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American Society of Nephrology
1510 H Street, NW, Suite 800
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Phone 202-640-4660, Fax 202-637-9793
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Role of PAD4 and NETs in Ischemia Reperfusion Injury in the Kidney

William Brian Reeves,1 Wesley M. Raup-Konsavage,1 Weiwei Wang,1 Jinqun Sun,2 Yanning Wang,2 1Div of Nephrology, Penn State College of Medicine, Hershey, PA; 2Biochemistry and Molecular Biology, Penn State Univ, Univ Park, PA.

Methods: CADPE induces NAD(P)H oxidase and MAPK-mediated neutrophil degranulation. Neutrophil degranulation is a defense against infection but may also contribute to tissue injury. The role of NETs in ischemic AKI is unknown. Peptidyl arginine deiminase 4 (PAD4) is essential for NET formation and regulates gene expression through the citrullination of histones. Methods: Wild-type (WT) mice and PAD4 KO mice were subjected to renal ischemia. Renal function, histology and circulating cell-free DNA were measured.

Results: PAD4 KO mice were markedly resistant to ischemic injury as measured by serum BUN (WT 136±14 vs KO 49±9 mg/dl, P<0.0001) and creatinine (WT 1.5±4 vs KO 0.6±0.7 mg/dl, P<0.0001). We assessed NET formation by measuring serum DNA levels. Serum DNA levels increased after IRI but were lower in KO than WT mice (1310±16 vs 1687±157 ng/ml, P<0.01). Additionally, we observed less citrullinated histone H3 in tissue from PAD4 KO vs WT mice. Kidney expression of TNF and IL-6 were lower, while IL-10 was higher, in KO vs WT mice. DNaseI has been used to reduce NET formation in vivo. Therefore, we treated WT mice with DNase just prior to ischemia and again 8 h after reperfusion. DNase treatment resulted in better preservation of kidney function (BUN: veh. 130±6 vs DNase 66.1±12 mg/dl and creatinine: veh. 1.48±0.24 vs DNase 0.84±0.06 mg/dl, P<0.0001). We determined if neutrophils were the major site of action for PAD4 in IRI, we transferred WT or PAD4 KO neutrophils into PAD4 KO mice prior to IRI. PAD4 KO mice which received WT neutrophils developed much greater injury than mice which received PAD4 KO neutrophils (BUN 136±9 vs 63±10 mg/dl, P<0.001). In contrast, neutrophils lacking TIFIR1 did not increase injury (BUN 73±6 mg/dl).

Conclusions: Our findings suggest that formation of NETs mediates IRI and that inhibition of PAD4 or degradation of NETs may reduce the severity of ischemic AKI. Moreover, neutrophils are targets of TNF in IRI, perhaps leading to NET formation.

Funding: NIDDK Support

Inhibition of Signal Transducer and Activator of Transcription 3 (STAT3) Proteins protects against Renal Ischemia-Reperfusion Injury

Jaewook Lee,1 Sun Moon Kim,2 Seung Hee Yang,1 Yun Su Kim,1 1National Cancer Center, Korea; 2Chungbuk National Univ Hospital, Korea; 3Seoul National Univ, Korea.

Background: STAT3 promotes survival of naïve T cells and differentiation of T helper 17 (Th17) cells. Cln three requiring 9 (Ctr9), a subunit of RNA polymerase II transcription factor complex, functions as a negative regulator of Th17 cells by repressing IL-17 (Th17) cells. Cln three requiring 9 (Ctr9), a subunit of RNA polymerase II

Methods: IR injury was induced in wild-type mice, wild-type mice pre-treated with CADPE (a STAT3 inhibitor), and mice with T cell-selective STAT3 deletion (Stat3flox/flox). Renal injury was assessed by serum creatinine and immunohistochemistry at 48 h. Activation of intrarenal Th17 cells was determined by intrarenal IL-17 concentrations and flow cytometry in intrarenal Th17 cells was determined by intrarenal IL-17 concentrations and flow cytometry in intrarenal Th17 cells. Changes in the proportions of Th17 cells following RNA interference of Ctr9 (Ctr9siRNA) were analyzed using flow cytometry. Primary human TECs were grown under hypoxia (1%, O2 for 6 h) with or without CADPE. Cytokine production was quantitated using real-time PCR and ELISA.

Results: Renal injury was significantly reduced in mice pre-treated with CADPE and Stat3flox/flox mice, both of which exhibited a significant reduction in intrarenal Th17 cells. Ctr9-siRNA treatment on intrarenal T cells further enhanced differentiation of Th17 cells, consistent with the inhibitory role of Ctr9 in Th17 differentiation. In cultured TECs, hypoxia upregulated Stat3, IL-17 receptor, and other markers of cell injury (e.g. IL-18). CADPE treatment significantly reduced STAT3 activation and the markers of cell injury. Interestingly, Ctr9 expression was also observed in TECs of normal kidneys and repressed with IR injury. Ctr9-siRNA treatment reduced the expression of STAT3 and Th17-related transcripts in TECs under hypoxia.

Conclusions: Inhibition of Stat3 protects against renal IR injury by reducing activation of Th17 cells and production of pro-inflammatory cytokines from TECs. Ctr9 is a negative correlate of Stat3 activity and functions as a negative regulator of IR-induced inflammation in both cell types.

Funding: NIDDK Support

Vagus Nerve Stimulation-Conditioned CD11b+ F4/80+ Cells Protect from Kidney Ischemia-Reperfusion Injury

Toshiyuki Inoue,1 Chikara Abe,1 Liping Xiong,2 Haruki Hatanaka,1 1Div of Nephrology and Center for Immunology, Inflammation and Regenerative Medicine, Univ of Virginia, Charlottesville, VA; 2Dept of Pharmacology, Univ of Virginia, Charlottesville, VA.

Background: We recently showed that prior vagus nerve stimulation (VNS) protects the kidney from ischemia-reperfusion injury (IRI) through the cholinergic anti-inflammatory pathway. The phenotypic change of macrophages (VNS induces M2 phenotype) in the kidney was observed by flow cytometry, however the causal role of these conditioned macrophages in vivo was not established.

Methods: CD11b+ splenocytes (MACS-enriched; 85% CD11b+ or peritoneal macrophages; 99% CD11b+ or peritoneal macrophages) positive for CD11b and CD11c were isolated from naive mice and alpha and 7 nioic acid cytosolcicin receptor (α7nAChR) knock out (α7KO) mice 24 h after electrical VNS (5 Hz, 50 for 10 min), then CD11b+ splenocytes or CD11b+F4/80+ peritoneal macrophages were transferred into the recipient mice. Kidney IR injury was performed 1 h after the adoptive transfer and kidney injury was evaluated 24 h later using plasma creatinine (Pcr), kidney-1 mRNA expression and histology (H&E).

Results: Adoptive transfer of CD11b+ splenocytes (1x106) cells from VNS-treated mice to recipient mice subjected to IRI provided greater protection than CD11b+ splenocytes (CD11b+F4/80+) peritoneal macrophages transferred (P<0.001). In contrast, the majority of saline transfused mice had higher creatinine than saline transfused VNS mice (1389±10 vs 1678±157 mg/ml, P<0.01). Additionally, we observed less citrullinated histone H3 in tissue from PAD4 KO vs WT mice. Kidney expression of TNF and IL-6 were lower, while IL-10 was higher, in KO vs WT mice. DNaseI has been used to reduce NET formation in vivo. Therefore, we treated WT mice with DNase just prior to ischemia and again 8 h after reperfusion. DNase treatment resulted in better preservation of kidney function (BUN: veh. 130±6 vs DNase 66.1±12 mg/dl and creatinine: veh. 1.48±0.24 vs DNase 0.84±0.06 mg/dl, P<0.0001). We determined if neutrophils were the major site of action for PAD4 in IRI, we transferred WT or PAD4 KO neutrophils into PAD4 KO mice prior to IRI. PAD4 KO mice which received WT neutrophils developed much greater injury than mice which received PAD4 KO neutrophils (BUN 136±9 vs 63±10 mg/dl, P<0.001). In contrast, neutrophils lacking TIFIR1 did not increase injury (BUN 73±6 mg/dl).

Conclusions: These data demonstrate that activation of CD11b+F4/80+ cells through α7nAChR is an important for the protective effect of VNS in AKI and extend our findings on the role of neuroimmune regulation of kidney injury through the inflammatory reflex pathway.

Funding: NIDDK Support, Government Support - Non-U.S.
Conclusions: Taken together, our data support that THP positively regulates macrophage proliferation and phagocytic activity. In addition to its effect on the epithelium, this emergent immuno-modulatory role could explain the protection conferred by THP in the setting of AKI.

Funding: VA Support

TH-OR006
Macrophage Extracellular Traps Induced by Mac-1 (CD11b/CD18) Dependent Platelet-Macrophage Interactions Promotes Acute Kidney Injury in Rhabdomyolysis Koshu Okubo, Matsuhiro Hayashi, Junichi Hirahashi. Apheresis and Dialysis Center; Keio Univ, School of Medicine, Tokyo, Japan.

Background: Rhabdomyolysis-induced acute kidney injury (AKI) is a critical complication after breakdown of skeletal muscles. Crush syndrome, an emergency condition caused by traumatic rhabdomyolysis, occurs commonly in natural disasters such as earthquakes and man-made disasters such as wars or terrorism. Recently, macrophages were implicated in disease pathogenesis, however, the detailed molecular mechanism remains unclear. Leukocytes release extracellular traps (ETs) composed of chromatin fibers and granule proteins to eliminate invading pathogens. However, ETs may also cause tissue damage.

Methods: We show that macrophages released ETs in a mouse model of rhabdomyolysis, and contributed to the pathogenesis of rhabdomyolysis-induced AKI.

Results: Administration of ET inhibitors, depletion of platelets, and genetic ablation of Mac-1 (leukocyte specific β2 integrin expressed on macrophages) ameliorated rhabdomyolysis-induced AKI. Herne-activated platelets enhanced macrophage extracellular traps (METs) production, involving intracellular ROS generation and histone citrullination. These results revealed an unanticipated role for platelets in rhabdomyolysis-induced AKI, and suggested that an interaction between platelets and Mac-1 contributed to disease pathogenesis.

Conclusions: Our findings provide a novel mechanism in rhabdomyolysis-induced AKI that Mac-1 may potentially be targeted for treatment of the disease.

Funding: Government Support - Non-U.S.

TH-OR007
FTY720 Regulates Mitochondria Biogenesis in Dendritic Cells to Prevent Acute Kidney Injury Elvira Kurnaeva, Kyle J. Alexander, Liping Huang, Amandeep Bajwa. Medicine, Univ of WA, Charlotteville, VA.

Background: FTY720, a S1PR agonist has been shown to protect kidneys from IRI. However, the mechanism of action remains unexplored.

Results: 50% two male Wistar rats were divided in: sham operated (S), right nephrectomy (RNx) and biIRI. Gli1+ cell numbers were higher in the outer medulla, the site of maximal injury. Although, the mRNA levels of AKI to CKD transition.

Conclusions: The FTY720 treatment resulted in the decrease of cell number via reducing HIF-1α signaling.

Funding: NIDDK Support, Private Foundation Support

TH-OR009
Early DNA Hypomethylation, HIF-1 α Reduction and Increased Oxidative Stress Promotes Acute Kidney Injury (AKI) to Chronic Kidney Disease (CKD) Transition Andrea Sanchez-Navarro,1,2 Norma Gonzalez Rubio,1 Rosalba Perez-Villalta,3 Norma Bobadilla.1 Molecular Physiology Unit, UNAM, UNAM, Mexico City, Mexico; Dept of Nephrology, Inst Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico.

Background: AKI is now recognized as an independent risk factor for CKD development. The mechanisms involved in the AKI to CKD transition are poorly understood and even less is known about the temporality of renal alterations along the transition. The aim was to analyze the time course response of inflammation, oxidative stress, hypoxia, and fibrosis, as well as, epigenetic modifications in the AKI to CKD transition.

Results: Fifty-two male C57BL/6 mice were divided into: sham operated (S), right nephrectomy (UNx) and nephrectomy plus left renal ischemia (45 min, UNx+IR) groups. The animals were sacrificed and studied at 1, 2, 3 or 4 months. At the end of each period, mean arterial pressure, creatinine clearance, and renal blood flow were determined. Mitochondrial and oxidative stress was assessed monthly. In the UNx+IR, the mRNA levels of hypoxia, hypoxia and fibrosis markers, as well as, the global DNA methylation were assessed since 1 to 4 months. Renal histopathological alterations were also examined.

Conclusions: After 4 months, the UNx+IR group developed CKD characterized by progressive proteinuria, renal dysfunction, glomerular hyper trophy, tubular dilatation and tubulointerstitial fibrosis. These alterations were not seen in S and UNx groups. Since 1-month after AKI, there was a significant increase in oxidative stress by 2-fold and a reduction in the global DNA methylation by 15% that remained along the study. HIF-1α and VEGF were completely depressed by 99% in the 1st and 2nd month, and then recovered in the UNx+IR group compared to control group. Whereas TGF-β and IL-6 were up-regulated lately and occurred when the renal fibrosis was detected.

Funding: Government Support - Non-U.S.

TH-OR010
The Gli1+ Kidney MSC Population Is Not Fixed but Dynamically Acquires Gli1 Expression after AKI Flavia G. Machado, Gizey C.S. Moreira,1,2 Koghamin O Hainmhire,1 Benjamin D. Humphreys,1,3 Div of Nephrology, Washington Univ in St. Louis, St. Louis, MO; 2Renal Div. of Sao Paulo, Sao Paulo, SP, Brazil.

Background: We have shown that Gli1+ expression in kidney defines a population of MSC-like pericytes that are the major myofibroblast progenitor population in kidney fibrosis. It is unclear whether this population is fixed, or if interstitial cells can dynamically gain Gli1 expression and myofibroblast differentiation capacity after injury.

Methods: We performed bilateral ischemia reperfusion injury (biIRI) in Gli1−/−;GFP reporter mice and evaluated the distribution and density of Gli1+ cells, over a 14 day time course. We investigated whether the Gli1+ population proliferated or if Gli1 expression occurred in a previously Gli1− population. In vitro, we cultured fibroblasts from normal renal (NRK-49F) with TGFβ and evaluated Gli1 expression.

Results: Using a moderate, reversible biIRI model (24 h BUN, 121 + 20, avg. + SD), Gli1 mRNA was progressively upregulated during days 1, 3, 7 and 14 after IRI reaching a maximal level of 14-fold over control mice on day 14. Quantitation of mRNA expression by automatic analysis revealed a double analysis peak by day 14 in the cortex, from 0.31±0.01 cells/mm2 in control vs 0.57±0.08 cells/mm2 in d4 IR1. Gli1+ cell numbers were higher in the outer medulla, the site of maximal injury. There, Gli1+ cells rose from 0.50±0.05 cells/mm2 at baseline to 1.64±0.15 cells/mm2 by day 14. As expected, all Gli1 cells were PDGFR+; Gli1 cells differentiated into myofibroblasts during AKI repair as well, reflected by acquisition of sMAMA expression by double immunofluorescent staining. Despite the overall increase in Gli1 cell number, there was no more than 0.5% of Gli1/Ki67 co-positive cells in cortex, and no more than 0.1% of Gli1/Ki67 co-positive cells in medulla at all time points.

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

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Conclusions: During AKI repair, stomal cells can acquire Gli1 expression de novo. Since Gli1 expression defines a myofibroblast progenitor population, these results indicate that myofibroblast progenitors are recruited from a Gli1-negative stomal cell pool, rather than the proliferation of a fixed Gli1-positive population.

Funding: NIDDK Support

TH-OR011

Novel Biomarkers Predict Progressive Nephropathy in Patients with Type 2 Diabetes after Acute Coronary Syndrome: The EXAMINE Trial

David M. Charytan,1 Muthiah Vaduganathan,1 William B. White,2 Craig A. Wilson,3 Stuart Kuper,$ Faiez Zannad,4 Christopher Paul Cannon,4 George L. Bakris,5 Brigham & Women’s Hospital; 1Univ of Connecticut; 2Takeda Development Center; 3Univ of Chicago; 4Univ de Lorraine and Centre Hospitalier Universitaire.

Background: Novel biomarkers may improve identification of individuals at risk of progressive nephropathy in type 2 diabetes (DM2), but prior studies are limited in size.

Methods: Filtration (Cystatin C) and urine tubular injury markers (neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule-1, [KIM1]) were collected in >90% and urine protein/Cr ratio [PCR] in >58% of 5,380 patients with DM2 and recent acute coronary syndrome enrolled in the EXAMINE trial. eGFR was estimated with the CKD-EPI equation. End-stage renal disease was defined as a requirement for dialysis or ESRD or 50% decline in eGFR ≤0.03 for all comparisons).

Results: Median follow-up was 18 mo and 71% had eGFR ≥60 mL/min/1.73m2.

Background: Over 30% of systemic lupus erythematosus (SLE) patients have kidney impairment. Urinary epidermal growth factor (uEGF), a marker representing tubular cell regenerative potential, adds prognostic value to estimated glomerular filtration rate (eGFR) and proteinuria in chronic kidney disease (CKD) patients. However, uEGF as a non-invasive biomarker for kidney function and CKD incidence in SLE has not been studied.

Results: In MILES SLE cases, uEGF was inversely correlated with baseline eGFR (r=-0.62, p<0.001) and its level distinguished CKD (AUC=0.80 by uEGF vs 0.62 by proteinuria). Further, uEGF distinguished ESRD in cases and controls (AUC=0.88). In C-PROBE, the inverse correlation of uEGF with eGFR was validated in LN cases (r=0.83, p<0.001), and over 3.5 years, uEGF correlated with change in eGFR (r=0.56, p<0.001).

Conclusions: This is the largest study to date of novel and traditional biomarkers and suggests they allow early identification of DM2 patients at risk for worsening kidney function.

Funding: Pharmaceutical Company Support - Takeda

TH-OR012

Plasma Biomarkers and Progressive GFR Decline in Early and Established Diabetic Kidney Disease: Analyses from ACCORD and VA NEPHRON-D Studies

Charles J. Wessohn,1 Jessica M. Pruszynski,1 Joseph S. Gordon,1 Charles F. Berthier,1 Stuart D. Faiez,2 Sioban D. Harlow,3 Wendy Marder,1 William Joseph Mceune,1 Faith M. Strickland,1 Charles Helmeric,2 Caroline Gordon,1 Celine C. Berthier,1 Matthias Kretzler,1 Afton L. Hasselt,1 Suzie Zick,2 The Michigan Kidney Translational Core,1 Wenzun Ju,3 Emily C. Somers,1 1U of Michigan; 2CDC; 3Internal Medicine, U of Birmingham.

Background: For the first time, in a high CKD risk population, we show that uEGF is superior to traditional biomarkers for kidney function and CKD incidence in SLE.

Methods: We recruited 108 smokers (n = 108), continued smokers (n = 83), and quitters (n = 25) were followed 5 years after starting ACE inhibition with yearly eGFR (P3<0.03 for all comparisons).

Results: Similarly, in VA NEPHRON-D, the adjusted ORs for sustained eGFR decline ranged from 1.7-2.4 per log increase in sTNFR1, sTNFR2, and KIM1-1. The other 3 biomarkers were not significantly associated with the renal outcome in either cohort.

Conclusions: Although the absolute concentrations differed, 3 plasma biomarkers (sTNFR1 and 2, and KIM1) were independently associated with higher risk of eGFR decline in T2DM persons with both early (ACCORD) and established DKD (VA NEPHRON-D).

Funding: NIDDK Support, Other NIH Support - CSTA UL1TR000433; CDC; NIH/NEIH, Other U.S. Government Support

TH-OR013

Urinary Epidermal Growth Factor Is Inversely Associated with Impaired Kidney Function in a Population-Based Lupus Cohort

Michelle R. Smith,1 Vijji Nair,2 Sioban D. Harlow,3 Wendy Marder,1 William Joseph Mceune,1 Faith M. Strickland,1 Charles Helmeric,2 Caroline Gordon,1 Celine C. Berthier,1 Matthias Kretzler,1 Afton L. Hasselt,1 Suzie Zick,2 The Michigan Kidney Translational Core,1 Wenzun Ju,3 Emily C. Somers,1 1U of Michigan; 2CDC; 3Internal Medicine, U of Birmingham.

Background: Over 30% of systemic lupus erythematosus (SLE) patients have kidney impairment. Urinary epidermal growth factor (uEGF), a marker representing tubular cell regenerative potential, adds prognostic value to estimated glomerular filtration rate (eGFR) and proteinuria in chronic kidney disease (CKD) patients. However, uEGF as a non-invasive biomarker for kidney function and CKD incidence in SLE has not been studied.

Methods: We measured 6 biomarkers: sTNFR1, sTNFR2, and KIM1, Cystatin C, NGAL, and PCR strongly associated with combined ESRD or 50% decline in eGFR and mean change in eGFR (P<0.03 for all comparisons).

Results: Similarly, in VA NEPHRON-D, the adjusted ORs for sustained eGFR decline ranged from 1.7-2.4 per log increase in sTNFR1, sTNFR2, and KIM1-1. The other 3 biomarkers were not significantly associated with the renal outcome in either cohort.

Conclusions: Although the absolute concentrations differed, 3 plasma biomarkers (sTNFR1 and 2, and KIM1) were independently associated with higher risk of eGFR decline in T2DM persons with both early (ACCORD) and established DKD (VA NEPHRON-D).

Funding: NIDDK Support, Other NIH Support - CSTA UL1TR000433; CDC; NIH/NEIH, Other U.S. Government Support

TH-OR014

Cigarette Smoking Partially Negates the Kidney Protective Effect of ACE Inhibition in Stage 2, Non-Diabetic, Hypertension-Associated CKD

Bethany Roehm,1 Jan Simoni,2 Jessica Pruszyinski,3 Donald E. Wesson,4 1Internal Medicine, Tifts Medical Center, Boston, MA; 2Surgery, Texas Tech Univ HSC, Lubbock, TX; 3Biostatistics, Scott and White Healthcare, Temple, TX; 4Internal Medicine, Scott and White Healthcare and Texas A&M HSC College of Medicine, Temple, TX.

Background: Cigarette smoking appears to exacerbate nephropathy progression but by unknown mechanisms.

Methods: We recruited 108 smoking and 108 non-smoking, non-diabetic adults with CKD due to hypertension-associated nephropathy, stage 2 eGFR (60-89 mL/min/1.73 m2), and urine albumin (mg)-to-creatinine (g) ratio (albCr <200). Smokers received substance abuse counseling, nicotine patch, and oral bupropion to encourage quitting by pre-specified reductions of urine cotinine. Non-smokers (n = 108), continued smokers (n = 83), and quitters (n = 25) were followed 5 years after starting ACE inhibition with yearly eGFR (CKD-EPI), albCr, and urine (mg)-to-creatinine (g) isoprostane 8-isoprostaglandin F2α (8-iso/Cre), a measure of oxidative stress.

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

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Results: There was no difference in entry eGFR (p=0.53), albumin/creatinine ratio (p=0.30), or systolic and diastolic blood pressure (p=0.06 and 0.38, respectively) and no difference in either blood pressure at 5 years (p=0.45 and 0.25). Entry 8-isooxyl was higher (p<0.01) in continued smokers (4.3 µg/g) and quitters (4.1 µg/g) than non-smokers (1.6 µg/g). At 1 year, non-smokers had lower than entry albumin/creatinine (35±143 vs 424±148, p<0.01), consistent with ACE-related reduced kidney injury. By contrast, at 1 year continued smokers had higher albumin/creatinine (453±152 vs 42±138, p<0.01), consistent with increased kidney injury despite ACE. One-year albumin/creatinine (356±178 vs 367±160, p=0.15) was not different from entry. One year urine 8-isooxyl was higher in continued smokers (3.6±0.8) than non-smokers (1.6±0.3, p<0.01) and quitters (1.6±0.3, p<0.01). At 5 years, eGFR was lower (p<0.01) in continued smokers (54±9.6 ml/min) than non-smokers (66±8.5 ml/min) and quitters (64±1.6 ml/min).

Conclusions: Continued cigarette smoking in CKD partially negates kidney protection associated with ACEI possibly by inducing oxidative stress, an effect which appears to be ameliorated by smoking cessation.

Funding: Pharmaceutical Company Support - Texas Tech University

TH-OR015

Risk and Protective Metabolomic Signatures Associated with Albuminuria in Type 1 Diabetes (T1D): A Joslin Kidney Study

Adam Smiles, Melissa Major, Stephanie E. Croall, Andrzej S. Krolewski, Monika A. Niewczas, Medicine, Veterans Affairs Boston Healthcare System, Boston, MA; Genetics and Epidemiology, Joslin Diabetes Center, Boston, MA.

Background: Albuminuria and renal function impairment are intermediate phenotypes of diabetic nephropathy. We aimed to investigate whether these two phenotypic features would be associated with distinct metabolomic signatures in a large study of subjects with T1D of a long duration.

Methods: Plasma metabolites were analyzed via mass spectrometry-based global platform in a cross-sectional study of 419 subjects (T1D duration: median, 25th, 75th percentile: 24, 18-31 years). We examined the associations of metabolites with albumin/creatinine ratio (ACR) and renal function (eGFR) in the following study groups with normal renal function: nonalbuminuric (Resistors, n=92), microalbuminuric (n=44) and proteinuric (n=189)) and in subjects with proteinuria and CKD stage 3 (n=94).

Results: Of the 580 detected metabolites, 383 metabolites were measured at ≥ 80% frequency in the study subjects. With Bonferroni correction, 55 metabolites were significantly associated with ACR (26, 291). Among the 26 metabolites that levels were higher in the Resistors than in subjects with microalbuminuria and proteinuria; 13 metabolites (50%) belonged to the lipid class. Top protective lipid metabolites included pyroglutamate (e.g. undecanoyl) and dicarboxylic (e.g. decanecarboxylic) medium chain fatty acids. 28 metabolites were significantly elevated in the presence of an impaired eGFR. There were 12 metabolites that were associated with both, albuminuria and eGFR.

Conclusions: Metabolomic signatures associated with albuminuria and renal function impairment in diabetic kidney disease are uncoupled to a major degree. Our study suggests that medium chain fatty acids may play a protective role against albuminuria in T1D subjects.

Funding: NDDK Support, VA Support, Private Foundation Support, Clinical Revenue Support

TH-OR016

Association between Soluble Klotho and Change in Kidney Function: The Health ABC Study


Background: Chronic kidney disease (CKD) is a condition of soluble klotho deficiency. Despite associations between low soluble klotho and higher degrees of oxidative stress and fibrinosis, conditions that promote kidney damage, the longitudinal association between soluble klotho levels and change in kidney function has not been well studied.

Methods: Serum soluble u-klotho was assayed in 2,496 participants within the Health Aging and Body Composition Study, a cohort of well-functioning older adults. Kidney function was determined by cystatin C at baseline and years 3 and 10. Associations between baseline soluble klotho levels and rapid decline in kidney function (defined as either estimated glomerular filtration rate (eGFR) decline of greater than 30% or decline in eGFR greater than 3 ml/min/year) and incident CKD (incident eGFR < 60 ml/min/1.73 m² and at least 1 ml/min/year decline) were evaluated. Models were adjusted for demographics, baseline eGFR, UACR, comorbidity, and measures of mineral metabolism including FGF-23.

Results: Mean (SD) age was 75 years (3), with 52% female, and 38% African American. Median klotho level was 630 pg/ml (25%—75% = 477 – 817 pg/ml). In fully adjusted continuous models, each two-fold higher klotho had significant associations with lower odds of rapid decline in kidney function (30% decline: OR = 0.78 [0.66, 0.93] and > 3 ml/min/year decline: OR = 0.85 [0.73, 0.99]) but was not significantly associated with incident CKD (IRR = 0.90 [0.78, 1.04]).

Conclusions: Higher soluble klotho concentrations are independently associated with a lower risk of decline in kidney function. Future studies should replicate these results in those with advanced CKD and evaluate the mechanism underlying these findings.

Funding: Other NIH Support - NIA

TH-OR017

Lung Function and Incident Kidney Disease: The Atherosclerosis Risk in Communities (ARIC) Study

Keiichi Sumida, Lucia Kwak, Morgan Grams, Kunihiro Yamagata, Csaba P. Kovessy, Josef Coresh, Kunhiro Matsushita, Johns Hopkins Univ, Baltimore, MD; Univ of Tsukuba, Ibaraki, Japan; Univ of Tennessee Health Science Center, Memphis, TN.

Background: Reduced lung function is associated with various clinical outcomes like cardiovascular disease. Little is known about its association with incident ESRD and CKD.

Methods: In 14,946 ARIC participants aged 45-64 years at baseline (1987-89), we examined the associations of race- and sex-specific quartiles of percent-predicted forced vital capacity (FVC) and the proportion of forced expiratory volume in 1 second in FVC (FEV1/FVC) with subsequent risk of ESRD (initiation of dialysis therapy, transplantation, or death due to CKD) and CKD (ESRD <25% decline in eGFR reaching <60 mL/min/1.73 m², or CKD-related hospitalizations) through 2012, using Kaplan-Meier method and Cox proportional hazards models with adjustment for potential confounders.

Results: During 25 years of follow-up, 526 and 3,704 cases developed ESRD and CKD, respectively. The incidence of ESRD was higher in those with lower percent-predicted FVC and FEV1/FVC with subsequent risk of ESRD (initiation of dialysis therapy, transplantation, or death due to CKD) and CKD (ESRD <25% decline in eGFR reaching <60 mL/min/1.73 m², or CKD-related hospitalizations) through 2012, using Kaplan-Meier method and Cox proportional hazards models with adjustment for potential confounders.

Conclusions: Reduced lung function, particularly lower percent-predicted FVC, is independently associated with CKD progression.

Funding: Other NIH Support - NHLBI
**TH-OR018**

A Peptide Transporter 2 (PEPT2) Gene Variant Predicts the Severity of Porphyria-Associated Chronic Kidney Disease

Nicolas Pallet, Alexandre Karrai, Alexandre Thervet, Hervé Puy

**Background:** CKD occurs in the majority of patients with AIP (Acute Intermittent Porphyria). During AIP, d-aminolevulinic acid (ALA) is excreted in urine, where it promotes apoptosis of proximal tubular cells, leading to tubulointerstitial damage. The peptide transporter 2 (PEPT2, also known as SLC15A2) is expressed by renal proximal tubular cells and mediates the reabsorption of ALA. A functional single nucleotide variant is associated with a lower affinity of the transporter for ALA.

**Methods:** To test if PEPT2 variants impact the severity of AIP induced CKD, we followed a cohort of 122 patients with AIP for 10 years. PEPT2 has been genotyped for the T/C substitution at the position 1048 in exon 13, and the T/C substitution at position 1225 (exon 15) (total linkage disequilibrium). The allelic frequency of the variants was 0.53, and the distribution was in accordance with the Hardy Weinberg equilibrium.

**Results:** Carriers of the PEPT2*1*1 genotype experienced significantly worse renal function compared to *2 carriers (p=0.41: 66.6±2.7 and 78.1±3.8 ml/min/1.73m², p=0.004). eGFR loss was -11 ml/min/1.73m² over the follow-up period for PEPT2*1*1 carriers, compared to -2.4 ml/min/1.73m² for the PEPT2*1*2 genotype and +3.4 ml/min/1.73m² for PEPT2*2*2 patients (p=0.0016). During the follow-up, incident renal dysfunction (defined by eGFR<60 ml/min/1.73m²) was diagnosed in up to 20% PEPT2*1*1 patients, 14% of the PEPT2*1*2 and 0% of the PEPT2*2*2 carriers (p=0.007). At the end of the follow-up, 68% of the PEPT2*1*1 had eGFR<60 ml/min/1.73m² compared with 37% of the PEPT2*1*2, and 15% of the PEPT2*2*2 (p=0.002). In multiple regression models, PEPT2*1*1 genotype remained significantly associated with eGFR<60 ml/min/1.73m², with an odds ratio of 10.7. Losartan, a specific inhibitor of PEPT2, reduces ALA intracellular accumulation and inhibits ALA-induced apoptosis in proximal tubular cells in culture.

**Conclusions:** PEPT2 is critical to the severity of AIP-induced CKD and is a potential therapeutic target. Since PEPT2 transports peptide-like molecules such as antiviral nucleoside prodrugs, it may represent a susceptibility factors for the nephrotoxicity of these drugs.

**TH-OR020**

Multiple Proteins of TNF Superfamily Contribute to Progression to ESRD in Diabetes in a Global Profiling Study

Monika A. Nieczewaz, John J. Tsay, Adam Smiles, Melissa Major, Joseph V. Bonventre, Andrzej S. Krolevics

**Background:** We previously showed, using a targeted approach, that Tumor Necrosis Factor Receptors 1 & 2 (TNFRs) are robust predictors of renal function decline in diabetes. Here, we aimed to determine a comprehensive inflammatory signature associated with risk of ESRD using global profiling.

**Methods:** Our study group included 219 Joslin Kidney Study participants with T1D, proteinuria stage CKD Stage 3 that were followed up to 12 years. Non-Progressors (eGFR decline ≤ 2.5 ml/min/1.73m²) accounted for 34% of the cohort (n=76), whereas Rapid Progressors (eGFR decline > 5 ml/min/1.73m²) comprised 38% (n=84). Proteomic profiling of inflammatory proteins (n=210) was performed on an aptamer-based platform (Somascan).

**Results:** In the multivariate analysis 38 proteins differed between Progressors and Non-Progressors (Bonferroni corrected p value <0.05). A roster of significant proteins was enriched with TNF family members that included receptors: TNFR1 and TNFR2, TAJ, DR6, and ligands TWEAK or TNFSF15. TNFα and β were not associated with the outcome. Correlations among TNF superfamily members (figure: orange to blue) did not correspond to their known ligand-receptor interactions (figure: black open squares).

**Conclusions:** Our global proteomic profiling study confirmed associations of TNFRs as robust predictors of renal function decline in T1D. Further, it revealed that TNF superfamily members accounted for a major part of the inflammatory signature contributing to the progression of diabetic nephropathy. Mechanisms regulating circulating levels of this family and their contributions to the disease progression urgently need to be determined.

**Funding:** NIDDK Support, Private Foundation Support

**TH-OR019**

Glycoprotein A (GlyA), a Pro-Inflammatory Marker of Protein Glycosilation, Is Associated to Albuminuria Independently of Cardiovascular Risk Factors and C-Reactive Protein: Results from ELSA-Brasil

Silvia M. Titin, Roberto Pecoits-Filho, Isabela M. Bensoner, Paulo Lotufo

**Background:** Systemic inflammation has been implicated in several chronic diseases. GlycA is a new nuclear mass resonance (NMR) spectroscopy-derived biomarker of systemic inflammation that reflects protein glycosilation. We evaluated the role of GlycA in CKD, using albuminuria as a surrogate marker.

**Methods:** The association between GlycA, measured by NMR, LabCorp, (Raleigh, NC) and overnight 12-hour albuminuria was evaluated among 5050 participants from the Sao Paulo site of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

**Results:** GlycA was higher among older, women, smokers, alcohol abusers, obese and those with a history of diabetes, dyslipidemia or dysplasias. In addition, albuminuria was positively associated with GlycA. In linear regression, GlycA was significantly associated to log albuminuria (B 0.0008; 95%CI 0.0007–0.0009, P<0.0001), remaining significant after adjustment for age, sex, diabetes, SBP, smoking, alcohol and lipids. Importantly, the association between GlycA and albuminuria remained significant after hsCRP was added to the model. In logistic regression, GlycA was positively related to the risk of being micro or macroalbuminuric (versus normoalbuminuric), even after adjustments including hsCRP (OR 1.008, 95%CI 1.000–1.010, p=0.0001). By repeating this model with a stepwise procedure, GlycA was left in the model, while hsCRP was not. In the ROC curve, GlycA had a higher AUC in comparison to hsCRP (p=0.06, for association to micro or macroalbuminuria).

**Conclusions:** In conclusion, the present study demonstrates that GlycA is associated with albuminuria, independently of other major risk factors for CKD progression, including (and with a stronger association than) hsCRP. Our results suggest that GlycA may be an interesting novel marker of CKD progression, through its protein glycosylation-induced inflammation properties.

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

**TH-OR021**

Akt Is a MultiFaceted Protein in Albumin Endocytosis

Elif Erkan, Cory S. Newland

**Background:** Albumin in the glomerular filtrate is received by receptor mediated endocytosis (RME) in proximal tubule epithelial cells. We reported a link between albumin endocytosis and cell signaling protein, protein kinase B (Akt). Akt1 and Akt2 both mediate albumin endocytosis in proximal tubule epithelial cells in culture. We propose that Akt mediates albumin endocytosis through its interaction with clathrin associated sorting proteins.

**Methods:** Inhibition of Akt1 and Akt2 in proximal tubule epithelial cells is accomplished by generation of Akt1/2 lox/lox SGLT2 cre mouse. Urinary albumin and creatinine excretion is measured as 24-hour urine collection. Renal expression of megalin, cubilin and clathrin HC is evaluated by western blotting and immunofluorescence. Protein-protein interactions are assessed by communoprecipitation experiments.

**Results:** Global knock-out (KO) of Akt1 or Akt2 causes down regulation of megalin and cubulin expression in the proximal tubule epithelial cells associated with increased urinary albumin excretion and low molecular proteinuria. In order to eliminate systemic effects of genetic inhibition Akt1 and Akt1, we generated a mouse with targeted deletion of Akt1 (KOx) and Akt2 (Akt1/2lox/lox SGLT2 cre mouse). Protein expression of clathrin heavy chain was evaluated by western blotting and immunofluorescence. Protein-protein interactions are assessed by communoprecipitation experiments.

**Conclusions:** Global knock-out (KO) of Akt1 or Akt2 causes down regulation of megalin and cubulin expression in the proximal tubule epithelial cells associated with increased urinary albumin excretion and low molecular proteinuria. In order to eliminate systemic effects of genetic inhibition Akt1 and Akt2, we generated a mouse with targeted deletion of Akt1 and Akt2 (Akt1/2lox/lox SGLT2 cre mouse). Protein expression of clathrin heavy chain was evaluated by western blotting and immunofluorescence. Protein-protein interactions are assessed by communoprecipitation experiments.

**Funding:** NIH/OD ID:R01DK107062, NIDDK Support, Private Foundation Support
Mixed Lineage Kinase Domain-Like (MLK) Mediates Necroptosis in humans Nina Himmerkus,1 Hannes Olauson,2 Ina Maria Schieszl,3 Jan U. Becker,4 Karl Kunzelmann,1 Markus Bleich,1 Joel M. Weinberg,1 Andreas Linkermann.5 1Inst of Physiology, Christian-Albrechts-Univ, Kiel, Germany; 2Div of Renal Medicine, CLINTEC, Karolinska Inst, Stockholm, Sweden; 3Dept of Pathology, Univ of Regensburg, Regensburg, Germany; 4Inst of Pathology, Univ Hospital of Cologne, Cologne, Germany; 5Dept of Internal Medicine, VA Ann Arbor Healthcare System, Univ of Michigan, Ann Arbor, MI; 6Clinic for Nephrology and Hypertension, Christian-Albrechts-Univ, Kiel, Germany.

Background: Necrosis is a pathophysiological hallmark of diseases including myocardial infarction, stroke, sepsis, acute tubular necrosis, autoimmunity and cancer. Necroptosis is a form of regulated necrosis mediated by receptor-interacting protein kinase 3 (RIPK3) and pseudokinase mixed lineage kinase domain-like (MLK), a RIPK3 target. Activation of necroptosis is required for necroptosis execution in vitro, but the role of MLK in vivo has not been investigated in preclinical disease conditions or humans.

Methods: In vivo mouse models, ex vivo investigation of freshly isolated nephron segments, human kidney transplant biopsies.

Results: We demonstrate that MLK-deficient mice are protected from all necroptosis-related in vivo mouse models such as TNFα-mediated severe inflammatory response syndrome (SIRS) and renal ischemia-reperfusion injury (IRI). Freshly isolated perfused proximal tubules of MLK-deficient mice showed reduced single cell death events and a delayed onset in synchronized tubular necrosis. Moreover, intratubal microscopy revealed a strongly elevated peritubular capillary blood flow in MLK-deficient mice in comparison to wild type littermates. In matched human kidney transplant biopsies, the activated form of MLK (pMLKL) was detected in endothelial cells within two hours after transplantation and in parenchymal cells within four days.

Conclusions: In summary, MLK deficiency protects mice from renal damage by i) the prevention of parenchymal necroptosis and ii) an increase in capillary blood flow. In addition, this is the first detection of activation of the necroptosis pathway in humans.

TH-OR024

Pik3c3 Mediates Nephron Loss-Induced Compensatory Nephron Hypertrophy Ting Liu,1 Jinxuan Xu,1 Benjamin D. Humphreys,2 Caihong Xu,1 Jian-Kang Chen.3 Cellular Biology & Anatomy and Medicine, Medical College of Georgia at Augusta Univ, Augusta, GA; 1Div of Medicine, Washington Univ School of Medicine, St. Louis, MO.

Background: Nephron loss stimulates the residual nephrons to undergo compensatory nephron hypertrophy (CNH), which is implicated in progressive nephron damage. Activation of the mechanistic (formerly mammalian) target of rapamycin complex 1 (mTORC1) mediates uninephrectomy (UNX)-induced CNH. We recently observed class 3 phosphatidylinositol 3-kinase (Pik3c3) activation in the remaining kidney after UNX. However, whether Pik3c3 activation is essential for mTORC1 activation and CNH remains undefined.

Methods: We created a Pik3c3−/− mouse model and crossed it to Slc34a1 CreER2T2 mice to generate tamoxifen-inducible proximal tubule-specific Pik3c3 knockout (KO) mice, which have a genotype of Pik3c3−/−,Slc34a1 CreER2T2 (+). Gender-matched Pik3c3−/−,Slc34a1 CreER2T2 (+) littermates were used as controls (Ctrl).

Results: Upon induction with tamoxifen (120 mg/kg IP at 6 weeks of age), KO mice but not Ctrl mice showed Pik3c3 deletion only in the proximal tubules (mainly in the S1 and S2 segments). The KO mice did not exhibit any apparent phenotype, with a mean body weight and kidney-to-body weight ratio similar to those of Ctrl littermates. It is known that in response to UNX, all components of the nephron may hypertrophy to a certain degree but the proximal tubule undergoes the most prominent hypertrophy. Interestingly, when subjected to UNX, KO mice developed significantly less renal hypertrophy compared to Ctrl mice, revealed by UNX-induced increases in kidney-to-body weight ratio (Ctrl: 33.15±1.97 vs. KO: 15.81±2.82%; p<0.001, n=7) and protein-to-DNA ratio (Ctrl: 25.00±0.40 vs. KO: 9.78±2.38%; p<0.05, n=7). Signaling studies with immunoblotting and immunostaining indicated that Pik3c3 knockout inhibited UNX-induced mTORC1 activation in the proximal tubules, particularly in the S1 and S2 segments.

Conclusions: This study provides the first genetic evidence of Pik3c3 activation as a major mechanism mediating nephron loss-induced residual nephron hypertrophy upstream of mTORC1 activation.

Funding: NIDDK Support

TH-OR025

Bone Marrow Is Central to the Severity of Gadolinium-Associated Systemic Fibrosis Brent Wagner,1 Chunyan Tan,2 Viktor Drel,2 Jeffrey L. Barnes,2 Yves C. Gorrin,3 Doug Yoon Lee.1 1Medical Service, South Texas Veterans Health Care System, San Antonio, TX; 2Medicine (Nephrology), Univ of Texas Health Science Center at San Antonio, San Antonio, TX.

Background: Gadolinium-based magnetic resonance imaging contrast induces systemic fibrosis in humans and rodents. Cumulative doses correlate with severity. Bone marrow–derived fibrocytes accumulate in the dermis. Whether target organs liberate chemokines to recruit these cells or if they are stimulated to home to the affected tissue is unknown.

Methods: Transgenic (tagged) donor rats were treated with gadolinium–based contrast. Bone marrow was obtained from the treated animals and age–matched controls. Rats with subcutal nephrectomies were lethally–irradiated followed by salvage transplantation with either the contrast–naïve or contrast–exposed bone marrow. Bone marrow recipients were transplanted into control or contrast–exposed recipients. The respective ligands, monocyte chemotactant protein and C-C chemokine receptors 2 and 7, and oxidative stress were all increased in skin from the contrast–treated animals—all parameters more severe in recipients of contrast–treated animals. The respective ligands, monocyte chemotactant protein 1 and C-C motif ligand 19, were both elevated in the skin from contrast–treated animals. When a C-C chemokine receptor inhibitor was co-administered with contrast, the severity of skin disease (including dermal cellularularity) was reduced. Neutralizing antibody to monocyte chemotactant protein 1 suppressed myocardial infiltration (using an in situ skin punch biopsy/labeled bone marrow co-culture assay).

Conclusions: These data demonstrate that the dermal liberation of specific chemokines recruits circulating myofibroblasts. The systemic fibrosis is augmented by bone marrow transfer from a contrast–treated mouse. This multiorgan fibrosis results from an increased propensity to apoptosis, with reduced expression of NRF2, glutathione content, decreased mitochondrial membrane potential and Bcl-2 expression. Overexpression of a constitutively active form of NRF2 (caNRF2) in NOX4-depleted cells rescued most of this phenotype in cultured cells, implying that NRF2 regulation by ROS from NOX4 may play an important role in its anti-apoptotic property in kidney tubular cells.

Conclusions: NOX4 protein displays anti-apoptotic properties in renal tubular cells subjected to injury. NOX4 deletion aggravates IRI lesions and renal function in mice. Baseline NRF2 regulation by NOX4 may play an important role in this phenotype, whereas other pathways are not excluded. NOX4 inhibition may aggravate tubular injury in stress conditions.

Funding: Government Support - Non-U.S.
TH-OR027

Kim1 Mediates the Upstage of Exosomes and Transfer of MHC II to Bart J. Kramers, Craig R. Brooks, Drhuti P. Chen, Alberto Lazarro Fernandez, Joseph V. Bonventre, Renal Div, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; Medicine, UVA Hospitals Case Medical Center, Cleveland, OH; Renal Physiopathology, Hospital G.U. Gregorio Marañon, Madrid, Spain.

Background: Urinary exosomes (EXO) are lipid membrane bound structures that mediate intercellular signaling through the transfer of proteins, miRNA and other factors. Kidney injury molecule 1 (Kim-1) acts as a phosphatidylserine (PS) receptor, inducing the uptake of apoptotic cells and necrotic debris. We hypothesize that Kim-1 acts as an endocytosis receptor, taking up EXO containing PS and mediating the intercellular exchange of signaling molecules, such as MHC II.

Methods: LLC-PK1 cells expressing Kim-1 (PK1-Kim1) and cells expressing empty vector (PK1-pcDNA) were incubated with liposomes composed of PS and fluorescein labeled phosphatidylcholine (PC) or EXO isolated from LLC-PK1 cells, mouse dendritic cells (DC) or human urine by ultracentrifugation. EXO were fluorescently labeled with CytoTracker dye or MHC II-FITC. Uptake was quantified by measuring fluorescence intensity and flow cytometry. EXO were characterized by western blot and electron microscopy. MHC II expression levels in urinary EXO from healthy subjects and CKD patients were determined by western blot.

Results: PK1-KIM-1 took up significantly more liposomes than PK1-pcDNA. EXO derived from LLC-PK1 cells, DCs and urine were positive for EXO markers HSP70, Flipt-1 and TSG101. The diameter of EXO were between 30-150 nm. Kim-1 expressing cells took up significantly more EXO than empty vector expressing cells independent of the source of EXO. Urinary EXO from CKD patients were found to carry MHC II while EXO from healthy subjects were MHC II negative. We found the transfer of MHC II to primary PTCs to be greater in cells expressing Kim-1 after incubation with DC-derived EXO compared to LLC-PK1 cells. Urinary receptor for EXO from PK1-KIM-1 mice carried MHC-II, while urinary EXO in healthy subjects did not. MHC-II on EXO can be transferred to and presented by Kim-1 positive cells, suggesting EXO may serve to link DC activation to PTC MHC II expression and antigen presentation cells in inflammatory settings.

Funding: NIDDK Support

TH-OR028

RTN1A Is a Key Mediator for Progression of Acute Kidney Injury to Chronic Kidney Disease through Endoplasmic Reticulum Stress Ying Fan, Wenzhen Xiao, Kyung (Kim) Lee, Jiejun Wen, Jie Zhang, Niansong Wang, Jiong H. Chen; 1Dept of Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People’s Hospital, Shanghai, China; 2Dept of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: A large body of evidence suggests that severe acute kidney injury (AKI) could progress to chronic kidney disease (CKD). ER stress has been considered as a key pathological process leading to tubular cell injury in AKI. However, it remains unclear whether sustained and maladaptive ER stress contributes to the progression from AKI to CKD. Recently, we reported that RTN1A expression is highly associated with the progression of human kidney disease and increased RTN1A expression in renal tubular epithelial cells (RETECs) induces apoptosis and renal fibrosis in the ULO mouse through induction of ER stress. Based on these findings, we hypothesized that RTN1A mediates the progression of AKI to CKD through induction of maladaptive ER stress in RETECs.

Methods: To test this, we generated doxycycline-inducible RTN1A RTEC-specific knockdown and over expression mice. Meanwhile, we studied the expression of RTN1A and other ER stress markers in kidney biopsies of 50 AKI (ATN and AIN) patients at various disease stages.

Results: We found that induction of RTN1A knockdown in RETECs had reduced ER stress and apoptosis of RETECs at the AKI stage and minimal renal fibrosis at the late stage in mice with folic acid nephropathy (FAN) or aristolochic acid nephropathy (AAN). In contrast, induction of RTN1A overexpression in RETECs at the AKI stage resulted more ER stress and apoptosis of RETECs at the AKI stage and more renal fibrosis at the late stage in these mice with FAN or AAN. Then, we validated that in patients with AKI there was also a significant association between renal expressions of RTN1A and ER stress markers (Phospho-PERK and CHOP). Interestingly, we found in 10 patients with progression of AKI to CKD, RTN1A and CHOP expressions were significantly higher than those without progression to CKD.

Conclusions: In conclusion, our data suggest that RTN1A is a key molecule mediating the progression of AKI to CKD through induction of sustained and maladaptive ER stress in renal tubular epithelial cells.

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

TH-OR029

Proximal Tubule Deletion of Dynamin Related Protein 1 Protects against Renal Ischemia-Reperfusion Injury Heather M. Perry, Hong Ye, Liping Huang, David Kashatus, Mark D. Okusa; 1Dept of Medicine, Div of Nephrology, Center for Immunology, Inflammation and Regenerative Medicine, UVA; 2Dept of Microbiology, Immunology and Cancer Biology, UVA, Charlottesville, VA.

Background: Mitochondrial dysfunction plays a crucial role in the pathogenesis of kidney disease. A key mediator of mitochondrial function is the GTPase, dynamin related protein 1 (DRP1). Pharmacological inhibition of DRP1 in mice has shown to protect against ischemia mediated AKI. Yet, the specific cellular target of DRP1 inhibition in AKI has not been determined. Proximal tubule cells are highly dependent on mitochondrial function. Thus, we hypothesize that the genetic deletion of DRP1 in proximal tubules (PT) protects against renal ischemia-reperfusion injury (IRI) in mice.

Methods: PckCre+ Drp1−/− (PT-Drp1 KO, n = 9) and littermate control PckCre+ Drp1+/− (n = 8) mice were subjected to 26′ of bilateral renal ischemia or sham operation. After 24hr of reperfusion, plasma was collected to quantify PC as a measure of kidney function and kidneys were prepared for assessment of acute tubular necrosis (ATN) by H&E staining, TUNEL and Ki67 positivity by immunofluorescence, quantification of mRNA transcripts by RT-qPCR and neutrophils (CD45+ CD11b+Ly6G+) by flow cytometry.

Results: PT-Drp1 KO mice had attenuated IRI-induced PC levels compared to control mice (1.44 vs. 0.35 mg/dl respectively, p < 0.001). Consistent with preserved kidney function, PT-drp1 KO mice had attenuated renal injury indicated by ATN and transcript levels of tubule injury markers Kim1 and Ngal compared to controls. Lastly, PT-Drp1 KO mice had reduced renal inflammation characterized by fewer neutrophils and transcript levels of Il6 and Ccl2 compared to control mice. Mechanistically, kidneys from PT-Drp1 KO mice had fewer TUNEL+ and increased Ki67+ epithelial cells.

Conclusions: Loss of PT DRP1 directs epithelial cells from IRI induced cell death pathways to proliferation, enhancing renal recovery. Recovered tubules prevent tubular damage and subsequent neointimal formation. Targeting DRP1 and mitochondrial function may be a therapeutic strategy to divert PT cells from cell death to recovery pathways, mitigating AKI.

Funding: NIDDK Support

TH-OR030


Background: Acute kidney injury (AKI) causes severe morbidity and mortality and chronic kidney disease (CKD). Mortality is particularly marked in the elderly and with pre-existing CKD. To date, therapeutic targets based models of AKI have failed to translate into preventative or therapeutic treatments. Oxidative stress is a common theme in models of AKI induced by ischemia/reperfusion injury (I/R) or sepsis. We recently characterized an intracellular isoform of matrix metalloproteinase-2 (MMP-2) induced by oxidative stress-activated expression of an alternate promoter in the first intron of the MMP-2 gene. This generates an N-terminal truncated MMP-2 isoform (NTT-MMP-2) that is retained intracellularly and is localized to the mitochondria. Significantly, the NTT-MMP-2 isoform is expressed in the proximal tubules of older mice (14 months) and in models of CKD. We recently determined that NTT-MMP-2 is induced in human renal transplants with delayed graft function and that NTT-MMP-2 expression correlates with tubular epithelial cell injury, validating NTT-MMP-2 as a potential target.

Methods: To determine mechanism(s) of action, we generated proximal tubule cell-specific NTT-MMP-2 transgenic mice.

Results: While morphologically normal at the light microscopic level at 4 months, there was evidence for increased mitochondrial oxidative stress. Ultrastructural studies revealed foci of epithelial cell necrosis, loss of the mitochondrial permeability transition and mitophagy. To determine if NTT-MMP-2 expression enhances sensitivity to I/R injury, we performed limited unilateral I/R, sufficient to induce mild tubular injury in wild type mice. In contrast, expression of the NTT-MMP-2 isoform resulted in a dramatic increase in tubular cell necrosis, inflammation and fibrosis. NTT-MMP-2 mice had enhanced expression of innate immunity genes and prolonged release of danger associated molecular pattern (DAMP) molecules.

Conclusions: We conclude that NTT-MMP-2 “primes” the kidney to enhanced susceptibility to I/R injury via induction of mitochondrial dysfunction. NTT-MMP-2 may be a novel AKI preventative or treatment target.

Funding: NIDDK Support, VA Support
TH-OR031 Treatment of Myeloma Cast Nephropathy: A Randomized Trial Comparing Intensive Hemodialysis with High Cutoff or Standard High-Flux Dialyzers (The MYRE Study) Frank Brudux,1 Pierre-Louis Carron,2 Eric Alamartine,3 Marie-Noëlle Peraldi,4 Alexandre Karras,5 Cécile M. Vigneur,1 Alain Wynckel,6 Nolwenn Rabot,7 Christian Combe,8 Sylvie Chevet,9 Jean-Paul Fermard.10

Background: Multiple myeloma (MM) is often revealed by acute kidney injury (AKI) usually related to cast nephropathy (CN). Recovery of renal function is a key prognostic factor. With novel anti-myeloma agents, hemodialysis (HD) independence occurs in about 30% of patients (pts) with severe AKI, advocating for the use of additional strategies to rapidly remove serum monoclonal free light chains (FLC).

Methods: We designed a prospective randomized phase III trial to compare the HD independence rate in pts with inaugural severe AKI secondary to biopsy-proven CN, treated with intensive HD (8 sessions of 3 hours over the first 10 days, then twice a week) using either high cutoff (HCO) or conventional high-flux dialyzer. In both groups, pts received 21 day-courses of bortezomib and dexamethasone (BD) reinforced by cyclophosphamide after 3 cycles in the absence of hematological response.

Results: Between 2011 and 2015, 98 pts were randomized. One pt withdrew consent and 3 had main exclusion criteria. Baseline characteristics in the control arm (n=48) and HCO arm (n=46) were close, including similar high FLC levels (median 6,015 mg/L). All 46 and 36 (76.6%) in the HCO and HD group respectively. At 3 months, 75% and 70% of pts met the criteria for CN. At 12 months, 10 and 8 pts had died, respectively.

Conclusions: This randomized trial demonstrates that in MM pts with CN and severe AKI treated with bortezomib-based chemotherapy, intensive HCO HD increases renal response rate at 6 months, compared to similar HD dose with conventional high-flux dialyzers.

Funding: Pharmaceutical Company Support - Janssen; Baxter, Government Support - Non-U.S.

TH-OR032 European Trial of Free Light Chain Removal by Extended Haemodialysis in Cast Nephropathy (EuLITE); Survival and Renal Outcomes Colin A. Hutchinson,3 Paul Cockwell,1 Niels Heyze,2 Katja C. Weisel,3 Lesley B. Fifer,4 Julian D. Gillimore,4 Arthur R. Bradwell,4 Mark Cook.5

Background: Myeloma cast nephropathy (MCN) is caused by a pathogenic immunoglobulin serum free light chain (sFLC). High cut-off haemodialysis (HCO-HD) can remove large quantities of sFLC and retrospective uncontrolled clinical trials reported very good partial response or above at 3 months, based on FLC, was 48% in control and 56% in the HCO arm (n=46) were close, including similar high FLC levels (median 6,015 mg/L).

Methods: We carried out a prospective multi-centre RCT in patients with newly diagnosed MM and associated MCN who required acute dialysis, comparing HCO-HD and standard high flux (HF)-HD, and using bortezomib based chemotherapy. 90 patients were randomised and followed for 2 years. Results are reported as intention to treat (ITT).

Results: The groups were similar for demographics, myeloma type (light chain only vs intact Ig), and sFLC isotype. At 3 weeks sFLC levels were similar between groups. 24/43 (56%) in the control arm and 28/43 (65%) in the HCO arm had very good partial response or above at 3 months, based on FLC, was 48% in control and 56% in the HCO arm (n=46) were close, including similar high FLC levels (median 6,015 mg/L). All 46 and 36 (76.6%) in the HCO and HD group respectively. At 3 months, 75% and 70% of pts met the criteria for CN. At 12 months, 10 and 8 pts had died, respectively.

Conclusions: In this RCT, HCO-HD compared to HF-HD did not improve outcomes in patients requiring acute dialysis for MCN.


Background: The public health significance of the reported higher incidence of CKD with intensive SBP lowering in high-risk hypertensive adults without CKD in SPRINT is unclear.

Methods: In 6662 SPRINT participants without CKD (eGFR ≥ 60 ml/min/1.73 m²) at baseline, the effects of intensive SBP control (goal <120 vs. standard <140 mm Hg) on incident CKD and the composite of CV outcome or all-cause death were examined. Incident CKD was defined as a ≥30% decrease in eGFR to a value <60 ml/min/1.73 m². CV outcome was defined as the first occurrence of MI, ACS, stroke, heart failure, or CV death.

Results: Mean age was 66 ± 9 yrs, 34% were women and 34% were Black. Mean eGFR was 81 ± 16 ml/min/1.73 m². The SBP difference between the two arms after 6 months of follow-up was 15.0±2.0 mm Hg. The slopes of eGFR were -5.42±0.50 (intensive) vs. -0.23±0.50 (standard) ml/min/1.73 m² in the first 6 months (p<0.001). After 6 months, eGFR slopes were similar (0.79±0.13 vs. 0.68±0.13; p=0.51). Numbers needed to treat for harm (NNTB) for incident CKD and the numbers needed to treat for benefit (NTTB) for CV event/death over the 3.26 yrs of median follow-up are summarized in Table.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive arm incidence*</th>
<th>Standard arm incidence*</th>
<th>Hazard ratio [95% CI]</th>
<th>% Absolute risk reduction [increase] [95% CI]</th>
<th>NNTH (NTTB) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident CKD</td>
<td>1.32 (140/10583)</td>
<td>0.37 (40/10570)</td>
<td>3.55 [52, 5.11]</td>
<td>(3.01) [3.78, 2.26]</td>
<td>(40/10750)</td>
</tr>
<tr>
<td>CV event or all-cause death</td>
<td>1.80 (192/10647)</td>
<td>2.51 (266/10046)</td>
<td>0.72 [0.60, 0.87]</td>
<td>2.17 [1.03, 3.69]</td>
<td>(34) [64]</td>
</tr>
</tbody>
</table>

* events per 100 person years of follow-up. (N events/ total years of follow-up)

For each CV event/ death prevented, there were 1.4 incident CKD events (3.01/2.17). None in either arm reached ESRD.

Conclusions: As asymptomatic incident CKD is much more benign than CV event/ death, the risk of incident CKD appears to be outweighed by CV benefits. When the SPRINT intervention is adopted in routine clinical practice, the incidence and consequent prevalence of CKD will need to be determined over the long-term.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA, NINDS

TH-OR034 Folic Acid Therapy Delays the Progression of Chronic Kidney Disease: The Renal Substudy of the China Stroke Primary Prevention Trial (CSPPT) Xun Xu,1 Xianhui Qin,1 Youbao Li,1 Yong Huo,2 Fan Fan Hou.1 2Div, Nanfang Hospital, Southern Medical Univ; National Clinical Research Center for Kidney Disease; 3Dept of Cardiology, Peking Univ First Hospital.

Background: The efficacy of folic acid therapy on renal outcomes has not been previously investigated in populations without folic acid fortification. This study was to test whether treatment with enalapril and folic acid is more effective in slowing renal function decline than enalapril alone among Chinese adults with hypertension.

Methods: A randomized, double-blinded clinical trial was conducted in 20 communities in Jiangsu province in China, enrolling 15104 eligible CSPPT participants with an eGFR≥30 ml/min/1.73 m², including 1671 patients with CKD. Participants were randomized to receive a daily tablet containing 10mg enalapril and 0.8mg folic acid (n=7554) or 10mg enalapril alone (n=7559). The primary outcome was progression of CKD, defined as a decrease in eGFR of ≥30% and a slower rate of eGFR decline (1.28% vs 1.42% per year, P=0.02). Among the participants with CKD at baseline, folic acid therapy resulted in a 21% reduction in the odds of the primary event (OR,0.79; 95%CI,0.62-1.00), and a slower rate of eGFR decline (1.28% vs 1.42% per year, P=0.02). Among those without CKD at baseline, there was no between-group difference in the primary endpoint.

Conclusions: Enalapril-folic acid therapy, compared with enalapril alone, can significantly delay the progression of CKD among patients with mild to moderate CKD.

Funding: Government Support - Non-U.S.
TH-OR035

Effect of Folic Acid Supplementation on the New-Onset Proteinuria: New Insight from a Randomized Controlled Trial

Yousouf Li, Xianhui Qin, Binyan Wang, Yong Huo, Fan Fan Hou, Xin Xu.

Nantong Hospital, Southern Medical University; National Clinical Research Center for Kidney Disease; Peking First University Hospital.

Background: The efficacy of folic acid supplementation for the preventing the new-onset proteinuria was still inconclusive. We aimed to test the hypothesis that treatment with enalapril and folic acid is more effective in preventing the new-onset proteinuria than enalapril alone among Chinese adults with hypertension.

Methods: This was a sub-study of the China Stroke Primary Trial (CSPTT). A total of 14538 eligible CSPTT patients without overt proteinuria, including 1866 patients with diabetes, were randomly assigned to receive a single tablet daily containing 10mg enalapril and 0.8mg folic acid (n=7212) or 10mg enalapril alone (n=7326) in 20 communities in Jiangsu province in China. The primary outcome was the new-onset proteinuria, defined as a urine dipstick reading ≥ 1+ at exit visit.

Results: Median follow-up was 4.4 years. The primary event occurred in 260 (4.4%) and 242 (4.1%) participants, respectively, in the enalapril group and the enalapril-folic acid group. Compared with the enalapril group, the enalapril-folic acid group had no significant effect on the primary event (OR, 0.93; 95% CI, 0.77, 1.11). Among the participants with diabetes at baseline, folic acid therapy resulted in a significant reduction in the risks for the primary event (8.5% in the enalapril group vs. 5.6% in the enalapril-folic acid group; OR, 0.63; 95% CI, 0.42-0.94). Among those without diabetes at baseline, there was no between-group difference in the primary endpoint.

Conclusions: Folic acid supplementation, compared with enalapril alone, can significantly prevent the new-onset proteinuria in hypertensive patients with diabetes.

Funding: Government Support - Non-U.S.

TH-OR036

Correction of Metabolic Acidosis Improves Insulin Resistance in Chronic Kidney Disease

Antonio Bellasi, Lucia Di Micco, Luca Di Lullo, Mario Cozzolino, Giorgio De Risi, Assunta Lariana, Paola Landolfi, Ospedale Parodi Delfino; Univ of Milan.

Background: Correction of metabolic acidosis (MA) with nutritional therapy or bicarbonate administration is widely used in chronic kidney disease (CKD) patients. However, it is unknown whether these interventions reduce insulin resistance (IR) in diabetic patients with CKD. We sought to evaluate the effect of MA correction on endogenous insulin action in diabetic type 2 (DM2) CKD patients.

Methods: Sub-study evaluation of the first 145 CKD subjects (83 men e 62 women) with DM2 treated with oral anti-diabetic drugs recruited in the ongoing BIC study (NCT01640119) who completed 12 months follow-up. All patients were randomly assigned 1:1 to either open-label (A) oral bicarbonate to achieve bicarbonate levels of 24-28 mmol/L (treatment group) or (B) no treatment (control group). The Homeostatic model assessment (HOMA) index was used to evaluate IR at study inception and conclusion. Parametric and non-parametric tests as well as linear regression were used.

Results: At baseline no differences in demographic and clinical characteristics between the 2 groups was observed. Average dose of bicarbonate in the treatment group was 0.7±0.2 mmol/kg. Treated patients showed a better metabolic control as confirmed by lower insulin levels (13.4±5.2 vs 19.9±6.3; for treated and control subjects respectively; p<0.001), Homa-IR (5.9±5.0 vs 6.3±5.8; 2-p<0.001) and need for oral anti diabetic drugs. The serum bicarbonate and HOMA-IR relationship was non-linear and the largest HOMA-IR reduction was noted for serum bicarbonate levels between 24-28 mmol/L. Adjustment for confounders, suggests that serum bicarbonate rather than treatment drives the effect on HOMA-IR.

Conclusions: Serum bicarbonate is related to IR and the largest HOMA-IR reduction is noted for serum bicarbonate between 24-28 mmol/L. Treatment with bicarbonate influences IR. However, changes in serum bicarbonate explains the effect of treatment on HOMA index. Future efforts are required to validate these results in diabetic and non-diabetic CKD patients.

Funding: Government Support - Non-U.S.

TH-OR037

Rapid Onset of Action of Orally Administered C5aR Inhibitor CCX168 in Randomized Clinical Trial in ANCA-Associated Vasculitis (CLEAR)

Vladimir Tesar, David R. W. Jayne, Annette Bruchfeld, Lorraine Harper, Matthias Schäfer, Patrick Hamilton, Volker Rolf Burst, Franziska Grundmann, Michel Y. Jadoul, Istvan Szombati, Antonia Portaceli, Thomas J. Schall, Mario Cozzolino, Charlene Karle, vd Borolan Institut, Sweden; Univ of Birmingham, United Kingdom; Univ Hosp Heidelberg, Germany; Manchester Univ, United Kingdom; Univ of Cologne, Germany; Cliniques Saint-Luc, Belgium; Budai Irgalmasrendi Korhaz, Hungary; Charles Univ, Czech Republic; ChemoCentryx, Inc.

Background: CCX168 is being developed for anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV).

Methods: This was a randomized, placebo-controlled trial in AAV. The aim was to reduce or replace steroid treatment with CCX168 without compromising efficacy. There were three treatment groups: (1) High dose (60 mg) prednisone standard of care control, (2) CCX168 30 mg b.i.d. low dose (20 mg) prednisone, and (3) CCX168 30 mg b.i.d. no prednisone. All patients received CYC, 15 mg/kg IV q2 to 4 wks, or RTX, 375 mg/m2 IV weekly for 4 wks. Primary endpoint: treatment response at wk 12, based on Birmingham Vasculitis Activity Score (BVAS) decrease from baseline of ≥50% and no worsening in any body system.

Results: 67 patients were enrolled. Mean age was 57–59 yrs, BVAS 13 to 14. The primary endpoint was met: BVAS response at wk 12 was higher and statistically non-inferior to SOC control (P = 0.002 and P = 0.01 for each CCX168 group vs. control), with a rapid onset of action (see figure).

The incidence of events likely associated with steroids, e.g., diabetes, psychiatric disorders, weight gain, fracture, and cataract was lower in patients on CCX168 (34%) vs. control (52%), OR = 0.63 (0.42–0.94). CCX168 was generally well tolerated.

Conclusions: CCX168 successfully replaced glucocorticoid treatment, with a more rapid onset of action based on BVAS, UACR, and HRQOL, and a lower incidence of steroid-related adverse effects.

Funding: Pharmaceutical Company Support - ChemoCentryx, Inc.

TH-OR038

Exercise Training in Hypertensive Patients with Chronic Kidney Disease: A Randomized Controlled Trial

Franklin Correa Barcellos, Annelise Reges, Marcela Bohle, Medicine Faculty, Univ Federal of Pelotas, Pelotas, Brazil; Medicine School, Univ Catholic of Pelotas, Brazil.

Background: Chronic kidney disease (CKD) is a progressive illness that leads to end-stage renal disease and renal replacement therapy. These patients are at increased risk for cardiovascular events and progression to kidney failure. Observational studies have found that higher physical activity is associated with slower rates of glomerular filtration rate (GFR) decline. However, there is no definitive evidence on exercise-programmed programs. The purpose study was evaluated the effects of exercise in cardiovascular risk factors and progression of kidney disease in hypertensive patients with CKD non-dialysis.

Methods: Randomized controlled trial. Participants: Non-diabetic patients with high blood pressure and renal dysfunction. Among 935 eligible individuals, 150 individuals were randomized into the intervention or control group. Intervention: Exercise training of the resistance and aerobic exercises, three times per week for 16 weeks. Outcomes: Glomerular filtration rate estimated, blood pressure, weight, fasting glucose, lipid profile, high-sensitivity C-reactive protein, hemoglobin levels and health-related quality of life. Data were obtained using linear mixed-effects models for repeated measurements over time.

Results: 76 participants were allocated to the intervention and 74 to the control group. The decrease in GFR was faster in the control group than in intervention group (2.6 against -1.9 mL/minute/1.73m2), but the between-groups difference was not significant (+0.7; -4.0 to 5.4 mL/minute/1.73m2) considering time and intervention interaction. C-reactive protein, mean body weight and fasting glucose levels had a significant reduction (p<0.01) throughout the study in the intervention, but not the control group. Blood pressure decreased in both groups, physical fitness increased in the intervention group and there were no changes in quality of life.

Conclusions: Sixteen weeks of physical training exercise reduced C-reactive protein, body weight and fasting glucose levels in this high-risk population. However, have no impact on eGFRs decline in non-diabetic hypertensive patients with renal dysfunction.

Funding: Government Support - Non-U.S.
A Randomized Controlled Trial of Care Management in Late Stage CKD – Preparation for ESKD  Candice Halinski,1 Sofia Agoritis,1 Vipulbhai Saljiya,1 Leah Balsam,1 Steven Fishbane,1 1Div of Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY; 2Div of Nephrology, Nassau Univ Medical Center, East Meadow, NY.

Background: Healthy Transitions (HT) is a care management and informatics program to improve late stage CKD care (stages 4/5). Nurses partner with nephrologists guided by a clinical informatics system. A primary goal is improved education / preparation for ESKD. In the current analysis, the program impact on ESKD initiation was evaluated.

Methods: Patients with stage 4/5 CKD were randomized to the HT intervention or usual care (UC) at four clinical sites. The only exclusions were for dementia, metastatic cancer or no consent. All patients were followed for up to 18 months. The primary outcome of this analysis was the proportion of patients reaching ESKD who initiated treatment with home dialysis or kidney transplantation with secondary outcomes including initiating hemodialysis (HD) without hospitalization and access type for HD.

Results: 65 patients were randomized to each group. There were no significant differences in baseline characteristics. The mean eGFR at baseline was 18.5±6.4 ml/min and 19.9±6.7 ml/min (HT/UC). 25 HT patients and 23 UC patients initiated RRT. The home dialysis or kidney transplantation with secondary outcomes including initiating hemodialysis (HD) without hospitalization and access type for HD.

For HD, a catheter was the sole access in 3/15 (20%) HT and 8/20 (40%) UC (p=0.28). A 65 patients were randomized to each group. There were no significant differences in baseline characteristics. The mean eGFR at baseline was 18.5±6.4 ml/min and 19.9±6.7 ml/min (HT/UC). 25 HT patients and 23 UC patients initiated RRT. The home dialysis or kidney transplantation with secondary outcomes including initiating hemodialysis (HD) without hospitalization and access type for HD.

Conclusions: The HT intervention significantly increased utilization of home dialysis and kidney transplantation and outpatient, nonhospital starts compared to UC. Further studies will help evaluate the cost effectiveness and scalability of the HT approach.

Cognitive Function and Kidney Disease: Baseline Data from the SPRINT Trial  Daniel E. Weiner,1 S. Gaussoin,2 John W. Nord,3 Alexander P. Aucus,10 G. Chelune,4 Michel Chonchol,2 Laura H. Coker,1 William E. Haley,4 Anthony Alexander Killean,2 Paul L. Kimmel,4 Alan J. Lerner,11 Mohammad G. Saklayen,2 Yelena Slinin,4 Clinton Wright,1 Manjula Kurella Tamura,9 Tufs; 1Utah; 2Colorado; 5Mia; 6Minnesota; 7NH; 8Dayton VA; 9Wake Forest; 10Sanford; 11Mississippi; 1Case Western.

Background: People with kidney disease are at high risk of cognitive impairment. The nature of this relationship remains uncertain.

Methods: To explore the relationship among kidney disease, cognitive function, and cerebrovascular disease, we evaluated baseline data from the Systolic Blood Pressure Intervention Trial (SPRINT) cognition substudy, SPRINT-MIND. Five cognitive domains were defined based on 11 cognitive tests using z-scores, and the associations of both urine albumin to creatinine ratio (ACR) and estimated GFR with cognitive performance and brain abnormal white matter volume quantified by MRI were evaluated using linear and quantile regression, respectively.

Results: Among 9361 SPRINT-MIND participants, 2800 were administered an expanded cognitive battery at baseline and 2707 had complete data; 637 had brain imaging. Mean age was 69 years, 37% were women, 30% were black, and 20% had known CVD. Mean eGFR was 71±21 ml/min/1.73 m² and median urine ACR was 9.7 (IQR 5.7, 22.5) mg/g. In analyses adjusted for demographic and clinical characteristics, higher ACR was associated with worse performance on tests of global cognitive function, executive function, memory and attention, such that each doubling of urine ACR explained similar declines in cognitive performance as with 7 months, 10 months, 6 months, and 14 months of increasing age, respectively per domain. Lower eGFR was independently associated with worse performance on tests of global cognitive function and memory. In adjusted models, higher ACR (p=0.001) but not lower eGFR (p=0.38) was associated with larger abnormal white matter volume; the association was present at low ACR levels (30 mg/g). In older adults, higher urine ACR and lower eGFR have additive effects on global cognitive performance with different patterns of affected domains. Albuminuria, even at low levels, identifies a higher burden of abnormal brain white matter disease, suggesting that vascular disease may mediate these relationships.

Conclusion: SPRINT-MIND participants had increased albuminuria and eGFR, with more advanced kidney disease, and higher prevalence of cognitive impairment, compared to prior reports. Further work is needed to understand the relationship among kidney disease, cognitive impairment, and cerebrovascular disease.

Philosophers On: The future of care for people with kidney disease and dementia

Impact of a Primary Care Registry on Chronic Kidney Disease Management in a Safety-Net Setting  Delphine S. Tuong,1 Charles E. McCulloch,2 Alexandra Velasque,3 Dean Schillinge,4 Chi-Yuan Hsi,5 Neil R. Powe.6 Univ of California, San Francisco, San Francisco, CA.

Background: Early stage CKD is asymptomatic; detection by primary care providers (PCPs) is critical to prevent disease progression via blood pressure (BP) control, minimization of albuminuria and prescription of angiotensin-converting enzyme inhibitors (ACEI/angiotensin receptor blockers (ARB)). In a randomized control trial (KARE, NCT01536958), we examined the impact of implementing a primary care CKD registry on delivery of guideline-concordant care in a racially/ethnically diverse low-income patient population. At point of care, the registry identified patients with CKD, those with uncontrolled BP (>140/90 mmHg), those not on ACEI/ARBs, and whose albuminuria had not been quantified in the past year. Quarterly feedback pertinent to these metrics was also provided to PCPs/health care teams.

Methods: PCPs were randomized to receive the registry or usual care for one year. Mixed models and generalized estimating equations adjusted for age, gender, race/ethnicity and clinic, were used to account for PCP and patient clustering and repeated measures, to assess the impact of the registry, time, and their interaction on change in systolic BP and change in proportion of patients with BP control, prescription of ACEI/ARB and quantification of albuminuria in the prior year.

Results: Patients whose providers were randomized to the registry (n=22 PCPs, 263 patients) had no significant change in systolic BP or change in proportion of patients with BP control compared to those randomized to usual care (n=61 PCPs, 551 patients). Randomization to the registry was associated with greater prescription of ACEI/ARB over time (p=0.01) with a post-intervention average of 82% for patients with registry vs 72% without registry, p=0.04 and increased albuminuria quantification over time (p=0.009), with a change from 7% to 43% with registry vs. 10 to 34% without registry, p=0.04.

Conclusions: A primary care CKD registry can improve processes of care (ACEI/ARB use and albuminuria quantification) for safety-net patients with CKD.

Cognitive Function and Kidney Disease: Baseline Data from the SPRINT Trial  Daniel E. Weiner,1 S. Gaussoin,2 John W. Nord,3 Alexander P. Aucus,10 G. Chelune,4 Michel Chonchol,2 Laura H. Coker,1 William E. Haley,4 Anthony Alexander Killean,2 Paul L. Kimmel,4 Alan J. Lerner,11 Mohammad G. Saklayen,2 Yelena Slinin,4 Clinton Wright,1 Manjula Kurella Tamura,9 Tufs; 1Utah; 2Colorado; 5Mia; 6Minnesota; 7NH; 8Dayton VA; 9Wake Forest; 10Sanford; 11Mississippi; 1Case Western.

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Conclusion: SPRINT-MIND participants had increased albuminuria and eGFR, with more advanced kidney disease, and higher prevalence of cognitive impairment, compared to prior reports. Further work is needed to understand the relationship among kidney disease, cognitive impairment, and cerebrovascular disease.
TH-OR043
Association of Pre-ESRD Depression with Post-ESRD Mortality: A Transition of Care in CKD Study

**Background:** Depression in CKD patients is often undiagnosed, empirically overlooked, and often associated with worse outcomes including higher mortality; however, prior studies have been limited to either pre- or post-ESRD diagnoses of depression separately. We sought to examine the association of pre-ESRD depression with post-ESRD mortality in patients who transition to dialysis.

**Methods:** From a nation-wide cohort of 46,877 US veterans who transitioned to dialysis between 10/2007-09/2011, we identified 13,565 patients with a pre-dialysis depression diagnosis (from ICD9 codes) during the pre-dialysis period and modeled it as a predictor of all-cause mortality within the first 6 months, 1 and 2 years after maintenance dialysis therapy initiation using Cox hazards models adjusting for case-mix covariates, residential region, initial dialysis modality, BMI, and averaged laboratory values including eGFR.

**Results:** Patients were 72±11 years old (mean±SD) and included 5% females, 45% diabetics, and 23% African Americans. 29% of the cohort had been previously diagnosed with depression prior to transition to ESRD. Compared to those not reporting depression, depressed patients had a 16% higher 1-yr mortality risk in the unadjusted model (HR 95% CI): 1.16 (1.12, 1.20). Upon further adjustment for demographic characteristics and laboratory measures, this risk was attenuated to 8% [1.08 (1.04, 1.12)].

**Conclusions:** Pre-ESRD depression is associated with increased risk of post-ESRD mortality in veterans transitioning to dialysis. Intervention studies are warranted to examine whether management of pre-ESRD depression can improve ESRD outcomes.

Funding: NIDDK Support

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TH-OR045
Medicare Payments for Parts A and B Claims in Home Hemodialysis, In-Center Hemodialysis, and Peritoneal Dialysis Patients

**Background:** The United States Renal Data System (USRDS) annually publishes Medicare costs per person per year (PPP) for hemodialysis (HD) and peritoneal dialysis (PD) patients, but does not publish costs for home HD (HHD) and in-center HD (IHD). Such costs are relevant to the Comprehensive ESRD Care Model. We assessed Medicare Parts A and B payments for HHD, IHD, and PD during 2012.

**Methods:** We analyzed USRDS data. We identified all patient-days in 2012 that were marked by HHD, IHD, or PD treatment and coincided with Medicare as primary payer, which were linked to the USRDS registry, whereas IHD and PD patient-days were identified from USRDS data. Payments were ascertained from Medicare Parts A and B claims.

**Results:** Cumulative MPP-patient-years for HHD, IHD, and PD were 2,659, 273,848, and 24,076, respectively. Medicare payments PPPY are shown in the table. Compared to IHD, HHD was associated with lower inpatient/post-acute and physician/supplier payments, but higher outpatient dialysis payments. Compared to PD, HHD was associated with similar inpatient/post-acute payments and higher payments for other cost centers. Excluding outpatient dialysis payments, HHD was roughly $10,000 PPPY less than IHD and $5,000 PPPY more than PD.

**Conclusions:** Medicare payments for HHD, IHD, and PD are heterogeneous. Home dialysis modalities are associated with lower inpatient/post-acute and physician/supplier costs, whereas IHD is associated with higher outpatient dialysis costs, likely due to payment for extra HD sessions. Additional analyses are needed to characterize geographic variability of between-modality cost differentials, as well as Medicare Part D payments with each dialytic modality.

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TH-OR046
Gender Disparities in CKD Progression: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

**Background:** In the US, men have 1.5 times higher incidence of end-stage renal disease (ESRD), despite having lower prevalence of chronic kidney disease (CKD) compared with women. Prior studies suggest that men have more rapid CKD progression, but this finding has not been consistent. We evaluated gender differences in ESRD progression.

**Methods:** In this prospective, longitudinal study of 1778 women and 2161 men enrolled in the CRIC Study, we used Cox proportional hazards models to investigate the association of gender (women vs. men) with incident ESRD (dialysis or transplantation), and linear mixed effects models to evaluate gender differences in estimated glomerular filtration rate (eGFR) slope.

**Results:** Mean age was 58 years, 42% were non-Hispanic black and 13% Hispanic. At entry, women were significantly more likely to have never smoked (53 vs 39%), be physically inactive (33 vs 28%), have higher body mass index (33 vs 31 kg/m²), lower eGFR (44 vs 46 ml/min/1.73m²), and lower proteinuria (113 vs 268 mg/24h). Over median follow-up of 6.9 years, 844 participants developed ESRD. In fully-adjusted mixed effects models, the difference in eGFR slope in women vs. men was −0.17 ml/min/1.73m²/year (p=0.05). The table summarizes failure-time analyses.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>P Interaction Gender*Age</th>
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<tbody>
<tr>
<td>ESRD model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>0.80 (0.69-0.93)</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>0.81 (0.69-0.96)</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>0.92 (0.78-1.09)</td>
<td>0.03</td>
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**Adjusted HR (95% CI) stratified by age**

<table>
<thead>
<tr>
<th>Age</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>21-45 y</td>
<td>1.36 (0.96-1.93)</td>
</tr>
<tr>
<td>46-60 y</td>
<td>0.87 (0.68-1.12)</td>
</tr>
<tr>
<td>61-74 y</td>
<td>0.79 (0.61-1.03)</td>
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**Adjusted for clinical site, demographics, nephrology care and health insurance.**

**Conclusion:** In this large and diverse CKD cohort, the lower risk of ESRD in women relative to men was explained by differences in lifestyle factors, and this association was modulated by age.

Funding: NIDDK Support

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
TH-OR047

Food Environment and Risk of Kidney Function Decline among Urban African Americans: The Achieving Blood Pressure Control Together (ACT) Study
Deidra C. Crewe,1 Patti Ephraim,1 Yang Liu,1 Raquel C. Greer,1 Jessica Ameling,2 Kathryn A. Carson,1 Laptops Lewis Boyer,3 Lisa A. Cooper,2 L. Ebony Boulware,3 Johns Hopkins U, MD,1 U Michigan, MI,1 Duke U, NC.

Background: Studies suggest that dietary factors influence risk of kidney function decline. Barriers may hinder urban African Americans (AA)s abilities to follow healthful diets that could mitigate the increased risk of kidney function decline, yet these barriers have not been well-examined.

Methods: In a randomized trial of urban AA s with uncontrolled hypertension, we assessed, at enrollment, food environment factors including healthy food access [Healthy Food Availability Index (HFAl)] of stores near participants homes; higher-better] and participants dietary patterns [food insecurity (i.e. skipping meals due to lack of money), directly assessed presence of fresh or frozen fruits/vegetables in participants’ homes; and Block fruit/vegetable screener (measure of dietary intake; higher=better)]. We used logistic regression to quantify the association of each factor with eGFR decline >4 ml/min/1.73m2 (ml) over 1 yr, adjusting for age, sex, diabetes, albuminuria, and study arm.

Results: A majority (120 out of 159 participants) had eGFR=15ml at baseline and completed follow up labs. Mean age was 58, 74% were female, 41% had diabetes. Many lacked fresh/frozen fruits (40%) or vegetables (22%) in their homes. Median baseline eGFR was 85ml (IQR 67-104) and 16% had eGFR<60ml. Median eGFR decline over 1 year was 4ml and 46% declined >4ml.

Conclusions: Among urban AA s, greater availability of healthful foods in neighborhood stores and healthful dietary intake patterns were associated with a trend towards lower risk of eGFR decline. The impact of the food environment on kidney function in vulnerable populations warrants further study.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-OR048

Emergency Department Use among Patients with Chronic Kidney Disease: A Population-Based Analysis
Paul E. Ronksley, Robert G. Weaver, Chandra Mary Thomas, Jennifer M. MacRae. Univ of Calgary, Calgary, AB, Canada.

Background: While prior studies have observed high resource use among patients with chronic kidney disease (CKD), there is limited exploration of emergency department (ED) use in this population and the proportion of encounters related to CKD care.

Methods: We identified all adults (≥18 years) with eGFR<60 ml/min/1.73m2 (including dialysis-dependent patients) in Alberta, Canada between Apr 1, 2010 and Mar 31, 2011. Patients with CKD were linked to administrative data to capture clinical characteristics and frequency of ED visits, and followed until death or end of study (Mar 31, 2013). Within each CKD category we calculated adjusted rates of overall ED use, as well as rates of potentially preventable ED encounters (defined by CKD-specific ambulatory care sensitive conditions (ACSCs); heart failure, hyperkalemia, volume overload, malignant hypertension).

Results: During mean follow-up of 2.4 years, 111087 patients had 294113 ED encounters. 66) visits/1000 p yrs. In contrast, rates of ED use for hyperkalemia increased over 80% of all potentially preventable ED events among patients in categories 3A, 3B, and 4 CKD, while hyperkalemia accounted for almost half (48%) of all ACSCs among dialysis patients. Adjusted rates of ED events for heart failure showed a U-shaped relationship with rates peaking among category 4 CKD patients (61.9% CI: 56-66) visits/1000 p-yrs. In contrast, rates of ED use for hyperkalemia increased in parallel with CKD category; rates were highest among category 5 patients who were dialysis-dependent (22 (95% CI: 17-28)) and those not receiving dialysis therapy (23 (95% CI: 17-29)) visits/1000 p-yrs.

Conclusions: ED use is high among patients with CKD, although only a small proportion of these encounters are for potentially preventable CKD-related care. These findings suggest that strategies to reduce ED use among CKD patients will need to target other conditions besides CKD-specific ACSCs.

TH-OR049

Trajectories of Multidimensional Quality of Life among Patients Receiving Chronic Dialysis: Fluctuation, Gradation, and Improvement over Time
Mi-Kyung Song,1 Sudeepa Paul,1 Sandra E. Ward,2 Constance A. Gilet,3 Gerald A. Hallock,1 1School of Nursing, Emory Univ, GA; 2School of Nursing, Univ of Wisconsin-Madison, WI; 3UNC Kidney Center, Univ of North Carolina at Chapel Hill.

Background: Other than dialysis patients, no population must receive an invasive treatment every day or every other day to sustain life, yet inadequate attention has been paid to patient-reported multidimensional QOL over time in these patients.

Methods: 227 patients on chronic dialysis recruited from 12 clinics completed hour-long monthly measures of physical functioning, physical and emotional symptoms, cognitive functioning, and spiritual wellbeing for 12 months. Sessions were conducted by phone on a non-diagnosis day if patients were on hemodialysis (n=216, 95.2%). Mean patient age was 59 years (SD=12.6) and they had been on dialysis for M=4.3 years (SD=5.3). 74% (n=168) were African Americans. Baseline Charlson Comorbidity Index (CCI) score was M=7.3 (SD=2.1). Linear mixed models were used in analysis.

Results: Patient-reported physical functioning, symptoms, cognitive functioning, and spiritual wellbeing fluctuated severely from month to month. Activities of Daily Living (ADL) gradually worsened over time (p<0.05) while Instrumental ADL was unchanged. Moderate to severe pain remained unchanged (n=129, 56.8%) while fatigue slightly improved over time (p=0.01). Anxiety symptoms (STAI) improved gradually (p<0.01) whereas depressive symptoms (CESD-10) were stable. Stable CCI predicted these physical functioning and symptom scores (all p<0.01) while months on dialysis did not. Self-reported cognitive functioning and spiritual wellbeing (FACT-Sp) slightly improved over time (all p<0.001). While race was associated with higher fatigue and lower spiritual wellbeing, and older age was associated with lower anxiety and depression and higher spiritual wellbeing.

Conclusions: While physical functioning worsened over time, older and African American patients reported improved emotional and spiritual wellbeing, possibly reflecting adaptation to their situation. Further analysis is needed to glean hypotheses regarding ways to direct clinical management.

Funding: Other NIH Support - NIH, R01NR013359

TH-OR050

A Comparison Study on Clinical Features and CKD Related Quality of Life between CKD G3a and CKD G3b Patients in China
Zhanghe Peng,1 Qiongying Yuan,1 Jinwei Wang,2 Luxia Zhang,2 Qiaoling Zhou,3 1Renal Div, Dept of Medicine, Xiangya Hospital, Central South Univ, Changsha, Hunan, China; 2Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, China.

Background: A new classification of chronic kidney disease (CKD) was proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) in 2012. The major point of revision of this classification was the previous CKD stage 3 was subdivided into two stages (G3a and G3b). Furthermore, a two-dimensional staging of the CKD according to the level of albuminuria in addition to the GFR level was introduced. We compared the clinical features and CKD related quality of life between CKDG3a and CKDG3b patients in China to validate the necessity of the new classification.

Methods: Data of patients with CKD3 collected at baseline of the Chinese Cohort of Chronic Kidney Disease (C-STRIDE) which was performed in 3 000 pre-dialysis CKD patients aged between 18 and 74 years from 2011.09 to 2015.02.

Results: A population of 1277 patients with CKD3 was recruited for the study. 499(39.08%) patients were classified as CKD G3a group, 778(60.92%) patients were classified as CKD G3b group. We compared the clinical characteristics, laboratory parameters and overall rating of quality of life between CKD G3a and G3b patients. We found that serum PTH, uric acid, hemoglobin, serum HDL cholesterol and systolic blood pressure were significantly elevated in the G3b group compared with G3a group (P<0.05). Serum bicarbonate, serum total cholesterol were significantly decreased in the G3b group compared with G3a group (P<0.05). The proportions of subjects with hyperuricemia, anemia were significantly higher in the G3b group than in the G3a group (61.41% vs.52.03%, 26.35% vs.17.85 %, P<0.05). Most importantly, the overall rating of quality of life was significantly decreased in the G3b group compared with G3a group (P<0.05). Subsequently, we classified patients with CKD G3a and G3b according to the levels of ACR. We found that hyperuricemia, anemia were significantly more common in the later stages of both the eGFR and albuminuria (P < 0.01).

Conclusions: There are differences in the clinical features and quality of life between CKDG3a and CKDG3b patients in China.

Funding: Government Support - Non-U.S.
**TH-OR051**

Results from the ATLAS Trial: A Phase 2 Study to Evaluate Efficacy and Safety of BIBB023 in Subjects with Lupus Nephritis

Brad H. Rovin, David Wofsy, David R.W. Jayne, Eduardo Mysler, Karen V. Smirnakis, Jeremy Stuart Duffield, Nathalie Franchimont, Fei Shi, *Nephrology, The Ohio State Univ Wexner Medical Center, Columbus, OH; Rheumatology, Univ of California San Francisco, CA; Ixchel and Luisita Service, Addenbrooke’s Hospital, Cambridge, United Kingdom; Organizacion Medica de Investigacion, Buenos Aires, Argentina; Biogen, Cambridge, MA.

**Background:** BIBB023 is a humanized monoclonal antibody against TNF-related weak inducer of apoptosis (TWEAK). TWEAK has been linked to inflammation, mesangial proliferation, tubular cell death and fibrosis in lupus nephritis (LN). TWEAK acts through its receptor, Fn14. Fn14 is upregulated in LN kidney, but not expressed on T or B cells. Blocking TWEAK/TWEAK-FN14 pathway may attenuate inflammation and enhance the renal response (RR) to standard-of-care (SOC) therapy without adding to immunosuppression.

**Methods:** ATLAS was a phase II, placebo controlled, double blind, RCT to determine whether addition of BIBB023 (3 mg/kg or 20 mg/kg qwk) to MMF+steroids improved complete or partial RR at 1yr. Patients with biopsy proven (centralized) proliferative LN, UPCR >1 and were treated with SOC for 12 wks. Only patients with a UPCR >0.5 after 12 wks of SOC were randomized.

**Results:** ATLAS enrolled 188 subjects, 145 finished BIBB023/placebo infusions through wk 52. Complete and partial RR were seen in 11% and 17% of placebo and BIIB023 treated patients, respectively. There was no difference in RR between placebo or BIIB023 treated patients, respectively. 5 patients with proliferative LN compared to control. These included miRNA-451 showed a significant correlation with urine protein (r=0.31, p=0.008).

**Conclusions:** Urine exosome miRNA profiling was carried out in proliferative LN patients and healthy controls. Several differentially-expressed miRNAs were identified in LN exosomes and verified by RT-PCR. These data demonstrate the feasibility of developing urine exosomes as non-invasive biomarkers of LN activity. *Funding:* NIDDK Support

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**TH-OR054**

Molecular Imaging of Glomeruli from Serial Kidney Biopsies in Lupus Nephritis

Samar Parikh, Ana Malvar, Huijuan Song, John P. Shapiro, Valeria Gabriela Alberton, Jianying Zhang, Michael T. Eadon, Brad H. Rovin, *Nephrology, The Ohio State Univ Wexner Medical Center, Columbus, OH; Nephrology, Hospital Fernandez, Buenos Aires, Argentina; Nephrology, Indiana Univ, Indianapolis, IN.

**Background:** Proliferative lupus nephritis (LN) is managed using only clinical and histologic data. We postulated that molecular profiling of kidney biopsies could provide novel information to improve management strategies. Here we present results of glomerular profiling.

**Methods:** A kidney biopsy was done at flare (Bx1) and after induction therapy (Bx2) in 5 patients with proliferative LN. Biopsies of living donor kidney transplants were controls (n=2). Glomeruli were isolated using laser capture microdissection, and glomerular RNA was extracted. The expression of 569 immune-response genes was profiled using Nanostring technology. Clinical response after induction was assessed by proteinuria and creatinine (SCr), and all patients achieved complete or partial remission. Urine exosome miRNA from 6 healthy control, and 12 biopsy naïve B cell ratio was higher in MR (1.52±2.19 vs.0.21±0.33, p=0.011). miRNA profiling showed that 19 miRNAs were significantly increased in LN compared to control. The top upregulated transcripts included top 1 (miRNA-1285-5p and miRNA-451) and other miRNAs that were previously identified in LN, such as miR-155-5p and miR-451a, and other miRNAs not previously described in LN, such as miRNA-21-5p and miRNA-1285. RT-PCR confirmed Nanostring findings. For example, miRNA-451 was 30-fold higher in LN (p<0.0098). miRNA-21-5p and miRNA-1285-5p were over 200-fold higher in LN than control (p=0.0072 for both). miRNA-21-5p and miRNA-1285-5p were correlated with eGFR (r=0.77 and p<0.0001). miRNA-451 showed a significant correlation with urine protein (r=0.31, p=0.008).

**Conclusions:** Urine exosome miRNA profiling was carried out in proliferative LN patients and healthy controls. Several differentially-expressed miRNAs were identified in LN exosomes and verified by RT-PCR. These data demonstrate the feasibility of developing urine exosomes as non-invasive biomarkers of LN activity. *Funding:* NIDDK Support

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**TH-OR055**

Microbiota Profile in IgAN Is Associated with Differences in Immunologic Function and Disease Severity

Heather N. Reich, David Guttman, Bryan Coburn, Jan Novak, Ping Lam, Scott Gray-Owen, Christoph Licht, Michelle Altmann, Susanne Allgeier, Beat Schaffner, Daniel Costabel, Rulan S. Parekh, Krzysztof Kiryluk, Pauline Wang, Rupert Kaul, Kenneth Croitoru, Jennifer Gommerman, *Univ of Toronto, Univ Health Network; Hospital for Sick Children; UBC, Univ of Alberta; Columbia Univ.

**Background:** There is a reciprocal relationship between host commensal microbiota and the immune system, suggesting that study of microbiota can reveal functional differences in immune responses that underlie susceptibility to IgA nephropathy (IgAN) and disease progression. To better understand the immunopathogenesis of IgAN, we characterized the microbiota of patients with IgAN and healthy control subjects. We characterized the immune and clinical phenotype associated with microbiota profile.

**Methods:** The cohort included 120 adults with IgAN and 60 healthy controls (primarily household-matched). Tonsil microbiota was characterized using V4 16s rRNA sequencing and qPCR. Galactose-deficient (Gd) IgA1 was quantified using ELISA.

**Results:** Overall abundance of *Neisseria* genus is significantly increased in tonsils of IgAN patients (p=0.01) however *N.meningitidis* (Nme) is underrepresented in IgAN (0.23 vs.0.17 ×10^9). *Nme* carriage is associated with a milder clinical phenotype as characterized higher eGFR, and by lower levels of Gd-IgA1(Fig1). *Nme* carriage is associated with differential tonsil colonization by *Neisseria* and *Nme*. The association of *Nme* carriage with milder clinical phenotype and decreased Gd-IgA1 is compelling and merits further exploration. Non-pathogenic (non- *Nme*) *Neisseria* may contribute directly to pathogenesis of IgAN and/or *Nme* carriage may be a biomarker of a milder immunologic phenotype. Current work to investigate mechanisms explaining these associations includes evaluating complement and cytokine profiles in relation to *Neisseria* status.

**Conclusions:** IgAN is associated with differences in Immunologic Function and Disease Severity with r^2=0.31, p=0.008).

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
**TH-OR056**

**Systematic Analysis of IgA1 Glycosylation in IgA Nephropathy, Membranous Nephropathy and Healthy Subjects and the Effects of Ethnicity**

Karen Molyneux, David Harry John Wimbury, Daniel P. Gale, Patricia Higgins, Peiran Yin, Xueqing Yu, Jonathan Barratt.

*Infection, Immunology & Inflammation, Univ of Leicester, Leicester, United Kingdom; 2UCL Centre for Nephrology, Univ College, London, United Kingdom; 3Inst of Nephrology, SunYat-Sen Univ, Guangzhou, China.*

Background: IgA nephropathy (IgAN) is characterised by the deposition of galactose deficient IgA1 (Gd-IgA1)-containing immune complexes in the mesangium. IgAN is especially common in East Asia, and while the diagnostic criteria are the same worldwide, there are marked regional differences in gender distribution and clinical outcomes, suggesting that the biology of the condition is not uniform. The aim of this study was to compare levels of Gd-IgA1 in serum from Caucasian and Chinese patient and control cohorts.

Methods: An ELISA-based method was used to measure binding of the lectin Helix aspersa agglutinin to IgA captured from serum from: 1091 UK IgAN patients, 998 Chinese IgAN patients, 360 UK membranous nephropathy (MN) patients, 193 UK controls and 80 Chinese controls.

Results: UK IgAN patients exhibited higher Gd-IgA1 levels than UK controls with levels highest in patients with progressive renal damage (p<0.05 compared with non-progressors). Gd-IgA1 was lower in UK MN patients compared to both IgAN patients (p=0.0001) and the healthy subjects (p=0.0001) from the UK. Among Chinese individuals, Gd-IgA1 levels were higher in IgAN patients compared to healthy controls (p<0.05), but levels were lower in the Chinese compared to the UK cohort, in both IgAN patients (p=0.0001) and controls (p=0.0001).

Conclusions: Gd-IgA1 levels are associated with IgAN in Caucasian and Chinese patients but the difference in prevalence of IgAN cannot be attributed to differences in Gd-IgA1 levels between these populations. Results also presented at this meeting show that a C1GALT1 haplotype, common in Caucasians but rare in Chinese people, is strongly associated with elevated Gd-IgA1 levels and the reduced Gd-IgA1 in the Chinese population is consistent with reduced frequency of this haplotype. These data support the hypothesis that the causes of IgAN vary across the world.

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

**TH-OR057**

**The MEST Kidney Biopsy Score Predicts Renal Outcome in STOP-IgAN Trial Patients - A Post-Hoc Study**

Jürgen Floege, Thomas Rauen, Judith Isabel Schimpf, Christina Fitzner, Frank Eiter, Hermann-Josef Groene, Ralf-Dieter Hilgers.

1Nephrology, RWTH Aachen, Aachen, Germany; 2Medical Statistics, RWTH Aachen, Aachen, Germany; 3Bayer AG, Wuppertal, Germany; 4German Cancer Research Center, Heidelberg, Germany.

Background: Since the Oxford-MEST classification of IgA nephropathy (IgAN) was introduced, still there is limited information on its predictive power in randomized clinical trials.

Methods: We retrospectively re-analyzed renal biopsies from STOP IgAN trial participants (Rauen et al, NEJM 2015) using the MEST criteria (available biopsies in 70/162 patients). The analyses were performed by researchers blinded to the clinical outcome of patients. Biopsies had been obtained at a median of 9.9 months prior to randomization. MEST scores were correlated with trial endpoints. Analyses were done with Welch, ANCOVA and Fisher's exact tests.

Results: Mesangial hypercellularity (M1 score) significantly correlated with the subsequent annual eGFR loss during the 3 year trial and showed a weak association with full clinical remission and an eGFR-loss≥15 ml/min. T1/2 scores were significantly associated with ESRD onset in the group with additional immunosuppression, but not in the group with supportive-care only. Baseline eGFR was significantly lower when tubulointerstitial fibrosis (T1/2) was present (45.2±15.7 vs. 74.6±28.2 ml/min; p<0.0001), whereas initial proteinuria did not differ between the histological groups. Endocapillary hypercellularity (E) or glomerular segmental sclerosis (S) had no influence on any clinical outcome parameter.

*Funding: Private Foundation Support*
**TH-OR060**

**Eculizumab in Secondary Atypical Hemolytic Uremic Syndrome**

Teresa Cavero Escribano, Santiago Rodriguez de Cordoba, Manuel Praga.

*Background:* Complement hyperactivity can be observed in thrombotic microangiopathies (TMA) other than atypical hemolytic uremic syndrome (aHUS), which may explain why some patients with aHUS associated with secondary TMA (secondary aHUS), have been successfully treated with eculizumab.

*Methods:* We included 3933 participants with CKD in CRIC for longitudinal analysis. Weight, height, and a creatinine C statistic were measured annually. We used segmented, mixed-effects regression for modeling the repeated measures of BMI as a function of estimated GFR (using 2012 CKD-EPI cystatin C equation). We then examined the association between weight loss and risk factors including age, race, sex, diabetes, and heart failure.

*Results:* During mean longitudinal follow-up over 7.6 years, BMI increased by 0.15 kg/m² (95% CI 0.11-0.18) with every 10 mL/min/1.73 m² decline in renal function until eGFR of approximately 30 mL/min/1.73 m². When eGFR dropped below 30 mL/min/1.73 m², a 0.9 kg/m² (95% CI 0.88-1.1) decline in BMI was noted with every 10 mL/min/1.73 m² decline in eGFR. (An 0.9 point decline in BMI is ~3 kg loss in a 5'10" adult.) The associations between eGFR and BMI before and after an eGFR of 30 mL/min/1.73 m² were statistically significantly different (p<0.001).

*Conclusions:* In adults with CKD, weight loss mostly occurs when eGFR is ≤30 mL/min/1.73 m². Further research is needed to determine whether interventions to prevent weight loss during advanced stages of CKD may improve outcomes.

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

**TH-OR062**

**Associations of Sarcopenia and Its Individual Criteria with Mortality among Patients on Hemodialysis**

Pyawwn Kittikulthummalan, Glenn Matthew Chertow, Juan Jesus Carrero, Cynthia Delgado, George A. Kaysen, Kirsten L. Johansen, UCSF; Stanford Univ; Karolinska Inst; UC Davis.

*Background:* Sarcopenia is defined as low muscle mass combined with reduced strength or physical performance. The relative importance of sarcopenia and its individual components as independent predictors of mortality in dialysis population have not been determined.

*Methods:* ACTIVE/ADIPOSE enrolled prevalent HD patients from San Francisco and Atlanta from 2009 to 2011. We estimated whole-body muscle mass using bioimpedance spectroscopy (n=645; age 56.7±14.5 years). We defined low muscle mass as≤2SD below sex-specific means for young adults from NHANES and indexed to height², body weight, BSA, or BMI. We evaluated the association of sarcopenia, low muscle mass by four indexing methods, weak grip strength, and slow gait speed with mortality outcome.

*Results:* Seventy-eight deaths (12.1%) were observed during a mean follow-up of 1.9 years. Sarcopenia was not associated with mortality after adjusting for covariates. No muscle mass criteria were associated with death, regardless of indexing metrics. In contrast, having weak grip strength or slow gait speed was associated with mortality in adjusted model.

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

*Underline* represents presenting author.
Healthy Eating Patterns, Mortality, and End-Stage Kidney Disease: A Meta-Analyses of Cohort Studies; Suontia Paljeme,1 Jaimon T. Kelly,1 Shu Ning Wai,1 Marinella Ruopolo,2 Juan Jesus Carrero,3 Giovanni F.M. Strippoli,4 Karlo de Cardakis,4 University of Otago Christchurch; 5Bond University; 6Diverum Medical Scientific Office; 7Amedeo Avogadro University of Eastern Piedmont; 8Karolinska Ins; 9Univ of Sydney; 10Univ of Bari; 11Univ of Queensland.

Background: Patients with CKD are advised to follow dietary recommendations that restrict individual nutrients. Emerging evidence suggests that whole dietary patterns may be more important than single nutrients in influencing clinical outcomes. RCTs in the general population showed that adherence to a Mediterranean diet lowers mortality risk factors for kidney disease. Further studies are warranted to corroborate these findings in pre-dialysis CKD patients.

Methods: A systematic review and meta-analysis of cohort studies of dietary patterns in adults with CKD was conducted. Electronic databases (Medline, Embase, Cochrane) were searched without language restriction in November 2015 by two independent authors. Risk ratios were summarized using random effects meta-analysis. Primary outcomes were all-cause mortality and ESKD.

Results: Seven studies (n=15,285 patients) were included. Healthy eating patterns were higher in fruit and vegetables, fish, legumes, cereals, whole grains, and fiber in people consuming less red meat, salt, and refined sugars. Health eating patterns were consistently associated with lower mortality (relative risk 0.73, CI 0.63-0.83; absolute risk 46 fewer deaths (CI 29-63) among 1000 patients after 5 years).

Conclusions: Healthy eating patterns are associated with clinically-important reductions in mortality for people with CKD. Dietary advice on whole food approaches encourages consumption of fruit and vegetables, fish, legumes, whole grains, and fiber, while reducing red meat, sodium, and refined sugar consumption could be an effective strategy to lower mortality in CKD. A randomized trial of interventions to support healthy eating patterns would be of clinical relevance in the CKD population.

Protein Intake and Long-Term Change in eGFR in the Jackson Heart Study; Rakesh Malhotra,1 Loren Lipworth,1 Karlo de Cardakis,2 Adolfo Correa,3 Talat Alp Ikizler,4 Edmond Kato Kabagambé.1 1VUMC; 2UW; 3Diaverum; 4UMMC.

Background: Dietary protein intake could have deleterious renal effects in populations at risk for chronic kidney disease such as those with diabetes. Here, we examined whether higher percent of energy intake from protein (P% of energy from protein) is associated with decline in kidney function and whether this decline varied by diabetes status.

Methods: Participants were African Americans (n=5301) who enrolled in the Jackson Heart Study between 2000 and 2004. Dietary intake was assessed using a validated FFQ at baseline (visit1) and 8 years later (visit3). Estimated glomerular filtration rate (eGFR) was baseline and follow-up were compared using the CKD-EPI equation. Participants with an eGFR<60 mL/min/1.73 m2 at baseline or sCR was measured at baseline (visit1) and 8 years later (visit3). Estimated glomerular filtration rate (eGFR) was baseline and follow-up were compared using the CKD-EPI equation. Participants with an eGFR<60 mL/min/1.73 m2 at baseline or sCR was measured at baseline (visit1) and 8 years later (visit3). Estimated glomerular filtration rate (eGFR) was baseline and follow-up were compared using the CKD-EPI equation. Participants with an eGFR<60 mL/min/1.73 m2 at baseline or sCR was measured at baseline (visit1) and 8 years later (visit3). Estimated glomerular filtration rate (eGFR) was baseline and follow-up were compared using the CKD-EPI equation. Participants with an eGFR<60 mL/min/1.73 m2 at baseline or sCR was measured at baseline (visit1) and 8 years later (visit3). Estimated glomerular filtration rate (eGFR) was baseline and follow-up were compared using the CKD-EPI equation.

Results: Of 3,165 subjects, 64% were women, 57% hypertensive and 19% diabetic. The median percent energy intake from protein was 14.3 (12.4, 16.4). During a median up of 8.0 (7.4, 8.3) years, eGFR declined by 10.5% from a mean (SD) of 97.4 (17.5) to 49.8 (24.7). There was no evidence of a significant association between healthy eating patterns and risks of ESKD (RR 1.04, CI 0.68-1.63). Protein intake was positively associated with decline in eGFR, particularly among those with diabetes at baseline.

Conclusions: Protein intake and eGFR were positively associated and higher declines in eGFR after accounting for risk factors for kidney disease. Further studies are warranted to corroborate these findings and to elucidate the underlying mechanism.

Sarcopenia, Obesity, and Mortality in U.S. Adults with and without Chronic Kidney Disease; Matthew K. Abramowiz,1 Lagu A. Androga,1 Afolarin Ayomide Amudoi,2 Deep Sharma,1 1Albert Einstein College of Medicine/ Montefiore Medical Center, Bronx, NY; 2Seton Hall Univ School of Health and Medical Sciences, St. Francis Medical Center, Trenton, NJ.

Background: In pre-dialysis chronic kidney disease (CKD), the association of muscle mass with mortality is poorly defined, and no study has examined outcomes related to the co-occurrence of low muscle mass and excess adiposity (sarcopenic-obesity). We hypothesized that associations of sarcopenia and sarcopenic-obesity with death would be stronger in persons with CKD than in those without, as CKD-induced muscle wasting is likely a poor prognostic factor.

Methods: We examined abnormalities of muscle and fat mass using dual-energy x-ray absorptiometry measurements in adult participants of the National Health and Nutrition Examination Survey 1999-2004 to define sarcopenia, obesity, and sarcopenic-obesity. Cox proportional hazard models were created to determine whether associations of body composition with all-cause mortality differed between participants with CKD compared to those without.

Results: CKD modified the association of body composition with mortality (p=0.04 for interaction). In participants without CKD, both sarcopenia and sarcopenic-obesity were independently associated with increased mortality compared with normal body composition (hazard ratio (HR) 1.44 (95%CI 1.07-1.93) and 1.64 (95%CI 1.26-2.13), respectively). These associations were not present among participants with CKD (HR 1.24 (95%CI 0.89-1.71) and 1.05 (95%CI 0.75-1.46) for sarcopenia and sarcopenic-obesity, respectively; p=0.16 for interaction by CKD status: sarcopenia, p=0.22; sarcopenic-obesity, p=0.003). Conversely, obese persons had the lowest adjusted risk of death among persons with CKD, with an increased risk among those with sarcopenia (HR 1.43 (95%CI 1.05-1.95)) but not sarcopenic-obesity (HR 1.21 (95%CI 0.89-1.65)), compared with obesity.

Conclusions: In conclusion sarcopenia is associated with increased mortality regardless of eGFR, but excess adiposity modifies this association among people with CKD. Future studies of prognosis and weight loss and exercise interventions in CKD patients should consider muscle mass and adiposity together rather than in isolation.

Funding: NIDDK Support

TH-OR065


Background: Malnutrition is common in chronic kidney disease (CKD) and especially end-stage renal disease (ESRD) patients and may be partially mediated by olfactory defects. We characterized these defects in renal patients and tested a novel intervention to improve olfaction.

Methods: We quantified olfaction in CKD (n=56) and ESRD patients (n=100) and healthy volunteers (nH, n=25) using the validated Univ. of Penn. Smell Identification Test (UPST, through which subjects were categorized as normosmic, mildly, moderately or severely microsmic or anosmic) and the Small Threshold Test for 2-phenylethanol detection (Sensonics, Inc.). We then performed a pilot study to test the effect of nasal thalidomide on olfactory impairment.

Results: Most HVs were normosmic or mildly microsmic. CKD patients were equally distributed among normal and mild, moderate and severe microsmic categories, and 1 patient was anosmic. Strikingly, only 8% of ESRD patients were normosmic and 10% were anosmic. Odor threshold was not affected in CKD, but was impaired in ESRD patients (p=0.015 vs. CKD). Nutritional markers (total cholesterol, LDL, albumin and transferrin) showed a modest but statistically significant association with UPSIT categories (R² range: 0.10-0.16; p range: 0.001-0.006). We next enrolled 6 ESRD patients in a 6-week pilot clinical trial for nasal thalidomide (CT# NCT02479451). Compared to baseline, the mean UPSIT score increased in 5 patients by 2-10% during treatment. Patients reached maximum scores of 123.5% above baseline; 3 patients improved by 1 UPSIT category.

Conclusions: CKD and ESRD patients have olfactory defects that may correlate with malnutrition. Nasal thalidomide should be further tested to determine if this novel intervention improves olfactory defects and potentially nutritional status.
Intramuscular Myostatin Gene Expression Following Aerobic and Combined Exercise in Chronic Kidney Disease

Douglas W. Gould,1 Emma L. Watson,1 Thomas James Wilkinson,1 Soteris Xenophontos,1 Alice C. Smith,1,2 Joao L. Viana,1,2 1Leicester Kidney Exercise Team, Univ of Leicester, United Kingdom; 2Univ Inst of Matia.

Background: Muscle wasting is common in chronic kidney disease (CKD) and is associated with poor physical function and mortality. Myostatin (MSTN) is a potent negative regulator of muscle mass. It acts through the ActIVin B2 Receptor (AC2BR), eliciting both increased protein catabolism and reduced protein synthesis. The differential effects of aerobic exercise (AE) and resistance exercise (RE) on catabolic and anabolic pathways in CKD are poorly understood. Therefore we investigated the effects of AE or combined resistance and exercise (CExE) on muscle mass, protein synthesis and protein breakdown in patients with stage 3–4 CKD.

Methods: At baseline, 20 patients with stage 3–4 CKD were randomized to 12 weeks of AE (2x/week, n=10) or CExE (AE + RE 2x/week, n=10). Nutritional status, muscle mass, body composition and circulating inflammatory markers were measured at baseline and post-intervention.

Results: After 12 weeks, we observed significant increases in muscle mass (29% at baseline, 34% at 12 weeks, p<0.05) and RE improved muscle mass and protein synthesis to a greater extent than AE. AE or CExE decreased muscle protein breakdown (51% at baseline, 45% at 12 weeks, p<0.05) and RE was associated with greater muscle protein synthesis than AE. AE or CExE had no significant effects on muscle protein synthesis.

Conclusions: AE or CExE improved muscle mass and reduced protein breakdown in patients with stage 3–4 CKD, with greater benefits observed with RE. These findings highlight the importance of incorporating RE into aerobic exercise programs for patients with stage 3–4 CKD.

Background: Hemodialysis (HD) patients have elevated risk of bone fractures, partly due to impaired bone metabolism and bone-energy parameters. Protein supplementation has shown to improve bone health in older adults, but this effect has not been explored in HD patients.

Methods: We performed a post-hoc analysis of the HIOPE trial. In short, HD patients (n=138; >60y: 48±9y, 54% male, 88% African American; ≥60y: 67±7y, 63% male, 80% African American) were randomized for 12 months to: placebo (CON), protein supplementation (PRo) or protein + exercise training (PRo+Ex). Patients in PRo+Ex received 30 gams of whey protein every HD session, while the PRo+Ex group also cycle at moderate intensity for 30-45 minutes during HD. Patients where then divided into >60y (n=80) and ≥60y (n=58). Dietary intake and bone and body composition, measured by DEXA were assessed at 0, 6 and 12 months. No differences were observed between PRo and PRo+Ex in the variables measured, so the groups were collapsed for analysis.

Results: In patients ≥60y, PRo had higher total protein intake on dialysis days compared to CON at 6 and 12 months (≥60y CON: 0.58±0.35 vs. PRo 0.73±0.36, p=0.032, and 0.50±0.35 vs. PRo 0.70±0.31, p<0.001). After 12 months, 60% of CON vs. 80% of PRo and PRo+Ex increased the percentage of protein intake on dialysis days, respectively (p=0.001). After 12 months, there was a trend for increased BMD (p=0.063) and a significant increase in CSA measured at 12 months (p=0.004) in PRo+Ex compared to CON. After 12 months, a significant increase in bone density was observed in PRo+Ex compared to CON at both T-t-score (p=0.032) and Z-score (p=0.005). No differences between CON and PRo were observed in BMD at 12 months.

Conclusions: Intradialytic PRo supplementation improved protein intake and attenuated the decrease in h-BMD, a predictor of fractures, in older HD patients. Future studies should aim to explore the effect of whey protein on fracture rates in older HD patients.
reproducibility due to more precise seeding of cell numbers. We generated kidney organoids by applying the temporal and genetic cues that go into the induction system during development. The 3-dimensional structures are formed by re-aggregation and contain structures derived from both ureteric epithelium and metanephric mesenchyme progenitor populations.

**Results:** The self-organizing organoids are positive for markers of the glomerulus, proximal and distal tubule, and collecting duct. In addition to this, we identified endothelial cell networks in the organoids. Scanning electron microscope analysis demonstrated the presence of glomerulus-like structures containing podocytes with foot processes. However, we could not detect vascularization inside the glomerulus structures. To further explore the possibility of vascularization of the organoids, we transplanted them under the renal capsule. Preliminary analysis showed the integration of mouse endothelial cells into the PSC-derived organoid, possibly promoting further maturation of the glomerulus-like structures.

**Conclusions:** We demonstrated the generation of kidney organoids and their vascularization upon transplantation. These mini-kidneys are an important step forward for future applications in the development of a bioengineered kidney.

**TH-OR074**

**Kidney Organoids Derived from Human Pluripotent Stem Cells Contain Multiple Kidney Compartments and Model Polycystic Kidney Disease**

**Yang Ruiyu,1,2 Navin R. Gupta,1 Albert Q. Lam,1,2 Benjamin S. Freedman,1,2 M. Todd Valerius,1,2 Joseph V. Bonventre.1,2 Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 1Harvard Stem Cell Inst, Cambridge, MA.**

**Background:** We generated nephron progenitor cells (NPCs) from human pluripotent stem cells (hPSCs) with 80–90% purity. These NPCs subsequently formed segmented nephron structures containing a glomerulus, proximal tubules, loops of Henle, and distal tubules juxtaposed to interstitial cells. To utilize this novel platform for studies of human kidney diseases, we further characterized kidney organoids and demonstrated the feasibility of modeling polycystic kidney disease.

**Methods:** Kidney organoids were evaluated by qRT-PCR and immunostaining for solute transporters and organ specific proteins to evaluate the existence and functionality of multiple kidney compartments. We developed modified differentiation protocols for hiPSCs derived from patients with autosomal recessive polycystic kidney disease (ARPKD). Kidney organoids were generated from hESCs/hiPSCs (HDF), and three lines of ARPKD hiPSCs.

**Results:** Kidney organoids highly expressed erythropoietin, 1-α-hydroxylase, ciliary proteins (PKD1, PKD2, PKHD1), and proximal tubule (AQP1, SGLT2, MDR1), distal tubule (SLC12A3), and collecting duct (AQP2) transporters. Immunostaining revealed CDH1+AM/FP proximal tubules, Endomucin+ or PDGFRβ+ vascular structures, and α-SMA+ interstitial cells, indicating the presence of collecting duct cells, endothelia, pericytes, myofibroblasts, and fibroblasts. More than 80% of organoids derived from ARPKD hiPSCs exhibited cyst formation in response to forskolin within 4 weeks of differentiation while only 13% of AR PKD hESC organoids formed from CDH1+ tubules and were negative for FITC and KIM-1, indicating distal nephron derivation.

**Conclusions:** Kidney organoids derived from hiPSCs contained nephron glomerular and tubular structures with many transporters present in the adult human nephron. In addition the organoids contained collecting duct and interstitial cells with multiple functional proteins. ARPKD patient-derived hiPSCs exhibited cystic phenotypes at high enough frequency serve as models of ARPKD.

**Funding:** NIDDK Support, Private Foundation Support, Government Support - Non-U.S.
Conclusions: This data provides a framework for removing sources of unwanted experimental variation in the analysis of expression data, thereby increasing the utility of this approach for personalised medicine and functional genomics.

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

TH-OR076
Isolation and Maturation of Glomeruli in Human Induced Pluripotent Stem Cell-Derived Kidney Organoids

Lorna J. Hale, Peter Farlie, Pei Xuan Er, Jessica May Vanslambrouck, Ed G. Stanley, Andrew G. Elefanti, Minoru Takasato, Thomas A. Forbes, Irene Ghobrial, Melissa H. Little, Murdoch Childrens Research Inst, Melbourne, Victoria, Australia.

Background: An essential function of the glomerular filtration barrier (GFB) is to limit the permeability of proteins from the blood to the urinary space. The GFB is composed of two highly specialised cell populations, the glomerular endothelial cells and podocytes, both of which contribute to the formation of the basement membrane, completing this three-layer structure. Defects in this barrier are a common feature of glomerulopathies, including Alport syndrome and nephrotic syndrome, however the cellular and structural complexity makes modeling of glomerulopathies in vitro challenging. We have generated kidney organoids from human iPSC that contain developing nephrons. This segment into distal tubules, proximal tubules and glomeruli with a primitive Bowman’s capsule and podocytes with forming primary and secondary foot processes.

Methods: Glomeruli were isolated from human iPSC kidney organoids using mechanical disruption and sieving, followed by in vitro culture. The kidney organoids contain a network of endothelial cells, however there is only limited vascularisation of the glomeruli. To investigate whether we can overcome this issue, kidney organoids were transplanted onto the chorioallantoic membrane (CAM) of chicken embryos in ovo.

Results: When placed into culture, podocyte outgrowth from glomeruli was comparable to that seen from glomeruli isolated from postnatal human or mouse kidney. These podocytes form confluent monolayers with accurate polarity and podocyte-specific markers including CD2AP, Podocin, Synaptopodin and WT1. Organoids transplanted onto CAMs showed vascular ingrowth from the host embryo within 24-36h, with organoid vascularisation increasing over time. The capacity for this exogenous blood supply to form glomerular capillaries and facilitate podocyte and GBM maturation was then investigated.

Conclusions: In conclusion, we have developed an in vitro method for the vasculisation of iPSC-derived kidney organoids. This will facilitate the modelling of human glomerular disease using patient-derived iPSC.

Funding: Government Support - Non-U.S.

TH-OR077
Human Pluripotent Stem Cell Derived Kidney Model for Toxicity and ADME Studies

Piyush Baija, Claire Stepan, David Rodrigues, Thomas Schroeter. PDM-NCE, Pfizer Inc, Groton, CT, U.S.

Background: In vitro models of kidney function have been challenging to develop. Both primary and immortalized kidney cells quickly lose the apicobasal transporters and key proteins when grown in conventional culture systems. Therefore, a need exists to develop more physiologically relevant in vitro human cell models which could be used to support efficacy, safety and ADME testing.

Methods: Pluripotent stem cells were differentiated into podocytes and proximal tubule cells (PTCs) by mimicking elements of renal developmental biology and prior literature. The stem-cell derived cells were characterized in terms of gene expression, immunocytotoxicity, and functionality. Presence of several key renal transporters was confirmed by gene expression. When exposed to the NP reprogramming protocol, these cells displayed key markers of NPs and epithelial-to-mesenchymal-transformation, as well as morphological and functional characteristics of endogenous NP cells.

Conclusions: These results not only demonstrate the feasibility of transplanted-based disease modeling, but also bring us closer to realizing patient-specific reprogramming to NP cells for cellular therapies, bioengineering applications and nephrotoxicity screening.

Funding: Government Support - Non-U.S.

TH-OR078
PiggyBac Transposon-Mediated Direct Transcriptional Reprogramming to Neprhon Progenitors

Jennifer May Vanslambrouck, Lauren Elizabeth Woodard, Norsela Suhaimi, Matthew H. Wilson, Melissa H. Little, Murdoch Childrens Research Inst, Royal Children's Hospital, Melbourne, Australia; Dept of Veterans Affairs and Dept of Medicine, Div of Nephrology and Hypertension, Vanderbilt Univ School of Medicine, Nashville, TN; School of Biomedical Sciences, The Univ of Queensland, Brisbane, Australia.

Background: Reprogramming holds great promise for the development of desperately needed novel treatments for chronic kidney disease (CKD). All nephrons in the kidney arise from embryonic nephron progenitors (NPs). However, this population is depleted near birth rendering the mature kidney unable to form new nephrons regardless of damage or disease. Recreation of NPs may allow regeneration of entire nephrons, making them an ideal target for regenerative approaches to generate alternate NPs to generate alternate CKD treatments. Using a low-expressing, transmeditated screen, we previously identified 6 transcription factors (SIX2, SIX1, HOXA11, OSR1, EYA1 and SNAIL2) sufficient to re-impose a NP-like state when co-expressed in adult human kidney epithelial cells (Hendry et al., JASN, 2013). To improve reprogramming and transdifferentiation to in vivo models, we have developed a multicellular transposon construct.

Methods: The transposon was generated by engineering reprogramming factors into a piggyBac construct with intervening 2A sequences, a tetracycline response element for doxycycline inducibility and a fluorescent reporter (mCherry) for enrichment. To assess functionality, the transposon was co-transfected with tetracycline-activator and piggybac transposase constructs. Reprogramming was induced with doxycycline exposure in combination with brief valproic acid treatment.

Results: Transfected adult kidney cells showed tightly regulated, inducible mCherry expression when exposed to the NP reprogramming protocol, these cells displayed key markers of NPs and epithelial-to-mesenchyme-transformation, as well as morphological and functional characteristics of endogenous NP cells.

Conclusions: These data provide a framework for removing sources of unwanted variability in the analysis of expression data, thereby increasing the utility of this approach for personalised medicine and functional genomics.

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

TH-OR079
Convoluted Proximal Tubule Modeling Enabled by Microfluidics and Bioprinting

Kimberly Homan, David Kolesky, Jessica E. Herrmann, Annie Moisan, Jennifer A. Lewis, The Wyss Inst, Harvard Univ, Cambridge, MA; Roche Pharma Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland.

Background: Three-dimensional models of kidney tissue that recapitulate human responses are needed for drug screening, disease modeling, and, ultimately, kidney organ engineering.

Methods: We present a bioprinting method for creating functional 3D human renal proximal tubules in vitro that are fully embedded within an extracellular matrix and housed in perfusable tissue chips, allowing them to be maintained for greater than four months. Their convoluted tubular architecture is circumscribed by proximal tubule epithelial cells and actively perfused through the open lumens at physiological shear stresses.

Results: These engineered 3D proximal tubules exhibit significantly enhanced epithelial morphology and functional properties relative to the same cells grown on 2D surfaces with or without perfusion. The proximal tubule cells in 3D printed and perfused conduits rebuild their own basement membrane over time and maintain a high barrier. Additionally, epithelial cells in curved regions of the convoluted tubule uptake albumin more than nearby straight regions. Lastly, upon introducing the nephrotoxin, Cyclosporine A, the epithelial barrier is disrupted in a quantifiable, dose-dependent manner.

Conclusions: In addition to the enhancement in morphology and function of tubule cells observed in our chips, the bioprinted platform is versatile and could be customized to incorporate perfusable vasculature and multiple cell types in predefined locations, enabling both drug screening and drug toxicity mechanistic studies at user-defined levels of complexity.

Funding: Pharmaceutical Company Support - Roche, Private Foundation Support

TH-OR080
Rapid Iterative Development of Blood Conduits for Artificial Kidney

Eliminates Thrombosis


Background: Implanted blood contacting devices, particularly dialyzers, tend to require pharmacologic anticoagulation of the patient to avoid local thrombosis and distant thromboembolism. Macrovascular encapsulation of islet cells utilizing a U-shaped device as a biointerface microchannel was largely abandoned due to complications such as microthrombosis. Improved design and manufacturing of devices might avoid the risks and costs of chronic anticoagulation and allow for the successful development of an artificial organ.

Computational modeling and in vitro imaging facilitated rapid iterative development of a high throughput blood conduit.

Methods: Following 3-90 day sustained preclinical implantation trials of hemofilter cartridges, correlations between low shear rates in silicon and areas of clot nucleation in vivo

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

Underline represents presenting author.
led to modifications of outflow tract geometry. Computational fluid dynamics simulations of steady flow trajectories in design variations were followed by flow field imaging in vitro. The design with least recirculation and stasis was machined from medical grade polycarbonate and implanted in a Class A dog for 30 days without warfarin or heparin. Serial Doppler ultrasound examinations verified patency of the blood conduits. At postoperative day 30, the animal suffered no complications of surgery. No hemolysis or distal embolization was noted. The optically transparent cartridge had no visible thrombosis.

**Results:** Robustness and reliability were established and examined for thrombosis. The animal suffered no complications of surgery. No hemolysis or distal embolization was noted. The optically transparent cartridge had no visible thrombosis.

**Conclusions:** The gold standard for the diagnosis of idRTA. The furosemide/fludrocortisone (F/F) test has been widely used as a test with improved tolerability. Due to the lack of comparative studies, the F/F test is the gold standard for the diagnosis of idRTA. The F/F test had a positive predictive value of 37% and a negative predictive value of 97% for the diagnosis of idRTA. Furthermore, comparison of fasting urinary pH and urinary acidification capacity during F/F and NH4Cl tests indicates that only a morning fasting urinary pH of <5.3 reliably excludes idRTA.

**Conclusions:** Thus, the F/F test is an excellent screening test for idRTA diagnosis in recurrent SF with a high negative predictive value. Due to low positive predictive value, however, patients with a pathological F/F test need confirmation by the NH4Cl test for idRTA diagnosis. In the absence of provocative testing, a diagnosis of idRTA can only be ruled out confidently with a morning fasting urinary pH <5.3.

**TH-OR083**

**Hydroxyproline Metabolism and Oxalate Synthesis in Primary Hyperoxaluria**

**Sonia Fargue,** 1 John Knight, 1 Dawn S. Milliner, 1 Julie B. Olson, 2 W. Todd Lownher, 3 Ross P. Holmes. 1 1Dept of Urology, Univ of Alabama at Birmingham, Birmingham, AL; 2Hyperoxaluria Center, Mayo Clinic, Rochester, MN; 3Dept of Biochemistry, Wake Forest School of Medicine, Wake Forest, NC.

**Background:** The primary hyperoxalurias (PH) are severe inherited diseases of glyoxylate metabolism characterized by increased endogenous production of oxalate. A major source of glyoxylate in humans is hydroxyproline (HPy), a collagen breakdown product. To quantify the contribution of HPy turnover to oxalate synthesis, we infused labeled HPy in fasting PH patients and healthy subjects.

**Methods:** Patients with PH type 1 (n: 7), 2 (n: 4), 3 (n: 8), and normal subjects (n: 9) were infused with $^{15}$N-HPy (750 mmol/kg) for 6 h continuously. Urine and plasma were collected hourly for analysis of $^{15}$N-HPy by GC/MS, total HPy by HPLC, HPy, and $^{15}$C-oxalate and glycolate by IC/MS.

**Results:** Basal HPy concentrations and fluxes were lower in PH patients as compared to controls [table1A,B]. The contribution of HPy metabolism to urinary oxalate excretion was assessed by giving the PH patients compared to PH1 patients (16%) and controls (11%) [figure1C]. The contribution of HPy to urinary glycolate was significantly decreased in PH2 and PH3 and marginally decreased in PH1 [figure1D].

**Conclusions:** Hydroxyproline contributes to glycolate and oxalate metabolism in humans confirming its potential as a therapeutic target in PH and the potential usefulness of dietary restrictions in PH2. The heterogeneity seen between PH3 patients highlights the complexity of oxalate synthesis in PH3. These data suggest other yet to be determined pathways are important to the increased synthesis of oxalate in PH.

**Funding:** NIDDK Support

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**Table TH-OR082**

**Comparison of Furosemide/Fludrocortisone with Ammonium Chloride Test in the Diagnosis of Incomplete iRTA in Recurrent Stone Formers: A Prospective Study**

**Nasser Dhanat,** Ganesh Pathare, Bruno Coe, Elaine M. Worcester, Nephrology Section, Univ of Chicago, Chicago, IL.

**Background:** In a General Clinical Research Center, we investigated whether the F/F test has a positive predictive value of 37% and a negative predictive value of 97% for the diagnosis of idRTA. Furthermore, comparison of fasting urinary pH and urinary acidification capacity during F/F and NH4Cl tests indicates that only a morning fasting urinary pH of <5.3 reliably excludes idRTA.

**Methods:** We measured U/P and determinants of acid-base regulation in 14 normal subjects (7 M). We collected 15 urines and 20 blood samples over a 15 hour day; diet was fixed. Gi alan excretion (GIAE) = [(Na-K+Ca+Mg) - (Na+K+P)] in urine (mmol/hr).

**Results:** U/P of W exceeded that of M; U/P rose with meals in W but not M (Table). Serum ultrafilterable (UF) CO2 and GIAE rose with meals in W, not M; urine CO2 excretion and GIAE exceeded M. Lower U/P in M was accompanied by higher net acid excretion (NEA) and higher titratable acid (TA) and NH3. Urinary citrate (cit) and fractional excretion (FE) of cit was higher in W even adjusted for filtered load (FL) of cit, indicating reduced renal reabsorption of cit in W vs M.

**Conclusions:** W have higher Gi alkali absorption and GIAE than M which translates into increased urinary CO2 and higher U/P. The sex difference in U/P is due not to diet, but is related to ingestion of food.

**Funding:** NIDDK Support

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**Table TH-OR083**

**Hydroxyproline Metabolism and Oxalate Synthesis in Primary Hyperoxaluria**

**Figure 1A** Plasma concentration of Hyp (white) and glycolate (gray) before infusion; (1B) Hyp flux; (1C) contribution of Hyp to urine oxalate and (1D) glycolate. Results (median, range); **p<0.05/0.01/0.001 with Kruskall-Wallis test.
Results: ob mice have significantly higher (≅5-fold) urine 17C-oxalate compared to controls, indicating increased intestinal oxalate absorption in vivo. Observing a greater oxalate absorption in vivo compared to ex vivo suggest the possibility of increased paracellular permeability along the entire gut. ob mice have significantly higher urinary excretion of succinate (≅1.7-fold) and succurazole (≅2.2-fold), reflecting increased proximal gut (and colon) faecal oxalate (and succinate). In addition, ob mice also have significantly higher urinary excretion of lactulose (≅4.4-fold), mannitol (≅3-fold), and lactulose:mannitol (≅1.52-fold), reflecting enhanced small intestinal paracellular permeability. Using qpcr, significantly reduced mRNA expression of the tight junction proteins occludin (37±3%) and ZO-1 (28-62%) is observed in the stomach, duodenum, jejunum, ileum, cecum, and distal colon of ob mice.

Conclusions: We conclude that obese mice have significantly higher paracellular permeability along the entire gut, which would likely contribute to the observed hyperoxaluria, since there is a favorable transepithelial oxalate concentration gradient.

Funding: NIDDK Support

TH-OR085
A Dose Finding Study with ALLN-177 in a Porcine Model of Hyperoxaluria (20HO) Induced by a Human-Like Western Diet
Dana Grupi, Craig B. Langman, Katerina Goncharova, Lee Brettman, Stefan Pierzykowski, Allena Pharmaceuticals; Northwestern Univ; Lund Univ. Sweden.

Background: Secondary hyperoxaluria is a known risk factor for recurrent urolithiasis and progressive chronic kidney disease. Dietary modifications have limited effectiveness and new therapeutic options are needed.

Methods: To induce mild hyperoxaluria 24 pigs were fed the WLD for an initial pre-treatment period of 7 days and then randomized based on daily urinary oxalate (Uox) in a parallel 7d study to one of three treatment arms: ALLN 22,500 units/day (high dose, HD, n=8), 11,250 units/day (low dose, LD, n=8), or no treatment (n=6). The primary endpoint was the change in Uox level, defined as the difference between the normal range on record for the time period before and after treatment. A control group of 6 pigs was fed a regular pig feed (RF) to estimate the impact of HDx Uox vs RF alone and to establish a normal Uox excretion.

Results: Twice daily oral Rx with ALLN-177 significantly reduced mean Uox by 15mg (17%) and 11mg (12%) with HD and LD respectively, when compared to WLD alone (HD: 85.08±15.0 to 70.60±10.1; LD 87.94±15.0 to 77.23±10.1 mg/gCr/d; p<0.001) whereas the mean Uox did not change in the WLD control group. Importantly, with the HD Rx, Uox excretion decreased in 24h Uox (mg/g cr/24h) calculated from days 3.5 and 7 collected during the pre-treatment and treatment periods. A control group of 6 pigs was fed a regular pig feed (RF) to assess the impact of RX on Uox vs RF alone and to establish a normal Uox excretion.

Conclusions: Orally administered ALLN-177 with meals was well tolerated and normalized Uox with the 22,500 units/d. This porcine model that mimics 20HO in patients, was tested in a porcine dietary model of 20HO induced with a Western like diet (WLD) with average oxalate and calcium levels. Pigs were chosen due to their physiological similarities to humans in GI and renal functions.

Funding: Clinical Revenue Support

TH-OR086
Claudin-2 Knockout Mice Spontaneously Develop Calcium Phosphate Deposition within the Renal Papilla
Alan S.I. Yu, Joshua N. Curry, Lei Pci, Peter S.N. Rowe.

Molecular and Integrative Physiology, Univ of Kansas Medical Center; Kansas City, KS; Kidney Inst, Univ of Kansas Medical Center; Kansas City, KS; Anatomy and Cell Biology, Indiana Univ School of Medicine, Indianapolis, IN.

Background: The proximal tubule (PT) is where the majority of calcium reabsorption in the kidney occurs by an unknown mechanism. Physiologic studies have shown this reabsorption to be predominantly passive. The tight junction proteins called Claudins are important determinants of paracellular permeability and passive reabsorption in the kidney. In the PT, the highest Claudin expression is that of Claudin 2, which forms cation-selective pores in vitro studies. Previous studies have shown that Claudin-2 KO mice have an increase in urine calcium. We hypothesize that Claudin-2 loss leads to defective PT calcium reabsorption and nephrocalcinosis.

Methods: Renal calcification was quantified by micro-CT (Scanco). Mineral composition of renal stones was determined by micro-Fourier Transform infrared spectroscopy. Transmission electron microscopy was performed on 2% glutaraldehyde fixed parietal sections.

Results: We found that Cldn2-2 KO mice develop nephrocalcinosis concentrated within the renal papilla that is absent from wild type littermates. Using micro-FTIR analysis, these deposits were determined to be composed primarily of hydroxyapatite (calcium phosphate). Localization of these deposits was determined to be intraluminal by immunohistochemistry and transmission electron microscopy.

Conclusions: Randall’s plaques are hydroxyapatite plaques which develop within the renal papilla in human kidney stone formers. Claudin-2 KO mice may develop nephrocalcinosis in a similar manner. Physiologic analyses will help us further determine whether the observed increase in urine calcium is due to a defect in PT calcium reabsorption in Cldn2-2 KO mice.

Funding: NIDDK Support

TH-OR087
Insulin Resistance and the Risk of Calcium Kidney Stone Zeyar Myint, Jie Tang, Nephrology, Brown Univ, Providence, RI; Nephrology, Univ Medicine, Brown Univ, Providence, RI.

Background: Insulin resistance is associated with a higher risk of uric acid kidney stone. But its role in calcium kidney stone formation is not clear.

Methods: We performed a cross-sectional study of 43 non-diabetic calcium kidney stone formers, and examined the associations between insulin resistance and 24-hour urine stone risk parameters. The homeostatic model assessment (HOMA)-IR and HOMA-B were used to quantify insulin resistance and pancreatic beta-cell function respectively. Both HOMA-IR and HOMA-B were log transformed and were modeled using univariate and multiple linear regression methods.

Results: All study participants had confirmed calcium kidney stones. Among them, 61% were male, 86% were Caucasian, 33% had prevalent hypertension and 12% had prevalent dyslipidemia. The median age was 53 years (range 21-76), and the average body mass index (BMI) was 26.8 (Standard Deviation, 5). The mean serum 25-OH-vitamin D level was 25 ng/ ml, the median HOMA-IR was 5.25 (range 1.4-68.4), and the median HOMA-B was 176.9 (range 52.25-2421). Both HOMA-IR and HOMA-B associated significantly with BMI, even after adjusting for hypertension, dyslipidemia and 25-OH-vitamin D (P<0.02). HOMA-IR associated significantly with uric acid (P=0.001), uric acid (P=0.001) and uric acid (P=0.017) in univariate linear models. After adjusting for age, gender, race and BMI, only uric acid associated significantly with HOMA-IR (P<0.009). HOMA-B associated significantly with urine calcium (P=0.039) and urine uric acid (P=0.017) in univariate linear models. After adjusting for age, gender, race and BMI, the associations were no longer significant. Neither HOMA-IR nor HOMA-B had significant associations with urine pH, sodium, phosphorus, oxalate, and citrate in univariate analysis (P>0.05).

Conclusions: Neither HOMA-IR nor HOMA-B appeared to be associated with an increased risk of calcium kidney stone formation. The significance of the association between HOMA-IR and urine uric acid among calcium stone formers is not clear.

Funding: Private Foundation Support

TH-OR088
The Live Donor Champion Program: A Novel Approach to Identifying Live Kidney Donors
Elizabeth A. King, Dorry L. Segev. Surgery, Johns Hopkins Univ, School of Medicine, Baltimore, MD.

Background: The Live Donor Champion (LDC) program is a clinical program offered to kidney waitlist candidates at our transplant center. The five-month program provides education and advocacy training for candidates and a friend or family member chosen to serve as an advocate, or “Live Donor Champion”, on each candidate’s behalf. The goal of the program is to increase awareness of live donation and to identify potential live donors.

Methods: We studied 163 adult kidney transplant candidates that have participated in the LDC program at Johns Hopkins Comprehensive Transplant Center between October 2013 and May 2016. Paired t-tests were used to estimate the difference in knowledge about live donation and comfort approaching others about live donation before and after participation in the LDC program. We compared time to first live donor referral for candidates that participated in the program with matched controls from our waiting list using a cox proportional hazard model. We used 1:3 iterative expansion ratio matching to choose controls based on age at listing, time on waitlist without a live donor, sex, race, and ABO blood type.

Results: Participation in the LDC program was associated with a statistically significant increase in knowledge of live donation among candidates participating alone, candidates participating with a LDC, and LDCs (all p < 0.001). Comfort approaching others about live donation also increased significantly among all three groups (all p-values <0.001). Among LDC participants, there were a total of 81 live donor referrals. Participation in the LDC program was associated with 3.5-fold increase in having at least one donor referral compared to matched controls (aHR 5.92, 95% CI 3.42-7.95, p<0.001).

Conclusions: The LDC program is associated with increased knowledge of live donation, comfort approaching others about live donation, and live donor referrals.

Funding: Clinical Revenue Support

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21A
Pre-Transplant Recipient Transcriptomic Profile May Predict Delayed Graft Function (DGF) in Kidney Transplantation
Paola Pontrelli,1 F. Rascio,2 Francesco Pesce,1 Matteo Accetturo,1 Giuseppe Castellano,1 Gianluigi Zaza,1 Marco Fiorentino,1 Loreto Gusaudo,1 G. Stallone,1 Giuseppe Grandaliano,1
1 Univ of Bari, 2Univ of Foggia, 3Univ of Verona.

Background: DGF is associated with a reduced long-term graft survival. Inflammation-reperfusion damage and donors’ features have been always considered as key pathogenic factors in this setting. The aim of our study was to evaluate the role of recipients’ characteristics in the development of DGF.

Methods: We prospectively enrolled 538 kidney graft recipients, 176 of whom experienced DGF. We selected 10 couples of DGF/early graft function (EGF) recipients for high throughput analysis. Peripheral blood mononuclear cells (PBMC) were harvested by qPCR in an independent group (DGF n=10; EGF n=10).

Results: Using the 5 years prior to the LKD as a baseline, there were 11 DGFs from CMDBH in this period, 4 of which were in Māori or PP. In total, there were 7 DLDTs, 4 of which were in Māori or PP. Accounting for underlying prior 5-year trends in KT or LDKT, the DGF program is associated with an increase in KT by 1.84 (1.21-2.79) fold, and in LDKT by 1.60 (1.73-2.49) fold.

Conclusions: A whole-systems approach with a multifaceted health service delivery improvement program is an effective way of increasing LDKT, particularly in disadvantaged populations.
Funding: Government Support - Non-U.S.

Crossing the Valley of Death: A Validation Study of Noninvasive Diagnosis of Acute Cellular Rejection by a Composite Signature of 3-mRNAs and 4 Metabolites in Urine
Mohammad M. Alkadi, Catherine Snopkowski, Carol Y. Li, Liana S. Perry, Matthew Magruder, Kanan Jatwani, John R. Lee, Steven Salvatore, Darshana Dadhania, Surya V. Seshan, Hua Yang, Adhiraj Mathukumar, Karsten Suhr, Manikbam Suthanthiran, Well Cornell Medicine.

Background: Most biomarkers fail to be validated in an independent cohort- the valley of death encountered also during transitions from Phase I safety to Phase III efficacy trials. We investigated whether our 3-gene urinary cell RNA signature and the metabolite signatures for the noninvasive diagnosis of acute cellular rejection (ACR) are validatable in an independent cohort of kidney graft recipients.

Methods: We collected 118 biopsy-matched urine specimens from 95 kidney recipients (22 from 22 recipients with ACR; 96 from 73 recipients with no rejection). We isolated RNA from the urine cell pellets and quantified the absolute abundance of CD3+ mRNA, CXCL10 mRNA and 18S rRNA using qPCR assays. We measured the metabolites 3-sililactate, xanthosine, quinoline and X-16397 in the corresponding cell-free urine supernatants using comprehensive GC/MS and LC/MS/MS platforms.

Results: Urinary cell 3-gene signature discriminated patients with ACR from no rejection (AUC: 0.81). The ratio of 3-sililactate/xanthosine (AUC: 0.63) and quinoline/X-16397 (AUC: 0.74) discriminated ACR from no rejection. The combined mRNA and metabolite signature also discriminated patients with ACR from those with no rejection (AUC: 0.86).

None of the AUCs differed significantly from the AUCs in our original biomarker studies (P>0.05, DeLong test).

Conclusions: To our knowledge, this is first-in-kind validation of urine-based biomarkers diagnostic of ACR using: (i) an independent cohort of kidney recipients, and (ii) a locked prediction model, i.e., using the same discovery study validation in the study. Our observations support consideration of these biomarkers in the clinical management.

TH-OR092
Urine Fibrosis Markers and Risk of Cardiovascular Events and Death in Kidney Transplant Recipients: The FAVORIT Trial
Yasuyo Takada,1 2 Yuki Kamiyama,3 Yuka Mihayama,4 Jan M. Hughes-Austin,5 Francis B. Gabbai,6 Chi-Tuan Hsu,7 Nisita Bamsai,1 Andrew Bostom,1 Orlando M. Gutierrez,5 Mark J. Sarnak,4 Andrew S. Levey,2 Joachim H. I.,3 UCSF; 2U. Washington; 2U. Sydney; 3Kidney Society Auckland, Auckland, New Zealand; 4Kidney Society Auckland, Auckland, New Zealand.

Background: Cardiovascular disease (CVD) risk is high in kidney transplant recipients (KTR) despite improvement in eGFR after transplant. Urine markers of kidney fibrosis may help to reveal mechanisms of this risk.

Methods: In a case-control cohort study among stable KTR who participated in the FAVORIT trial, we measured 4 urine proteins known to correlate with kidney biopsy tubulo-interstitial fibrosis (alpha 1 microglobulin [α1m], monocyte chemoattractant protein-1 [MCP-1], procollagen type I [PINP] and type III [PIIINP] N-terminal amino peptide). We used spot urine specimens collected at baseline in a randomly selected subcohort (N=488) and in an independent cohort of kidney graft recipients.

Results: Urine α1m, PINP, and PIIINP were strongly associated with CVD events and death, after adjusting for demographics, CVD/CKD risk factors, eGFR, and ACR (Table 1). Relative to the lowest quartile, the highest quartile of urine α1m [HR 2.95 (1.43, 5.57)] and PINP [HR 2.88 (1.61, 5.16)] were associated with CVD events. All 3 markers were also associated with death in adjusted models: HR Q4 v. Q1 α1m 3.89 (2.05, 7.23), PINP 1.95 (1.02, 3.75), PIIINP 2.27 (1.35, 3.79). After adjustment, urine PIINP was not associated with CVD events [HR Q4 v. Q1 1.97 (0.52, 1.82)] or death [1.63 (0.92, 2.90)] in either continuous or quartile analyses.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Higher concentrations of urine mIgM, MCP-1, and PINP identify KTR at risk for CVD events and death. Fibrotic processes in the transplanted kidney may reflect systemic fibrosis and CVD risk in KTR.

Funding: NIDDK Support

TH-OR093

Emerging Safety and Tolerance with Obinutuzumab, a Type 2 Anti-CD20 Monoclonal Antibody for the Desensitization of Renal Transplant Candidates

Robert R. Redfield,1 Stanley C. Jordan,2 Thomas Schindler,3 Ha N. Tran,4 Caroline Looney,5 Cherie Green,6 Alyssa Morimoto,7 Richa Rajwanshi,8 Paul Brunetta,9 Dominic Boric,10 University of Wisconsin, Madison, WI; Cedars-Sinai Medical Center, Los Angeles, CA; P. Hoffman-La Roche AG, Basel, Switzerland; Genentech, South San Francisco, CA.

Background: Allosensitization in end-stage renal disease (ESRD) patients (pts) may restrict the deceased donor pool, resulting in long waiting times, or prevent living donor kidney transplantation. B-cell depletion with rituxanab (RTX) appears to be effective in desensitizing pts and enabling transplantation; however, B-cell depletion is incomplete in lymphoid organs despite complete peripheral depletion, and high antibody titers are only moderately reduced. Greater B-cell depletion in tissue may be more effective in allosensitization reduction. Obinutuzumab (Obi) is a glycoengineered anti-CD20 monoclonal antibody that binds CD20 differently from RTX and displays increased antibody-dependent cellular cytotoxicity and enhanced direct cell death compared with RTX, resulting in increased in vitro and in vivo B-cell depletion.

Methods: The type I, open-label, phase 1b THEORY study assessed the safety, pharmacokinetics, and pharmacodynamics of Obi in hypersensitized ESRD pts awaiting renal transplantation. The first cohort of patients (n=5) received 1,000 mg Obi on day 1 and high-dose IVIG on days 22 and 43. Safety and tolerability were reviewed when the last enrolled patient had 4 weeks of follow-up.

Results: Most (4/5) pts were women, aged 34-54 years, who had been waitlisted for 2-11 years and had calculated panel reactive antibody values of 74%-100%. Obi resulted in depletion of peripheral B cells by FACS (5/5) and to less than or equal to the lower limit of quantification of high-sensitivity flow cytometry (3/5). Obi appeared well tolerated and safe. Main adverse events (AEs) were grades 1 and 2 infusion related reactions in 3 pts that were manageable and did not prevent complete Obi administration. A serious AE of severe hypotension was managed with IV fluids and resolved. A serious AE of increased creatinine clearance with 4/5 pts was manageable and did not prevent complete Obi administration. A serious AE of decreased creatinine clearance was managed with 4/5 pts and did not prevent complete Obi administration. A serious AE of increased creatinine clearance was managed with 4/5 pts and did not prevent complete Obi administration. A serious AE of increased creatinine clearance was managed with 4/5 pts and did not prevent complete Obi administration.

Conclusions: Emerging experience with Obi indicates acceptable tolerability in ESRD patients requiring desensitization.

Funding: Pharmaceutical Company Support - Genentech, Inc.

TH-OR094

Efficacy and Safety of 3 Different Treatment Regimens in De Novo Renal Transplant Patients: 5 Year Follow-Up Data of the HERAKLES Trial on Efficacy and Safety of 3 Different Treatment Regimen in De Novo Renal Transplant Patients

Petra Everolimus-Based Immunosuppression in De Novo Renal Transplant Patients: 5 Year Follow-Up Data of the HERAKLES Trial on Efficacy and Safety of 3 Different Treatment Regimen in De Novo Renal Transplant Patients

TH-OR095

Timing of Eculizumab Treatment and the Need for Dialysis in Patients with aHUS Who Receive a Kidney Transplant

Andrew M. Siedlecki,1 Nicole Isbel,2 Johan Vande Walle,3 Varant Kupelian,4 David J. Cohen,5 Brigham and Women’s Hospital;6 The Univ of Queensland and Princess Alexandra Hospital, Australia;7 Ghent Univ Hospital, Belgium; 8 Alexion Pharmaceuticals, Inc.; 9 Columbia Univ Medical Center.

Background: Patients (pts) with atypical hemolytic uremic syndrome (aHUS) are at risk of thrombotic microangiopathy (TMA) and graft loss following transplantation. Eculizumab (Ecu), a complement C5a inhibitor, is effective in preventing and treating TMA and is increasingly used post-kidney transplant (KTs) in pts with aHUS. We report data on the timing of Ecu initiation and subsequent dialysis and TMA in aHUS patients undergoing KT.

Methods: Our analyses utilized data from a Global aHUS registry (NCT01522183) with 1122 pts enrolled as of March 2016, of whom 252 (24%) had at least one KTx. Overall, 94/252 pts had a KTx between December 1, 2011 and December 1, 2014) and received Ecu. Pts were grouped by use of Ecu (prior to or at time of transplant [pre-transplant]; n=57 vs started post-KTx [n=96]). Pts were monitored for up to 12 months post-KTx.

Results: Pts starting Ecu post-KTx were older, less likely to have a family history of aHUS, and had undergone fewer prior transplants (Table). Fewer pts treated pre-KTx with Ecu required any dialysis (4% vs 33%) and the median time to any dialysis was longer (15.3 vs 1.6 months) than in pts receiving Ecu post-KTx. The pts starting Ecu post-KTx had a higher rate of TMA (61% vs 4%) and TMA occurred earlier (after a median of 3.0 vs 11.4 months), compared with those starting Ecu pre-KTx.

Table Characteristics of pts with their last transplant between 01 December 2011 and 01 December 2014

Conclusions: HERAKLES 5 year data show that immunosuppressive regimen using ECU in reduced-dose or without CNI reflect an efficacious and safe therapeutic approach offering the opportunity for an individualized immunosuppression to minimize CNI-exposure.

Funding: Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.
TH-OR096

Effect of Denosumab on Peripheral Compartmental Bone Density, Microarchitecture and Estimated Bone Strength in De Novo Kidney Transplant Recipients: The POSTOP-HRpQCT Bone Microarchitecture Ancillary Study

Rudolph P. Wuthrich,1 Ursina Meyer,2 Diana P. Frey,3 Nicole Graf,4 Heike A. Bischoff-Ferrari,5 Marco Bonan,1 Div of Nephrology, Univ Hospital, Zurich, Switzerland; 2Div of Geriatrics and Aging Research, Univ Hospital, Zurich, Switzerland; 3Div of Rheumatology, Univ Hospital, Zurich, Switzerland; 4Graf Biostatistics, Winterthur, Switzerland.

Background: In a randomized controlled clinical trial in kidney transplant recipients (NCT01377764) we have recently shown that RANKL inhibition with denosumab significantly improved areal bone mineral density (aBMD) when given during the first year after transplantation. The effect of denosumab on skeletal microstructure and bone strength in kidney transplant recipients is not known.

Methods: The purpose of the present analysis was to investigate high-resolution peripheral quantitative computed tomography (HRpQCT) data from the distal tibia and distal radius in 24 study patients that had been randomized to receive either two injections of denosumab 60 mg at baseline and after 6 months (n=10) or no treatment (n=14).

Results: Denosumab reduced biomarkers of bone turnover, and significantly increased aBMD at the lumbar spine (median difference of 4.7%; 95% CI 2.6–7.8; p=0.001). Bone quality as assessed by total and cortical volumetric bone mineral density (Tot.vBMD, Ct.vBMD) and cortical thickness (Ct.Th) increased significantly at the tibia. The trabecular volumetric BMD (Tb.vBMD), separation (Tb.Sp) and number (Tb.N) and the cortical porosity (Ct.Po) at the tibia and the radius did not significantly change in both treatment groups. Micro-finite element analysis (mFEA) showed that bone stiffness increased significantly at the tibia (median difference 5.6%; 95% CI 1.8%–9.2%; p=0.002) but not at the radius (median difference 2.9%; 95% CI -3.7%–9.1%; p=0.369). Likewise, failure load increased significantly at the tibia (median difference 5.1%; 95% CI 2.1%–8.1%; p=0.002) but not at the radius (median difference 2.4%; 95% CI -3.2%–8.5%; p=0.336).

Conclusions: Denosumab improves bone density and bone quality in first-year kidney transplant recipients at risk to develop osteoporosis.

Funding: Clinical Revenue Support

TH-OR097

Kidney Failure Risk Projection for the Young Living Kidney Donor Candidate

Jayme E. Locke,1 Rhiannon D. Reed,2 Deirdre L. Sawinski,2 Paul A. Maclennan,1 Vinette Kumar,1 Shikha Mehta,3 John Jeffrey Carr,3 James Gregory Terry,2 Allan Massie,1 Meredith Kilgore,1 Robert S. Gaston,1 Roslyn B. Mannon,1 Dorry L. Seges,4 Cora E. Lewis,5 1Univ of Alabama at Birmingham; 2Univ of Pennsylvania; 3Vanderbilt Univ; 4Johns Hopkins Univ.

Background: Living kidney donor selection practices aim to identify risk for chronic kidney disease (CKD). Assessment has evolved from examination of individual risk factors to a risk calculator that incorporates multiple candidate characteristics. Due to limited long-term data, current risk tools lack precision with regard to young living donor candidates (LKDC).

Methods: We identified a cohort of potentially acceptable, young (18-30yo) LKDCs with no absolute contraindications to kidney donation (diabetes, hypertension, malignancy, heart disease, kidney problems, or pregnancy at year 0 exam) from the longitudinal cohort study CARDIA. Risk associations for CKD were identified and assigned weighted points, resulting in calculation of a risk score (c-statistic: 0.74).

Results: 3,554 LKDCs were identified; mean age 24.8yrs; 48.8% black; median follow-up of 24.9yrs (IQR: 24.5-25.2). For an 18yo LKDC 15yrs from transplantation the median risk was 0.74 (95% CI 0.66–0.83; c-statistic: 0.74).

Conclusions: Denosumab reduced biomarkers of bone turnover, and significantly increased aBMD at the lumbar spine (median difference of 4.7%; 95% CI 2.6–7.8; p=0.001). Bone quality as assessed by total and cortical volumetric bone mineral density (Tot.vBMD, Ct.vBMD) and cortical thickness (Ct.Th) increased significantly at the tibia. The trabecular volumetric BMD (Tb.vBMD), separation (Tb.Sp) and number (Tb.N) and the cortical porosity (Ct.Po) at the tibia and the radius did not significantly change in both treatment groups. Micro-finite element analysis (mFEA) showed that bone stiffness increased significantly at the tibia (median difference 5.6%; 95% CI 1.8%–9.2%; p=0.002) but not at the radius (median difference 2.9%; 95% CI -3.7%–9.1%; p=0.369). Likewise, failure load increased significantly at the tibia (median difference 5.1%; 95% CI 2.1%–8.1%; p=0.002) but not at the radius (median difference 2.4%; 95% CI -3.2%–8.5%; p=0.336).

Conclusions: Denosumab improves bone density and bone quality in first-year kidney transplant recipients at risk to develop osteoporosis.

Funding: Clinical Revenue Support

TH-OR098

Cultural Competency of a Mobile, Customized Patient Education Tool for Improving Potential Kidney Transplant Recipients’ Knowledge and Decision-Making

Crystal Anderson,1 David A. Axelrod,2 David Wojciechowski,3 Marie Jacobs,3 Krista L. Lentine,1 Mark Schnitzer,1 John Devin Peipert,1 Amy D. Waterman,1 1David Geffen School of Medicine, Univ of California, Los Angeles, Los Angeles, CA; 2Ayn Management Inc., Boerne, TX; 3Dept of Medicine, Massachusetts General Hospital, Boston, MA; 4Dept of Internal Medicine, St. Louis Univ, St. Louis, MO.

Background: After Kidney Allocation System (KAS) reforms, patients have to decide between deceased donor kidney transplant (DDKT), living donor kidney transplant (LDKT) and dialysis. My Transplant Coach (MTC) is a mobile, iOS based tablet education tool that presents didactic animated videos and individualized charts derived from multivariate models of pre-transplant mortality rate, median waiting time to transplant, and post-transplant survival based on kidney donor profile index (KPDI) and transplant type. We assessed whether patients found the application helpful and culturally sensitive; whether transplant knowledge and informed decision-making improved; and how patients’ race and comfort with technology were associated with changes.

Methods: In two US transplant centers, 81 patients (White: 27%, African American: 25%, Hispanic: 15%, Asian: 25%) varying in their experience with technology (51% were comfortable using internet) viewed the animated content and their own graphs and completed pre- and post- intervention knowledge assessments (0-20 scale) and usability questionnaires. Results: 86% reported MTC helped them understand their options, 85% would recommend the app, and 78% felt more comfortable talking to their doctor about their treatment options. High proportions of patients said the app was suitable for people of their race/ethnic group (67%–85%; P<0.79). After reviewing MTC, patients reported having a greater ability to make informed DDKT (52%–55%, P<0.001) and LDKT decisions (40%–72%, P<0.001). Knowledge increased (9.1 to 13.8 questions correct, P<0.001), with similar increases for patients of all races and levels of comfort with technology levels.

Conclusions: MTC was helpful for a diverse group of transplant candidates and resulted in increased transplant knowledge and informed decision-making.

Funding: Private Foundation Support

TH-OR099

Impact of Patient Navigators and Enhanced Personal Health Records on Health Literacy in Those with CKD

Stacey Jolly,1 Sankar D. Navaneethan,2 Jesse D. Schold,1 Susana Arriagin,1 Georges Nakhoul,1 Victoria Konig,1 Jennifer Hyland,1 Yvette K. Burrucker,1 Priscilla Davis Dunn,1 Barbara H. Tucky,1 Joseph V. Nally,1 1Cleveland Clinic; 2Baylor College of Medicine.

Background: The recognition of and education for patients with CKD is a public health need as patients with limited health literacy may have difficulty processing medical information and traversing an increasingly complex health system. There is a lack of...
translational research in CKD that incorporates educational tools. We developed a CKD Patient Navigator program and an enhanced online personal health record (PHR) with links to publicly available NKEP and NKF education materials. We report CKD health literacy survey results from our randomized-controlled clinical (RCT) trial.

Methods: 209 patients with CKD from 6 outpatient clinics were randomized in a 2x2 factorial design to CKD Patient Navigator or enhanced PHR, their combination, or usual care. Baseline survey was done at time of enrollment in person. An exit phone survey was done at the end of the 2-year follow-up. Survey included literacy, computer skills, and detailed CKD knowledge items. Results: Mean age was 66.7 years with 75% whites and 22% blacks. Majority were CKD Stage 3b (n=156) (70%) at enrollment. 194 completed exit survey (deceased = 11; declined/no response/unable to reach = 4). Some pre-/post-survey results are shown in Table 1.

<table>
<thead>
<tr>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigator (n=53)</td>
<td>ePHR (n=50)</td>
</tr>
<tr>
<td>need help with medical forms</td>
<td>11(21%)</td>
</tr>
<tr>
<td>difficulty understanding when doctor talks about CKD</td>
<td>21(40%)</td>
</tr>
<tr>
<td>know your eGFR (yes)</td>
<td>9(17%)</td>
</tr>
<tr>
<td>need help with medical forms</td>
<td>3(6%)</td>
</tr>
<tr>
<td>difficulty understanding when doctor talks about CKD</td>
<td>2(4%)</td>
</tr>
<tr>
<td>know your eGFR (yes)</td>
<td>12(24%)</td>
</tr>
</tbody>
</table>

Conclusions: We successfully conducted a RCT trial using educational tools. Health literacy improved in all groups. For some measures, we were able to evaluate the tools, for which CKD educational links were most utilized, CKD Patient Navigators role in addressing barriers, patient satisfaction with the intervention.

Funding: NIDDK Support

TH-OR102


Background: Perceived adequacy of the pediatric nephrology (PN) workforce varies considerably worldwide. Likewise, training for qualification as a pediatric nephrologist varies from country to country. No comendium of these requirements exist. In the United States (US), PN workforce concerns have generated a discussion of whether a year option, as opposed to 3 years, is advisable in order to increase the number of trainees. The purpose of our study is to synthesize and compare PN training requirements worldwide, and describe the opinions of pediatric nephrologists on the value of a 2 versus 3 year fellowship.

Methods: In the spring of 2013, survey invitations were sent to members of the American Society of Pediatric Nephrology (ASPAN) and the American Academy of Pediatrics (AAP) section on Pediatric Nephrology. In the Fall of 2015, survey invitations were sent to members of International Pediatric Nephrology Association (IPNA). E-mail messages were sent to pediatric nephrologists in countries with ≥ 25 contacts listed in the online IPNA member directory. Qualitative and quantitative analyses were performed, and data cross-referenced when possible.

Results: The AAP survey was sent to 766 pediatric nephrologists and had a 66% response rate. Forty nine percent of respondents favored a 2 year option for PN fellowship training and 34% were opposed to a change in training duration. Prominent themes in support of a 2 year fellowship were a perceived need for more clinicians in the PN workforce and a desire to limit the financial and time burdens of the third year of training. The IPNA survey was sent to 2304 valid e-mail addresses and had a 15% response rate. In some countries, the duration and intensity of training varies with the PN responsibilities that the graduates are anticipated to assume.

Conclusions: We summarize the requirements for PN training in most areas of the world as of the beginning of 2016. Three years is the common duration of PN fellowship and recently has become the new minimal recommendation in Europe, Australia, and New Zealand. Due to concerns of a potentially inadequate workforce, many U.S. pediatric nephrologists wonder if a 2 year clinical track should be considered.

TH-OR103

An Integrated Pathology and Ultrasonography-Based Simulation Is an Effective Educational Tool for the Performance of a Kidney Biopsy Juan Carlos Q. Vélez,1 Vandanana Niyayar,1 Kevin D. Phelan,1 Nithin Karakala,2 Kevin W. Creamer,3 Kelly W. Creamer,3 M. John M. Arthur,3 Shree G. Sheth,1 MD,1 Div of Nephrology, Medical Uni of South Carolina, Charleston, SC; 2Renal Div, Emory Univ, Atlanta, GA; 3Div of Nephrology, Univ of Arkansas Medical Sciences, Little Rock, AR; 4Arkana Laboratories, Little Rock, AR.

Background: Proficiency in performance of percutaneous kidney biopsy (PKB) is required for accreditation in nephrology. Medical practice trends and limitations in trainees’ duty hours have diminished the interest and exposure of nephrology fellows to PKBs. We hypothesized that a novel integrated nephrology-pathology-led simulation may be an effective educational tool.

Methods: A 4-hour PKB simulation workshop (KBWS) was led by 2 ultrasonography (US)-trained nephrologists and 1 pathologist and consisted of 6 stations: diagnostic kidney US with live patients, kidney pathology with embedded torso crosses sections, US-based PKB with cadaver, US-based PKB with embalmed cadavers and tissue retrieval adequacy examination by microscopy. A 10-question survey [6 multiple-choice questions assessing knowledge acquisition, 4 five-scale questions assessing procedural confidence gain] was administered pre and post KBWS.

Results: Twenty-one participants (4 nephrologists, 17 trainees) attended the KBWS and completed the survey. The percentage of correct answers increased numerically in 5 of 6 knowledge questions, reaching statistical significance in 3 of them (p=0.0003–0.04). The percentage of correct answers increased from 55 to 83% (p=0.016). The number of Extremely Confident answers increased from 0-5% to 19-28% in all 4 questions (p=0.02–0.04), and the number of Not At All Confident answers significantly decreased from 14-62% to 0-5% in 3 out of 4 questions (p=0.0001–0.03).

Funding: Private Foundation Support

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

Underline represents presenting author.
Conclusions: A KBSW utilizing US-based training on patients, mannqueins and cadavers, along with simultaneous pathology instruction, is an effective educational tool to gain proficiency in PKB performance. This novel approach could regain interest among trainees in performing PKBs.

TH-OR104
A Novel Quality Improvement Collaborative to Reduce Acute Kidney Injury Incidence and Progression in a Large Teaching Hospital in England

Lynne F. Sykes, Robert Niph.
Clinical Research, Salford Royal Foundation Trust, Salford, United Kingdom.

Background: Acute kidney injury (AKI) is a common condition which is associated with significant mortality and cost according to the NCEPOD report of 2009. The Quality Improvement Collaborative was established to review and improve both the recognition and management of AKI.

Methods: We designed a program of education and learning events to reduce all cause AKIs by 10%, reduce hospital acquired AKIs by 25% and reduce progression of AKI 1 to either AKI 2 or 3 by 50%. A driver diagram was developed for this improvement program based on the Institute for Healthcare Improvement’s Breakthrough Series Collaborative Model. An information banner was inserted into the electronic patient record, modifications made to the admission document, post ward round and discharge summary forms, and an AKI review template introduced. A team of selected doctors, nurse champions, pharmacists and quality improvement staff implemented an AKI bundle, based on the acronym ‘SALFORD’, to the collaborative wards.

Results: Whilst there was an increase overall in AKI seen, especially AKI 1, over the study (November 2015 to May 2016), there were several statistically significant results following the interventions made by the collaborative. A 15.56% reduction in overall hospital acquired AKI, with a 22.32% reduction on collaborative wards. Although there was normal variation shown for the overall hospital rates of progression of AKI 1 to AKI 2/3 there was a 48.47% reduction in AKI progression on the collaborative wards.

Conclusions: This is the first quality improvement project of its kind focussing on AKI. It has achieved statistically significant reductions of hospital acquired AKI and AKI progression particularly on the collaborative wards and is an effective to an effective quality improvement programme that is universally applicable and a step towards tackling AKI. 

Funding: Other NIHR Support - National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care (NIHR CLAHRC)

TH-OR105
Estimating Sodium Intake in Hemodialysis Patients to Help Assist Dietary Habits

Amar V. Patel,1 Jenner M. George,1 Sahia Tahir,2 Carla Boutin-Foster,3 Subodh J. Saggi.1 1Div of Nephrology, SUNY Downstate Medical Center, Brooklyn, NY; 2Long Island Univ, Brooklyn, NY; 3Div of Internal Medicine, SUNY Downstate Medical Center, Brooklyn, NY.

Background: Sodium restriction is encouraged in almost all patients on hemodialysis due to its easy and effective preventative therapy, which facilitates control of thirst, water overload, inter-dialytic weight (IDW) gains, hypertension, and cardiac failure. However this strategy is often neglected by patients. Our primary aim was to validate salt intake estimation equation in ESRD patients on dialysis and making these patients aware and our secondary aim was to evaluate changes in sodium intake after being counseled on their sodium restriction died to 2g/day.

Methods: In this pilot study, data regarding sodium intake of 13 patients on hemodialysis was gathered during 3 consecutive months (January 2016 to March 2016). Each patient was counseled regarding sodium restriction in the first month and the subsequent two months were recorded to evaluate sodium intake. Sodium intake was estimated using the following formula: Sodium intake = V × ([Na]pre – [Na]post) + (ΔW × [Na]pre) where V= total body water and ΔW = interdialytic weight gain.

Results: Referring to table 1 you will see that the mean sodium intake was 3.7 ± 1.3 g in January, 4.1 ± 1.2 g in February, and 4.2 ± 1.3 g in March.

There was tremendous variability in salt intake and a single counselling session over 3 month period was not associated with adherence to salt restriction (p = 0.54) or IDW gains.

Conclusions: Further solutions to improve sodium intake need to be considered such as motivational behavioral therapy and provide access to low salt foods. We have assumed that the participants were anaphoric and had insignificant amount of GI and insensible fluid loss.

Funding: Baxter Health Corp

TH-OR106
Therapeutic Game-Based Exercise during Hemodialysis to Improve Balance: A Pilot Randomized Controlled Trial

Abdulhamid S. Al-Ali,1 He Zhou,2 Talal Talal,2 Sergio Nicolas Sardon Melo,3 Mohamed Amin Elesnawi,1 Rania Abdelaziz Ibrahim,1 Bijan Najafi,2 1Nephrology, Hamad Medical Corporation, Doha, Qatar; 2Baylor College of Medicine, Houston, TX; 3Podiatry, Hamad Medical Corporation, Doha, Qatar.

Background: Balance, mobility and falls are serious problems for older patients with end stage renal disease on hemodialysis (HD) especially with diabetic neuropathy. HD visit time provides an optimal opportunity for exercise intervention to improve balance and mobility and decrease falls.

Methods: Eleven HD subjects (age: 65±6 years) with confirmed diabetic peripheral neuropathy were consented and recruited. They were randomized to intervention (n=7) or control (n=4) group (CG: n=4-8 weeks' ankle and knee exercise program, twice per week for duration of 30 minutes during HD. The IG received exercise via the Exergame platform developed by our team, which integrates data from wearable sensors attached to subject’s feet and legs into a human-computer interface designed for game-based motor adaptation training. The CG received same exercises without technology. The feasibility, acceptability, perception of benefit, and enhancement in balance in different conditions were examined.

Results: One subject in IG was dropped out due to travelling. The rest finished all exercise sessions during HD sessions indicating its feasibility. The participants gave an average score of 3.7 out of 4 for entertainment and ease of use of the Exergame platform. All participants in IG felt more energetic at home and perceived the balance program effective. Balance improved in IG compared to baseline in almost all tested balance conditions with highest effect size (ω=0.21) observed for hip stability during semi-tandem eyes closed test. The improvement in tested balance conditions in IG was on average 32% higher than CG with the highest effect size difference observed for semi-tandem eyes-closed (ω=0.26).

Conclusions: Our pilot trial provide proof of concept for the feasibility and benefits of an interactive ankle and knee exercise program based on wearable technology. The program was perceived to be beneficial, easy and enjoyable to perform during hemodialysis sessions by target subjects.

Funding: Government Support - Non-U.S.

TH-OR107
“Home Run” Results of a Chronic Kidney Disease Telemedicine Patient Education Study

Andrea K. Fason, Manisha Singh, John M. Arthur. U of AR for Medical Sciences, Mabelvale, AR.

Background: Comprehensive pre-dialysis patient education (CPE) facilitates the choice of renal replacement therapy modalities and can slow progression of disease but it is not clear if education via telemedicine is comparable to face-to-face education (FT/TF).

We present the two year results of a pilot randomized controlled study evaluating the effectiveness of CPE through telemedicine TM to FTF in patients with stage 4-5 CKD.

Methods: An 82 page CKD Workbook was created with corresponding slides and used to provide education to 82 patients in the FTF group and 58 patients the TM group over three, 2-3 hour visits. Patient choice of dialysis modality is the primary endpoint of the study. Three assessment tools were used to compare groups: CKD Knowledge Questionnaire (based on the workbook and completed pre on visit 1 and post on all visits), S-TOFHLA on visit 1 and KDQoL on visits 1 and 3. All groups have quarterly phone follow-up. There are 7 telemedicine sites across the state.

Results: Of the 170 patients enrolled, 25 (15%) were initial drop outs. These results include data from 118 patients. Most patients were interested in transplant initially (90% FTF, 98% TM). Patients were randomised to either FTF (n=71) or TM (n=99) and 55% of the TM group, 58% of the patients that started therapy were either transplanted or started a home modality. The results show that TM can be an effective CPE strategy.

Conclusions: By the end of their 3rd visit, 97% of the FTF group and 85% of the TM group were able to choose a modality. Home modalities were chosen by 71% of the FTF group and 55% of the TM group, 58% of the patients that started therapy were either transplanted or started a home modality. The results show that TM can be an effective educational tool for CPE.

Funding: Pharmaceutical Company Support - Baxter Health Corp
GLomerulosclerosis, Imploding Glomerulopathy and Podocytes

TH-OR110

Compound Effects of Aging and Experimental FSGS on Glomerular Parietal Epithelial Cells and Podocytes in Mouse Kidneys

Remington Schneider, Diana G. Eng, Jeffrey W. Pippin, Stuart J. Shankland. Nephrology, Univ of Washington, Seattle, WA.

Background: Impaired kidney function is more common in the elderly, and occurs disproportionately in people >65yrs. Glomerular parietal epithelial cells (PECs) and podocytes (podo) undergo substantial changes with advanced age. This study tested the hypothesis that advanced aging adversely impacted PEC and podo responses in mice with FSGS.

Methods: Experimental FSGS was induced in young adult (Y-FSGS) or aged (A-FSGS) (2-3m) and aged (Y-BL) and aged (A-BL) (5-6m) mice without FSGS as served as baselines. Podo density was measured by unbiased stereology on p57/PAS stained kidney sections; Desmin marked podo injury. Fibrosis was quantified using Collagen IV staining. Activated PECs (Pax8/CD44+) were examined for their localization along Bowman’s Capsule (BC) and migration onto the glomerular tuft.

Results: As expected, podo density was lower in A-BL mice (P<0.01 vs. Y-BL). Upon induction, podo density decreased by >40% in both Y-FSGS and A-FSGS mice (P<0.05). However, Desmin expression increased further in podo in A-FSGS mice. Although the density of activated PECs along BC was higher in A-BL mice (P<0.05 vs. Y-BL), PEC increase along BC was 4 fold higher in A-FSGS mice (P<0.01 vs. Y-FSGS). The number of activated CD44-positive cells on the tuft was also higher in A-BL mice (P<0.01 vs. Y-BL). Thus, Desmin expression increased further in podo in A-FSGS mice. Although the density of activated PECs along BC was higher in A-BL mice (P<0.05 vs. Y-BL), PEC increase along BC was 4 fold higher in A-FSGS mice (P<0.01 vs. Y-FSGS). The number of activated CD44-positive cells on the tuft was also higher in A-BL mice (P<0.01 vs. Y-BL). Thus, Desmin expression increased further in podo in A-FSGS mice.

Conclusions: In conclusion, CD44-dependent proliferating glomerular cells, most likely PECs, are essential in the pathogenesis of scarring glomerular disease.

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

TH-OR111

Sonic Hedgehog Links Podocyte Injury to Mesangial Cell Activation in Glomerular Disease

Dong Zhou, Haiyan Fu, Youhua Liu. Dept of Pathology, Univ of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: Glomerular disease is often characterized by podocyte injury-triggered proteinuria, followed by glomerulonephrosis caused by mesangial activation and matrix over-production. However, how podocyte injury is linked to mesangial cell activation remains largely unknown. In this study, we have identified sonic hedgehog (Shh) as a novel factor that mediates podocyte-mesangial communication (PMC), which plays a crucial role in the pathogenesis of glomerulosclerosis after initial podocyte injury.

Methods: See results section.

Results: Shh was specifically induced in podocytes in animal models of glomerular diseases induced by adriamycin (ADR) and anti-GBM antibody, and in kidney biopsy specimens from patients with glomerular diseases. Using Gli1+/- knock-in mice, we identified mesangial cells as the major Shh-responsive cells in diseased glomeruli. Incubation of mesangial cells with Shh activated canonical Shh/Gli1 signaling pathway and promoted cell proliferation and extracellular matrix (ECM) accumulation in a time- and dose-dependent manner, as assessed by cell counting, MIT and BrDU incorporation assay, and induced numerous proliferation- and fibrosis-related genes. Furthermore, Shh promoted mesangial cells activation and fibrosis in cultured glomeruli. However, Shh had little effects on podocyte proliferation. We further generated mice with podocyte-specific deletion of Shh, and found that conditional ablation of Shh had little effect on proteinuria in 1 and 5 weeks after ADR injection. However, loss of Shh in podocyte markedly ameliorated glomerulosclerosis. Consistently, blockade of Shh signaling by cyclopamine, an inhibitor of Smo or Shh, inhibited mesangial cells proliferation, reduced ECM accumulation and attenuated glomerulosclerosis after ADR injection at 5 weeks.

Conclusions: These studies demonstrate that podocyte-derived Shh acts as a previously unknown paracrine mediator to positively promote mesangial cell cell proliferation and matrix overproduction, leading to glomerulosclerosis. Our studies uncover a new pathway by which podocyte injury leads to glomerulosclerosis, and should have significant implication in designing future therapy for glomerular diseases.

Funding: NIDDK Support

TH-OR112

Single Kidney Cell Transcriptomics Applying Microfluidic Droplet Generation Technology (Drop-Seq)

Edward A. Otto, Rajasree Menon, Celine C. Berthier, Matthias Kretzter. Internal Medicine - Nephrology, Univ of Michigan, Ann Arbor, MI.

Background: Microfluidic droplet-based technology (Drop-Seq) allows to uniquely barcode mRNA transcripts of thousands of individual cells derived from a complex tissue for downstream analysis. The technique involves processing of individual cells with barcoded beads in separate nanoliter-sized droplets in the course of flowing oil, beads, and cells through a droplet-generator device via three syringe pumps. Health: Healthy and disease derived from 19 human kidney tissue specimens from patients with glomerulonephritis were enzymatically and mechanically dissociated into single cell suspensions. Cells were processed according to the DropSeq workflow described by the McCarroll lab. Individual cells were identified by barcodes, and all transcripts were tagged with Unique Molecular Identifiers (UMIs) in order to determine absolute transcript abundance. Paired-end RNA-Seq was performed on a HiSeq2500 platform. Bioinformatics analysis was done using the tools embedded in Picard tools developed by the Broad Institute and unsupervised clustering algorithms were executed using the R package tool kit “Seurat” from the Satija lab.

Results: Single cell transcriptome analyses of 3,000 cells enabled the distinction of various cell types which correspond to specific nephron segments according to the RNA-seq analysis of Microdissected Rat Kidney Tubule Segment dataset. Principal component analysis revealed cells showing high expression of ALDOB and GBA3 corresponding most likely to segment S1 of the proximal convoluted tubules, SLCL243 and PWCL2 stains distal convoluted tubule (DCT) and UM022 and EGF2 indicates GT1 nephron segment cell origin. About 10% of the cells expressed hemoglobin indicating the presence of red blood cells in the preparation.

Funding: NIDDK Support
Degradomic Analysis Dissects Intracellular Protease Signaling in Podocytes
Markus M. Rinsch1, Pitter F. Huesgen,2 Thomas Benzing1, Internal Medicine, Univ Hospital Cologne, Germany; 2Forschungszentrum Juelich, Germany.

Background: Proteases are successful therapeutic targets in many human diseases. Proteases are also crucial for the maintenance of a physiological podocyte function. Based on previous system-wide analyses, thromine proteases are expressed at very high levels in podocytes both on the proteome and transcriptome levels. However, the intracellular protease targets are not completely characterized. The aim this study was to delineate posttranslational protease networks in podocytes.

Methods: Terminal Amine Isotope Labeling of Substrates (TAILS) is an innovative technology that allows identification and quantification of cleavage and native protein N-termini in various conditions using high-accuracy tandem mass spectrometry. We applied this technology to native glomeruli perfused with protease inhibitor to demonstrate the physiological presence of novel proteaseforms originating from posttranslational proteolytic processing. Second, we performed a quantitative degradomic analysis of cultured podocytes under normal and stressed (PAN injury) conditions.

Results: In renal glomeruli, we discovered thousands of termini by TAILS proteomic analysis. Among these, we found a novel podocin proteaseform lacking its N-terminal 60 amino acids. Novel proteoforms were also discovered for Nephrin, Synaptopodin and Actinin-4. Degradomic analysis of stressed podocytes demonstrated a distinct perturbation of protease signaling. Differentially regulated protease substrates were mainly cytoskeletal proteins, including ACTNA, further actin-associated and intermediary filament proteins. The data also determined preferential protease motifs during this damage and indicated that specific protease classes are activated during PAN injury. Novel proteoforms were also confirmed by differential migrational behavior on SDS PAGE gels.

Conclusions: The technology utilized here is crucial to identify protease classes and their intracellular targets involved in renal and podocyte disease. We demonstrate that a tightly regulated protease network strongly affects cytoskeletal and slit diaphragm proteins in podocytes. Funding: Government Support - Non-U.S.

Endothelial SIRT1 Inactivation Enhances Capillary Rarefaction and Fibrosis following Kidney Injury through Notch Activation
Yujiro Kida1, Joseph A. Zullo1,2, Michael S. Goligorsky3,1, Medicine, New York Medical College, Valhalla, NY; 2Pharmacology, New York Medical College, Valhalla, NY; 3Physiology, New York Medical College, Valhalla, NY.

Background: Peritubular capillary (PTC) rarefaction, along with tissue fibrosis, is a hallmark of progression of chronic kidney diseases (CKD). Although previous studies have demonstrated that functional loss of endothelial sirtuin 1 (SIRT1) aggravates renal fibrosis, mechanisms that afford renal protection are not completely elucidated. Recently, SIRT1 was found to deacetylate Notch intracellular domain-1 (NICD1, active form of Notch1) and accelerate its degradation. In this study, we hypothesized that impaired endothelial SIRT1 function induces Notch activation that exacerbates renal injury.

Methods: We created mice with deleted SIRT1 catalytic domain in endothelial cells (Sirt1 mutant mice). Both wild-type (WT) control and Sirt1 mutant mice were subjected to unilateral ureteral obstruction (UUO). For in vitro studies, we isolated microvascular endothelial cells (MVECs) from WT and Sirt1 mutant kidneys, which enabled our in vitro studies.

Results: In Sirt1 mutant mice, kidney injury enhanced apoptosis and senescence of PTC endothelial cells with impaired endothelial proliferation and expanded myofibroblast population and collagen deposition. Compared to WT kidneys, Sirt1 mutant kidneys showed increased expression of DLL4 (a potent Notch ligand), Hey1 (Notch target gene), and NICD1 in PTC endothelial cells post-injury. Sirt1 mutant primary MVECs reduced motility and enhanced senescence compared to WT MVECs. This phenotypical difference was negated with Notch inhibition. Dll4 and Tgfi-1 synergistically increased transdifferentiation of primary kidney pericytes into myofibroblasts.

Conclusions: Functional loss of endothelial SIRT1 aggravates PTC rarefaction via excessive Notch activation and tissue fibrosis through increased expression of endothelial DLL4. Endothelial SIRT1-Notch1 axis could be a novel therapeutic target to prevent progression of CKD.

Funding: NIDDK Support, Private Foundation Support

Osteopontin Deficiency Reduces Alport Pathology
Wen Ding, Keyvan Yousefi, Jayant Singh, Stefania Conoclabas, Bradley J. Goldstein, Lina Shedeade. Univ of Miami.

Background: Alport Syndrome is characterized by progressive renal failure, hypertension, proteinuria, hearing loss, and cardiovascular dysfunction. The COL4A3 mouse phenocopies these symptoms, making it an ideal Alport model. Osteopontin (OPN), a secreted phosphoprotein, has never been studied in Alport Syndrome. We elected to investigate the role of OPN in Alport pathology.

Methods: OPN protein expression from wild type (WT) and Alport mice (n=3-6) was analyzed by western blot. We generated Alport mice with hetero- or homo-zygous OPN deletion and evaluated effect on life span. At 8-9 weeks of age, WT, OPN−/−, COL4A3−/−, COL4A3−/−OPN−/− and COL4A3−/−OPN+−/− mice were studied. Urine from all groups was analyzed by Albumin and Creatinine Elias, blood was analyzed for mean corpuscular hemoglobin concentration (MCHC), plasma was analyzed by Gelactin-3 Elisa, kidney injury molecule-1 (KIM-1) protein expression was analyzed by immunofluorescence, blood pressure was recorded by a tail cuff system, and hearing thresholds were determined by auditory brainstem responses to pure tone (4-16 kHz) or click stimuli. Heart function was assessed by echocardiography. Basement membrane morphology in kidneys and cochleas was analyzed by electron microscopy.

Results: OPN was increased in plasma (FC=1.4, p<0.03) and kidneys (FC=2.3, p<0.003) of Alport versus WT mice. COL4A3−/−OPN−/− and COL4A3−/−OPN+−/− mice significantly outlived the Alport mice (16 versus 10 weeks), with increase in body weight (FC=1.2, p=.0001). COL4A3−/−OPN+/− mice significantly outlived the Alport mice (16 versus 10 weeks), with increase in body weight (FC=1.2, p=.0002), MCHC (FC=1.2, p=.0003) and renal cortical thickness (FC=1.2, p=.0001). Albumin and creatinine were increased (FC=1.4, p<0.003) and (FC=1.4, p<0.003), respectively.

Conclusions: This is the first study reporting that reduction of OPN can improve lifespan, proteinuria, hypertension, renal and cochlear histology, cardiac function and hearing ability in Alport mice. Our data suggest OPN as a therapeutic target for Alport Syndrome.

Funding: Private Foundation Support

Role of Macula Densa Cells in Tissue Remodeling in Renovascular Hypertension
Toshiki Doi, Anne Riquier-Brison, Janos Petti-Peterdi.
Physiology and Biophysics, Univ of Southern California, Los Angeles, CA.

Background: Renovascular disease (RVD) accounts for an important proportion of secondary hypertension and is associated with progressive renal dysfunction. There is no specific cure for RVD and the resulting progressive, chronic kidney disease. Since robust alterations in tissue composition and renal are established features in RVD, this study tested the hypothesis that the cells of the juxtaglomerular apparatus (JGA) play an important role in vascular and glomerular remodeling in RVD.

Methods: Genetic cell fate tracking using in vivo serial multiphoton microscopy (MPM) of the same glomeruli, and histology in tamoxifen-induced NG2CreERT2-Tomato mice and Ren1CreConfetti mice was performed to evaluate mesenchymal progenitor cell-
mediated tissue remodeling. Mice underwent either sham operation or renal artery cutting (two-kidney, one-clip, 2K1C model of RVD) and were treated with specific inhibitors of macula densa (MD) cell-specific nitric oxide synthase (NOS1, 7-Nitroindazole (7-NI), 20 mg/kg/day ip), and cyclooxygenase (COX-2, 6 mg/L SC58236 in drinking water), or control (vehicle) groups, and sacrificed 3 weeks later.

Results: 2K1C mice showed high blood pressure, a significant decrease in the weight of the clipped kidney, and a significant increase in the weight of the non-clipped kidney compared with sham group. The number of NG2-derived cells, Ki-67 or renin positive cells increased more than 2-fold in the JGA in the clipped kidney. Some NG2-derived cells were co-labeled for Ki-67 or renin. On the other hand, 7-NI and COX-2 inhibitors attenuated these alterations. At baseline, RenI-Confetti cells existed at glomerular vascular pole, mesangium, Bowman’s capsule, and in the proximal tubule. Serial MPM showed the migration of RenI-Confetti cells from vascular pole into glomerulus.

Conclusions: Our results suggest that mesenchyme-derived cells, including cells of the renin lineage have important roles in vascular and glomerular remodeling in RVD. Also, MD-derived (from COX-2 and nNOS) paracrine factors promote the migration of these cells to the JGA and glomerulus. In conclusion, MD cells may be important regulators of vascular and glomerular remodeling in RVD.

**Funding:** NIDDK Support

### TH-OR119

**Choice of Vascular Access (VA) and Clinical Outcomes among Elderly Hemodialysis Patients**

**Patients:** Timmy C. Lee,1 Mae Thamer,1 Qian Zhang,2 Michael Allon,1 Yi Zhang.1 1Univ of Alabama at Birmingham; 2Medical Technology and Practice Patterns Inst.

**Background:** Current guidelines recommend placing an AVF rather than an AVG in HD patients. Our observational study compared VA and patient outcomes among elderly patients who initiated HD with a dialysis catheter (CVC), and subsequently had an AVF or AVG placed.

**Methods:** Using an observational equivalent of an intention-to-treat design, we identified ESRD patients from the USRDS age ≥67 who initiated HD from 7/1/2010-6/30/2011 with a CVC and no secondary VA, and who received an AVF (n=7,016) or AVG (n=2,228) within the ensuing 6 months. We evaluated CVC dependence during the 6 months after VA placement and used propensity score (PS)-weighted Cox proportional hazard models to evaluate the association of AVF vs AVG use with patient survival.

**Results:** Patients receiving an AVF were more likely to be female, black, and have high comorbidities. Those receiving an AVG had lower CVC use in the first 6 months after VA surgery (figure 1).

**Conclusions:** In the PS-adjusted analysis of the entire cohort, patients with an AVF had a lower risk of death versus those with an AVG (OR 0.79, 95% CI 0.74-0.83). The survival difference between CONV and AVG persisted when patients were stratified by age and race (table 1).

**Funding:** NIDDK Support, Private Foundation Support

### TH-OR120

**Cost Comparisons of Hemodialysis Access Modalities among Patients Starting with Tunneled Catheters**

**Patients:** Jason Kane Wagner, Larry Fish, Theodore H. Yoo. Vascular Surgery, Univ of Pittsburgh, Pittsburgh, PA.

**Background:** Arteriovenous fistula (AVF) is the ideal hemodialysis (HD) access, but most patients start with tunneled dialysis catheter (TDC). AVF and arteriovenous graft (AVG) surgery may reduce TDC use and also increase procedural expenses. We compared Medicare costs associated with AVF, AVG, and TDC.

**Methods:** Using the US Renal Data System (USRDS), we identified incident HD patients in 2008 who started with TDC, survived at least 90 days, and had adequate Medicare records for analysis. We followed them until death or end of 2011; access modality was determined by Medicare records. We used multivariate linear regression models predicting Medicare expenditures, censoring costs when patients died; we included all payments to physicians and institutions. We also created algorithms to identify access-related costs.

**Results:** There were 113,505 patients in the USRDS who started HD in 2008, of whom 51,002 Medicare patients met inclusion criteria. Of that group, 41,532 (81%) began with TDC; 27,064 patients were in the final analysis file. In the first 90 days after HD initiation, 6,100 (22.5%) received an AVF, 1,813 (6.7%) AVG, and 19,151 (70.8%) stayed with TDC. Annualized access costs by modality were: TDC $13,625 (95% CI $13,426-13,828); AVG $16,664 (95% CI $16,533-17,194); and AVG $20,961 (95% CI $20,867-21,854) (P<.001). Multivariate linear regression demonstrated that staying with TDC had lowest access-related costs, AVF was intermediate, and those who underwent AVF surgery were highest (P=.021).

**Access type was not significantly associated with total costs. Additional AVF and AVG**
creation ($3,525 and $3,804 per access per year, respectively) and open and endovascular access ($3,012 and $3,569 per procedure per year, respectively) (all $P<0.001) were important predictors of increased cost.

Conclusions: Among patients starting HD with TDC, continued TDC use is associated with lowest access-related cost. Both endovascular and open interventions are associated with significant additional costs. Further investigation is warranted to develop efficient patient-centered strategies for HD access.

Funding: Other NIH Support - KL2-TR000146, T32-HL098036, Clinical Revenue Support

TH-OR121
Access Blood Flow Surveillance in Native-Arteriovenous Fistula: Reduction in Thrombosis Rate and Improvement in Assisted and Secondary Patency. A Randomized Clinical Trial
Ines Aragoncillo,1 Soraya Abad,1 Silvia Caldes,2 Antonio Cirugeda,1 Almudena Vega,1 Cristina Fernandez,2 Cristina Moratilla,2 Nicolas Macias,1 Juan Manuel Lopez Gomez,2 Fernando De Alvaro Moreno.1
1Nephrology, H Gregorio Marañon, Madrid, Spain; 2Nephrology, H Clinico, Madrid, Spain.

Background: Thrombosis is the main cause of arteriovenous fistula (AVF) failure. It is still unclear if surveillance based on Vascular Access Blood Flow (Qa) enhances AVF function and longevity.

Methods: 3-year follow up randomized, controlled, multicentric, open-label trial, comparing Qa surveillance (pre-emptive repair of subclinical stenoses with angioplasty and/or open surgery) with standard monitoring/surveillance (intervention based on classic criteria) in mature autologous AVFs. AVFs were randomized to either control group (surveillance based on venous pressure, recirculation, dialysis dose...) or to Qa group. Qa was measured quarterly using doppler ultrasound (M-Turbo) and ultrasound dilution method (Transonic). The criteria for intervention in Qa group were 25% reduction in Qa, Qa <500 ml/min or significant stenosis with >50% reduction in vessel lumen and haemodinamic repercussion [Peak Sistolic Velocity (PSV)>400 ml/min or PSV stenosis/PSV pre-stenosis >3].

Results: Significant reduction in thrombosis rate (0.025 thrombosis/patient/year in the Qa group compared with 0.086 thrombosis/patient/year in control group. p=0.007) Significant improvement in assisted primary patency rate and secondary patency rate in Qa group (HR 0.30 CI 0.11-0.82, p=0.011 / HR 0.49 CI 0.26-0.93, p=0.030) No differences in non-assisted primary patency rate between groups (HR 0.98 CI 0.57-1.61, p=0.935). Higher needs of central venous catheter and hospitalizations related with VA in control group (p=0.001 / p=0.003). - Higher total VA related costs in control group (217.845 € vs 124.186 €. p=0.029).

Conclusions: QA based surveillance combining doppler ultrasound and ultrasound dilution method prevents thrombosis, increases assisted and secondary patency rate in AVF and it is cost effective.

TH-OR122
Comparison of Postoperative Ultrasound Criteria to Predict Unassisted Clinical Arteriovenous Fistula (AVF) Maturation. Tommy C. Lee,1 Michelle L. Robbins,1 Steven K. Burke,2 Andrew T. Blair,2 Missy Magill,2 Michael Allon.3 1Univ of Alabama at Birmingham; 2Protein Therapeutics.

Background: AVF maturation failure is a major clinical problem. A postoperative ultrasound (US) may provide objective measures to predict unassisted clinical AVF maturation and guide interventions to salvage nonmaturing AVFs. We compared predictive values of the NKF KDOQI and University of Alabama (UAB) maturation criteria for unassisted clinical AVF maturation from data in a multicenter, randomized- clinical trial.

Methods: We analyzed prospective data from “A Study of PRT 201 Administered Under Arteriovenous Fistula Creation in Patients with Chronic Kidney Disease,” which enrolled 151 subjects. We excluded 14 subjects with a missing 6-12 week postoperative US and 32 subjects with indeterminate clinical AVF maturation. The remaining 105 subjects were analyzed. Two US criteria were assessed: (1) NKF/AVF diameter ≥6 mm and blood flow ≥600 ml/min and (2) UAB:AVF diameter ≥6 mm and blood flow ≥500 ml/min. Unassisted clinical AVF maturation was defined as successful cannulation for ≥30 days without requiring prior surgical or percutaneous interventions. Sensitivity and specificity were calculated for both criteria.

Results: 44% of AVFs were radioisotope (RCF) and 56% brachioisotope.

Table 1

<table>
<thead>
<tr>
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<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>AR-AVF (N=105)</td>
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<tr>
<td>UAB Criteria</td>
<td>0.83</td>
<td>0.48</td>
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<tr>
<td>NKF Criteria</td>
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<td>0.74</td>
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<tr>
<td>Radioisotope AVF (N=46)</td>
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<tr>
<td>UAB Criteria</td>
<td>0.82</td>
<td>0.85</td>
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<tr>
<td>NKF Criteria</td>
<td>0.59</td>
<td>0.92</td>
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</table>

Table 1 summarizes the sensitivity and specificity of both US criteria for unassisted clinical AVF maturation. Collectively, the UAB criteria had higher sensitivity and lower specificity for unassisted AVF maturation, as compared to the NKF criteria. For patients with a RCF AVF, the UAB criteria had higher sensitivity and similar specificity to the NKF criteria.

Conclusions: In the total population, the UAB criteria would minimize unnecessary early interventions in AVFs likely to clinically mature without an intervention, but delay interventions that may be indicated in AVFs that are unlikely to be clinically mature. However, for RCF AVFs, using the UAB criteria would reduce unnecessary early interventions without delaying necessary interventions.

TH-OR123

Background: The pathophysiology of arteriovenous fistula (AVF) maturation failure is unknown but impaired outward remodeling and intimal hyperplasia are both considered to contribute. RP105 is an important regulator of inflammatory TLR4 signaling, expressed on numerous cell types. In the present study, we defined cell specific effects of RP105 on vascular smooth muscle cells (VSMCs) and macrophages (mRF) in vitro and in vivo effects of RP105 on AVF maturation in a murine model of AVF failure.

Methods: All in vitro experiments were performed on primary cells isolated from RP105-/- and wild type (WT) mice. AVFs were created in an end-to-side manner between sjugularis and carotid a. in RP105-/- (n=13) and WT (n=11) mice. AVFs were harvested at day 14 and processed for morphometric analysis and immunohistochemistry. MMPSense probe was used to measure in vivo MMPa activity.

Results: In vitro, anti-inflammatory (M2) mRF of RP105-/-mice showed increased IL10 (ELISA) compared to WT. Venous VSMCs from WT mice exhibited increased mRNA of RP105 and TL84 compared to arterial VSMCs, whereas proliferation rate of venous VSMCs was 50% lower in RP105-/- cells. In vivo, a shift towards M2 mRF and a 70% reduction in CD4+ T cells was observed in RP105-/- mice(fig.a,b). MMP-activity was reduced by 50% in RP105-/- (fig.c). Amount of SMA/Ki67- VSMCs was decreased by 31%. Overall, RP105-/- mice showed 26% smaller circumference of the external jugular vein (fig.d).

Conclusions: Deletion of RP105 results in a marked decrease in venous outward remodeling in AVF. The latter might relate to a shift towards M2 mRF, reduction in MMP activity and decreased VSMC proliferation in the venous outflow tract of AVF, illustrating the complex interactions between inflammation and VSMC biology in AVF maturation.

Funding: Government Support - Non-U.S.

TH-OR124
Loss of GATA4 Enhances CKD-Induced Arteriovenous Fistula Failure. Ming Liang, William E. Mitch, Jizhong Cheng. Medicine/Nephrology, Baylor College of Medicine, Houston, TX.

Background: A functioning arteriovenous fistula (AVF) is the “dialysis lifeline” but progressive neointima formation reduces AVF functions leading to AVF failure. We have found that chronic kidney disease (CKD) accelerates AVF failure. CKD induces oxidative stress leading to accumulation of the reactive toxin, 4-hydroxy-2-nonenal (4-HNE). This process is linked to CKD-suppressed expression of n-glutathione transferases (GSTs).

Methods: we created CKD and AVFs in GATA4 KO mice and mice overexpressing GATA4, we studied how GATA4 can suppress CKD-induced AVF failure. In cultured VSMCs, we examined how 4-HNE induces VSMC proliferation and whether GATA4 modulates these responses.

Results: GATA4 expression measured as mRNA or protein was decreased and 4-HNE level was increased in AVFs in CKD mice. In GATA4 (GATA4 KO) mice, CKD increased both 4-HNE and pc-JUN levels in VSMCs, and stimulated VSMC proliferation and neointima formation in AVFs. Using a combined Tet-On/Cre induction system, a transgenic mice was generated to transiently overexpress GATA4 in VSMCs. The overexpression of

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Underline represents presenting author.

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GTA4 resulted in lower levels of 4-HNE and decreased MAPK activation. There were reduced accumulation of SMA+ VSMCs and PCNA-positive cells in neointima in AVFs created in GTA4 transgenic mice. The outcome was a reduction in the CKD-induced neointima formation and improved AVF maturation. In ex-vivo experiments, the loss of GTA4 expression is accompanied with increased VSMC migration and outgrowth. In cultured cells, treatment with 4-HNE was found to exclude p21<sup>WAF1</sup> from the nucleus to promote VSMC proliferation. 4-HNE also upregulated MAPK activation (pERK/1,2 and pJNK). Both responses were amplified when GTA4 was knocked down, but were blocked when GTA4 was overexpressed.

Conclusions: CKD complications decrease GTA4 expression resulting in 4-HNE accumulation in AVFs. This increase in 4-HNE stimulates the proliferation of VSMC to stimulate the MAPK signaling pathway. When GTA4 was specifically overexpressed in VSMCs, there was suppression of CKD-induced 4-HNE accumulation and VSMC proliferation. These results demonstrate that increased expression of GTA4 can suppress CKD-induced neointima formation and AVF failure.

Funding: NIDDK Support

TH-OR125


Background: Recent high arteriovenous fistula (AVF) failure rates (20-60%) may be associated with vessel trauma incurred at the time of surgery. Vessel trauma may be mitigated by a novel approach to AVF creation endovascularly (endoAVF) using magnet-based catheter technology and radiofrequency energy (RFE). NEAT aimed to evaluate the safety and efficacy of this new technology in a prospective, multi-center study. We report key 6 mo outcomes.

Methods: 80 CKD V patients (60 study cohort;20 roll-in) from sites in Canada, Australia and New Zealand were enrolled. EndoAVFs were created using two magnetic catheters to create a channel between a vein and artery using RFE. Key inclusion criteria included: inability for a distal forearm AVF, target vein and artery diameters > 2.9mm, no central vein stenosis. Primary endpoint was percentage of endoAVF physiologically mature (brachial artery flow >500 ml/min, vein diameter > 4mm) or 2 needle cannulation within 3 months. Patient satisfaction was evaluated via a validated survey (SF-VAQ). Only study cohort patients (n=60) were evaluated and reported.

Results: 65% of patients were men, mean age 60 yrs, mean BMI 28, 65% had diabetes and 57% were predialysis at the time of procedure. An endoAVF was successfully created in 98% (59/60) of patients; 5 (8.3%) patients had a serious device or procedure related adverse event. Physiological maturation was 91% (52/57) of endoAVFs within 3 months. Mean brachial artery flow rate was 918ml/min at 3 months and sustained to 6 months. Cephalic, basilic, and median cubital vein diameters (mm) increased to 5.4, 5.8 and 6.1 at 6 months, respectively. 2-needle cannulation of endoAVF occurred in 90% (9/10) of predialysis patients who required dialysis and 73% (1622) of patients who were already on dialysis at baseline. 6mo primary and secondary patency rates were 79% and 90%, respectively. 83% of patients were satisfied with their endoAVF at 6 months.

Conclusions: The NEAT reveals that endoAVF results in high physiological maturation success and ability to cannulate with 2 needles for dialysis. Patients were satisfied with their endoAVF. Ongoing follow-up will reveal the long-term durability of the endoAVF.

Funding: Pharmaceutical Company Support - TWA Medical

TH-OR126

The Effect and Mechanism of Chitosan Inhibiting Vascular Smooth Muscle Cells Hyperplasia of uremia Patients Yan Yan. Nephrology, The First Affiliated Hospital of Nanchang Univ; NanChang, JiangXi, China.

Background: The most common complication of arteriovenous fistula(AVF) is stenosis. The pathological characteristic of stenosis is intimal hyperplasia. Our previous studies have found that chitosan can inhibit the internal jugular fistula intimal hyperplasia of rabbit. Our aim was to investigate the effect and mechanism about chitosan have on cultured vascular smooth muscle cell(VSMCs) of uremia patients with AVF.

Methods: Adopting the second generation VSMCs of uremia patients with AVF and normal person which cultured with improved adherent method of tissue explants, VSMCs from myofibroblast-vessel cells and VSMCs from uremia patients cultured with 20%FBS and 100/ug/ml chitosan respectively were control group and experimental group. -SMA were detected by immunohistochemistry method. The migration and invasion’s ability of VSMCs were detected by scratches and transwell method. The mRNA expressions of TLR4 and PCNA were measured by Real-time PCR. VSMCs of uremia patients with AVF were intervened with different doses of chitosan(10, 100, 500ug/ml), the protein expressions TLR4, MyD88 and NF-kB were detected by Western blotting.

-n-SMA was staining compared to blank control group. Compared experimental group with control group, the level of -SMA was significantly decreased. The ability of migration and invasion of VSMCs after the intervention of chitosan were decreased significantly (P < 0.05). The mRNA expressions of TLR4 and PCNA decreased (P < 0.05); TLR4, MyD88 and NF-kB protein expression were reduced by chitosan in the certain concentration range. Similarly, the rates of catheter dysfunctions were significantly lower in the Taurolock™ regimen (18.7/1000 catheter days) vs. 4% citrate (44.3/1000 catheter days; p= 0.001). As a consequence, patients in the citrate 4% group needed alteplase rescue intervention in a significantly higher rate (38 vs. 3.8/ 1000 catheter days Citrate 4% versus TauroLock™; p< 0.001).

Conclusions: Chitosan not only decreases the ability of migration and invasion but also inhibits the proliferation of VSMCs of uremia patients with AVF, the mechanism may be concerned in the decreased expression of TLR4,MyD88 and NF-kB.

Funding: Government Support - Non-U.S.

TH-OR127

Taurolidine/Urokinase Based Locking Regimen Significantly Reduces Catheter-Related Blood Stream Infections and Dysfunction of Tunneled Haemodialysis Catheters when Compared to 4% Citrate Wolfgang Wündick, Gurkan Sengoege, Dept of Medicine III, Div of Nephrology and Dialysis, Medical Univ of Vienna, Vienna, Austria.

Background: Catheter infections and dysfunctions cause morbidity and mortality in haemodialysis patients. There are data showing that taurolidine containing catheter lock solutions may reduce the risk of both of these complications. Yet, there are no consistent guidelines for the use of lock solutions in haemodialysis patients with tunneled central lines. We aimed to study whether a TauroLock™ based locking regimen reduced the incidence of catheter-related blood stream infections (CRBSI, at least one positive blood culture with no other source of infection) and catheter malfunction (inadequate blood flow during dialysis - defined as blood flow < 200ml/min or >30% less than the average of the previous 10 sessions or necessity of catheter rescue with alteplase).

Methods: In this randomized controlled trial with 106 haemodialysis patients with a newly inserted tunneled central line a taurolidine based locking regimen with Taurolock™, Hep500 2x/week after the first two dialysis sessions and TauroLock™U25.000 1x/ week before the long interval was compared to 4% citrate (CitraFlow™) used after each dialysis 3x/w.

Results: 52 patients were assigned to Taurolock™ (6982 catheter days) and 54 patients to 4% citrate (6788 catheter days). Catheter-related blood stream infections occurred in 11.4% of patients in TauroLock™ and in 33.3% of patients in 4% citrate-group, corresponding to rates of 0.67 and 2.6 episodes of CRBSI per 1000 catheter days, respectively (p= 0.003). Similarly, the rates of catheter dysfunctions were significantly lower in the Taurolock™ regimen (18.7/1000 catheter days) vs. 4% citrate (44.3/ 1000 catheter days; p= 0.001). As a consequence, patients in the citrate 4% group needed alteplase rescue intervention in a significantly higher rate (38 vs. 3.8/ 1000 catheter days Citrate 4% versus TauroLock™; p< 0.001).

Conclusions: The use of a taurolidine based locking regimen significantly reduced the incidence of catheter-related blood stream infections as well as catheter malfunction in tunneled central venous haemodialysis catheters when compared to 4% citrate.

TH-OR128

Renal Olfactory Receptor 1393 Contributes to Glucose Reabsorption Blythe D. Shepard,1 Lydie Cheval,2 Zita Peterlin,3 Stuart Firestein,4 Hermann Koepssel,5 Alain Doucet,3 Jennifer L. Pluznick,3 Johns Hopkins Univ SOM, Baltimore, MD;1 Univ Wurzburg, Julius-von-Sachs-Inst, Wurzburg, Germany;2 Centre de Recherche des Cordeliers UMRS 872, Paris, France;3 Columbia Univ, New York, NY.

Background: Olfactory receptors (ORs) are G protein-coupled receptors that detect odorants in the nose but also have functions beyond odorant detection; we previously determined that ORs (including Orfl1393) are expressed in the kidney.

Methods: Orfl1393 renal localization was determined by RT-PCR on RNA from microdissected renal segments and with overexpressed MDCK cells. We generated whole-animal knockout mice (KO) and measured plasma electrolytes by tail cuff, GFR by elimination of plasma sinistrin, blood glucose by glucometer and

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Underline represents presenting author.

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urinary glucose and creatinine by VetACE Clinical Chemistry System. Sodium-glucose co-transporter (Sglt1 and Sglt2) were examined by western blotting and confocal microscopy of kidney cytocosmid.

**Results:** Olfr1393 is expressed in the renal proximal tubule (S1, S2, S3, n=3 mice), and is found on the apical plasma membrane, but not cilia, when expressed in polarized MDCK cells. Olfr1393 KO are similar to wild-type (WT) V1aR in regards to plasma electrolyte, blood pressure and GFR. However, KO's exhibit urinary glucose wasting (1.4x increase in glucose/creatinine vs WT; P = 0.01) despite normal blood glucose (fed and fasted) and insulin levels. KO's also perform better in a glucose tolerance test (area under curve: WT 20.4±1.6 vs KO 16.3±1.6; P = 0.008) implicating a role in renal glucose handling. In support of this, KO's have a 22% decrease in luminal Sglt1, but not Sglt2, in the proximal tubule (confocal) despite similar total renal expression (western blot). Olfr1393 and Sglt1 co-immunoprecipitate when overexpressed. KO of the Sglt5 genes has been shown to attenuate diabetes-induced hyperfiltration due to increased distal Na+ delivery. In preliminary data, the hyperfiltration induced after 16 weeks on high fat diet in WT mice appears to be attenuated in KO (GFR/BW: WT 576mL/min n=4, KO 435mL/min n=9; P=0.09).

**Conclusions:** These data suggest that Olfr1393 is a regulator of Sglt1 and presents a novel signaling pathway modulating renal glucose reabsorption.

**Funding:** NIDDK Support, Private Foundation Support

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**TH-OR129**

**Analysis of Vasopressin V1a Receptor Distribution and Function in the Mammalian Kidney Torsten Giesecke,1 Taka-Aki Koshimizu,2 Kaisa Sarna,1 Seiji Bachmann,3 Kerim Mutlu,3 Charité Universitätspital Berlin, Dept of Anatomy, Berlin, Germany; 1Jichi Medical Univ, Dept of Molecular Pharmacology, Shimotsuke-shi, Tochigi-ken, Japan; 2Kitasato Univ School of Medicine, Dept of Physiology, Kitasato, Sagamihara Kanagawa, Japan.

**Background:** From its effect on the renal concentrating mechanism, vasopressin (AVP) may affect acid-base regulation through its binding to the V1a receptor (V1aR). Activation of the V1aR appears to stimulate renal proton secretion, but information on this receptor's signaling is generally scarce. To extend available evidence, we have analyzed segmental expression and cellular distribution of V1aR in mouse, rat, and human kidneys and performed functional studies using a V1aR agonist.

**Methods:** Antibody to V1aR was generated and controlled using V1aR knockout mice. The antibody recognizes E175, E179, and Y184 in the extracellular domain of the receptor. We analyzed segmental expression and cellular distribution of V1aR in mouse, rat, and human kidneys and performed functional studies using a V1aR agonist.

**Results:** The V1aR antibody produced basolateral signal in n-type intercalated cells of connecting tubules and collecting ducts across the studied species. In contrast, beta-type intercalated cells showed punctate perinuclear and subapical V1aR signal which was partially colocalized with clathrin and the lysosomal marker, LAMP1. In the mouse kidney, macula densa cells were V1aR-positive as well. Administration of AO-4-67 to Brattleboro rats for 4h resulted in luminal trafficking of V-ATPase in alpha-type intercalated cells, whereas basolateral V-ATPase of luminal pendrin signals of beta-type intercalated cells were not affected by the stimulation.

**Conclusions:** Our findings show divergent cellular distribution patterns of V1aR in alpha- vs beta intercalated cells provide morphological support for distinct responsiveness of these cells to the V1aR-agonist. These results corroborate and extend data on the role of AVP in the renal acid-based handling.

**Funding:** NIH KO1DK084986, NYSTEM, and Howard Hughes Medical Institute.

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**TH-OR130**

**Physiological Study of Urea Transporters Using Mice Lacking All Urea Transporters and Computational Model Baoxue Yang,2 Tao Jiang,1 Yingjie Li,1 Anita T. Layton.1 1Dept of Pharmacology, Peking Univ, Beijing, China; 2Dept of Mathematics, Duke Univ, Durham, NC.

**Background:** Urea transporters (UT) are a family of transmembrane urea-selective channel proteins expressed in multiple tissues and play an important role in the urine concentrating mechanism of the mammalian kidney. UT inhibitors have been identified to support of this, KOs have a 22% decrease in luminal Sglt1, but not Sglt2, in the proximal tubule (confocal) despite similar total renal expression (western blot). Olfr1393 and Sglt1 co-immunoprecipitate when overexpressed. KO of the Sglt5 genes has been shown to attenuate diabetes-induced hyperfiltration due to increased distal Na+ delivery. In preliminary data, the hyperfiltration induced after 16 weeks on high fat diet in WT mice appears to be attenuated in KO (GFR/BW: WT 576mL/min n=4, KO 435mL/min n=9; P=0.09).

**Conclusions:** These data suggest that Olfr1393 is a regulator of Sglt1 and presents a novel signaling pathway modulating renal glucose reabsorption.

**Funding:** NIDDK Support, Private Foundation Support

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**TH-OR131**

**Src Kinase Inhibition by Dasatinib Induces Aquaporin-2 Membrane Accumulation in Kidney Principal Cells Richard Bouley, Pui Wen Cheung, Dennis Brown. Medicine/Nephrology, Massachusetts General Hospital, Boston, MA.

**Background:** Maintenance of water homeostasis is a vital function of the kidneys. In order to efficiently reabsorb water, the kidneys require a functional vasopressin (VP) signaling pathway to activate aquaporin-2 (AQP2). AQP2 trafficking is a balance between endocytosis and exocytosis, and src kinases are known to play important regulator roles in membrane protein endocytosis; therefore, we explored the role of dasatinib, a src inhibitor, on AQP2 trafficking, and to investigate its potential role for treatments of water balance diseases.

**Methods:** We treated LLC-PK1 cells stably expressing AQP2 (LLC-AQP2) and mutant S256A cells with the src inhibitor dasatinib, and used immunocytochemistry to study AQP2 trafficking. We used western blot with specific phospho-antibodies against S256, S261 and S269 to measure phosphorylation. We treated rat kidney slices with dasatinib to follow AQP2 localization in situ. The effect of dasatinib treatment on vasopressin-induced cell swelling was also studied using exocytosis and endocytosis assays, actin depolymerization assay and clathrin-transferrin internalization assays to provide mechanistic information on its mode of action.

**Results:** Dasatinib increased apical membrane AQP2 accumulation in collecting duct principal cells in our in situ kidney slice model, and led to an increase in AQP2 membrane accumulation in the LLC-AQP2 cells. Western blots showed that dasatinib did not increase phosphorylation of S256, and this S256-independent effect was confirmed when dasatinib was able to induce AQP2 membrane accumulation in mutant S256A cells. Similar to VP, dasatinib increased exocytosis and decreased endocytosis, and these effects were specific to AQP2 containing cells. In contrast to VP, dasatinib did not activate PKA or MAP kinase, and did not de-phosphorylate S261. To our surprise, however, we observed a dose-dependent increase in S269 phosphorylation upon dasatinib treatment.

**Conclusions:** Src inhibition by dasatinib induced AQP2 membrane accumulation in a non-canonical fashion. The signaling pathway differs from that induced by VP, and represents a new approach to stimulating VP-dependent AQP2 membrane accumulation.

**Funding:** NIDDK Support, Private Foundation Support

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**TH-OR132**

**CaSR and AQP2 Interplay in Pendrin/NCC dKO and the Impact on Water Excretion and Vascular Volume Depletion. Marianna Ranieri,1 Kamyar A. Zahedi,2 Grazia Tamma,3 Mariangela Centrone,4 Manoocher Soleimani,5 Giovanna Valenti,6 1Univ of Bari Aldo Moro; 2Univ of Cincinnati.

**Background:** Pendrin/NCC double KO (dKO) mice display significant calcium (and phosphate) wasting and develop severe volume depletion despite increased circulating vasopressin levels. It is known that high concentrations of urinary calcium in the renal collecting duct counteract vasopressin action, consequently impairing the trafficking of the vasopressin-sensitive water channel AQP2. This effect is mediated by the activation of the Calcium Sensing Receptor (CaSR) expressed in the luminal membrane of collecting duct cells. Here we tested the hypothesis that the vasopressin resistance in dKO mice is due to CaSR-mediated impairment of the AQP2 expression/trafficking. 

**Methods:** Ex vivo experiments were performed in kidney slices from pendrin/NCC dKO mice. Modulation of AQP2 phosphorylation was tested using phospho-specific antibodies. The calciuminsensitive RSN-586 and the calcilytic NPS2143 were used to activate or inhibit CaSR respectively.

**Results:** Pendrin/NCC dKO mice exhibit significantly reduced total AQP2 both at mRNA and protein levels. Interestingly, when normalized to total AQP2, dKO mice had significantly higher levels of AQP2-pS256 in viscosity WT mice, which paralleled higher levels of phosphorylated pS256 MAPK, an enzyme activated by CaSR and known to phosphorylate AQP2. S256A mice showed less AQP2 abundance, possibly through miRNA S269 to measure phosphorylation. We treated rat kidney slices with dasatinib to follow AQP2 vesicle trafficking. We treated rat kidney slices with dasatinib to follow AQP2 vesicle trafficking. We treated rat kidney slices with dasatinib to follow AQP2 vesicle trafficking.

**Conclusions:** Together, these results point to a critical role of CaSR in impairing both AQP2 abundance, possibly through miRNA S269 to measure phosphorylation. We treated rat kidney slices with dasatinib to follow AQP2 vesicle trafficking.

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

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**TH-OR133**

**Taming Fibrosis: The Role of the SRC-kinase Pathway in Renal Fibrosis. Grazia Ranieri,1 Mariangela Centrone,2 Manoocher Soleimani,3 Giovanna Valenti,3 Kamyar A. Zahedi,2 Grazia Tamma,3 Mariangela Centrone,4 Manoocher Soleimani,5 Giovanna Valenti,6 1Univ of Bari Aldo Moro; 2Univ of Cincinnati.

**Background:** Renal fibrosis is the final common pathway in chronic kidney diseases and is the most consistent predictor of irreversible loss of renal function. Previous studies have demonstrated that fibrosis reduces the amount of aquaporin (AQP-2) and AQP3. Taminofen binds to estrogen receptor (ER) and has been used as an anti-estrogen for the prevention and treatment of breast cancer. In this study, we investigated the effect of tamoxifen on unilateral ureteral obstruction (UUO)-induced fibrosis and its regulation of AQP3.

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

**Underline represents presenting author.**

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**Methods:** Fibrosis was induced by 7 days UUO in rats. Tamoxifen (50 mg/kg) was given intraperitoneally for 5 days before induction of renal fibrosis. Tamoxifen (TAM) treatment was continued for 7 days after UUO operation. Clearance experiments were performed and histologic changes were examined by HE stain and Masson’s trichrome stain. Expression of α-smooth muscle actin, fibronectin, AQP2 and AQP3 were evaluated by immunohistochemistry and western blot analysis.

**Results:** Renal fibrosis was increased after UUO. TAM treatment significantly reduced fibrosis and fibroblast activation as well as increased the anti-fibrotic bone morphogenetic protein 7 (BMP7) in rats subjected to UUO. Furthermore, TAM decreased cross-sectional area and glomerular size in the obstructed kidney. In the UUO kidneys, AQP2 phosphorylated Ser256-AQP2 and AQP3 protein expression was reduced and TAM administration attenuated downregulation of the AQP3s although no change was observed in expression of the vasoressin receptor V2R. In addition, the expression of ERa, ERβ and GPER was not affected by TAM treatment in UUO rats. Urine samples collected from the pelvis of the obstructed kidney treated with TAM exhibited a higher urine osmolality compared to untreated UUO kidneys. Plasma osmolality was not affected.

**Conclusions:** These findings indicate that TAM has beneficial effects on UUO-induced fibrosis and might have therapeutic potential in the management of obstruction-associated dysregulation of fluid metabolisms.

**Funding:** Private Foundation Support

**TH-OR134**

Metformin Improves Urine Concentration Ability in Rodent Models of Nephrogenic Diabetes Insipidus

**Background:** Urine concentration is regulated by vasopressin. Congenital nephrogenic diabetes insipidus (NDI) is characterized by excessive polyuria and caused by vasopressin receptor V2 (V2R) mutations. Present treatment options are limited. We studied AMPK as an alternate pathway to stimulate transporters involved in urine concentration.

**Methods:** Tolvaptan (10 mg/kg/day) was given by oral gavage to rats for 4 or 10 days, +/- metformin (800 mg/kg/day). Tolvaptan (selective V2R antagonist) was used to produce a rat model of NDI. Metformin was used to stimulate AMPK. Urine volume and osmolality were measured daily. Kidneys were dissected into inner medullary (IM) tip, base, outer medulla, and papilla, and TAT-A1, AQP2, pAQP2 and NKCC2 were analyzed by Western blot. Immunohistochemistry was used to localize the same transporters. Tamoxifen-induced V2R knockout-out mice (girl from Dr. Wess, NIH) were given metformin (600 mg/kg) or vehicle twice daily. Hourly and daily urine osmolarities were determined and transporter proteins analyzed.

**Results:** Metformin reduced urine volume in tolvaptan-treated rats by 110% in 3 days and the effect was stable for 10 days. Correspondingly, urine osmolality in tolvaptan-treated rats was restored to near control levels by metformin (mean: 130±12 mOsm/mL - met) vs 235±27 mOsm/mL (controls, 10 mg/kg/day). Metformin increased protein abundance of IM tip UT-A1 61% and AQP2 44% (p<0.05) in tolvaptan-treated rats but not in control rats. Outer medullary NKCC2 abundance was markedly increased (117%) with metformin in control rats (p=0.004) but not in tolvaptan-blocked rats. Immunohistochemistry showed increased membrane accumulation of AQP2 and pSer256-AQP2 with acute (1 hr) and chronic (4 days) AMPK stimulation, both in control and V2R-blocked rats. Metformin treatment of V2R knockout-out mice increased urine osmolality within 1 hr and was maintained for up to 10 hours. Repeated daily treatment maintained the higher 24-hr urine osmolality. Metformin increased AQP2 and NKCC2 in V2R knockout-out mice similar to the tolvaptan-treated rats.

**Conclusions:** AMPK activators, such as metformin, might provide a promising treatment for congenital NDI due to V2R mutations.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Otsuka Pharmaceuticals

**TH-OR135**

Genetic Deletion of ADP-Activated P2Y12 Receptor Ameliorates Lithium-Induced NDI in Mice

**Background:** Previously we reported that pharmacological blockade of P2Y12 receptor (R) significantly ameliorates Li-induced nephrogenic diabetes insipidus (NDI) in rodent models. To establish that the observed protection is mediated through P2Y12 receptor (R) we administered LiCl to mice with CD-specific deletion of P2Y12 and compared with control mice.

**Methods:** Wild-type C57BL/6J mice were treated with LiCl in drinking water at 0.1 M for 7 days. Then, mice were divided into two groups: control wild-type mice and CD-specific deletion of P2Y12 mice. The experiment was performed in 5 replicates. At the end of 7 days, mice were sacrificed, and the kidneys were collected for further analysis.

**Results:** As expected, Li caused marked increases in water consumption and urine output, and decreases in urine osmolality and AQP2 protein in the kidney medulla of WT mice. These alterations were significantly ameliorated in KO mice (Table; mean ± se).

**Conclusions:** To determine the CD2 is not sufficient to block the development of NDI in response to LiCl.

**Funding:** NIDDK Support, VA Support

**TH-OR136**

Soluble (Pro)Rein Receptor Targets Renal V2 Vasopressin Receptor to Enhance Urine Concentrating Capacity

**Background:** Previously we reported that pharmacological blockade of P2Y12 receptor (R) derived from collecting duct intercalated cells acts in a paracrine fashion to regulate water transport in the principal cells. The present study attempted to define the role of sPRR in vasopressin (AVP) signaling with emphasis on V2R regulation.

**Methods:** Primary rat IMCD cells were used to assess the direct effect of a recombinant sPRR-His on V2R expression. The sPRR-His was infused to mice with CD-specific deletion (CD PRR KO) and nephrogen-specific deletion (Neph PRR KO) of PRR.

**Results:** In primary rat IMCD cells, sPRR-His at 10 μM induced a 2.8-fold increase in V2R protein and a 2.5-fold increase in V2R mRNA. Following AVP treatment, V2R protein was increased by 3-fold, which was blunted by a PRR antagonist and a PRR neutralizing antibody. CD PRR KO mice developed a medium level of diabetes insipidus [urine volume (UV): KO: 2.2±0.4 versus Floxed: 1.2±0.3 ml/d; p<0.05], accompanied by a 60% reduction of renal V2R protein and a 25% reduction of urinary sPRR excretion. Administration of sPRR-His for 3 days almost completely rescued the polyuria phenotype (UV: KO+sPRR-His: 1.6±0.3 vs. KO: 2.4±0.5 ml/d; p<0.05) associated with restoration of renal V2 and AVP expression. Interestingly, Neph PRR KO mice exhibited more robust polyuria (UV:KO:7.3±1.1 vs. Floxed: 1.2±0.5 ml/d, p<0.01) accompanied by suppressed renal expression of AQP2, NKCC2, and V2R. Administration of sPRR-His to Neph PRR KO mice partially attenuated polyuria (UV:KO+sPRR-His:4.1±1.2 vs. KO: 7.3±1.1 ml/d; p<0.01) accompanied by restored expression of V2R and AQP2. In contrast, the downregulation of NKCC2 expression in the null mice was unaffected by sPRR-His nor did it increase urine concentrating ability. Hence, the role of autophagosome markers microtubule-associated protein 1A/1B light chain 3 (LC3B).

**Conclusions:** The sPRR selectively targets the CD to determine V2R expression and hence AVP sensitivity and urine concentrating capability, independently of autophagosome accumulation.

**Funding:** NIDDK Support, VA Support

**TH-OR137**

Medullary Class I HDACs Are Critical for Fluid-Electrolyte Balance and Blood Pressure Control during High Salt Feeding

**Background:** Our recent studies indicate that renal medullary class I HDACs are deranged HDAC activity is causally linked to cancer, where three HDAC inhibitors (HDACi) are of transcription through epigenetic modification of chromatin structure. Consequently, HDACi use include hypertension, hyponatremia, and hypokalemia suggesting fluid-electrolyte disturbances. Thus we hypothesized that renal medullary class I HDACs are deranged HDAC activity is causally linked to cancer, where three HDAC inhibitors (HDACi) are

**Methods:** Primary rat IMCD cells were used to assess the direct effect of a recombinant sPRR-His on V2R expression. The sPRR-His was infused to mice with CD-specific deletion (CD PRR KO) and nephrogen-specific deletion (Neph PRR KO) of PRR.

**Results:** In primary rat IMCD cells, sPRR-His at 10 μM induced a 2.8-fold increase in V2R protein and a 2.5-fold increase in V2R mRNA. Following AVP treatment, V2R protein was increased by 3-fold, which was blunted by a PRR antagonist and a PRR neutralizing antibody. CD PRR KO mice developed a medium level of diabetes insipidus [urine volume (UV): KO: 2.2±0.4 versus Floxed: 1.2±0.3 ml/d; p<0.05], accompanied by a 60% reduction of renal V2R protein and a 25% reduction of urinary sPRR excretion. Administration of sPRR-His for 3 days almost completely rescued the polyuria phenotype (UV: KO+sPRR-His: 1.6±0.3 vs. KO: 2.4±0.5 ml/d; p<0.05) associated with restoration of renal V2 and AVP expression. Interestingly, Neph PRR KO mice exhibited more robust polyuria (UV:KO:7.3±1.1 vs. Floxed: 1.2±0.5 ml/d, p<0.01) accompanied by suppressed renal expression of AQP2, NKCC2, and V2R. Administration of sPRR-His to Neph PRR KO mice partially attenuated polyuria (UV:KO+sPRR-His:4.1±1.2 vs. KO: 7.3±1.1 ml/d; p<0.01) accompanied by restored expression of V2R and AQP2. In contrast, the downregulation of NKCC2 expression in the null mice was unaffected by sPRR-His nor did it increase urine concentrating ability. Hence, the role of autophagosome markers microtubule-associated protein 1A/1B light chain 3 (LC3B).

**Conclusions:** The sPRR selectively targets the CD to determine V2R expression and hence AVP sensitivity and urine concentrating capability, independently of autophagosome accumulation.

**Funding:** NIDDK Support, VA Support

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

Underline represents presenting author.

33A
Randomized, Placebo Controlled Double Blind Clinical Trial of the Somatostatin Analog Pasireotide LAR for Patients with ADPKD or ADPLD with Severe Liver Involvement

Methods: Eligible participants were assigned (2:1 ratio) in a 1 year double blind randomized trial (stratified ADPKD & ADPLD) to receive SOM230 / placebo every 28 days. Primary endpoint (EP) was change in LV; secondary EPs were change in kidney volume (KV) eGFR & QOL.

Results: Forty eight subjects were randomized (20; 40; ADPLD n=8; of these, 40 completed the trial). Ambulatory blood pressure measurements at 12 mo. From baseline, there was a 3.3% decrease in annualized change in LV (4271±2433 to 4104±2265mL) in SOM230 group (n=28), compared with 6.3% decrease (4047±1298 to 4294±1341mL) in placebo group (n=12; p=0.001) (fig 1). 

Conclusions: SOM230 versus placebo treatment significantly decreased the annualized LV growth when compared with placebo in patients with PLD and ADPKD. The eGFR declined in both arms, thus larger studies are needed to determine the impact of SSTs analogs on eGFR. (NCT01670110)

Funding: Pharmaceutical Company Support - Novartis

FR-OR002

Efficacy and Safety of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease Including Chronic Kidney Disease G4

Methods: Among ADPKD patients with TLV administration from 2014 to 2016, serum creatinine and estimated glomerular filtration ratio (eGFR) were measured at 1 week, 1, 3, 6 months, and TKV was calculated immediately before and 6 months after TLV treatment. TKV was estimated using ellipsoid approximation. Urine volume at day 1, 3, 6 months, and urine osmolality at 0, 1 day, and each month until 8 months were evaluated.

Results: Chronic kidney disease (CKD) G2, G3 and G4 were 22%, 45% and 33%, respectively. ΔTKV was significantly decreased 6 months after TLV administration compared with the next day (3375(2723-3958) mL vs 3860(3468-4300) mL, P<0.05), whereas urine volume tended to increase between the same periods (3825(3210-5638) vs 3952(3588-4000) mL, P=0.07). The dose of TLV was larger in responders than non-responders when responders were defined as patients with improvement of TKV or eGFR after TLV administration. The dosage could not be increased because of hepatocytic dysfunction and polyuria in non-responders. TLV was discontinued in 2 cases with CKD G4, and both of them showed hepatocytic dysfunction 4-8 months after TLV initiation.

Conclusions: TLV was well tolerated in CKD G4. High dose TLV may mitigate TKV outgrowth.

Funding: NIDDK Support, Other NIH Support - NIH Program Project Grant on Endothelial Control of Renal Excretory and Hemodynamic Function (P01 HL54999) to D.M.P., J.S.P, and K.A.H.
FR-OR005
A New Clinical Entity: GANAB-Related Polycystic Kidney and Liver Disease
Emilie Concej-Le Gall,1 Vladimir Gainullin,1 Binu Porath,1 Yannick Le Meur,2 Marie-Pierre Audrezet,2 Peter C. Harris,3 Claude Fercé.2 Mayo Clinic;1 CHU Brest, France.

Background: Genetic variability in ADPKD/ADPLD has recently been refined with the description of a new gene, GANAB, encoding a subunit of the glucosidase II; mutations impair polycystin trafficking (Porath et al, AHG 2016). The aim of this study is to characterize the disease presentation in GANAB patients.

Methods: Molecular analysis of GANAB was conducted in 50 unresolved ADPKD/ADPLD unrelated patients. Clinical records and imaging data of recently reported and newly identified patients were reviewed.

Results: GANAB mutations were found in 2 new pedigrees. In the first (splice variant c.39-1G>C), a 75 y.o man was incidentally diagnosed with ADPKD at age 61 by a CT scan and had atrophic cystic kidneys (7.5 cm, ~20 cysts) and liver cysts. His two siblings had similar presentations at age 87 and 75 and did not require dialysis. In the second pedigree (frameshift variant c.2723del), a diagnosis of bilateral cystic kidneys was made in a 7 y.o boy following hematuria, and subsequently in his 9 y.o brother and 44 y.o father, who had normal kidney function and liver cysts. While all the 26 described GANAB patients (median age 50y (7-87), 14 males) had kidney cysts, kidney enlargement was only present in 18.5%, and was moderate, caused by a few large cysts. Kidney function was preserved, with 96% being CKD1-2 patients, and the only CKD3 patient (75y) had a partial nephrectomy at age 26. Hypertension was present in 39% of the adult patients. Liver cysts were reported in 81% of the adult patients and severe PLD was observed in 4 patients, clustered in 2 pedigrees, which tested positive for mutations in GANAB gene. We conclude that increased class (from A to E) was associated with increased proportion of patients with severe liver dysfunction.

Conclusions: In patients with normal-sized cystic kidneys and significant liver cysts, a GANAB diagnosis should be considered. GANAB patients typically present with milder kidney disease than PKD2 and do not seem at risk of CKD. As larger GANAB cohorts become available, better description of the disease penetrance and presentation will be possible. We are currently analyzing 200 other unresolved ADPKD/ADPLD cases.

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

FR-OR006
Trajectory of the GFR in Autosomal Dominant Polycystic Kidney Disease
Alan S.L. Yu,1 Chengli Shen,2 Doug Landsittel,2 Jared J. Grantham,1 Larry Cook,1 Vicente E. Torres,1 Arlene B. Chapman,1 Kyongtae Ty Bae,1 Michal Mrug,2 Peter C. Harris,1 Frederic F. Rahbari-Oskoui,1 Michael F. Flessner,1 William M. Bennett.1 U Kansas;1 U Pittsburgh;1 Mayo Clinic;1 U Chicago;1 Emory Univ;1 U Alabama;1 NIH;1 Legacy Good Samaritan Med Ctr.

Background: In autosomal dominant polycystic kidney disease (ADPKD), cyst growth and kidney injury occur throughout life, leading to ESRD. The shape of the GFR trajectory over this period spanning several decades is not well defined, and the factors that influence this are unclear.

Methods: CRISP is a 13 yr observational study of 241 ADPKD pts. To predict trajectories of renal decline, a novel classification of kidney growth rates, based on age and height-adjusted total kidney volume (Irazabal, et al., 2014), was used to stratify participants into 5 classes. Within each group, a quadratic polynomial function was fit to the individual GFR trajectories using linear mixed models with a subject random effect and fixed effects for age and other covariates. Conditional R² is the variance explained by fixed and random factors.

Results: Irazabal classes effectively separated the cohort into individuals with similar trajectories. The overall curvilinear trend included a period of relatively stable GFR followed by accelerating decline. Increasing class (from A to E) was associated with earlier and steeper decline.

Funding: NIDDK Support, Other NIH Support - RR000039, RR00585, RR23940, RR000032, RR025008, TR000454, RR024150, TR000135, RR033179, TR000001, RR025777, TR00165, TR001417, RR024153, TR000005

FR-OR007
Foam Sclerotherapy for Cystic Volume Reduction in Autosomal Dominant Polycystic Kidney Disease
Joan-Andrei Iluia, Beili Shi, Silvio Giancarlo Bruni, John Conklin, Moomita Barua, Korosh Khallili, Eran Shlomovitz, York P. Pei. Toronto General Hospital, Univ Health Network, Toronto, ON, Canada.

Background: Kidney volume (KV) in autosomal dominant polycystic kidney disease (ADPKD) expands exponentially during adult life at ~5%/yr on average. Patients with total kidney volume >1,500 mL are at high risk of developing end-stage renal disease. Large cysts may be particularly detrimental by impeding regional kidney blood and urine flow. We examined the safety and effectiveness of foam sclerotherapy (FS) on KV reduction.

Methods: Thirty-one patients with typical or atypical ADPKD were treated with 3% sodium tetradecyl sulfate FS targeting to 2 to 3 large (>5 cm) non-expoicytic cysts in one or both kidneys between August 2014 and April 2016. Serum creatinine (SCr), measured 24 hr clearance (Cr), and KV were assessed before and after each intervention.

Results: The mean age and baseline sCr of our typical (n=27) and atypical (n=4) PKD patients were 51 ± 63 years and 0.94 [95% CI: 0.81-1.58] vs. 0.93 [0.75-1.43] mg/dL, respectively. Over a mean time of 12.5 months, the volume of kidneys targeted by FS decreased by 375 mL (-24%; p<0.0001) while the volume of non-targeted kidneys increased by 88 mL (15%; p=0.003).

Funding: NIDDK Support

FR-OR008
Increased Risk of Kidney Cancer in Patients with Polycystic Kidney Disease: A Propensity Score Matching Analysis of a Nationwide, Population-Based Cohort Study
Tung-Min Yu,1 Kuo-Hsiung Shu,1 Mei-Ching Yu,2 Ya-Wen Chuang.1 Div of Nephrology, Taichung Veterans General Hospital, Taichung, Taiwan;2 Pediatric Nephrology, Chang-Gung Hospital, Taoyuan, Taiwan.

Background: Data regarding the risk of kidney cancer and cancer at other sites in patients with polycystic kidney disease (PKD) are scarce. Therefore, we conducted a nationwide cohort study to determine the risk of cancer in patients with PKD.

Methods: From the National Health Insurance Research Database (NHIRD), we included 7080 patients aged >20 years and diagnosed with PKD between 1998 and 2010 in NHIRD. For each patient with PKD, one patient aged ~20 years who was neither PKD nor cancer was randomly selected from the NHIRD, matched on the basis of the propensity score, and included as control group. The follow-up period was from the time of the initial PKD diagnosis until the date of the cancer diagnosis, censoring, or December 31, 2011. We used Cox proportional hazard regression models to analyze the risk of cancer.

Results: The overall incidence of cancer was significantly higher in the PKD cohort than in the non-PKD cohort [17.6 vs. 11.4 per 1000 person-years; crude hazard ratio (HR) = 1.82; 95% confidence interval (CI) = 1.61–2.06]. After adjustment for comorbidities including hypertension, chronic obstructive pulmonary disease, diabetes, alcoholism, alcoholic liver damage, and obesity, the patients with PKD had a higher overall risk of cancer [adjusted HR (aHR) = 1.74; 95% CI = 1.54–1.96]. The risk of kidney cancer was significantly higher in the PKD cohort than in the non-PKD cohort (aHR = 5.00; 95% CI = 2.98–7.59). After considering death as a competing risk factor, the risk of kidney cancer remained significantly higher in patients with PKD [adjusted subhazard ratio (aSHR) = 3.69; 95% CI = 2.41–5.67]. Of note, a significantly higher risk of kidney cancer was observed in younger patients with PKD (<49 year old; aSHR = 4.70; 95% CI = 1.78–12.4).

Conclusions: This study is the first to report the association of PKD with a higher risk of cancer, particularly kidney cancer. When treating patients with PKD, a high index of suspicion for cancer should be maintained.

Funding: NIDDK Support

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

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FR-OR009

Urinary Proteomic Analysis Revealed New Specific Medullary Sponge Kidney Disease (MSK)-Associated Proteins

Gianluigi Zaza,1 Antonio Fabris,1 Maurizio Bruschi,2 Giovanni Candiano,2 Simona Granata,1 Giovanni Gambard,3 Antonio Lupo.1 1Renal Unit, Univ of Verona, Verona, Italy; 2Laboratory of Nephrology of Uremia, Gaslini Inst, Genoa, Italy; 3Renal Unit, Columbus-Gemelli Hospital/Univ, Verona, Italy.

Background: MSK is a kidney malformation featuring nephrocalcinosis, recurrent renal stones, renal acidification and ectasias of pre-calcule ducts. It generally occurs sporadically, but an autosomal dominant inheritance have been reported. Previous studies have suggested a putative point mutations of the GDNF gene as a cause of MSK, but the precise molecular mechanisms leading to the disease remain poorly understood. Currently, MSK diagnosis is only radiographic and no molecular diagnostic biomarkers are available.

Methods: Therefore, we employed an innovative high-throughput methodology (proteomic analysis) to identify new specific MSK urinary diagnostic biomarkers. Briefly, urines from 21 MSK patients and 21 controls with idiopathic calcium nephrocalcinosis (ICN) were collected and processed for proteomic analysis and ELISA. The urine of 11 MSK and 10 controls, randomly selected, were processed/analyzed by the mass spectrometer LTQ-Orbitrap Velos Pro. Subsequently, several statistical algorithms and bioinformatic analysis were undertaken to select most discriminative proteins between the 2 study groups. ELISA, performed on the entire patients’ cohort, was used to validate proteomic results.

Results: After an initial statistical analysis, 249 (16%) and 396 proteins (26%) resulted exclusive for MSK and ICN (FC<2, p<0.001), respectively. Subsequently, several statistical algorithms and graphic representations (including Volcano Plot and ROC curve) restricted the number of proteins to 22 up- and 15 down-regulated in MSK compared to ICN. The use of a Support Vector Machine restricted the selection to 16 top ranked proteins (primarily involved in matrix remodeling and bone differentiation) hyper-expressed in urines of MSK (e.g., Glypican, Plexin). These biological elements were validated by ELISA.

Conclusions: Therefore, our study, for the first time, using a proteomic methodology was able to identify new diagnostic MSK urinary biomarkers possibly employable in future in the “day by day” clinical practice.

FR-OR011

Empagliflozin and Changes in Renal Function Decline in Type 2 Diabetes: Prespecified Slope Analyses from the EMPA-REG OUTCOME Trial

Christoph Wanner,1 Bernard Zinman,2 Silvio E. Inzucchi,3 John M. Lachin,4 Maximilian von Eynatten,5 Audrey Koitka-Weber,6 Michaela Mattheus,6 Erich Bluhmki,7 Hans-Juergen Woehrle,8 Ul Christian Broett,9 Per-Henrik Groop,4 Hidde Jan Lambers Heerspink,3 1Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany; 2Lunenfeld-Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, Canada; 3Section of Endocrinology, Yale Univ, New Haven, CT; 4Biostatistics Center, George Washington Univ, Rockville, MD; 5Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; 6Div of Nephrology, Helsinki Univ Central Hospital, Helsinki, Finland; 7Dept of Clinical Pharmacy and Pharmacology, Univ of Groningen, Groningen, Netherlands.

Background: CKD and progressive decline of renal function are common in patients with diabetes. In the EMPA-REG OUTCOME trial, empagliflozin (EMP) slowed CKD progression in patients with type 2 diabetes and high cardiovascular risk. Here we report treatment differences in the rate of change in eGFR by utilizing linear regression models yielding mean and individual slopes.

Methods: 7020 patients were randomized (1:1:1) to EMPA 10 mg, 25 mg or placebo on top of standard of care. Treatment differences in the average rate of change in eGFR (MDRD) for pre-specified time periods were assessed using a random intercept and time coefficient model.

Results: Mean slopes with EMPA showed an acute fall in eGFR during the first 4 weeks, followed by stable eGFR during chronic treatment and a rapid return towards baseline after drug cessation (Figure [lower panel]). Individual slopes revealed a uniform shift with EMPA compared to placebo during all three periods (Figure [upper panel]).

Conclusions: EMPA exerted a uniform treatment effect on eGFR across the entire distribution of renal function. Therefore, our findings suggest that EMPA has the potential to slow rate of GFR decline independent of the individual renal function trajectory.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

FR-OR012

Glycogen Synthase Kinase 3β Overexpression and Hyperactivity in Urinary Exfoliated Cells Predicts Progression of Diabetic Nephropathy

Hans-Juergen Woehrle,8 Ul Christian Broett,9 Per-Henrik Groop,4 Hidde Jan Lambers Heerspink,3 1Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany; 2Lunenfeld-Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, Canada; 3Section of Endocrinology, Yale Univ, New Haven, CT; 4Biostatistics Center, George Washington Univ, Rockville, MD; 5Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; 6Div of Nephrology, Helsinki Univ Central Hospital, Helsinki, Finland; 7Dept of Clinical Pharmacy and Pharmacology, Univ of Groningen, Groningen, Netherlands.

Background: Glycogen synthase kinase (GSK) 3β is a highly-conserved serine/threonine protein kinase that was originally identified as a key cellular signaling transducer involved in glycogenesis. Converging evidence recently points GSK3β as a key player in pathogenesis of diverse kidney diseases. However, its role in diabetic nephropathy (DN) remains unknown and was examined here.

Methods: The expression and activity of GSK3β were evaluated in kidney specimens from DN patients or db/db diabetic mouse models, and assessed in urinary exfoliated cells in patients with type 2 diabetes.

Results: In db/db mice, renal expression and activity of GSK3β were progressively elevated over time, in parallel with deterioration of signs of diabetic kidney injuries, clearly demonstrated by accumulation of extracellular matrix, accumulation in glomeruli, podocytopeny and renal interstitial fibrosis. In consistency, in cultured kidney cells, including podocytes, mesangial cells and tubular epithelial cells, high glucose exposure markedly amplified GSK3β expression and activity, associated with cytophatic changes. In kidney biopsy specimens procured from patients with varying stages of DN, GSK3β expression and activity were progressively augmented in glomeruli and renal tubules, and correlated with the severity of DN, as assessed by albuminuria and glomerular pathology. In a cohort of patients with type 2 diabetes that were followed for 5 years, elevated expression of GSK3β in urinary exfoliated cells was found to the progression of proteinuria in patients diagnosed with diabetic nephropathy. In contrast, urinary GSK3β levels remained normal in diabetic patients with no normoalbuminuria or stable microalbuminuria. Moreover, receiver operating characteristic curve analysis revealed that urinary GSK3β was likely superior to microalbuminuria in predicting the progression of DN.

Conclusions: In aggregate, our studies demonstrated that renal expression and activity of GSK3β are amplified in animal and human diabetic nephropathy. GSK3β in urinary exfoliated cells may serve as a novel biomarker for predicting progression of DN.

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

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

Underline represents presenting author.

36A
FR-OR013

BP Levels Lower Than 120/70 mm Hg Associate with Lower Risk of Renal Events in Type I Diabetes
Elaine K.1, Charles E. McClurchock,1 Michael Maurer,2 Barbara A. Grimes,3 Chi-Yuan Hsu.1 1UCSF; 2Univ of Minnesota.

Background: Optimal BP targets in diabetes continue to be debated. We compared different BP levels and their associations with adverse renal outcomes in type I diabetes (T1DM), and determined whether glycomic control modifies this association.

Methods: We included 1441 participants with T1DM ages 13-39 initially randomized to intensive vs. conventional glycomic control in the Diabetes Control and Complications Trial (DCCT) and subsequently followed in Epidemiology of Diabetes Interventions and Complications (EDIC) study. The predictors were time-updated systolic (SBP) and diastolic blood pressure (DBP) categories, ascertainment one year before outcomes of interest, which included macroalbuminuria, CKD stage III, and ESRD.

Results: During median follow-up of 24 years, 84 cases of CKD stage III, 169 cases of macroalbuminuria, and 26 cases of ESRD occurred. In adjusted Cox models, there was a stepwise graded association between higher BP and risk of macroalbuminuria and CKD stage III.

<table>
<thead>
<tr>
<th>SBP category</th>
<th>Risk of Macroalbuminuria Hazard ratio (95% CI)</th>
<th>Risk of CKD Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 140 mm Hg</td>
<td>2.64 (1.62-4.29)</td>
<td>2.61 (1.44-4.71)</td>
</tr>
<tr>
<td>130–140 mm Hg</td>
<td>Reference (Ref)</td>
<td>Ref</td>
</tr>
<tr>
<td>120–130 mm Hg</td>
<td>0.65 (0.41-1.02)</td>
<td>0.91 (0.49-1.71)</td>
</tr>
<tr>
<td>&lt; 120 mm Hg</td>
<td>0.46 (0.29-0.73)</td>
<td>0.23 (0.10-0.53)</td>
</tr>
</tbody>
</table>

Conclusions: BP levels lower than 120/70 mm Hg increase in SBP and DBP also associated with 1.73 (95% CI 1.42-2.11) and 1.67 times (95% CI 1.42-2.45) higher risk of ESRD, respectively. No interaction was noted between BP and glycomic control strategy (HbA1C <6% vs. conventional therapy) during DCCT (p > 0.10). Similar results were observed when analysis was limited to participants receiving BP medications.

FR-OR014

Intensified Multifactorial Intervention in Type 2 Diabetes and Microalbuminuria Reduces End Stage Renal Disease and Mortality: 21 Years Follow-Up of the Steno-2 Study
Jens Christian Ølgaard,1,2,3 Peter Gaede,1,3 Peter Rossing,1,3 Hans-Henrik Parving.1,3 Steno Diabetes Center, Gentofte, Denmark; 2Univ of Southern Denmark, Odense, Denmark; 3Steno Diabetes Center, Gentofte, Denmark; 4Univ of Aarhus, Aarhus, Denmark; 5Univ of Copenhagen, Copenhagen, Denmark; 6Novo Nordisk Foundation Center for Basic Metabolic Research, Univ of Copenhagen, Copenhagen, Denmark; 7Righospitalet, Copenhagen, Denmark.

Background: Despite declining rates of late diabetic complications in other organ systems, renal complication rates do not decline to the same extent according to epidemiological studies. We report renal outcomes over 21 years in patients with type 2 diabetes and microalbuminuria and the influence of intensified, multifactorial treatment including strict control of blood glucose, lipids and blood pressure.

Methods: 160 patients with type 2 diabetes and microalbuminuria assigned to conventional or intensified multifactorial intervention targeting multiple risk factors in a prospective, open-label trial. The treatment regimen was target-driven and included behavioral and pharmacological modifications. Duration of the intervention was 8 years, where after all patients were recommended intensified treatment. Total follow-up of up to 21 years of albuminuria and GFR (1C-EDTA-clearance) assessed at 6 visits study. Outcome measures were progression to macroalbuminuria (>500 mg/24h), decline-rate of GFR and progression to ESRD or death.

Results: Progression to macroalbuminuria was reduced in the original intensive-therapy group, HR 0.45 [95% CI 0.28–0.74; p = 0.003]. The decline in GFR was 3.1 ml/min/year in the intensive group vs. 4.1 in the conventional group [difference 0.5 – 1.5 ml/min/year; p = 0.001]. Progression to ESRD trended towards a decreased HR with an adjusted (age and sex) HR of 0.36 [95% CI 0.12–1.05; p = 0.061] (n 5 vs. 10) in the intensive group. ESRD combined with all-cause or cardiovascular mortality was reduced in the intensive group; adjusted HR 0.53 [95% CI 0.12–0.81; p = 0.003] and 0.35 [95% CI 0.19–0.65; p = 0.001], respectively.

Conclusions: Intensified, multifactorial treatment for 8 years in type 2 diabetes patients with microalbuminuria slows long-term progression in nephropathy and reduces the risk of ESRD and mortality.

Funding: Pharmaceutical Company Support - Novo Nordisk A/S

FR-OR015

Hypoglycemia-Related Hospitalizations and Mortality among Non-Dialysis Dependent CKD Patients Transitioning to Dialysis
Connie Rhee.1 Amy Seung You,1 Melissa Sooho,1 Elani Streja,1 John J. Sim,1 Danh V. Nguyen,1 Csaba P. Kovesdy,1 Kamyar Kalantar-Zadeh.1 1UC Irvine; 2Kaiser Perm. Southern CA; 3Univ of Tennessee Health Science Center.

Background: Diabetic kidney disease patients with declining kidney function are at heightened risk for hypoglycemia due to impaired insulin degradation and clearance, as well as decreased renal glucose reabsorption. We sought to examine how hypoglycemia in the pre-dialysis (prelude) period impacts post-ESRD mortality in this population.

Methods: Among US veterans with diabetic kidney disease who transitioned to dialysis over 2007-2011, we evaluated the occurrence and frequency of hypoglycemia-related hospitalizations during the 2-year pre-ESRD Prelude interval. We then examined whether occurrence and frequency of pre-ESRD hypoglycemia-related hospitalizations are associated with post-ESRD all-cause mortality using unadjusted, minimally adjusted, and case-mix adjusted Cox models. We conducted sensitivity analyses examining 1-year and 5-year prelude intervals.

Results: Among 30,321 patients in the 2-year prelude period, occurrence of a hypoglycemia-related hospitalization was associated with higher mortality risk in case-mix analyses (ref: no hypoglycemia): HR (95%CI) 1.21 (1.14-1.28). Increasing frequency of hypoglycemia-related hospitalizations were associated with incrementally higher mortality risk in case-mix analyses (ref: no hypoglycemia): HRs (95%CI) 1.17 (1.10-1.24), 1.44 (1.21-1.70), and 1.85 (1.37-2.49) for 1, 2, and ≥3 hypoglycemia-related hospitalizations, respectively. Similar findings were observed for 1-year and 5-year prelude periods.

Conclusions: In diabetic kidney disease patients transitioning to dialysis, there is a dose-dependent relationship between frequency of pre-ESRD hypoglycemia and post-ESRD mortality. Further studies are needed to determine modifiable risk factors for hypoglycemia, and whether correction of these factors improves survival.

Funding: NIDDK Support

FR-OR016

Angiotensin Receptor Blockers Confer Cardioprotection in Males but Not in Females with Type 2 Diabetes
Bauke Scheivink,1 Dick de Zeeuw,1 Peter G.M. Mol, Michelle Pena, Petra Denig, Hidde Jan Lambers Heerspink.1 Univ Medical Center Groningen.

Background: Previous studies showed that female patients with type 2 diabetes (T2D) have nearly 50% higher risk of cardiovascular (CV) complications compared to male patients. It is unclear if females also respond differently to therapy compared to males. We assessed gender differences in response to treatment with angiotensin receptor blockers (ARBs), a mainstay of cardiorenal protective therapy in T2D.

Methods: We used data from RENAAL and IDNT trials, which assessed the effect of ARBs on CV outcomes in T2D patients with nephropathy. The CV outcome in both trials was time to first event of a composite of stroke, myocardial infarction (MI) and heart failure (Table 1). Males also had a larger, albeit non-significant, interaction=0.027). This interaction was driven by treatment differences in myocardial infarction (MI) and heart failure (Table 1).

Results: Among 3737 males and 924 females were followed for a median 2.9 years. During follow-up 872 CV events were recorded. ARB treatment decreased CV risk in males (HR: 0.79, 95% CI: 0.67 - 0.94), but not in females (HR: 1.12, 95% CI: 0.88 - 1.43, p interaction=0.027). This interaction was driven by treatment differences in myocardial infarction (MI) and heart failure (Table 1). Males also had a larger, albeit non-significant, benefit for the renal endpoint of ESRD or doubling serum creatinine compared to females (Table 1).

Conclusions: ARB treatment confers cardioprotection in male but not female T2D patients. These results warrant more careful analysis of gender differences when determining treatment efficacy, as well as investigation of underlying mechanisms of drug response.

Funding: NIDDK Support

Table 1: Gender differences in the effect of ARBs on CV outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV risk</td>
<td>HR: 0.79, 95% CI: 0.67 - 0.94</td>
<td>HR: 1.12, 95% CI: 0.88 - 1.43</td>
</tr>
<tr>
<td>MI risk</td>
<td>HR: 0.79, 95% CI: 0.67 - 0.94</td>
<td>HR: 1.12, 95% CI: 0.88 - 1.43</td>
</tr>
<tr>
<td>Heart failure</td>
<td>HR: 0.79, 95% CI: 0.67 - 0.94</td>
<td>HR: 1.12, 95% CI: 0.88 - 1.43</td>
</tr>
</tbody>
</table>

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FR-OR017

Development of a Service Interface Method (Webservice) between Family Care Physicians (FCPs) Operating in a Primary Care Setting and Nephrologists (NPs), for the Prevention, Diagnosis and Treatment of Kidney Damage in Patients with Type 2 Diabetes Mellitus (T2DM)  
Stefano Bianchi, Chiara Bilanceri, Elisa Poderelli, Silvia Campatelli, Francesca Nistri, Giada Santini, Roberto Bigazzi.  
Nephrology and Dialysis, ASL Nordovest Toscana, Italy.

Background: Chronic kidney disease (CKD) due to T2DM is a common and costly chronic disease and its complications are a major driver of health care (HC) costs worldwide. Because of the large prevalence of such patients (pts), second care level of assistance (outpatient clinics and hospitals) is not able to screen and treat appropriately all of them. Information technology can be used effectively to track clinical and laboratory data and generate databases useful to follow these pts.

Methods: With this 3 years project (Italian HC system RF-2011-02346990) we realized a shared computerized (WEB connection) clinical chart (SCCC) allowing continuous updating of individual clinical data of pts with T2DM between NPs and FCPs. A SCCC allows an early diagnosis and would improve the treatment of DN and a reduction of cost of medications, diagnostic examinations and hospitalization rate.

Results: In the first year of the study, 106 FCPs have been enrolled, each of them caring for 1,000 pts. Therefore, the population of our study includes 106,000 subjects. We have screened 6,142 pts with T2DM, 2898 females and 3244 males, mean age 71.3±11.1 years. 3,071 out of 6,142 pts (50%) presented DN in different stage of CKD: 222 Stage I (3.6%), 856 Stage II (3.9%), 1227 Stage IIIa (20%), 579 Stage IIIb (9.4%), 147 Stage IV (2.4%) and 40 Stage V (0.6%).

Prevalence of renal damage (Stage of CKD) in 6,142 patients with type II Diabetes enrolled in the Study

Conclusions: A SCCC between NPs and FCPs is a feasible tool to early diagnose DN in pts with T2DM. DN has a high prevalence: 65% of pts with DN shows an advanced CKD stage. Screened T2DM pts with DN are now enrolled in a therapeutic protocol aimed to reduce the renal and cardiovascular complications of this high risk population.

Funding: Government Support - Non-U.S.

FR-OR018

Intensive Blood Pressure Control Associates with Lower Mortality Risk among Persons with High-Risk APOL1 Genotype  
Elaine Ku,1 Michael S. Lipkowitz,2 Lawrence J. Appel,2 Afshin Parsa,1 Jennifer J. Gassman,2 David V. Glicksen,1 Miroslaw Smogorzewski,2 Chi-Yuan Hsu.1 UCSC; 2AASK; 1Univ of Maryland.

Background: The association between APOL1 risk and risk of death in black CKD patients is not well known. We determined whether APOL1 status modifies the association between strict BP control and long-term mortality risk in former African American Study of Kidney Disease (AASK) trial participants.

Methods: We analyzed 682 AASK trial participants with CKD previously randomized to intensive (mean arterial pressure [MAP] <92 mm Hg) versus usual BP control (MAP ≥102-107 mm Hg) between 1995-2001. We determined risk of death by 1) APOL1 genotype and 2) prior BP target assignment in analysis stratified by APOL1 genotype. Deaths were ascertained through 2012 by linkage with the Social Security Death Index and US Racial Data System.

Results: During median follow-up of 14.5 years, risk of death did not differ between individuals with high- versus low-risk APOL1 genotypes (unadjusted HR= 1.00 [95% CI 0.76-1.33]). However, an interaction was detected between APOL1 risk group and BP control strategy during AASK trial (p=0.03). In the APOL1 high-risk group (N=157), risk of death in long-term follow-up was 0.58 times lower comparing intensive versus usual BP control (unadjusted 95% CI 0.35-0.97), but in the APOL1 low-risk group (N=523), risk of death was not different (unadjusted HR=1.09 [95% CI 0.84-1.43]).

In analysis adjusted for age, sex, baseline GFR, heart disease, smoking, and proteinuria, risk of death remained 0.48 times lower (95% CI 0.28-0.84) comparing intensive versus usual BP arms in the APOL1 high-risk group, but was not different in the APOL1 low-risk group (HR=0.99 [95% CI 0.74-1.28]).

Conclusions: Intensive BP control during CKD associates with lower risk of death in blacks with high-risk APOL1 genotype. Knowledge of APOL1 status may inform appropriate BP treatment targets in black CKD patients.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-OR019

Thyroid Functional Disease and Mortality in U.S. Veterans with Chronic Kidney Disease  
Connie Rice,1 Kaymar Kalantar-Zadeh,1 Vanessa A. Ravel,1 Elani Streja,2 Steven M. Brunelli,2 Danh V. Nguyen,3 Gregory Brent,3 Csaba P. Kovesdy,4 1UC Irvine; 2DaVita Inc; 3UCLA; 4Univ of Tennessee Health Science Center.

Background: Epidemiologic studies show that advanced chronic kidney disease (CKD) patients have a higher prevalence of thyroid dysfunction compared to their non-CKD counterparts. While hyper- and hypothyroidism have been associated with higher mortality in the dialysis population, no studies have examined the relationship between thyroid function defined by serum thyrotropin (TSH) and death risk in non-dialysis dependent chronic kidney disease (NDD-CKD) patients.

Methods: We examined the association of thyroid function with all-cause mortality among US veterans with Stage 3-5 NDD-CKD who underwent ≥1 TSH measure(s) over 2004-12. We examined the association between thyroid status, defined as hyper-, eu-, and hypothyroid (TSH levels <0.5, 0.5-5.0, and >5.0 mIU/L, respectively), with all-cause mortality across CKD strata using case-mix adjusted Cox models.

Results: Among 232,524 patients with Stage 3-5 CKD, 4% (n=8154), 90% (n=209,438), and 6% (n=14,932) of patients had hyper-, eu-, and hypothyroid, respectively. In the overall cohort, 1.0% (n=227,426), 2% (n=4248), and 0.4% (n=850) had Stage 3, 4, and 5 CKD, respectively. In adjusted analyses, hyperthyroidism was associated with higher mortality risk across all stages of CKD: HRs (95% CI) 1.17 (1.14-1.20), 1.20 (1.10-1.29), and 1.28 (1.13-1.39) for Stage 3A, 3B, and 4+5, respectively. Similarly, hypothyroidism was associated with higher mortality risk across all stages of CKD: HRs (95% CI) 1.17 (1.13-1.20), 1.17 (1.10-1.25), and 1.28 (1.13-1.45) for Stage 3A, 3B, and 4+5, respectively.

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

Underline represents presenting author.

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Conclusions: Among US veterans with Stage 3-3 CKD, hyper- and hypothyroidism were associated with higher mortality. Further studies are needed to determine whether treatment that normalizes TSH ameliorates death risk in NDD-CKD patients with thyroid dysfunction.

Funding: NIDDK Support

FR-OR020

Equations Based on a Set of Novel Metabolites Markers Provide a More Precise Determination of the Glomerular Filtration Rate (GFR) Than the Standard Equations in a Swedish Population with Measured GFR

Background: Creatinine and creatinine-based equations (eg, MDRD and CKD-EPI) are used in routine clinical practice to assess the kidney function. However, non-glomerular determinants affects the performance and clinical utility of creatinine-based equations. We previously identified new metabolites with high correlation with the measured (mGFR).

Methods: Using quantitative assays for these new metabolites we developed equations that had better precision than the MDRD and CKD-EPI equations in a cohort of adult Swedish patients with mGFR (n=482). The aim of this study is to verify the performance of these new equations in an independent set of 803 patients with mGFR.

Results: The MDRD and CKD-EPI equations performed similarly in this patient cohort: about 78% and 64% of the GFR estimates were within 30% and 20% of the mGFR values, respectively. In contrast, with an equation based on acetyl-threonine, pseudouridine and age, 87% and 75% of the GFR estimates were within 30% and 20%, respectively. The rate of CKD Stage misclassification due to an error of more than 30% was 18% with MDRD age, 87% and 75% of the GFR estimates were within 30% and 20%, respectively. The rate of CKD Stage misclassification due to an error of more than 30% was 18% with MDRD and CKD-EPI equations. In contrast, this rate was only 8.3% (more than 50% reduction) with the equation based on the new metabolites.

Conclusions: The potential for new metabolites to provide significantly more precise and accurate estimates of GFR was verified in this large independent cohort. Full clinical validation of the new metabolite markers is underway in a larger and diverse cohort.

Funding: Pharmaceutical Company Support - Metabolon, Inc.

FR-OR021

Multiple Metabolites Correlate More Strongly with Measured Glomerular Filtration Rate Than Creatinine: A Verification Study

Background: We previously showed that in 200 individuals from AASK measured glomerular filtration rate (mGFR) was highly correlated with many metabolites. We now test whether this is also true in a higher GFR range and evaluate which metabolites are strongly correlated with mGFR at both low and high GFR providing a foundation for improved GFR estimation.

Methods: Study Population: 265 white or African-American participants at the JHU MISA site with mGFR by plasma clearance of iohexol. Laboratory Methods: Untargeted GC/MS and LC/MS-based metabolomic quantification of serum (Metabolon) followed by development of targeted assays for 15 metabolites. Data Analysis Methods: Log metabolites were ranked by correlation with log mGFR and compared across AASK and MESA.

Results: In semi-quantitative untargeted metabolite assays more than a quarter of measured metabolites were significantly correlated (p<0.001) with mGFR in AASK and MESA, and 7 of 9 metabolites more negatively correlated than untargeted serum creatinine in AASK were also more negatively correlated in MESA (Figure). Targeted assays developed for promising metabolites showed higher correlations in the combined dataset with mGFR than creatinine (r=-0.82) for: acetyl-threonine (-0.90), pseudouridine (-0.89), acetyl-alanine (-0.84) and myo-inositol (-0.83).

Conclusions: We identified several metabolites which replicated as being more correlated with mGFR than serum creatinine across both a low and high GFR populations. Validation and testing of metabolite panels is underway with the goal of developing a more precise and robust GFR estimate. [Patents pending by Drs. Levey, Inker and Coresh and Metabolon].

Funding: NIDDK Support, Pharmaceutical Company Support - Metabolon

FR-OR022

Weak Performances of Glomerular Filtration Rate Equations in Stable Lung/Liver Transplant Recipients Compared to 51Cr-EDTA Clearance

Background: Performance of the most common GFR equations (i.e. MDRD and CKD-EPI) is poorly described in transplant recipients. These populations exhibit frequent non-renal characteristics that influence serum creatinine. Exogenous marker, such as 51Cr-EDTA, allows accurate GFR measurement but it remains cumbersome. Performance of MDRD-2006 and CKD-EPI-2009 equations was compared to the 51Cr-EDTA clearance in lung or liver transplant recipients.

Methods: Retrospective monocentric study (Jan 2011-Sept 2015). GFR was measured by the intercept slope method (3 samples: 90,150 and 210 min). Bias, precision and accuracy defined the performance of GFR equations (IDMS traceable serum creatinine values). Bias was the difference between estimated and measured GFR. Precision was the standard deviation of this difference. Accuracy was rated by the percentage of estimations within 30% of the measured GFR. Risk of misclassification between chronic kidney disease categories (KDIGO 2012) was defined.

Results: 753 GFR measurements were performed for lung (n=152) and liver (n=124) transplant recipients. Mean GFR was 56±42 ml/min/1.73m², mean age was 56 years and 56% were male. Under 60 ml/min/1.73m² (n=444), bias was lower for MDRD (11±24 versus 12.5±45 ml/min/1.73m²; p=0.001). Between 60-90 ml/min/1.73m² (n=238), bias was lower for CKD-EPI (-7±12 versus -17±25 ml/min/1.73m²; p=0.001). Accuracy was similar but strikingly poor (43% MDRD and 41% CKD-EPI). The subsequent risk of misclassification was 75% with both equations. GFR overestimation was associated with an age >60 years, malnutrition and lung transplant. GFR underestimation was associated with an age >60 years, BMI >30 kg/m² and liver transplant.

Conclusions: Accuracy of MDRD and CKD-EPI equations was inadequate in this population precluding valid use in clinical routine. Clinicians should be aware of these limitations that may lead to a high risk of misclassification.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
39A
**FR-OR024**

Absence of Renal Hypertrophy Imposes Adverse Pregnancy Outcome

Schoon Park, Ho Jun Chin, Ki Young Na, Dong Ki Kim, Kwon Wook Joo, Yon Su Kim, Hajeong Lee. Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea.

**Background:** Pre-gestational chronic kidney disease was related to worse pregnancy prognosis and failed hemodynamic adaptation was suspected to be the cause. However, the relationship between midrenal renal hypertrophy (RHF), a normal hemodynamic change during gestation, and adverse pregnancy outcome remains obscure.

**Methods:** This study included pregnancy cases from two tertiary hospitals in Korea from 2001 to 2016. We used CKD-EPI eGFR (estimated glomerular filtration rate, ml/min/1.73m²) in the second trimester of each pregnancy to assess midrenal RHF of mothers. Mothers were divided into four subgroups as follows: eGFR 60–90, 90–120, 120–150, and ≥150. Mothers with delivery done in the same trimester and eGFR<60 before or during pregnancy were excluded. Adverse pregnancy outcome was the composition of prematurity birth (gestational age<37 weeks), low birth weight (fetal birth weight=2.5 kilograms) and preeclampsia.

**Results:** A total of 1,936 deliveries were included in the study. Mothers with adverse pregnancy outcome had lower midrenal eGFR than those without gestational complications, although their pre-gestational eGFR were not significantly different. When classified into subgroups, mothers with midrenal eGFR 60–90 (adjusted OR 2.31, 1.41-3.79, P=0.001), eGFR 90–120 (adjusted OR 1.34, 1.00-1.80, P=0.047), and even mothers with eGFR<150 (adjusted OR 2.31, 1.79-13.72, P=0.001) showed increased risk of adverse pregnancy outcome when compared to those with eGFR 120-150. Overall, midrenal eGFR showed non-linear, U-shaped association with the risk of adverse pregnancy outcome. The results were similar with prematurity birth and low birth weight, respectively. In contrast, the risk of preeclampsia increased as midrenal eGFR decreased, and was higher in the subgroup with midrenal eGFR<60 (OR 8.27, 2.06-33.30, P=0.003).

**Conclusions:** We demonstrated a novel, non-linear, U-shaped relationship between midrenal eGFR and the risk of adverse pregnancy outcome. The absence of adequate midrenal RHF was a significant risk factor of worse pregnancy prognosis. Therefore, routine measurement of the midrenal renal function should be considered.

**FR-OR025**

Chronic Kidney Disease (CKD) and Peripheral Nerve Function in the Health, Aging and Body Composition (HABC) Study


**Background:** Peripheral neuropathy is prevalent in older adults and is associated with loss of mobility and balance. We hypothesize that CKD, akin to aging, will be associated with nerve function deficiencies.

**Methods:** We evaluated the cross-sectional relationship of CKD (defined by eGFR<60 ml/min/1.73 m2) with sensory, motor and autonomic function(Tables 1) in 1483 participants of the HABC Study, a longitudinal cohort of community-dwelling white and black Medicare beneficiaries with 1997-98 baseline. Multivariable logistic regression (LR) model was used. Variables significant at p<0.1 in univariate analyses were adjusted.

**Results:** Mean(SD) age was 75(3) yrs, 46.1% were men, 35.7% were black and 18.5% had CKD. Participants with CKD had higher odds for having vibration detection defects and abnormal autonomic function(Tables).

**Conclusions:** CKD patients. For the first time we describe longitudinal change in gait speed in patients with CKD.

**FR-OR026**

Association of Sleep Architecture and Stage of Chronic Kidney Disease in a Large Community Based Cohort Study

Ciaran Joseph McMullan, Susan Redline, John P. Forman. 1 Renal Div, Brigham and Women’s Hospital, Boston, MA; 2Div of Sleep and Circadian Disorders, Brigham and Women’s Hospital, Boston, MA.

**Background:** Individuals with progressive chronic kidney disease (CKD) frequently report increasing insomnia and poor sleep quality. There is also evidence that individuals with habitual sleep restriction have a more rapid decline in renal function. These findings indicate interplay between renal function and sleep which is not fully understood. To better understand the specific attributes of sleep disturbances that may associate with CKD, we performed a large cross-sectional analysis of polysomnography measures with stages of CKD.

**Methods:** In cross-sectional analyses of individuals from the Sleep Heart Health Study with sleep disturbances measured using polysomnography, we evaluated the association of baseline total sleep duration (primary exposure), arousal index, hypoxia index (% time sleep with oxygen saturation < 90%), and respiratory disturbance index (secondary exposures) with baseline estimated glomerular filtration rate (eGFR,N=3597) and albuminuria-creatinine ratio (ACR, N=1567).

**Results:** Lower eGFR was associated with shorter total sleep duration, and higher indices of arousal, hypoxemia and respiratory disturbance, p-trend <0.005 for all. After adjustment for age, gender, race, smoking and diabetes only total sleep duration remained significantly associated with decreased eGFR, p-trend = 0.007. Higher indices for arousal, and hypoxia were associated with higher ACR, which remained significant after adjustment for age, gender, race, smoking, and diabetes, p<0.005. Neither total sleep duration nor respiratory disturbance index was associated with albuminuria.

**Conclusions:** Individuals with lower eGFR appear to have decreased sleep duration as measured by polysomnography, independent of age, gender or race, while individuals with frequent arousals or hypoxic episodes tend to have higher albuminuria. Prospective studies are required to more fully examine the direction of these associations and to better assess whether or not they may be causal.

**Funding:** Other NIH Support - NHLBI, Private Foundation Support

**FR-OR027**

Gait Speed Trajectory among Patients with CKD

Baback Roshanravan, Kushang V. Patel, J. Hamaske, Annea Robinson-Cohen, Jonathan Himelfarb, Ian H. De Boer, Bryan R. Kestenbaum, Kidney Research Inst, Univ of Washington, Seattle, WA; Anesthesiology and Pain Medicine, Univ of Washington, Seattle, WA; Medicine, Vanderbilt Univ, Nashville, TN.

**Background:** Gait speed is an component of frailty and strongly associated with mobility disability and mortality across populations. Understanding the trajectory of gait speed decline and its determinants is critical to preventing functional impairment among CKD patients. For the first time we describe longitudinal change in gait speed in patients with CKD.

**Methods:** Longitudinal study of 213 participants with CKD I-IV enrolled in the Seattle Kidney Study without ADL disability, lower extremity impairment, or dialysis treatment at baseline. Gait speed was measured yearly. Generalized estimating equations were used to estimate associations with annual change in gait speed. Kidney function was measured using eGFRcysc. Multiple imputation was performed for missing variables.

**Results:** Mean age of participants was 57±13 years with 81% male, and 22% black. Mean eGFRcysc was 48±18. Median follow-up was 3 years IQR[2, 4]. Mean annual change was -0.021m/s/yr or -0.21% per SD lower eGFRcysc at baseline. After adjustment, lower eGFRcysc was associated with more rapid decline in gait speed (-0.021 m/s/yr or -0.22% per SD) (p<0.05, 0.04). Those with fastest tertile decline (17.5%/yr IQR[28.3, 12]) were more likely black, and had lower eGFRcysc at baseline. After adjustment, lower eGFRcysc was associated with higher albuminuria and lower arterial blood pressure.

**Conclusions:** Among persons with CKD, lower eGFRcysc, diabetes, and low hemoglobin are associated with faster decline in gait speed, underscoring the importance of screening for mobility impairment in more severe kidney disease.

**Funding:** NIDDK Support, Private Foundation Support

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Cap Mesenchyme Cell Migration during Kidney Development Is Influenced by Attraction, Repulsion, and Adhesion to the Ureretic Tip

Nrp1 function is vital in the glomerulus. In the beginning of kidney development, the cap mesenchyme is essential for ureretic branching, how the cap mesenchyme is specifically maintained at the tips is unclear.

Methods: Using ex vivo timelapse imaging we show that cells of the cap mesenchyme are highly motile. Results: Individual cap mesenchyme cells move within and between cap domains. They also attach and detach from the ureretic tip across time. Timelapse tracks collected for >800 cells showed evidence that this movement was largely stochastic, with cell autonomous migration influenced by opposing attractive, repulsive and cell adhesion cues.

Conclusions: What was formerly considered a static cellular environment has proven to be dynamic. Continuous cell movement within the niche results in a constant change in the likely signalling environment of any given CM cell. As a result, the niche does not appear to be neatly segregated into spatial subdomains required for a linear differentiation into specific nephron types.

Funding: Government Support - Non-U.S.

The Role of Megalin in Nephrogenesis and Its Expression in the Developing Human Kidney

Megalin is localized in the proximal tubule (PT) and rescues ligands like retinol-binding protein (RBP) and vitamin D-binding protein (VDBP) from urinary loss. RBP transports vitamin A, critical for kidney development. Premature neonates are at risk for CKD. Considering the role of megalin in vitamin conservation, we hypothesized that kidney development in premature neonates is compromised by a relative megalin deficiency and lipid loss. Our aim is to determine if premature neonates excrete megalin ligands due to a developmental expression of megalin and if megalin deficiency during nephrogenesis interferes with kidney development, increasing CKD risk.

Methods: To study megalin expression during human renal development along with the uptake and urinary excretion of megalin ligands, two human cohorts were assessed (1) deceased cohort (20-40 wks gestation) to quantify tissue megalin, RBP, VDBP and maturation PT and (2) living cohort (28-32 wk group) to measure urinary RBP and VDBP. Imaging software calculated the area of protein expression. To assess the role of megalin during nephrogenesis, we used a kidney specific megalin deficient model to analyze GFR, nephron number, PT fraction and renal morphology.

Results: Human megalin expression in the PT increased over gestation from 20 to 33 wks as does the tissue level of RBP and VDBP from 20 to 29 weeks. There was a significant correlation between megalin expression and RBP and VDBP uptake. Urinary RBP and VDBP were found in higher concentrations in the 28 wk group as compared with cyst formation. Ureteric bud branching was decreased by 45%. Tubular cell thickness was decreased by 65% (p < 0.001) using a specific vivo-morpholino. This finding was associated with cyst formation (p < 0.001). This phenotype recapitulated the patients’ renal phenotype. Another gene was a candidate to account for multicystic hypoplasia because of the identification of a homozygous, predicted as damaging nonsense variant in 3 fetuses from 1 family. Its expression in culture was decreased by 65% (p < 0.001) using a specific vivo-morpholino. This finding was associated with cyst formation. Ureteric bud branching was decreased by 45%. Tubular cell thickness was increased by 28%. The phenotype matched the patients’ phenotype.

Conclusions: This novel approach is fast, inexpensive, and reliable, especially on a multicystic frameshift variant segregating with renal cystic dystrophy in one family. Its expression in culture was decreased by 65% (p < 0.001) using a specific vivo-morpholino. This finding was associated with cyst formation. Ureteric bud branching was decreased by 45%. Tubular cell thickness was increased by 28%. The phenotype matched the patients’ phenotype.

Funding: NIDDK Support

A Novel Strategy to Identify the Role of Whole-Exome Sequencing Candidate Genes in Renal Hypo-Dysplasia

Methods: Candidate genes obtained by WES were sorted in silico (functional and biological significance). The expression of each candidate gene was knocked down in murine kidney cultures, using a specific vivo-morpholino. Kidneys were analyzed after culture using a multiphoton fluorescence microscope. Candidate genes whose knockdown in culture recapitulated the phenotype observed in the families were defined as confirmed candidates.

Results: Six WES candidate genes were tested, accounting for renal hypodysplasia in 7 unrelated families. One candidate gene was identified by the presence of a heterozygous frameshift variant segregating with renal cystic dystrophy in one family. Its expression in culture was decreased by 65% (p < 0.001) using a specific vivo-morpholino. This finding was associated with cyst formation (p < 0.001). This phenotype recapitulated the patients’ renal phenotype. Another gene was a candidate to account for multicystic hypoplasia because of the identification of a homozygous, predicted as damaging nonsense variant in 3 fetuses from 1 family. Its expression in culture was decreased by 65%. This was associated with cyst formation. Ureteric bud branching was decreased by 45%. Tubular cell thickness was increased by 28%. The phenotype matched the patients’ phenotype.

Conclusions: This novel approach is fast, inexpensive, and reliable, especially on a multicystic frameshift variant segregating with renal cystic dystrophy in one family. Its expression in culture was decreased by 65% (p < 0.001) using a specific vivo-morpholino. This finding was associated with cyst formation. Ureteric bud branching was decreased by 45%. Tubular cell thickness was increased by 28%. The phenotype matched the patients’ phenotype.

Funding: NIDDK Support

Regulation of Kidney Field Size by Transcriptional Regulation of microRNAs

Regulation of kidney field size by microRNAs was studied. Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

FR-OR028

FR-OR029

FR-OR030

FR-OR031

FR-OR032

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
potential interaction in the specification of the kidney field. To gain further insight of the mechanisms for Frz1 in the kidney field, we identified miRNAs regulated by the proteins using miRNA deep sequencing, & perturbed specification of the kidney field by expressing mimics for the identified miRNAs.

Conclusions: These results support a role of a Lhx1/Fry complex in specification of the kidney field by regulation of miRNAs expression.

Funding: NIDDK Support, Other NIH Support - 5T32DK011926-13

FR-OR035
Epigenomic Profiles Identify Age Associated Chromatin State Transitions in Nephrin Progenitors
Samir S. El-Dahr,1 Yuwen Li,1 Melody C. Baddoo,1 Jiao Liu,1 Zubaida R. Safiudeen,2 Mazhar Adli.2 Pediatrics, Tulane Univ, New Orleans, LA; 1Biochemistry, Univ of Virginia, Charlottesville, VA.

Background: Cited1+/Sicx2+ cells are lineage-restricted multipotent nephrin progenitor cells (NPC). Unlike young NPC, which are actively engaged in self-renewal and are resistant to inductive signals, old NPC differentiate at a faster rate limiting their life span. We hypothesized that “aging” alters the epigenomic landscape of NPC, which favors differentiation over renewal.

Methods: NPC were isolated using a magnetic activated cell sorting protocol from E13 and E19 CD1 mouse kidneys and expanded in NPEM growth factor medium for 4-6 days to generate pure Cited1+/Sicx2+/NPC. To identify genome-wide open chromatin regions (OCR - nucleosome-free active promoters and enhancers), NPC were subjected in triplicates to ATAC-seq (Assay for Transposable-Accessible Chromatin with high throughput sequencing). Peak calling, annotation, transcription factor binding motifs and overlapping between E13 and E19 samples were performed using HOMER and i-CifTarget. OCR were integrated with publicly available RNA-seq and ChIP-seq databases.

Results: We identified 956 and 1438 annotated genes carrying at least one OCR in E13 vs. E19 NPC, respectively, of which 5-7% are differentially expressed. OCR clustered around the transcription start site and at distant 5' or 3' or intragenic sites. Progenitor genes (e.g., c-Myc, Osr1, Sicx2, Meox1, Eyal, cell cycle and epigenetic regulators) featured age-related attenuation of OCR peak scores and density. Transcriptionally silent β-catenin target genes (e.g., Wnt4, Letf1, Axin2, Jag1, Pax8) consistently harbored OCR in curated enhancers as well as in novel candidate enhancers in old but not young NPC. AP-1, Sicx2, Sall1/2, WT1, Pa2x, Smads, c-Myc, p53, and E2F were amongst the most commonly identified transcription factors in OCR footprints.

Conclusions: Young and old Cited1+NPC exhibit distinct epigenomic landscapes. OCR footprinting identified candidate regulatory networks of transcriptional regulators in NPC. Chromatin of old NPC displays biochemical signals of epigenetic poising which may explain, at least partly, the enhanced propensity of old NPC to differentiation vs. self-renewal.

Funding: NIDDK Support

FR-OR036
RET Signaling Is Necessary for Survival of Progenitors in the Anterior Intermediate Mesoderm and Wolffian Duct - Cloaca Joining through a Novel Trans-Cloacal Cascade of Apoptosis before Ureteric Budding
Masato Hoshi1 Sanjay Jain,1,2 Dept. of Medicine (Renal), Washington Univ School of Medicine, St. Louis, MO; 2Dept of Pathology and Immunology, Washington Univ School of Medicine, St. Louis, MO.

Background: The mammalian collecting system is derived from the ureteric bud (UB) at the distal end of the Wolffian duct (WD). The UB progenitors originate in the anterior intermediate mesoderm (IM) at E8.5 in mouse. The specific mechanisms of how these IM progenitors generate WD and UB or join the cloaca before UB budding is not clear. These processes when disrupted are major causes of congenital anomalies of kidney and urinary tract (CAKUT). Global RET receptor tyrosine kinase signaling is required for UB induction and for WD to reach the cloaca. We recently showed that signaling through RET-Y1015 docking tyrosine inhibits ectopic UBs from WD and regulates CND apoptosis for ureter maturation after UB budding.

Methods: Here we used genetically encoded reporters, lineage tracing and mice deficient in RET-Y1062 or RET-Y1015 docking tyrosine activity to better understand the early events priming the formation of the metanephric kidney and its union with the cloaca beginning from the IM progenitors and through WD morphogenesis during the pronephros and the mesonephros stages of mouse.

Results: We discovered that RET-Y1062 signaling controls IM cell number, the survival of WD leader cells and their migration to reach cloaca. We discovered a novel cascade of spatio-temporally controlled trans-cloacal apoptosis before ureteric budding and branching morphogenesis during normal development. The cloacal apoptosis at the site of presumptive WD insertion did not occur in WDs that do not reach the cloaca and it was dependent on RET-Y1015 signaling in WD tip cells.

Conclusions: These novel findings decipher how progenitors in IM lay this plumbing under the cloaca and convey novel insights in the pathogenesis of CAKUT and rebuilding a kidney ex vivo.

Funding: NIDDK Support

FR-OR037
P13K Pathway Potentiates Nephrin Progenitor Cell (NPC) Renewal by Promoting Glycolysis
Zubaida R. Safiudeen,1 Jiao Liu,1 Francesca Edgington-Giordano, Pediatrics, Tulane Univ School of Medicine, New Orleans, LA.

Background: Energy metabolism pathways have emerged as critical regulators of stem/progenitor cell fate. We showed an age-dependent decrease in glycolysis in young (E13.5, predominantly self-renewing) vs old (P0, poised to differentiate) NPC. Glycolysis inhibition in organ culture promotes NPC differentiation. PI3K and mammalian target of PI3K signaling pathways maintain NPC in a Cited1+/Sicx2+ self-renewing state. PI3K inhibition or Bmp/ Smad activation promotes NPC differentiation. As the P13K pathway is a positive regulator of glycolysis, we hypothesized that PI3K and Bmp/ MAPK pathways converge on glycolysis to maintain NPC in a self-renewing state. To test our hypothesis we measured the glycolytic flux in isolated NPC after PI3K or Bmp/Smad pathway modulation.

Funding: NIDDK Support
Methods: E13.5 NPC were isolated by MACS, cultured in expansion (NPEM) or differentiation (DMEM) media and treated with 10µM PI3K inhibitor LY294002, 100µM Akt inhibitor MK2206, Wnt activator CHIR 2µm or NPEM minus Smad inhibitor LDN to activate the Hrp3/Smad pathway. Glycogen synthesis enzyme PFKFB3 inhibitor UCN 20µm was used as a positive control.

Results: Compared to NPC/NPEM, NPC/DMEM showed 3.5 fold ECAR decrease; 10- and 12-fold decreased Cited1 and Six2 expression and 6-fold increased Wnt4 expression.

In conclusion: inhibition of glycogen synthesis enzyme PFKFB3 inhibitor UCN 20µm was used as a positive control.

Conclusions: Glycolysis flux is a pivotal determinant of NPC fate. A high glycogen synthesis flux is an essential intermediary of PI3K-mediated NPC self-renewal. Glycogen inhibition promotes nephropenia via established β-catenin dependent pathways. Reduced glycolysis in itself is insufficient to activate NPC differentiation in the absence of β-catenin.

Funding: NIDDK Support

FR-OR038

Molecular Predictors of Proteinuria and Glomerular Filtration Rate in Patients with Focal Segmental Glomerulosclerosis Undergoing a Kidney Transplant


Katz Family Drug Discovery Center and Div of Nephrology and Hypertension, Univ of Miami, Miami, FL; Dept of Internal Medicine - Nephrology, Univ of Michigan, Ann Arbor, MI.

Background: We recently demonstrated that sphingomyelinase phosphodiesterase acid like 3b (SMPDL3b) is a key modulator of podocyte architecture and function. Decreased SMPDL3b expression in post-reperfusion kidney biopsies predicted post-transplant proteinuria and occurred in association with foot process effacement in retrospective studies.

Methods: Thirty-nine patients with biopsy proven FSGS undergoing a kidney transplant were enrolled in a prospective clinical trial. Pre (PRE) and post-reperfusion (POST) kidney biopsies were collected. Histological analysis, immunohistochemistry (IHC) for SMPDL3b, microarray analyses of isolated glomeruli from PRE and POST biopsies, analyses by electron microscopy (EM) to assess foot process effacement (FPE) and correlation analyses with protein/creatinine ratios (PCR) and estimated Glomerular Filtration rate (eGFR) at 12 months (eGFR-12) after kidney transplantation were performed.

Results: We found a positive correlation between SMPDL3b positive glomerular cells and eGFR-12 (p<0.05) in POST biopsies. The degree of FPE positively correlated with PCR and with worsened eGFR-12 (p<0.05). Inflammation and lipid-related pathways were found to be significantly regulated in POST when compared to PRE biopsies. Transcripts levels of several genes of these pathways significantly correlated with PCR or change in eGFR. In addition, the transcript levels of a subset of genes was found to correlate with the degree of FPE.

Conclusions: Decreases in SMPDL3b positive cells in POST biopsies is significantly associated with post-transplant loss of GFR in FSGS. FPE in POST biopsies is significantly associated with post transplant proteinuria and loss of renal function. Upregulation of certain genes associated with inflammation or lipid metabolism may predict the development of proteinuria or change in eGFR after transplantation.

FR-OR039

Molecular Significance of Peritubular Capillaritis in Early Transplant Kidney Biopsies of Donor-Specific Antibody Negative Patients

Maria Ajayu, Yi Bao, Enver Akalin. Montefiore Transplant Center, Albert-Einstein College of Medicine.

Background: Peritubular capillaritis (PTC) is a part of microvascular inflammation seen in antibody-mediated rejection (ABMR). However, it is observed in early transplant kidney biopsies with acute tubular necrosis (ATN) due to ischemia/reperfusion injury. We aimed to investigate intragraft gene expression of transplant kidney biopsies with PTC and ATN in transplant recipient without donor-specific antibody (DSA).

Methods: A total of 19 early transplant kidney biopsies with ATN for gene expression profiling comparing to 12 normal transplant kidney biopsies (Group 1). Biopsies with a diagnosis of acute or chronic rejection, recurrent or de novo glomerular disease, moderate to severe fibrosis or polyoma nephropathy were excluded. The gene expression profiles were analyzed by Affymetrix Mouse 1.0 ST expression arrays.

Results: Among the 19 biopsies with ATN, 7 patients (Group 2) had isolated PTC and 12 patients (Group 3) had no PTC. Both groups had similar demographics characteristics in terms of age, race, and sex, type of transplant, previous history of transplantation or acute rejection, donor characteristics, panel reactive antibody levels and immunosuppressive treatment. There was a statistically significant difference in gene expression profiles between the 3 groups including injury and response (IRIT), interferon-gamma and rejection associated transcripts (GRIT), cytoketic T cell (CAT), regulatory T cell (TREG), B-cell (BAT) natural killer cell transcripts (NKAT) Constitutive Macrophage (CMAT), donor-specific antibody (DSAT) and endothelial cell associated transcripts.

Pathogenesis Based Transcripts

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<th>G2 vs G3</th>
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Conclusions: Isolated peritubular capillaritis could be seen in early transplant kidney biopsies with ATN and intragraft gene expression profiles do not reflect immune activity.

FR-OR040

Molecular Evidence of Chronic Cellular Rejection in C4d and Microvascular Inflammation Negative Transplant Glomerulopathy

Michelle Labeckty, Yi Bao, Enver Akalin. Montefiore Center for Transplantation, Albert Einstein College of Medicine, Bronx, NY.

Background: Transplant glomerulopathy (TGP) is frequently found in the setting of chronic antibody mediated rejection along with microvascular inflammation (MVI) (peritubular capillaritis/glomerulitis score > 1) and/or post-c4d staining. We assessed the molecular profiles of TGP in the absence of microvascular inflammation and C4d staining as compared to TGP with positive MVI and/or C4d.

Methods: 42 cause renal allograft biopsies were studied using Affymetrix HuGene 1.0 ST expression arrays; 12 with normal biopsy findings (G1), 17 with a diagnosis of TGP, C4d positive and/or a MVI score >1 (G2), and 13 with a diagnosis of TGP and C4d negative and MVI score <=1 (G3).

Results: There was no difference in sex, race, or type of transplant between the 3 groups. More patients had DSA in TGP with MVI or C4d (G2, 82.4%), as compared with normal (G1, 8.3%) p<0.001 and TGP without MVI or C4d (G3), 38.4%, p=0.02. When comparing TGP with MVI and/or C4d (G2) to TGP without MVI or C4d (G3) and normal (G1), pathogenesis based transcripts revealed increased expression of gamma interferon and rejection (GRIT) and DSA associated transcripts (DSAT) consistent with the response seen in antibody-mediated rejection. However, when TGP without MVI or C4d (G3) compared to normal (G1), increased expression of Cytotoxic T cell (CAT), T-regulatory cell (TREG), and B cell associated transcripts (BAT) were observed but not GRIT or DSAT.

There was no difference in expression of natural killer cell and endothelial cell associated transcripts between the 3 groups.

Conclusions: Gene expression profiles of TGP in the absence of microvascular inflammation and C4d lack molecular features of antibody-mediated rejection but suggest chronic cellular rejection.

FR-OR041

Angiotensin II Type 1 Receptor Antibodies Are Associated with Elevated TNF-α, IL-1β, IL-8, and Poor Allograft Outcomes in Pediatric Renal Transplantation

Meghan Pearl, 1 Jonathan Grotts, 1 Maura Rossetti, 1 Qinghong Jennifer Zhang, 1 Miguel Fernando Palma Diaz, 1 Patricia L. Weng, 1 Elaine F. Reed, 1 Eileen W. Tsai. 1 1 Univ of California Los Angeles, Los Angeles, CA; 2Dept of Pediatrics, Duke Univ, Durham, NC.

Background: We recently identified that angiotensin II type 1 receptor antibody (AT-R-Ab) was associated with vascular injury and allograft failure in pediatric renal transplant recipients. TNF-α, IL-1β, IL-8, IFN-γ, IL-17, and IL-6 have been associated with vascular injury and AT-R activity, but their role in renal transplant patients with AT-R-Ab is unknown. We aimed to determine the relationship between cytokine profiles and AT-R-Ab on renal function and allograft survival in pediatric kidney transplant recipients.

Methods: 65 pediatric kidney transplant recipients were monitored for 2 years post-transplant from August 2005 to November 2014. AT-R-Ab (ELISA test, > 17 units/ml positive) and TNF-α, IL-1β, IL-8, IFN-γ, IL-17, IL-6 have been associated with vascular inflammation and AT-R activity, but their role in renal transplant patients with AT-R-Ab is unknown. We aimed to determine the relationship between cytokine profiles and AT-R-Ab on renal function and allograft survival in pediatric kidney transplant recipients.

Results: There was no difference in sex, race, or type of transplant between the 3 groups including injury and response (IRIT), interferon-gamma and rejection associated transcripts (GRIT), cytoketic T cell (CAT), regulatory T cell (TREG), B-cell (BAT) natural killer cell transcripts (NKAT) Constitutive Macrophage (CMAT), donor-specific antibody (DSAT) and endothelial cell associated transcripts.

Pathogenesis Based Transcripts

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<th>G2 VS G3</th>
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Conclusions: Angiotensin II Type 1 Receptor Antibodies Are Associated with Elevated TNF-α, IL-1β, IL-8, and Poor Allograft Outcomes in Pediatric Renal Transplantation

Michael Labeckty, Yi Bao, Enver Akalin. Montefiore Center for Transplantation, Albert Einstein College of Medicine, Bronx, NY.
patients positive for AT1R-Ab, even in patients without rejection (p=0.049, Figure 1b). Furthermore, AT1R-Ab positive patients with TNF-α were more prone to allograft loss (p=0.058, Figure 1c).

Conclusions: In pediatric renal transplant patients, AT1R-Ab is associated with poor allograft function, survival and higher IL-8, IL-1β, and TNF-α levels. AT1R-Ab monitoring used in conjunction with these cytokines may identify those at risk for poor allograft outcomes.

**Cytokines in AT1R-Ab Negative vs. Positive Patients**

**Figure 1a:** TNF-α, IL-1β and IL-8 in patients who were positive for AT1R-Ab in the first 2 years post-transplant compared to those who were negative (n=65).

**Change in eGFR from Baseline to Last Follow-Up**

**Figure 1b:** Median percent change in estimated glomerular filtration rate (eGFR) between baseline and last follow up in patients with and without AT1R-Ab with and without rejection.

**Cytokines in AT1R-Ab Positive Patients with and without Allograft Loss**

**Figure 1c:** TNF-α, IL-1β and IL-8 in AT1R-Ab positive patients (eMR) with and without graft loss.

**FR-OR042**

**Polyclonal Treg Adoptive Therapy for Control of Subclinical Kidney Transplant Inflammation: TASK Pilot Trial**

**Sindhu Chandran, Qizhi Tang, Minnie Sarwal, Zoltan G. Laszik, Amy Putnam, Tara Sigdel, Erica Christen Tavares, Jeffrey A. Bluestone, Flavio Vincenti. UCSF, CA.**

**Background:** Treg therapy can reverse established inflammation in animal models. We conducted a pilot safety & feasibility trial of Treg therapy for subclinical kidney transplant inflammation.

**Methods:** Peripheral blood CD4+CD25+CD127lo/- Tregs were isolated (FACS) & expanded *ex vivo* (anti-CD3/anti-CD28 stimulations/IL-2) in a deuterated glucose-containing medium. 320x10^6 Tregs were infused into kidney transplant recipients with subclinical inflammation on 6-month protocol biopsy. %Deuterium enrichment by GC-MS allowed estimation of levels of infused (labeled) Tregs in circulation. Inflammation was assessed on follow-up biopsies using Banff scoring and leukocyte common antigen positive (LCA+) cell density & in urine using common rejection module (uCRM), a biomarker of rejection.

**Results:** 3 patients on tac/MMF/prednisone received Treg infusions. Tregs expanded >100-fold (comparable to non-immunosuppressed patients) & met release criteria for infusion. One patient had transient lymphopenia (day 4-21) post-infusion. No infusion reactions or infections were seen & graft function remained stable. Infused Tregs peaked within week 1, up to 7.5% of all circulating Tregs. Decay of infused Tregs was similar to that seen in non-immunosuppressed patients (Fig 1A). Graft inflammation improved in two & uCRM scores improved in all cases (Table 1 & Fig 1B).

**Conclusions:** It is feasible to isolate & expand Tregs from transplanted patients. Infused Tregs were well tolerated & had pharmacokinetics similar to those in non-immunosuppressed patients. CTOT-21 will test the efficacy of Tregs for control of graft inflammation.

**Funding:** Private Foundation Support

**FR-OR043**

**A Molecular Approach to Chronic Active T Cell Mediated Rejection**

**Layla Kamal, Michelle Lubetzky, Maria Ajaimy, Yi Bao, Graciela De Boccado, Enver Akalin. Montefiore Einstein Transplant Center, Bronx, NY.**

**Background:** Banff classification only recognizes chronic allograft arteriopathy as chronic active T cell mediated rejection. We hypothesized that T cell-mediated immune injury plays role in two conditions; donor-specific antibody (DSA) negative transplant glomerulopathy (TGP) and interstitial fibrosis and tubular atrophy (IFTA) with inflammation (i>0). We investigated gene expression profiles of those biopsies compared to biopsies with antibody-mediated rejection (ABMR) and to biopsies with non-specific IFTA and no inflammation (i=0).

**Methods:** A total of 62 for-cause renal allograft biopsies were studied using Affymetrix HuGene 1.0 ST expression arrays in the following groups; G1: normal transplant kidney biopsy, n=12, G2: ABMR (including TGP with DSA), n=24, G3: TGP without DSA or IFTA with i score > 0 and G4: IFTA without inflammation (i=0).

**Results:** There was no difference in sex, race, or type of transplant between the 4 groups. G2 biopsies showed significantly increased expression of gamma-interferon and rejection associated (GRIT), Cytotoxic T cell (CAT), regulatory T cell (TREG), constitutive macrophage (CMAT), and DSA associated gene transcripts (DSAST) when compared to G1 biopsies. While there were no statistically significant differences in expression of any pathogenesis based transcripts studied in G4 compared to G1 biopsies, G3 biopsies showed increased intragraft expression of CAT and TREG, suggesting T cell mediated immune mechanisms in its pathogenesis.
Conclusions: DSA-negative TGP and IFTA with inflammation biopsies have a unique molecular signature with significant expression of cytotoxic and regulatory T cells. This suggests that DSA-negative TGP and IFTA with inflammation could be classified as chronic T cell mediated rejection.

FR-OR044
Identification of Urinary mRNA Expression for Diagnosing Acute Rejection by Meta-Analysis of Gene Expression in Kidney Transplantation 
Sang-Ho Lee,1 Yu Ho Lee,1 Haena Moon,1 Yang Guan Kim,1 Kyung-Hwan Jeong,1 Tae Won Lee,1 Chun-Gyoo Ihm,2 So-Young Lee,2 Dong Ho Yang,2 1Div of Nephrology, Dept of Internal Medicine, Kyung Hee Univ, Seoul, Korea; 2Div of Nephrology, Dept of Internal Medicine, CHA Bundang Medical Center, Seongnam, Korea.

Background: microarray data is a powerful source for identifying potential targets to diagnose acute rejection (AR) in kidney transplanted patients (KTPs). We performed a meta-analysis of gene expression profiles of stable graft function (STA) and AR from biopsy tissues in kidney transplantation and investigated expressions of candidate genes selected from meta-analysis in urine of KTPs.

Methods: The microarray data were obtained from the public repositories. Meta-analysis were conducted by 664 STA and 272 AR patients, with a total of 954 samples. 14 candidate genes were selected after meta-analysis as biomarker of AR in urinary cells of KTPs. 120 urine samples (23 stable, 34 acute cellular rejection (ACR), and 17 acute antibody-mediated rejection (AMR), 25 long-term graft survival (LGS), 17 chronic antibody-mediated rejection (CAMR), and 6 tolerance (Tol)) were collected after kidney transplantation. The expression levels of transcripts were determined in urinary cells using real-time PCR.

Results: 14 candidate genes were selected by meta-analysis of gene expression for AR diagnosis, including CXCL9, PSM9B, INPS5D, LCK, ISG, RUNX3, CD3e, IFN-10, TIM-3, Fosx3, IDO1, PTPRC and C1QB. We determined expression levels of mRNA isolated from urinary cells with 14 candidates. 3 (Tim-3, CXCL9, and LCK mRNA) among them were significantly elevated in patients with acute cellular rejection, while Tim-3 was significantly higher expressed and ISG20 and CX-40 were significantly decreased in patients with acute antibody-mediated rejection. In addition, the real change of CXCL9 mRNA level in biopsy tissue was confirmed by in situ hybridization. In ACR prediction model composed of 3 genes clearly discriminated the patients with acute cellular rejection from STA.

Conclusions: We developed ACR and AMR specific urine mRNA panel composed of 3 genes. We suggested that urinary mRNA is promising as a sensitive, non-invasive means to monitor kidney allografts.

Funding: Government Support - Non-U.S.

FR-OR045
The Association between Rapid BK Viremia Clearance and Graft Rejection in Kidney and Pancreas Transplant Recipients 
Massaki Yamada,1 Nissreen Elfadawy,2 Richard A. Fatricia,1 1Nephrology, Cleveland Clinic, Cleveland, OH; 2Internal Medicine, Univ Hospital, Cleveland, OH. 2Urology, Cleveland Clinic, Cleveland, OH.

Background: BK polyoma virus reactivation is a serious complication after transplantation with no definitive treatment except reduction of immunosuppression. Patients are at risk of graft rejection after BK viremia (BKV) and reduction of immunosuppression. There is no published data on the association between BKV clearance rate and incidence of graft rejection. The objective of this study is to assess the relation between the rate of BKV clearance and graft rejection after kidney transplantation.

Methods: We screened 595 kidney transplants (2007-2011) for BKV by PCR in blood. One hundred and sixty two out of total 595 patients (27.2 %) developed BKV any time after BKV transplantation, perhaps due to reconstitution of native immunity.

Conclusions: Rapid BKV clearance is associated with higher rates of graft rejection after BKV, perhaps due to reconstitution of native immunity.

FR-OR046
20-Year Trends in Clinical Outcomes of Kidney Transplantation 
William Irish,1 Akinolu O. Ojo,2 Neetu Agashivala,1 Larry M. Gache,1 1CTI Clinical Trial and Consulting Services, Inc.; 2Univ of Arizona Health Sciences; 3Novartis Pharmaceuticals Corporation.

Background: The short term outcomes of KTxs are excellent, but the long term outcomes have improved minimally despite advances in immunosuppression (IS). The purpose of this study was to examine historical trends using data from the United States Renal Data System (USRDS).


Results: 134,679 patients (77% 23% deceased [DD] living donor [LD]) were eligible: 21%, 27%, 16% and 16% in ERAs 1, 2, 3, 4, and 5. Across ERAs, donors were older, prevalence of hypertension and terminal Scr>1.5 mg/dl increased, donation after cardiac death and extended criteria donor organs increased. Across ERAs, recipients were older, more often had diabetes, had higher pre-transplant Charlson Comorbidity Index scores, had more 6-antigen mismatches and were more often African American. Maintenance IS shifted from cyclosporine- to tacrolimus-based regimens with decreased use of corticosteroids. Graft survival trends are shown. Similar trends were observed for DD and LD. Death-censored graft loss at 3-years post-KTx was reduced by –60% in ERA 5 compared to ERA 1 for DD and LD.

Conclusions: The net benefit of KTX has improved significantly across transplant eras despite worsening donor/recipient risk profiles.

Funding: Pharmaceutical Company Support - Novartis Pharmaceuticals Corporation

FR-OR047
Does Cognitive Function Predict Waitlisting for Kidney Transplant? 
Salem M. Al Matrood,1 V. Shane Pankratz, Yue-Hann Ng, Eduardo A. Alas, Christos Argyropoulos, Saeed Kamran Shaffi, Mark L. Unruh, Antonia Harford. 1Dept of Internal Medicine, Div of Nephrology, Univ of New Mexico Health Sciences Center, Albuquerque, NM.

Background: Cognitive dysfunction is common in patients with advanced kidney disease. Being cognitively intact is vital for post-transplant care and medical compliance. Few studies have examined cognitive function in pre-kidney transplant patients. We hypothesized that lower scores on the Montreal Cognitive Assessment (MoCA) would be associated with a decreased rate of transplant (TXP) listing.

Methods: MoCA was performed as a part of routine pre-kidney transplant evaluation and at annual follow-up. Demographic, comorbidity, and clinical parameters were collected on all patients. Different MoCA versions were utilized as appropriate. Scoring of the MoCA was performed as recommended by the test developers. Cox proportional hazards models were used to assess associations between baseline MoCA and the subsequent occurrence of TXP listing. Linear mixed effects models were used to test for longitudinal changes in MoCA.

Results: 329 subjects had at least 1 MoCA and 183 had 2 during a 28 month period. The baseline mean composite MoCA score was 24.3±4.2. Hispanics, Native Americans, advanced age, and ERSD secondary to diabetes were associated with lower MoCA scores. Conversely, higher education level, peritoneal dialysis, and non-Hispanic White ethnicity were associated with higher MoCA scores. In patients who underwent 2 MoCA tests (n=183), the mean score increased by 1.2 from the first to the second test (95% CI: 0.8 – 1.7, p<0.001). Among patients not already waitlisted for TXP, those with baseline composite MoCA scores below 26 had a hazard ratio for subsequent listing of 0.44 (95% CI: 0.24-0.82, p<0.01), compared to those with higher scores.

Conclusions: This study demonstrates that patients evaluated for kidney transplant suffer from mild cognitive function impairment compared to the general population. Lower MoCA scores were associated with decreased waitlisting for renal transplant. MoCA scores are a reasonable stable over time among patients evaluated for kidney transplant. Further studies are warranted to define cognitive changes in patients waiting for renal transplant.

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

45A
The IncRNA Tug1 Interacts Directly with PGC-1α to Regulate Mitochondrial Biogenesis in Diabetic Nephropathy

Jianyin Long,1 Shawn S. Badal,1 Zengchun Ye,2 Yin Wang,1 Farhad R. Danesh.1

Section of Nephrology, The Univ of Texas, MD Anderson Cancer Center, Houston, TX; 2Nephrology, 3rd Affiliated Hospital of Sun Yat-Sen Univ, Guangzhou, Guandong, China.

Background: The regulatory roles of long noncoding RNAs (lncRNAs) on transcriptional coactivators are still largely unknown. Here we show that the peroxisome proliferator-activated receptor γ (PPARγ) coactivator α (PGC-1α) is functionally regulated by a lncRNA, and describe a previously unknown regulatory role for this lncRNA in the transcriptional coactivators are still largely unknown. Here we show that the peroxisome proliferator-activated receptor γ (PPARγ) coactivator α (PGC-1α) is functionally regulated by a lncRNA, and describe a previously unknown regulatory role for this lncRNA in the regulation of podocyte mitochondrial function.

Methods: Using experimental models of diabetic nephropathy (DN), we performed unbiased RNA-Seq profiling of kidney glomeruli, and identified lncRNA Tug1 (Taurine upregulated gene 1) as a differentially expressed lncRNA in the diabetic milieu. To test the contribution of Tug1 to the progression of DN, we generated podocyte-specific transgenic mice to overexpress Tug1 within the diabetic milieu of Type 2 diabetic (db/db) mice. Mechanistically, we performed genome wide transcriptome studies, lncRNA genome wide DNA binding profiling (ChRP-Seq) and biochemical studies to investigate novel target pathways under the control of Tug1 RNA.

Results: Podocyte-specific overexpression of Tug1 in diabetic (db/db) mice improved albuminuria levels, reduced mesangial matrix expansion, improved podocyte foot process effacement and prevented podocyte loss as quantified by WTI positive podocytes. Unexpectedly, we found that podocyte-specific overexpression of Tug1 in diabetic mice rescued expression of PGC-1α mRNA, improved mitochondrial copy number levels and pathways under the control of Tug1 RNA.

Conclusions: We propose that a novel, physical interaction between PGC-1α protein and Tug1 RNA contributes to modulating mitochondrial bioenergetics in podocytes via regulation of PGC-1α gene expression.

Funding: NIDDK Support

FR-OR049


Background: Diabetes mellitus continues to be the leading cause of kidney disease.

Our purpose is to determine the role of the nuclear receptor farnesoid X receptor (FXR) and G protein coupled receptor TGR5 in prevention and treatment of diabetic kidney disease.

Methods: We have treated two distinct models of rodent diabetic nephropathy i) DBA/2J mice fed a western diet and made diabetic with streptozotocin and ii) db/db mice with a) FXR agonist INT-747 at 30 mg/kg/day, or b) TGR5 agonist INT-777 at 30 mg/kg/day, or c) FXR-TGR5 dual agonist INT-767 at 30 mg/kg/day, from 3 months of age until 6 months of age.

Results: All 3 agonists had no effects on the hyperglycemia but had very marked and significant effects to decrease urine albumin excretion, glomerular area and mesangial expansion, inflammatory cell infiltrates, glomerulosclerosis and tubulointerstitial fibrosis (determined by Mason’s trichrome and Picrosirius Red stains, immunostaining for extracellular matrix proteins, label free imaging with Two Photon Excitation and Second Harmonic Generation Microscopy, and expression of pro-fibrotic growth factors).

Further mechanistic studies indicated that these agonists also stimulate the mitochondrial transcription factors Nrf1 and Tfm, as well as AMPK, PGC-1α, Sirtuin 1, Sirtuin 3 and the nuclear receptor estrogen related receptor alpha (ERRα), major regulators of mitochondrial biogenesis and function. In fact there were increases in long-chain 3-hydroxy acyl-coenzyme A dehydrogenase (TGR5-LI CAD) and carnitine palmitoyltransferase 1A (CPT1A) which are mediators of mitochondrial fatty acid β oxidation, resulting in decreased lipid accumulation in the kidney (as determined by lipid stains and lipid composition analysis), and mitochondrial superoxide dismutase 2 (SOD2) which is an antioxidant resulting in decreased oxidative stress in the kidney (as determined by decreases in oxidized proteins and lipid peroxidation).

Conclusions: FXR and TGR5 agonists have renal protective effects independent of their effects on systemic glucose metabolism. They have a great potential for prevention and treatment of diabetic kidney disease by enhancing mitochondrial biogenesis and mitochondrial function.

Funding: NIDDK Support, VA Support, Pharmaceutical Company Support - Intercept Pharmaceuticals

FR-OR050

Enhanced Real-Time In Vivo Mitochondrial Redox in Diabetic Nephropathy Daniel L. Galvan,1 Shawn S. Badal,1 Paul T. Schumacker,2 Farhad R. Danesh.1

1Section of Nephrology, The Univ of Texas MD Anderson Cancer Center; Houston, TX; 2Dept of Pediatrics, Northwestern Univ, Chicago, IL.

Background: The role of mitochondrial reactive oxygen species (mROS) in the pathogenesis of diabetic nephropathy (DN) remains controversial. A major gap in further addressing the role of mROS in DN is the real-time measurement of ROS intrinsic to the mitochondrion.

Methods: To monitor mROS in vivo, we utilized a recently described mouse model in which the roGFP reporter sensor was specifically expressed in the mitochondrial matrix (nts). Transgenic CMV-nts-roGFP mice were intercrossed with mice harboring the Lepr db/fl−/− mutation to generate a type 2 diabetic mouse model with a genetic redox biosensor (db/db;Lepr db/fl−/−;roGFP), hereafter referred to as db/db;roGFP. We employed excitation of the roGFP biosensor at the prescribed laser wavelengths for the oxidized (720nm) and reduced (860nm) forms. Emission spectra were collected and ratios of the oxidized to reduced signals were measured.

Results: Using two-photon imaging, mitochondrial redox state was assessed in the kidneys of two different experimental models of diabetes. In 16-week old diabetic (db/db;roGFP) and control (db/db;ctrl) mice in vivo. Live animal imaging of these mice revealed increased mROS in kidneys of diabetic mice (~5-fold ratiometric increase). Pre-treatment with mitoTEMPO (10mg/kg for 3days) restored mROS to normal levels in diabetic podocytes. Podocytes isolated from diabetic mice reveal similar activity 1 activity in vitro, indicating that mROS might be generated by problems with electron transport at its entry point. Ectopic expression of yeast NADH-dehydrogenase (Ndi1), a mammalian complex I homolog, successfully prevented high-glucose induced increases in mROS.

Conclusions: We provide evidence that diabetic animals have increased levels of ROS within the mitochondrial matrix of the kidney in vivo. These increases in mROS could be ameliorated by quenching of the mROS, as well as by bypassing electron transport at complex 1.

Funding: NIDDK Support

FR-OR051

Pro-Oxidant Enzyme Nox5 Accelerates Renal Damage in Experimental Diabetes Jay Chandra Jha,1 Claudine Banal,1 Stephen P. Gray,1 Harald H. Schmidt,2 Mark E. Cooper,1 Rhian Touyz,2 Chris R. Kennedy,2 Hugh D. Dungan,1 Jerome C. Cooper,1,2 Diabetes Complications, Baker IDI Heart and Diabetes Inst, Melbourne, Victoria, Australia; 2Dept of Pharmacology, Maastricht Univ, Maastricht, Netherlands; 1Inst of Cardiovascular and Medical Sciences, Univ of Glasgow, Glasgow, United Kingdom; 2Dept of Medicine, Ottawa Hospital Research Inst, Ottawa, Canada.

Background: Reactive oxygen species (ROS) play crucial role in diabetic nephropathy (DN). The more recently discovered pro-oxidant enzyme, Nox5 could play a role in DN. Nox5 is present in humans but not in rodents. Thus, there is a paucity of information about the role of Nox5 in animal models of DN. We examined the effect of Nox5 in a model of human inducible Nox5 transgenic mice expressing Nox5 selectively in vascular smooth muscle cells including the mesangial cells (SM22+Nox5+) in the setting of diabetes. In vitro, we examined the effect of Nox5 silencing in human renal cells.

Methods: SM22-Nox5+ and SM22-Nox5- transgenic mice were diabetic via streptozotocin injections and followed for 10 and 15 weeks. Renal function including albuminuria and creatinine clearance, structural damage as well as gene and protein expression of markers of inflammation, fibrosis and oxidative stress were assessed. In vitro, Nox5 was silenced in human mesangial cells or in podocytes and exposed to high glucose and TGF-β for the measurement of ROS level and molecular analysis.

Results: Diabetes induced increase in albuminuria in Nox5 negative mice was further increased by 20% in Nox5 positive diabetic mice. In addition, a further increase in glomerulosclerosis and tubulointerstitial fibrosis (nitrityrosine and DHE) were found in diabetic SM22+Nox5+ mice when compared to diabetic SM22+Nox5- mice. Creatinine clearance was unchanged in both group of diabetic mice. Moreover, silencing of Nox5 in human renal cells resulted in decreased ROS production and down-regulation of proinflammatory and proinflammatory markers that are implicated in DN.

Conclusions: Collectively, these findings suggest that Nox5 derived ROS accelerates renal injury in diabetes and provide proof of principle for the innovation of a new renoprotective agent in diabetes.

FR-OR052

Myo-Inositol Oxygenase (MIOX) Accelerates Renal Tubular Injury via Oxidative Stress Utilizing Glucuronoxylohexose (GX) Pathway in Experimental Diabetes Ishu Sharma, Yashpal S. Kanwar. Dept of Pathology, Northwestern Univ, Chicago, IL.

Background: MIOX is exclusively expressed in renal proximal tubules. Subsequent to the ingestion of a carbohydrate rich meal it channels fructose into gluconoquinic acid via G-X pathway. During the various steps of this pathway there are perturbations in the ratios of NADPH:NADP and NAD:NADP, as a result there is an excessive generation of reactive oxygen species (ROS) via G-X pathway.

Methods: A diabetic state was induced by the administration of streptozotocin in wild type (WT), MIOX transgenic (TG) and MIOX−/− (KO) mice to assess the degree of MIOX-induced oxidant stress that influences the outcome of tubular injury among these animals. The mice with blood glucose >250 mg/dl were evaluated and sacrificed 8 weeks after induction of diabetes.

Results: The MIOX expression was highly accentuated in diabetic MIOX TG mice compared to WT and normoglycemic untreated or KO mice. Serum creatinine and urine levels were found to be significantly elevated in MIOX TG mice. The proximal tubules had relatively more cytology and apoptosis with thickened basement membranes and increased interstitial fibroconnectin and collagen I staining in TG mice compared WT and KO mice. The cellular redox in the kidney tissues was relatively more adversely affected in TG mice compared to other strains of mice, as highlighted by increased DHE staining. Also, a markedly decreased in reduced glutathione (GSH) levels were noted TG mice. Analyses of...
of various signaling events revealed an increased activation of p-p70S6K, p-p38 and AKT in kidneys of MIOX mice. Likewise expression of TGF-b and Smad4 along with HIF-1 alpha was relatively high in TG mice. All these parameters were minimally affected in MIOX KO mice. In vitro, HK-2 cells treated with MIOX-siRNA reduced the expression of all the above indicated signaling molecules and the ROS generation, as assessed by FACS analysis and DHE staining.

Conclusions: These data indicate that MIOX is another one of the newly discovered mediator in STZ induced tubular injury via Gi-X with accentuated generation of ROS in diabetic tubulopathy. Funding: NIDDK Support

FR-OR053

Stabilization of Endogenous Nrf2 by Minocycline Protects against Nrp3‑Inflammasome Induced Diabetic Nephropathy

Fabian Boek, Khurram Shahzad, Mohd Mohanad Ahmad Al-Dabe, Iisam Khan Gadi, Shrey Kohli, Berend Heinrich Isermann. 1Univ Klinikum Magdeburg, Inst of Clinical Chemistry and Pathobiochemistry, Magdeburg, Germany; 2Univ of Heidelberg, Dept of Internal Medicine 1 and Clinical Chemistry, Heidelberg, Germany;

Background: While a plethora of studies support a therapeutic benefit of Nrf2 activation and ROS inhibition in diabetic nephropathy, the Nrf2 activator barofoxolone failed in clinical studies in type 2 diabetic patients due to side effects. Intriguingly, the tetracycline antibiotic minocycline, which has been in clinical use for decades and limits mitochondrial dysfunction and apoptosis, has been shown to correct oxidative stress in diabetic patients. As the mechanism underlying minocycline’s nephroprotection remains unknown, we speculated that minocycline reduces renal ROS generation and inflammation, potentially through a Nrf2 dependent mechanism.

Methods: The effect of minocycline on inflammasome activation and oxidative stress was studied in murine models of diabetic nephropathy, db/db mice and the STZ diabetes model. We assessed albuminuria, glomerular extracellular matrix accumulation as well as expression of Nrf2 and inflammasome regulators. Nrf2-ubiquitination was analyzed by immunoprecipitation.

Results: Here we show that minocycline protects against diabetic TNF mouse models of type 1 and type 2 diabetes, while caspase-3,-6,-7,-8 and -10 inhibition is insufficient, indicating a function of minocycline independent of apoptosis inhibition. Minocycline stabilizes endogenous Nrf2 in kidneys of db/db mice, thus dampening ROS-induced inflammasome activation in the kidney. Indeed, minocycline exerts antioxidant effects in vitro and in vivo, reducing glomerular markers of oxidative stress. Minocycline reduces ubiquitination of the redox-sensitive transcription factor Nrf2 and increases its protein levels. Accordingly, minocycline stabilized the Nrf2-dependent antioxidant Nrf2 inflammasome inhibition and amelioration of DTN are abolished in diabetic Nrf2-/- mice.

Conclusions: Taken together, we uncover a new function of minocycline, which stabilizes the redox-sensitive transcription factor Nrf2, thus protecting from DN.

Funding: Government Support - Non-U.S.

FR-OR054

Renal Tubular ACE Affects Microalbuminuria in Early Diabetic Nephropathy

Masahiro Furuichi, Jorge F. Giani, Mercury Y. Lin, Tuana Lehim, Zhion Khan, Ellen S. Bernstein, Xiao Shen, Romer Andres Gonzalez-Villalobos, Kenneth E. Bernstein. 1Dep of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA; 2Pathology & Lab Medicine, Cedars-Sinai Medical Center, Los Angeles, CA; 3CVMETRU, Cedars-Sinai Medical Center, Grotton/Cambridge, MA.

Background: ACE inhibitors are mainstay treatment for diabetic nephropathy. Studies demonstrated that the intrarenal-angiotensin system plays a key role in the progression of diabetic nephropathy. However, the specific contribution of renal tubular ACE vs. other sources of ACE to diabetic nephropathy remains unknown.

Methods: To study this, we used two mouse models: 1) ACE mouse that specifically lacks ACE in renal tubular epithelial cells and ACE 3/9 in which renal ACE is only expressed in endogenous Nrf2 in kidneys of db/db mice, thus dampening ROS-induced inflammasome activation.

Results: Total renal ACE activity was decreased in both diabetic WT and diabetic ACE mice is 48% and 83% of WT mice; GFR is equivalent to WT mice. Diabetic nephropathy was induced with streptozotocin. Glomerular filtration rate (GFR), albuminuria and urinary KIM-1, a specific marker for tubular injury, were monitored. All data are presented as % of untreated WT control mice.

Conclusions: Total renal ACE activity was decreased in both diabetic WT and diabetic ACE 3/9 mice (54±15% and 56±7%, p<0.001, n=4 to 6). No changes in total renal ACE were observed between diabetic and non-diabetic i-ACE mice (46±7% and 48±p<NS). After 3 months of diabetes, both WT and i-ACE mice have increased GFR (142±11% and 147±7%, p<0.05). In contrast, ACE 3/9 did not increase GFR (107±6%). After 4 months of diabetes, microalbuminuria and urinary KIM-1 levels were significantly higher in both diabetic WT mice (220±17% and 49±8%) and ACE 3/9 mice (292±29% and 534±147%) compared to untreated WT mice. In diabetic i-ACE mice, despite glomerular hyperfiltration, depletion of renal tubular ACE reduced both microalbuminuria and urinary KIM-1 levels (127±27% and 236±38%) compared to diabetic WT mice.

FR-OR055

A Potent Pan-AMPK Activator Improves Renal Structure and Function in the ZSF-1 Rat Model of Diabetic Nephropathy


Background: Defects in mitochondrial function and renal metabolism have been hypothesized to play a causal role in the pathophysiology of diabetic nephropathy. Non-specific AMPK activators such as AICAR improve renal function in multiple animal models, which has been attributed to the ability of these agents to improve the metabolic state of the kidney. The goal of these studies was to determine whether a potent Merck pan-AMPK activator would be beneficial in animal models of diabetic nephropathy.

Methods: An intervention study was performed in the ZSF-1 rat in which the Merck AMPK activator (Cmpd A, potency 6-60 nM, dosed at 1 and 10 mpk in feed) was compared to enalapril (10 mpk in feed). Treatment was initiated at 20 weeks, a timepoint at which renal damage was evident, and continued for another 28 weeks. Cell based studies were performed in primary human renal proximal tubule cells to assess the direct protective effects of Cmpd A in the context of a lipotoxic challenge or a challenge with TGF-b.

Results: The 10 mpk dose of Cmpd A led to improvements in uPCR (48.6 vs 18.2 mg/ng), GFR (430 vs 779 ml/min/gm kid weight) and renal histology scores compared to vehicle. These effects were comparable to enalapril treatment. Treatment with Cmpd A was accompanied by decreases in plasma glucose, body weight, and plasma lipids. Distinct renal RNA expression profiles were noted between the enalapril and Cmpd A treatments, with the endothelin axis and oxidative phosphorylation more affected by Cmpd A, suggesting that pathways affected by these treatments were at least partially orthogonal. Cmpd A protected primary human proximal tubule cells from lipotoxic stress and attenuated collagen induction in response to TGF-b.

Conclusions: Treatment with a specific AMPK activator resulted in substantial improvements in renal function in the ZSF-1 model of diabetic nephropathy. Though the effects may be secondary to systemic metabolic improvement, cell based assays and RNaseq data suggest that some of the effects might be attributed to direct action on the kidney.

Funding: Pharmaceutical Company Support - Merck & Co.

FR-OR056

AdipoRon Prevents Diabetic Nephropathy through Improvement of Lipid Metabolism in db/db Mice

Yaei Kim, Sun Ryong Choi, Ji Hee Lim, Min Young Kim, Seong Deok Hwang, Yu Ah Hong, Yong-Soo Kim, Cheol Whee Park. Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: Adiponectin, one of the numerous adipokines produced by adipose tissue, interplays with others to exert the milieu of metabolic syndrome. Orally active synthetic molecules AdipoR agonists, AdipoRon binds to both AdipoR1 and AdipoR2 and ameliorates diabetic diabetic nephropathy (DN) in type 2 diabetes. The connection between adiponectin and lipid metabolism is apparent and the carboxylase species of shinglipolids have been related to inflammation, cell death, and insulin resistance, so called lipotoxicity. We investigated the possible role of AdipoRon in renal physiology in the view of prevention and development of DN in diabetic mice.

Methods: Male db/db and db/m mice were fed either a regular chow or a diet containing AdipoRon (30 mg/kg/day p.o. for 4 weeks from 17 to 20 weeks of age). Serum, urine and renal tissue were analyzed for changes in metabolic parameters, relevant levels and their association with regard to renal structure.

Results: AdipoRon fed db/db mice showed decreased amount of albuminuria and lipid accumulation in the kidney with no significant changes in the levels of serum adiponectin, glucose, insulin, creatinine, and body weight. Increased expressions of AdipoR1 and AdipoR2 in the renal cortex were observed in db/db mice with AdipoRon administration. Consistent up-regulations of p-AMPK, PPAR-α, p-Akt, p-ACC and p-NO and down-regulations of protein phosphatase 2A, SREBP-1c and iNOS levels were shown, which were related to a decrease in ceramide to sphingosine-1-phosphate ratio. In glomerular endothelial cells (GECs), AdipoRon treatment reduced lipotoxicity via attenuating palmitate-induced oxidative stress and apoptosis.

Conclusions: AdipoRon prevents lipotoxicity in the kidney as represented by decreased ceramide versus sphingosines ratio. The protective role of AdipoRon against the development of DN seems to occur through a direct action on the kidney independently of systemic effects of adiponectin. Its reduction of oxidative stress and apoptosis provides protection against renal damage via ameliorating endothelial dysfunction in DN.

Funding: Other NIH Support - R01HL110353, R21AI114965, R01DK098382

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

Underline represents presenting author.

47A
Fatty Kidney by Clinical 1H-Magnetic Resonance Spectroscopy: A Dietary Intervention and Validation Study in Porcine Kidneys

Jacqueline Jonker,1 Paul de Heer,2 Evyvelyn van Rosenberg,3 Celine Klessens,3 Hans J. Baade,1 Sietse Jan Koopmans,4 Paulo G. Coelho,5 Ingeborg M. Bajema,6 Treia C. M. Streetland,7 Hona Aleksandra Dekkers,8 Ton J. Rabelink,5 Patrick Rensen,6 Hildo Lamb,5 Aiko P.J. De Vries6,1 Nephrology, Leiden Univ Medical Center, Leiden, Netherlands; 2Radiology, Leiden Univ Medical Center, Leiden, Netherlands; 3Pathology, Leiden Univ Medical Center, Leiden, Netherlands; 4Veterinary Medicine, Wageningen Univ, Wageningen, Netherlands; 5Endocrinology, Leiden Univ Medical Center, Leiden, Netherlands; 6New York Univ.

Background: Renal lipid accumulation has been experimentally linked to obesity and type-2 diabetic nephropathy. Human translation has been hampered by lack of noninvasive biomarkers. 1H-MR spectroscopy is an established technique to study lipids in liver, muscle and heart and feasibility was shown for kidney, but few protocols underwent validation. We assessed agreement between our 1H-MRS protocol and enzymatically determined lipids in porcine kidneys.

Methods: Renal lipid content was measured in 27 porcine kidneys by 1H-MRS on a 7T scanner, of which 15 mini-pigs were randomized to either 9-months control diet, cafeteria diet (CAF), or CAF with low-dose streptozotocin (CAF-S) to induce obesity and insulin-independent diabetes, with the remaining being slaughter pigs. Renal biopsies were taken at the same location and lipids were measured enzymatically.

Results: Bland-Altman analysis of normalised data of all kidneys showed good agreement with bias of 0.0 (limits of agreement -0.8; 0.8) for 1H-MRS and enzymatically assessed lipid. After 9-month diet, renal triglyceride (TG) content was higher in CAF-S group (134.0±44.2 vs 45.2±8.1 mmol/mg protein) compared to the control group (36.0±36.2; P<0.001). Renal TG content was not significantly different between the control and cafeteria diet group. Notably, renal and hepatic TG showed significant positive correlation (r=0.97, P<0.001).

Conclusions: Our clinical 1H-MRS protocol agreed well with gold-standard assessment of lipids in porcine kidneys, which correlated closely with hepatic tissue. This offers unique opportunity to investigate the pathophysiology of fatty kidney clinically in obesity and diabetic nephropathy.

FR-OR057

Macrophage-Derived Wnts Contribute to Kidney Fibrosis after Injury

Yuan Tian,1 Dong Zhou,1 Haiyan Fu,2 Youhua Liu.1 Dept of Pathology, Univ of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: Activation of Wnt/β-catenin signaling plays a pivotal role in the pathogenesis of many forms of chronic kidney diseases (CKD). Wnt ligands are induced in a wide variety of kidney resident cells as well as infiltrated cells including macrophages. However, the relative contribution of Wnts from different sources in CKD progression is poorly understood. To address this issue, we utilized genetic approach by blocking Wnt secretion via conditionally knockout of Wntless (Wntl), a cargo receptor that is obligatory for further downstream secretion of Wnt in vivo. These results suggested that macrophage-derived Wnts does not affect the early kidney injury after ischemic AKI. However, it plays a critical role in promoting kidney fibrosis after UUO.

Funding: NIDDK Support

FR-OR059

A Critical Role for Rictor/mTORC2 in Promoting Macrophage Activation and Kidney Fibrosis

Jiia Ren,1 Chunsun Dai.1 Center for Kidney Disease, Nanjing Medical Univ.

Background: Our published study reported that Rictor/mTORC2 signaling mediates TGFB1-induced fibroblast activation and kidney fibrosis. However, the role and mechanisms for Rictor/mTORC2 in macrophage activation and kidney fibrosis are not clear.

Results: Here, a novel model demonstrated macrophage-specific deletion of Rictor and primary cultural macrophages from bone marrow (BMMs) were generated.

Conclusions: Together, these results suggest that Rictor/mTORC2 signaling plays an important role for promoting macrophage activation and kidney fibrosis.

Funding: Government Support - Non-U.S.
FR-OR062

**Fibroblast-Specific Loss of Krüppel-Like Factor 15 Exacerbates Kidney Fibrosis**

Xiaoguang Gu,1 Qiying Guo,2 Timothy W. Miller,3 John C. He,2 Sandeep K. Mallipatni,2 1Nephrology, Yuyuan Hospital of Integrated TCM and Western Medicine, Shanghai, China; 2MSSM, New York, NY; 3Medicine/ Nephrology, Stony Brook Univ, Stony Brook, NY.

**Background:** Regulation of fibroblast to myofibroblast differentiation in kidney fibrosis remains poorly understood. Krüppel-Like Factor 15 (KLF15), a zinc-finger transcription factor, has been demonstrated to play a critical role in progression of cardiac and kidney fibrosis. We sought to determine the mechanism by which the loss of KLF15 increases fibroblast to myofibroblast differentiation in kidney fibrosis.

**Methods:** To assess the role of KLF15 specifically in fibroblasts, we generated pericyte and renal fibroblast knock-out mice (Klf15ΔFoxd3 and Klf15ΔFoxcly) by crossing Klf15 ΔFoxd3 mice with Foxd1-Cre mice. We utilized unilateral uninephrectomy (UUN) for 3 and 7 days and Angiotensin II (Ang II infusion for 4 weeks) as murine models of fibrosis. Mouse embryonic fibroblasts (MEF) with stable knockdown of Klf15 (Klf15-shRNA) and empty vector (EV-shRNA) were generated using lentiviral delivery.

**Results:** Klf15ΔFoxd3 mice showed increased expression in pro-fibrotic markers (αSMA, Col1α1, fibronectin), and proliferation (Ki67 and MTT assay) as compared to fibroblasts incubated in AngII-treated wildtype mice. Gene-set enrichment analysis of genes with KLF15 binding sites identified an increase in the pathways involved in suppression of Wnt/β-catenin pathway. We initially confirmed that Klf15ΔFoxd3 mice showed an increased Wnt/β-catenin signaling (activated-phospho β-catenin, c-Myc), pro-fibrotic markers (αSMA, Col1α1, fibronectin), and proliferation (Ki67 and MTT assay) as compared to EV-shRNA MEFs after Wnt1 ligand treatment for 72 hours.

**Conclusions:** These data suggest that the loss of KLF15 in pericyte/resident fibroblast-specific accelerates fibroblast to myofibroblast differentiation in models of kidney fibrosis.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic Inc.

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FR-OR063

**Role of Lysophosphatidic Acid (LPA)/LPA Receptor in EGFR-Mediated Renal Fibrosis**

Jessica Marie Overstreet, Ming-Zhi Zhang, Raymond C. Harris, Medicine, Vanderbilt Univ, Nashville, TN.

**Background:** Excessive tissue scarring or fibrosis is a critical contributor to chronic kidney disease, which ultimately leads to organ failure. We have previously demonstrated that overactivation of EGFR in the proximal tubule epithelium of mice is sufficient to promote spontaneous, progressive renal fibrosis. The role of the lysosphosphatidic acid (LPA)/LPA receptor axis in epithelial-fibroblast crosstalk and renal fibrosis is less known.

**Methods:** For in vivo analysis, we generated male C57BL/6 mice with human HB-EGF selectively expressed in the renal proximal tubule epithelia (hHB-EGFΔFoxd1) to overactivate EGFR. hHB-EGFΔFoxd1 mice were crossed with Waved2 mice (hHB-EGFΔFoxd1; Waved2), which have a 90% reduction in EGFR kinase activity. Human proximal tubule epithelial cell line (hRPTEC) and mouse cortical fibroblasts were used for communication studies in vitro. Real-time immunohistochemical analysis revealed an increase in LPA, and autotaxin, an enzyme that produces LPA, in the interstitium surrounding the tubule epithelium of hHB-EGFΔFoxd1 mice compared to wildtype mice. The increased expression of LPA, and autotaxin observed in hHB-EGFΔFoxd1 mice was attenuated in hHB-EGFΔFoxd1; Waved2 mice. EGFR-induced LPA secretion from hRPTEC measured by high performance liquid chromatography. Conditioned media collected from EGFR-treated hRPTECs increased fibroblast proliferation and activation as indicated by increased fibronectin, α-smooth muscle actin (α-SMA), and cyclin D protein expression in comparison to fibroblasts incubated in conditioned media from untreated hRPTECs. Further, conditioned media derived from hRPTECs exposed to EGFR- Erlotinib, an EGFR kinase inhibitor, induced less fibroblast proliferation. Fibroblasts treated with EGFR-induced conditioned media Ki614625, an LPA/LPA inhibitor, prevented the increased proliferation seen with EGFR-induced conditioned media from hRPTECs.

**Conclusions:** These results suggest that EGFR activation in the proximal tubule promotes the secretion of paracrine factors driving fibroblast activation and proliferation, likely through a LPA/LPA receptor-dependent pathway.

**Funding:** NIDDK Support, VA Support

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FR-OR064

**Worn-out GBM Components, Particularly the Collagen IV-Alpha Chain, Account for Mesangial Matrix Expansion in Diabetic Nephropathy (DN) in Humans**

Wilhelm Kreis,1 Jana Loewen,1 Giuseppe Federico,2 Elisabeth Schloo,1 Hermann Josef Groene,3 1Dept of Neuroanatomy, Medical Faculty Mannheim, Univ of Heidelberg, Mannheim, Germany; 2Dept of Molecular Pathology, German Cancer Research Center, Heidelberg, Germany.

**Background:** Mesangial matrix expansion is a hallmark of DN and generally believed to emerge from the overproduction by mesangial cells; other sources have so far not been considered.

**Methods:** Re-evaluation of 918 biopsies of DN from the years 2007-2015 (types 1 and 2 diabetes) were evaluated using sequential electron microscopy (LM, TEM), immunofluorescence (IF) and in-situ hybridization (ISH).

**Results:** As seen by LM and TEM at least a major part of the accumulated matrix in the mesangium in DN is derived from the deposition of worn-out GBM-material. The process is as follows:

The DN specific thickening of the GBM causes a narrowing of the spaces within the GBM-inarrings prohibiting the solution of the podocytes therein. They retraction out of the GBM forming the knob shedded cytoplasmic material that become included into the innermost portions of the GBM. These portions disconnect from the GBM and are dropped into the mesangium. The inclusions of podocyte cytoplasmic remnants provide a label proving that this material is derived from the GBM.

If the knob is kept as original (activated-phospho β-catenin, c-Myc, Lef1) as compared to wildtype mice post UUO. We show that EGF inhibitor, prevents the increased proliferation seen with EGF treated wildtype mice as compared to AngII-treated wildtype mice. We initially confirmed that Klf15ΔFoxd3 mice showed an increased Wnt/β-catenin signaling (activated-phospho β-catenin, c-Myc), pro-fibrotic markers (αSMA, Col1α1, fibronectin), and proliferation (Ki67 and MTT assay) as compared to EV-shRNA MEFs after Wnt1 ligand treatment for 72 hours.

**Conclusions:** These findings put the turnover of the GBM into centre stage of the pathogenesis of DN. They support the view (Walker F. 1973, J Pathol 110: 233) that components of the GBM are synthesized by podocytes and endothelial cells and degraded within the mesangium.

**Funding:** Other NIH Support - K12 Child Health Research Career Development Award (NIH SK12HD034610-18)
FR-OR066
Cross-Talk of Anemia and Phosphate Metabolism via FGF23 in a Model of PKD
Erica Clinkenbeard, Hitesh Nidumunda, Pu Ni, Julia M. Hum, Yves Sbabgh, Kenneth E. White.
1Dept Medical and Molecular Genetics, Indiana Univ, Indianapolis, IN; 2Rare Diseases, Sanofi Genzyme, Framingham, MA.

Background: Fibroblast growth factor 23 (FGF23) is a bone-derived hormone responsible for maintaining phosphate homeostasis. We have found in addition to phosphate, FGF23 is also significantly induced with iron-deficiency anemia. Interestingly, patients with polycystic kidney disease (PKD) maintain EPO production during anemia, whereas patients with CKD-MBD often demonstrate anemia with loss of EPO production in concert with phosphate homeostasis dysregulation. Therefore, the purpose of our study was to test the associations between FGF23 and anemia in a mouse model of PKD and to determine the molecular mechanism driving the cross-talk between iron and phosphate homeostasis.

Methods: Juvenile cystic kidney (Jck) mice harboring a Nek8 mutation, were maintained on a normal chow and monitored from 4 to 20 weeks of age for complete blood counts, serum FGF23, erythropoietin (EPO) and total iron levels. Additionally, we tested factors important for iron handling on rat osteoblast cells (UMR-106) to determine EPO and FGF23 mRNA levels.

Results: Serum intact FGF23 becomes significantly increased in Jck mice over normal controls during the course of disease (13-fold, p<0.0005). Jck mice also exhibited anemia with reductions in red blood cells, hematocrit and hemoglobin. We found a negative correlation between total iron and FGF23 (p=0.005), and the reciprocal strong positive correlation between serum EPO and FGF23 (p<0.003) in Jck mice across time. In UMR-106 cell lines, FGF23 was upregulated in s.c. injection induced anemia, yet downregulated in stimulated EPO mRNA expression. Human EPO was transfected in the cells and upon EPO treatment initiated canonical JAK/STAT signaling which associated with increased FGF23 mRNA (p<0.05). Additionally, FGF23 promoter activity was stimulated by EPO administration.

Conclusions: During anemia, EPO is an independent regulatory factor for FGF23, and may be in part, responsible for elevated FGF23 in PKD, and EPO-treated CKD-MBD. This, in conjunction with iron deficiency may be modifiable risk factors in rare and common disorders of phosphate metabolism.

Funding: NIDDK Support, Private Foundation Support

FR-OR067
The FGF Receptor Inhibitor Decreases FGF23 Levels in Uremic Rats
Maria L. Pegues,1 Eva Gravenese,2 Anders Nordholm,3 Jacob Hofman-Bang,4 Klaus Olgaard,5 Ewa Lewin,1 Dept of Nephrology, Herlev Hospital, Copenhagen, Denmark; 2Dept of Nephrology, Rigshospitalet, Univ of Copenhagen, Denmark.

Background: The phosphaturic hormone fibroblast growth factor 23 (FGF23) is severely increased in uremia, where it is associated with increased cardiovascular complications and mortality. Our aim was to study whether inhibition of the FGF receptor (FGFR1) had a regulatory impact on FGF23, Klotho and PTH.

Methods: Chronic kidney disease was induced in Wistar rats by 5/6 nephrectomy. After 8 weeks of uremia, uremic rats (U) and age-matched control rats (C) were randomized to FGFRI (20mg PD173074) or vehicle. Plasma FGF23 and PTH were measured along with gene expression of FGF23 in bone and kidney expression of αKlotho, NaPi2a, NaPi2c and FGFRI1.[2]

Results: Uremic rats had increased p-creatinine (72±11 vs 32±1 μM), p-phosphate (2.57±0.18 vs 2.05±0.08 mM), p-PTH (932 ±(355-292) vs 224 (169-290) pg/ml) and p-FGF23 (1925±554 vs 367±21 pg/ml) (all p<0.05). FGFRI resulted in a significant decrease in p-FGF23 to 154±18 pg/ml in C rats and 738±174 pg/ml in U rats, and in down-regulation of the FGF23 mRNA in bone (C rats: 154±0.23 to 0.15±0.03; U rats: 2.79±0.61 to 1.41±0.03) (all p<0.01). Despite stable p-calciuric and p-phosphate, PTH rose significantly to 392 (281-2079) in C rats and to 2719 (1579-16912) in U rats after FGFRI (p<0.05). The present results didn’t support the concept of parathyroid resistance to FGF23 in uremia, but demonstrated renal resistance to FGF23. In the kidney of C rats FGFRI resulted in a significant increase in the expression of aklo (1.40±0.05 to 1.72±0.03), NaPi2a (1.48±0.05 to 1.72±0.05) and NaPi2c (1.44±0.03 to 1.73±0.11) (all p<0.05). In contrast, the kidney rudiment of U rats FGFRI had no effect on the expression of aklo (0.82±0.15 vs 0.87±0.13), NaPi2a (0.83±0.16 vs 0.83±0.14) and NaPi2c (0.80±0.16 vs 0.90±0.15). FGFRI did not affect the expression of FGFRI1.[1]

Conclusions: Inhibition of the FGF receptor has a powerful down-regulatory impact on FGF23 levels in both normal and uremic rats. The expression of Klotho was up-regulated in the normal kidney, but unchanged in the injured kidney by PD173074. These results demonstrate renal, but not parathyroid resistance to FGF23 in chronic uremia.

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

FR-OR068
Acute Parathyroid Hormone (PTH) Increases C-Terminal Fibroblast Growth Factor 23 Levels But Not Intact Fibroblast Growth Factor 23 Levels
Marta Christov,1 Vanessa Maria Knab,2 Braden A. Corbin,2 Olena Andrushkova,2 Julia M. Hum,2 Pu Ni,3 Seham M. Rabadi,1 Akira Maeda,2 Kenneth E. White,2 Reinhold Erben,1 Harald Jüppner,1 medicine, New York Medical College, Valhalla, NY; 2Medicine, Massachusetts General Hospital, Boston, MA; 3Medical and Molecular Genetics, Indiana Univ School of Medicine, Indiana, IN; 4Univ of Veterinary Medicine of Vienna, Vienna, Austria.

Background: The acute effects of parathyroid hormone (PTH) on fibroblast growth factor 23 (FGF23) in vivo are not well understood.

Methods: Injection of PTH into wild type and autosomal dominant hypophosphatemic rickets (ADHR) mice. Treatment of differentiated calvarial osteocytes with PTH.

Results: After a single s.c. PTH(1-34) injection (5nmol) in mice, FGF23 levels were measured in plasma using assays that measure either intact alone (FGF23) or intact/C-terminal FGF23 (εFGF23). Furthermore, FGF23 mRNA and protein levels were assessed in bone. In addition, we examined the effects of PTH treatment on FGF23 production in vitro using differentiated calvarial osteocytes. εFGF23 levels increased by 3-5 fold within two hours following PTH injection, which returned to baseline by 4 hours. In contrast, FGF23 levels remained unchanged for the first two hours, then declined to approximately 60% by 6 hours and remained suppressed before returning to baseline after 24 hrs. Using mice that are homozygous for the ADHR-FGF23 mutation or animals treated with a furin inhibitor, we showed that εFGF23 and FGF23 levels increased equivalently after PTH injection. These findings are consistent with increased FGF23 production in bone, yet rapid cleavage of the secreted intact protein. Using primary cultures of differentiated osteocytes, we showed that PTH(1-34) and FGF23 mRNA (although not FGF23 protein) were upregulated through cAMP/PKA, but not IP3/PKC signaling.

Conclusions: In conclusion, PTH injection rapidly increases FGF23 production in bone in vivo and in vitro. However, intact FGF23 is rapidly degraded. At later timepoints and through as yet unidentified mechanism there is a sustained decrease in FGF23 production.

Funding: NIDDK Support, Private Foundation Support

FR-OR069
Paricalcitol and FGF Blockade Synergistically Attenuate Uremic Cardiac Hypertrophy
Michael Freundlich,1 Christian Paul,2 Saurav Singh,3 Yasmir Quiroz,3 Brian A. Czaya,4 Keila Zulimi Yaguar,5 Fernando Rodriguez-Iturbe.1 Pediatric Nephrology, Univ of Miami, Miami, FL; 2Nephrology, Hospital Univ IVIC, Maracaibo, Venezuela.

Background: In uremic (U) rodents, FGF23 activates myocardial calcineurin/NFAT signaling causing cardiac hypertrophy (CH) that can be blocked by inhibiting FGF receptor (FGFR4) 4, and paricalcitol (Pc) improves CH by suppressing the myocardial renin-angiotensin-system (RAS). Since Pc suppresses NFAT with CH attenuation in non-U animals, we studied whether Pc inhibits myocardial NFAT in U rats and if FGFGR blockade amplifies the Pc effects.

Methods: 5/6 nephrectomized rats receiving Pc alone (0.3 mg/kg x3/week) or Pc+paricalcitol blocker PD173074 (PD; 1mg/kg), were compared to untreated (Nx) and sham (S).

Results: After 4 weeks, we analyzed heart weight/body weight (HW/BW) ratio, myocardial expression RT-PCR profiles, blood pressure (BP), and blood levels of creatinine and FGF23.

Results: Pc or Pc+PD versus Nx significantly attenuated renal dysfunction, hypertension and HW/BW with further elevation of FGF23. Pc+PD versus Pc significantly lowered HW/BW and Pc+PD versus NP significantly lowered blood pressure. Moreover, we investigated heart weight/body weight (HW/BW) ratio, myocardial expression RT-PCR profiles, blood pressure (BP), and blood levels of creatinine and FGF23.

Conclusions: In conclusion, PTH injection rapidly increases FGF23 production in bone in vivo and in vitro. However, intact FGF23 is rapidly degraded. At later timepoints and through as yet unidentified mechanism there is a sustained decrease in FGF23 production.

Funding: NIDDK Support, Private Foundation Support

FR-OR070
Endothelial Dysfunction in Experimental Chronic Kidney Disease Is Caused by FGF23
Melissa Verkaik,1,2 Pieter M. Ter Wee,1 Etto C. Eringa,1 Brian C. Valtchanov,1,3 Department of Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; 2Dept of Physiology, VU Univ Medical Center, Amsterdam, Netherlands; 3Inst of Cardiovascular Research ICaR-VU; 4On Behalf of the NIGRAM Consortium.

Background: Cardiovascular causes account for approximately 50% of mortality in patients with chronic kidney disease (CKD). FGF23, a phosphate-lowering protein and protein in CKD, is associated with endothelial dysfunction and cardiovascular mortality. We hypothesized that CKD impairs vascular function and that this can be attributed to FGF23.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Seven weeks old male wild type C57Bl/6 mice were subjected to partial nephrectomy (5/6Nx) surgery. After 6 days with intact arteries were isolated and subjected to a pressure myograph setup to test ex vivo vascular function. A second non-CKD group received either PBS or FGF23 i.p. injections for 7 consecutive days twice daily. To assess whether FGF23 mediates CKD-induced endothelial dysfunction, a third group received FGF23 antibodies by i.p. injections, in combination with a low phosphate diet, 6 days following 5/6Nx surgery. A control group received control antibodies and a normal diet. To assess eNOS uncoupling, femoral arteries were used to determine eNOS monomer and dimer protein expression by low-temperature SDS-PAGE.

Results: Plasma FGF23 significantly increased after 5/6Nx surgery (1.7-fold p=0.01), as well as fractional excretion of phosphate (FEP) (4-fold p=0.003). 5/6Nx blunted ex vivo vasodilator responses to acetylcholine (p=0.002), whereas responses to sodium nitroprusside (SNP) or endothelin were normal. Seven days in vivo FGF23 injections completely mimicked this vascular endothelial defect (p<0.01), and in accordance, responses to SNP and endothelin were not altered. Short-term ex vivo FGF23 administration to isolated vessels did not change vascular reactivity. FGF23 antibodies in CKD mice prevented development of endothelial dysfunction (p=0.048). eNOS uncoupling was not observed after 5/6Nx or FGF23 injections.

Conclusions: Impaired endothelium-dependent vasodilatation in CKD mice is mediated by FGF23 and can be prevented by blocking FGF23. These data corroborate FGF23 as a main target to combat in cardiovascular disease in CKD.

FR-OR071
Regulation of Phosphate Homeostasis by the Central Nervous System
Daniela Egli-Spichtig,1 Martin Y.H. Zhang,2 Komuraia Myakala,2 Evgenia Dobriniskii,3 Moshe Levi,2 Farzana Perwad.1 1Pediatric Nephrology, Univ of California San Francisco, San Francisco, CA; 2Dept of Medicine, Univ of Colorado, Aurora, CO.

Background: Phosphate (Pi) homeostasis is determined by dietary intake, intestinal absorption, renal excretion and skeletal turnover and is tightly regulated by parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) and 1,25 dihydroxyvitamin D3. Although several Pi cotransporters have been identified, Pi sensing mechanisms are still unknown. We hypothesize that Pi sensing in the central nervous system (CNS) plays a role in the regulation of systemic phosphate homeostasis in mice.

Methods: 12 weeks old C57BL6 mice were fed a low Pi (0.02%), 0.3%, and received intracerebroventricular (ICV) injections of either vehicle (ICV-Veh) or 20 nmol potassium dibasic phosphate (ICV-Pi).

Results: Sodium-dependent Pi (NaPi) uptake and NaPi-Ile protein abundance in the brain were reduced by 30% and urinary Pi excretion increased by 3-fold in ICV-Pi compared to ICV-Veh injected mice after one hour. Serum Pi and FGF23 levels were not significantly different in the two groups. We next determined whether increasing cerebrospinal fluid (CSF) Pi concentrations with ICV-Pi injections or by manipulating dietary Pi intake regulates CNS Klotho expression. We observed a 35% decrease in Klotho protein expression in the choroid plexus in ICV-Pi compared to ICV-Veh injected mice. In mice fed an acute high Pi (1.65%) diet which is known to increase CSF Pi, we observed a 56% decrease in Klotho protein abundance in the choroid plexus compared to mice fed a low Pi diet. As expected, serum Pi concentrations and urinary Pi excretion increased by 6- and 300-fold, respectively, in mice fed the high Pi diet compared to the low Pi diet group.

Conclusions: ICV Pi injections stimulate urinary Pi excretion independent of serum Pi and FGF23 levels providing evidence for a CNS-kidney signaling axis. Increased CSF Pi levels in response to high dietary Pi intake suppresses Klotho expression in the choroid plexus. Our study provides evidence that Pi regulates CNS Klotho expression and suggests Pi sensing in the CNS plays a role in the regulation of systemic phosphate homeostasis in mice.

FR-OR072
Dietary Magnesium Supplementation Prevents and Reverses Vascular and Soft Tissue Calcifications in Uremic Rats
Mariano Rodriguez,1 Juan R. Munoz-Castaneda,2 Alan Peralta-Ramirez,3 Yolanda Almaden Peña,4 Maria Encarnacion Rodriguez Ortiz,2 Ignacio Lopez,2 Carmen Maria Herencia,2 Noemi Vergara Segura,2 Sonja Steppan,2 Julio Manuel Martinez Moreno,2 Juan M. Diaz Tacodos,1 Antonio Canalejo,1 Escolastico Aguilera-Tejero,1 Medicina y Cirugía Animal, Univ Cordoba, Cordoba, Spain; 2Univ Naz Autónoma de Nicaragua, Leon, Nicaragua; 3Servicio de Nefrología (Red in Ren), IMIBIC/Hosp Univ Reina Sofia/Univ Cordoba, Cordoba, Spain; 4Univ Naz Autónoma de Nicaragua, Leon, Nicaragua; 5Proprietary Company Support

Background: A moderate increase in dietary Mg (0.3%) was associated with a reduction in arterial Ca and P content by 20% and 30%, respectively, in mice fed a high P diet (1.2%).

Methods: To investigate the effect of different levels of dietary Mg intake (from 0.1 to 1.1%) on the prevention and treatment of VC in vivo studies through 5/6 Nx rats were used with a high P diet (2.5%).

Results: A moderate increase in dietary Mg (0.3%) was associated with a reduction in arterial Ca content together with an improvement in mineral metabolism parameters. In comparison with a restricted phosphate diet (P 0.7%), Mg supplementation (0.6%) reduced mean arterial pressure, plasma Ca and P content. The effects of Mg on VC were not only limited to phosphate binder action, finding a reduction of blood pressure and improving renal function. In a second study, uremic rats with established VC (Mg 0.1%, Day 14) were fed a diet with calcium normal (Mg 0.1%, Day 28) or moderately increased Mg (Mg 0.6%, Day 28). Dietary Mg supplementation reduced VC and mortality.

Conclusions: Dietary Mg prevented and reversed both VC and mortality in uremic rats.

FR-OR073
The Kidney Is the Major Site for Fibroblast Growth Factor-23 Disposal in Humans
Giacomo Garribotto, Daniela Verzola, Francesca Ansoldo, Samantha Milanesi, Francesca Viazzi. Dept of Internal Medicine, Nephrology Div, Genoa Univ and IRECCS AOU San Martino-IST, Genoa, Italy.

Background: Fibroblast Growth Factor 23 (FGF-23) accumulates in blood of patients with chronic kidney disease and is associated both with cardiovascular complications and disease progression. However, our knowledge of the sites and mechanisms which regulate plasma FGF-23 is still incomplete.

Methods: We measured plasma FGF-23 (ELISA assay Endo Millipore, Darmstadt, Germany) across the kidney, splanchic organs and lung in nine patients (4 males, 5 females, median age 72 yrs, eGFR 65±16 ml/min) during elective diagnostic cardiac catheterizations.

Results: Arterial FGF-23 levels were in the normal range (median 14.3, range 10.5-32.7 pg/ml). Renal vein FGF-23 concentrations were remarkably lower (by ~21.6 %, p < 0.01) than the corresponding arterial values, indicating that plasma FGF-23 decreases substantially after a single pass across the kidney. Surprisingly, the fractional extraction (FE) of FGF-23 across the kidney was similar (p=NS) to that of creatinine (18.5%). FGF-23 level in the liver vein was quite similar (14±9±2 pg/ml) to that of arterial FGF-23. Arterial FGF-23 levels were almost identical to systemic venous (pulmonary artery) whole body levels (15.7±2 pg/ml), documenting zero balance of FGF-23 across these organs systems.

Conclusions: Our data show that the human kidney is the only site for FGF-23 removal from blood. Besides providing a better understanding of physiology of FGF-23 metabolism, the data reported in this study could be useful to understand the alterations in FGF-23 that are observed in CKD and many systemic and organ diseases.

Funding: Government Support - Non-U.S.

FR-OR074
Deletion of the Gene Encoding Transient Receptor Potential Canonical 1 (TRPC1) Channel in Mice Produces the Phenotypes of Familial Hypocalciuric Hypercalcaemia (FHH) and Skeletal Parathyroid (PTH) Resistance
Kari Lau,1 Bonnie Eby,1 Marybeth Humphrey,1 Leonidas Tsiokas,2 Medicine, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK; 2Medical Service, VA Medical Center, Oklahoma City, OK; 3Cell Biology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background: Previously we showed TRPC1 deficiency induces hypercalcemia, high PTH but increased bone mass, indicating TRPC1 controls Ca entry & cell [Ca] in concert with CaSR to regulate PTH secretion. Our 1st aim was to test the thesis that TRPC1 deficiency replicates FHH phenotypes. Our 2nd aim was to study skeletal resistance in mice.

Methods: We studied wild-type & null mice by standard metabolic, clearance (Cl) & micro-CT techniques. Serum (S) PTH, 1,25 di(OH) vit D (D, 25 D), & calcium were analyzed by ELISA; alkaline (Alk) & acid phosphatases (Phase), creatinine (creat), Ca, Mg, P, & urine (U) hydroxiproline (UHP) by published method.

Results: We confirmed high Sca & high PTH in null mice from 2nd to 12th m, without changes in S creat, 1,25 D, creatin, P or Mg. At 7 m, null mice were normocalciuric but hypercalciuric [Uca (1 vs. 2 mg/d), Ucra/creat (2 vs. 3), CaCl (14 vs. 26 ul/mn)]. In null females, Sca (10 vs. 8.5 mg %) was up, PTH inversely related to Sca, & low urine Ca (1 vs. 1.6 mg/d), Ucrea (2 vs. 3) & CaCl (13 vs. 22 ul/mn). In null males & females, S AlkPhase was down by 20-40 % from 2nd-16th m. Osteoclastic activities were down (30% down in tetratate-resistant acid Pase, 45% down in UHP, 3-fold up in trabecular
connectivity density, 37% more trabecular #, & 25% less trabecular spacing). At both 3 & 19 m, bone volume/tissue volume was higher in null mice. At 11 m, their hind limbs were 25% heavier.

Conclusions: 1. TRPC1 deficiency impairs Ca entry, reduces cell [Ca] & stimulates PTH to cause hypercalcemia. 2. Similar to FHH, 1,25 D, P & Mg are normal, but hypocalcemia is prominent in both sexes like CaSR inactivation. 3. Despite chronic PTH excess, due to resistance, resorption is down & bone volume is up in null mice. 4. These data support the key roles TRPC1 plays in PTH secretion, Ca absorption & bone biology.

_Funding:_ NIDDK Support, Private Foundation Support

**FR-OR075**

**Projecting End Stage Renal Disease (ESRD) Incidence and Prevalence in the United States through 2030**

Kei McCullough,1 Hal Morgenstern,2 William H. Herman,2 Rajiv Saran,2 Bruce M. Robinson,1,2 *Arbor Research Collaborative for Health;* 1Univ of Michigan.

**Background:** End-stage renal disease (ESRD) can be defined by receipt of chronic dialysis or transplantation. While the age-sex-race-adjusted incidence rate of ESRD has declined slightly since 2006, the crude incidence rate has risen. Future trends in the crude ESRD incidence are important because of the impact on healthcare utilization and cost. This analysis models incidence and prevalence of ESRD in the US through 2030.

**Methods:** We used an open compartmental simulation model to project diabetes, hypertension, and ESRD trends stratified by age and race categories using restricted cubic spline estimates of time-varying flow parameters optimized based on annual incidence. Future trends in population-level obesity were assumed to either plateau and start to decline or increase linearly; this range should cover every reasonable obesity prevalence scenario. We assumed ESRD mortality would either remain constant at 2013 levels or to continue to decline proportionately. We used data from the National Health and Nutrition Examination Survey, Centers for Disease Control and Prevention National Health Interview Survey, US Census, and United States Renal Data System, including population projections through 2030.

**Results:** While age-specific rates are projected to stay relatively constant or decline, the total crude annual ESRD incidence rate is projected to rise to 381-410 per million/year, a 5-13% increase, depending on obesity trends.

**Conclusions:** While progress in meeting the HP 2020 CKD and ESRD goals has exceeded the targets, not all groups of patients have benefited equally. Goal development for HP 2030 should consider ever-more-aggressive targets as well as changes in goal paradigms, such as tailoring goals by geographic region.

_Funding:_ Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by the following participating provider organizations: American Renal Associates, Atlantic Dialysis Management Services, DaVita HealthCare Partners, Dialysis Clinic, Inc., Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Satellite Healthcare, The Rogosin Institute, U.S. Renal Care, and Wake Forest University

**FR-OR077**

**Optimal Outcomes with Targeted Chronic Kidney Disease Management**

Meghan Martin Cockrell,1 Todd Prewitt, Yanting Dong,2 Hyui Hines,1 Gilbert Haugh,1 Stephen D. McMurray,1 Eric Franco,2 *Humana Inc., Louisville, KY;* 1Village Health.

**Background:** Unprepared patient transitions from chronic kidney disease (CKD) to end stage renal disease (ESRD) can result in avoidable hospitalizations and initiation of dialysis with non-preferred central venous catheters (CVC). Our objective was to evaluate the impact of integrated care management (ICM) on dialysis transitions with preferred modality (peritoneal dialysis vs. hemodialysis) and vascular access (arteriovenous fistula or graft).

**Methods:** Between 2012 and 2015, Humana Medicare enrollees with CKD who were most likely to transition to ESRD within a year were identified and referred to ICM using clinical rules (e.g., glomerular filtration rate ≤20) and a predictive model. The program ensured nephrologist oversight and patient education on CKD, modality and vascular access through telephone and in-person contact. For patients who transitioned to dialysis in 2015, descriptive statistics were used to report the number of transitions with preferred modality and access.

**Results:** In 2015, an average of 3,552 patients per month with CKD participated in ICM with a total of 690 transitioning to dialysis. Of those who transitioned, 338 (48.9%) started dialysis with preferred modality or access. Another 151 (21.7%) started dialysis with a maturing fistula or graft, for a total of 749 starting dialysis with preferred modality or access option in place or underway. Among all ICM patients who transitioned to dialysis and had at least 6 months of ICM enrollment, an additional 15% had nephrologist oversight, 44% had selected a modality, 47% had a vascular access plan, and 43% had permanent access in place or underway. Among all ICM patients who transitioned to dialysis, 338 (48.9%) started dialysis with preferred modality or access. Another 151 (21.7%) started dialysis with a maturing fistula or graft, for a total of 749 starting dialysis with preferred modality or access option in place or underway. Among all ICM patients who transitioned to dialysis and had at least 6 months of ICM enrollment, an additional 15% had nephrologist oversight, 44% had selected a modality, 47% had a vascular access plan, and 43% had permanent access in place or underway.

**Conclusions:** The observed outcomes of ICM were satisfactory for the health plan to continue the program. When these findings are viewed in context of national data from the 2015 Annual Data Report by the United States Renal Data System, patients in the ICM program had a 22.4% higher rate of transition to dialysis with preferred modality or access (48.9% vs. 26.5%), which can be extrapolated to 155 avoidable CVC placements with ICM. Focused, systematic care for patients with this high risk condition can have demonstrable clinical benefits.

_Funding:_ Pharmaceutical Company Support - Humana Inc.
FR-OR078
Hospitalization Rates among In-Center Hemodialysis (HD) Patients by Day of the Week Rajiv Saran,1 Patrick J. Alberts,1 Kevin He,1 Francesca Tentori,2 Brahmadej K. Nallamothu,1 Yi Li,1 KECC, Univ of Michigan; 2Arbor Research Collaborative for Health.

Background: Higher mortality on Monday/Tuesday has been reported in patients on thrice weekly hemodialysis, but the risk of other clinical outcomes remains uncertain. Therefore, we examined USRDS data to study the association of day-of-week with all-cause hospitalization and emergency department (ED) visits among Medicare-covered HD patients.

Methods: Prevalent in-center HD patients with Medicare as primary payer from 2013 with 3x/week dialysis sessions were identified in the USRDS database. Patients were followed through the end of 2013 for hospitalizations and ED visits, identified in Medicare claims. Poisson regression was used to calculate event rates and associated 95% confidence intervals (CI), characterized by the week day and stratified by dialysis schedule (Mon/Wed/Fri [MWF] or Tues/Thurs/Sat [TTS]), which was determined by the day of the week of a patient’s first HD session. The model was adjusted for age, sex, race, ethnicity, and primary cause of ESRD.

Results: For 237,920 prevalent in-center 3x/week HD patients in 2013, 371,346 hospitalizations and 16,530 ED visits occurred. With adjustment, hospitalization rates were highest on Mondays for MWF patients (risk ratio: RR=1.92; 95% CI:[1.89,1.96]) and on Tuesdays for TTS patients (RR=1.82 [1.79, 1.85]) (Fig. 1). Similarly, rates of emergency department visits after adjustment were highest on Mondays (RR= 1.55 [1.44, 1.68]) and on Tuesdays (RR=1.54 [1.42, 1.67]) for MWF and TTS patients, respectively.

Conclusions: These findings, when combined with prior reports of higher mortality rates early in the week, call for a serious reconsideration of policy and practice with respect to the widely prevalent paradigm of the thrice weekly hemodialysis.

Funding: NIDDK Support

FR-OR080
The Hemodialysis Schedule Affects Hospitalization by Day of the Week for Acute Cardiovascular Diseases: 20 Years’ Experience Masatake Banshodani, Hideki Kawanishi, Misaki Morishi, Sadanori Shintaku, Shinichiro Tsuchiya. Artificial Organs, Tsuchiya General Hospital, Hiroshima, Japan.

Background: An increase in deaths has been identified after a 2-day break (longest interdialytic gap) in hemodialysis (HD) in previous reports, and frequent HD has recently been recommended. However, no reports have evaluated how the dialysis schedule affects day-of-week hospitalization on a long-term basis.

Methods: We analyzed 11,111 hospitalizations of 1,955 HD patients and 1,969 hospitalizations of 497 peritoneal dialysis (PD) patients to clarify the association between the day-of-week hospitalizations for acute CVDs including pulmonary edema, cerebrovascular disease, heart failure, ischemic heart disease, cardiac arrhythmia, and aortic and peripheral vascular disease (HD: 1,705 times; PD: 261 times) and the dialysis schedule at our institution between January 1995 and December 2014.

Results: In HD patients, the rate of hospitalizations for acute CVDs on 1st HD day (Monday or Tuesday, 42%) was significantly higher than that on 2nd (Wednesday or Thursday, 24%) and 3rd (Friday or Saturday, 22%) HD days (P<0.001), while there was no significant difference for PD patients. However, in the HD group, the hospitalization rate on the 1st HD day has been decreasing in recent years (1st 5yr, 48%; 2nd 5yr, 41%; 3rd 5yr, 39%; P<0.001; 3rd 5yr, 39%; P<0.001). Moreover, the rates of acute CVD contributing to overall hospitalizations have been decreasing in HD patients (1st 5yr, 33%; 2nd 5yr, 19%; P<0.001; 3rd 5yr, 13%; P<0.001; 4th 5yr, 9.6%; P<0.001). Frequent HD (>4 times/week) at our institution increased from 1.0% (1st 5yr) to 5.3% (4th 5yr) (P<0.001), and the rate of hospitalizations for acute CVDs on 1st HD day significantly decreased from 37% pre- to 24% post-initiative (P=0.04).

Conclusions: Day of-week hospitalization was affected by the HD schedule, but the risk decreased over time. This result may be attributed to the advantages of frequent HD. Our findings can guide clinical management practices for CVDs in dialysis patients.

FR-OR081
Obstructive Sleep Apnea in Incident Hemodialysis Patients Significantly Increases Risk for Sudden Cardiac Death and Cardiovascular Mortality Eric S. Kerr1, Esther D. Kim2, Lucy A. Moon1, Stephen M. Sozio3, Bernard G. Jaar,1 Michelle M. Estrella2, Rulan S. Parikh3,2 Ghada Bourjily,1 1Brown Univ, Providence, RI; 2Univ of Toronto, Toronto, ON, Canada; 3Johns Hopkins Univ, Baltimore, MD.

Background: Mortality in ESRD approaches 20% per year predominantly from sudden cardiac death (SCD). Obstructive sleep apnea (OSA) is characterized by abnormal breathing during sleep and oxygen desaturations and is highly prevalent in patients with ESRD. Whether OSA increases the risk for SCD, cardiovascular (CV) and all-cause mortality in HD is unknown.

Methods: In a prospective cohort of 558 incident HD patients from the Predictors of Arrhythmogenic and Cardiovascular Risk in ESRD (PACE) study, we examined the association of OSA diagnosis ascertained by physician chart review with all-cause mortality, CV mortality, and SCD using Cox proportional hazards model. SCD was defined as out of hospital, non-ischemic coronary events adjudicated by the end point committee.

Results: Sixty-six incident HD patients (12%) were identified as having OSA. Median age and sex were similar in OSA and non-OSA groups. Those with OSA had fewer African Americans (53% vs 71%), and higher median BMI (37 [IQR 31, 42] vs 27 [IQR 24, 32]), median Charlson comorbidity index (6 [IQR 5, 7] vs 5 [IQR 4, 7]), prevalence of diabetes (76% vs 56%), coronary artery disease (47% vs 34%), and median left ventricular mass index (76 [IQR 59, 93] vs 61 [IQR 50, 79]) (all p <0.05). During 1080 person-years of follow-up, there were 104 deaths, including 30 CV and 16 SCD. OSA was associated with a higher risk of all-cause mortality, CV mortality, and SCD after adjustment.

Conclusions: Incident HD patients with a known diagnosis of OSA are at significantly increased risk for all cause and CV mortality and SCD. Future studies should assess the impact of screening for OSA and OSA-targeted interventions on morbidity and mortality in ESRD.

Funding: NIDDK Support

FR-OR079
Quantifying Risk of Increased All-Cause Hospitalization for Adult Hemodialysis Patients Who Skipped Seasonal Flu Vaccination Nien-Chen Li, Udday Oonta, Norma J. Ofshtun, Jeffrey L. Hyenes, Franklin W. Maddux, Fresenius Medical Care, Fresenius Kidney Care North America, Waltham, MA.

Background: It is well known that skipping seasonal flu vaccination is at a risk of increased hospitalization. The study attempts to quantify such risk for adult hemodialysis (HD) patients (pts).

Methods: We selected active HD pts aged ≥ 18 years at Fresenius Medical Care North America for three flu seasons: 2013-14, 2014-15, and 2015-16. Each season covered August 1 to July 31 of the following year. Active pts were those who had records of treatments or laboratory work within 40 days prior to August 1. We calculated hospitalization rate per 1000 HD (≥4 times/week) at our institution grew from 1.0% (1st yr) to 2.58% (all p<0.001) in three seasons, respectively.

Results: The total active pts were 158,326, 202,793, and 220,031, and % pts vaccinated were 60.1, 75.6, and 80.4 for seasons 2013-14, 2014-15, and 2015-16, respectively. The estimated RR for hospitalization for non-vaccinated vs. vaccinated were 1.53, 1.87, and 2.58 (all p<0.001) in three seasons, respectively.

Conclusions: Our model showed the risk of increased all-cause hospitalization for adult hemodialysis patients who skipped seasonal flu vaccination were 53 to 158% higher in terms of average hospitalization rate. An aggressive program for promoting flu vaccination is well warranted.

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

53A
FR-OR082

High Efficiency Hemodiafiltration (HDF) versus Hemodialysis (HD): A Comparison of Clinical Outcomes in EuroDOPPS

Angelo Karaboyas,1 Francesco Locatelli,2 Ronald L. Pisoni,1 Bruce M. Robinson,3 Joan Fort,4 Raymond C. Vanholder,5 Hugh C. Rayner,6 Werner Kleophas,7 Stefan H. Jacobson,8 Christian Combe,9 Friedrich K. Port,9 Francesca Tentori,10 1Arbor Research Collaborative for Health, Ann Arbor, MI; 2Alessandro Manzoni Hosp, Lecco, Italy; 3U of Michigan, Ann Arbor, MI; 4U Hosp Vall d’Hebron, Barcelona, Spain; 5U Hosp, Gent, Belgium; 6Heart of England NHS, Birmingham, United Kingdom; 7MVZ DaVita, Dusseldorf, Germany; 8Heinrich-Heine U, Dusseldorf, Germany; 9Danderyd Hosp, Stockholm, Sweden; 10Centre Hosp U de Bordeaux, France; 11Vanderbilt U, Nashville, TN.

Background: Online HDF is considered the most efficient dialysis technique, though only 1 of 3 recent randomized trials demonstrated a survival benefit vs. HD. Post-hoc analyses of all 3 studies showed that patients who received the highest convection volumes had lower risk of adverse events. Use of high-volume HDF has consequently increased in many European countries, while online production of replacement fluid is not available in North America.

Methods: We analyzed n=8567 patients from 7 European countries in DOPPS phases 4-5 (2009-2015) with vintage ≥90 days. Among n=2023 (23%) HDF patients, about half had replacement fluid volume ≥20L. Adjusted Cox regression was used to estimate the association between mortality and HDF (vs. HD).

Results: Median follow-up was 1.6 years, and 2043 patients died. The adjusted HR (95% CI) or mortality was 1.13 (1.00-1.28) for any HDF vs. HD and 1.08 (0.92-1.26) for HDF ≥20L vs. HD. Results were similar for CV and infection-related mortality. We did not observe lower mortality risk among facilities prescribing HDF to a greater % of patients.

Conclusions: Our results do not support the notion that online HDF achieves better patient survival vs. HD, even focusing on HDF with convection volumes ≥20L. Further trials specifically designed for testing the effect of increased convection of online HDF vs. HD on clinical outcomes are necessary before superiority of HDF can be accepted.

FR-OR083

Time Course of Reduction in Itch Intensity during and following Treatment with Nalbuphine ER Tablets: A Randomized, Placebo-Controlled Trial in Patients with Uremic Pruritus

Thomas Richard Sciascia,1 Howard Hart,1 Vandana S. Mathur,2 Trevi Therapeutics, New Haven, CT; 2Mathur Consulting, Woodside, CA.

Background: Clinical trials in uremic pruritus (UP) patients are typically powered to compare differences in itching intensity between the active treatment and placebo at the end of the treatment period. However, understanding the time course of loss of effect following treatment withdrawal is also important. Patients with severe baseline itching are of particular interest because they are the population with the greatest medical need.

Methods: This was a 3-arm randomized, double-blind, placebo-controlled trial comparing nalbuphine ER tablets 120 mg bid (NAL 120) and 60 mg BID (NAL 60) to placebo in 373 hemodialysis patients with UP. We measured change from baseline to weeks 7 and 8 in the worst itching intensity using an 11-point numerical rating scale (NRS) (0 = no itching; 10 = worst possible itching). The primary endpoint compared NAL 120 to placebo at the mean of Weeks 7 and 8. After completion of treatment, NRS data was additionally collected for 2 weeks.

Results: Among all patients and those with severe baseline itching (NRS ≥7.0), NAL 120 consistently reduced itching from the end of the 2 week titration through the end of the treatment period. In the NAL 120 group, the mean (SEM) reduction in itching intensity at the end of treatment and end of washout was 3.8 (0.3) (p = 0.017 vs. placebo) and 2.2 (0.3) (p = NS vs. placebo) in the overall population and 4.7 (1.0) (p = 0.01) and 3.1 (0.4) (p = 0.05) in the severe pruritus population.

Conclusions: In this randomized, controlled trial, NAL 120 significantly reduced itching in patients with moderate or severe pruritus. Among patients with severe pruritus, the anti-pruritic effects of NAL remained significantly better vs. placebo for at least 2 weeks after the last dose.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

FR-OR084

Timing of Hospice Enrollment and End-of-Life Utilization and Spending among Patients with ESRD

Melissa Wacherman, Susan M. Hailpern,7 Nancy L. Keating,1 Manjula Kurella Tamura,2 Ann M. O’Hare,2 Harvard Medical School; 2Univ of Washington; 2Stanford Univ.

Background: Rates of hospice enrollment in patients with ESRD have increased over time, although remain low compared with the general population. Less is known about timing of hospice enrollment in ESRD patients. Because Medicare will not pay concurrently for dialysis and hospice for patients whose life-limiting illness is ESRD, these patients may be less often referred to hospice in a timely fashion. We examined the frequency and timing of hospice enrollment and patterns of end-of-life utilization and spending among ESRD patients.

Methods: Using USRDS data, we identified all ESRD patients who died between 2000 and 2012 who had Medicare Part A & B. Patients were grouped according to whether and when they enrolled in hospice before death. We used a generalized linear model to examine the association of timing of hospice with healthcare utilization and spending at the end of life after adjustment for patient characteristics.

Results: Of the 739,689 ESRD patients who died, 19% were receiving hospice at the time of death, increasing from 10% in 2000 to 26% in 2012. Among hospice enrollees, 42% enrolled ≤3 days before death, decreasing slightly from 43% in 2000 to 40% in 2012. Adjusted measures of spending and utilization were significantly lower for those who received >3 days of hospice than for patients who did not use hospice (all p<.001). For patients who received ≤3 days of hospice, spending was not significantly different than for hospice non-users (p = .97), and hospital admission, length of stay, and ICU utilization were significantly higher (all p<.001).

Funding: Other NIH Support - K23AG049088 from National Institute on Aging, VA Support
Efficacy of Endothelin Receptor Blockade in Experimental Podocin Nephropathy
Tania Tamara Wlodkowski, 1 Mansoureh Tabatabaiefar, 1 Helga Denc, 1 Geraldine Mollet, 2 Corinne Antignac, 2 Franz S. Schaefler, 2
1Pediatric Nephrology Div, Heidelberg Univ Hospital, Heidelberg, Germany; 2InsERM U1163-Imagine Inst, Paris Descartes Univ; Paris, France.

Background: Renal endothelin-1 expression is increased in various kidney diseases. Selective ET receptor blocker (ERA) improves renal function in various animal models of kidney disease. Here, we investigated antiproteinuric and nephroprotective effects of the ET receptor blocker Atrasentan in a mouse model of the most common human hereditary podocytopathy. Hemizygous R133Q-NPHS2 knock-in mice develop heavy proteinuria, podocyte loss, focal segmental glomerulosclerosis (FSGS) and progressive renal failure. 

Methods: In C57BL/6 mice with Nphs2<sup>R133Q</sup>/<sup>C</sup> CRE-hemizygosity for mutant podocin was induced by tamoxifen injection. In a pilot study the animals were administered Atrasentan encompassing a sixfold dose range with food from time of induction or remained untreated (U). Furthermore, animals treated with a 4-week delay (D) (delayed, n=14) were analyzed. Weight, blood pressure (MAP) and proteinuria were monitored weekly. Biochemical parameters and histopathological changes were examined after 4-week treatment.

Results: Prophylactic ERA blockade demonstrated no attenuation in proteinuria and histological lesions at any dose level. Notably, intraperitoneal ET-1 expression increased only gradually as disease progressed, reaching significance by wk 5. When Atrasentan was administered at the time of maximal proteinuria and strong ET1-1 expression, proteinuria decreased progressively and MAP was lowered significantly (wk7: 80.4 (D) v. 99.5 (U) mmHg, p=0.001) Preliminary histological evaluation (n=9) demonstrates attenuation in glomerulosclerosis (GSH: 1.69 (D) v. 2.27 (U wk 8), p=0.0008) and tubulointerstitial fibrosis (TIF % of total area: 4.18 (D) v. 7.56 (U wk 8), p=0.008) podocyte numbers tended to be better preserved (podocytes per glom: 54% (D) v. 32% (U wk 8) of healthy controls, n.s.). Furthermore, podocin protein abundance and mRNA expression was partly preserved in the treated animals.

Conclusions: In an in vivo model of hereditary podocin nephropathy, treatment with Atrasentan showed a beneficial effect on glomerulosclerosis and tubulointerstitial fibrosis. 

Funding: Pharmaceutical Company Support - AbbVie

FR-OR085

Genomic Imbalances Associate with Cognitive Impairment and Anxiety/ Depression in Children with Chronic Kidney Disease
Amy Kogon, 1,2 Miguel Verbitsky, 1,3 Matthew Matheson, 1 Craig S. Wong, 4 Bradley Warady, 5 Susan L. Furtth, 5 Ali G. Harihavi, 1,2 National Institute of Child Health and Human Development, Washington, DC; 1CCTR, Nationwide Children’s Hosp; 2Columbia Univ; 3Chronic Kidney Disease in Children Study Group.

Methods: We examined the relationship of GIs to NP performance using data from the Chronic Kidney Disease in Children Study. GIs were defined as genomic variations that have the ability to modify susceptibility to a variety of human disorders such as cancer, obesity, and common diseases. GIs were detected by chromosomal microarrays and defined as definitively pathogenic or likely pathogenic per American College of Medical Genetics recommendations for interpretation of microarray data (Verbitsky et al, JCI 15). Linear regression determined associations of GIs with NP scores after controlling for GFR, age, and maternal education, low birth weight, sex, and genetically defined ancestry using genomic SNP data. NP measure score ≥1 standard deviation worse than the standardized mean was considered at risk.

Results: Analysis included 31 children with and 388 children without GIs. There were no differences in age or kidney disease parameter differences between the groups. By adjusted regression analyses, associations associated with a 7.6 point lower IQ score (p=0.006), 6.6 point worse IP score (p=0.003) and 5.8 point worse GEC score (p=0.01). 40% of children with GIs were at risk for intellectual disability, 46% for anxiety/depression and 57% for executive function. 

Conclusions: GIs may predict NP function in children with CKD. Identifying pathogenic CNVs may provide opportunity for early diagnosis and personalized intervention for this at-risk subgroup.

Funding: NIDDK Support

FR-OR086

DNA Copy Number Variations Associated with Vesicoureteral Reflux and Its Sequelae
Dong Liang, 1 David S. Hains, 1 Andrew L. Schwadener, 2 "Innate Immunity Translational Research Center, Le Bonheur Children’s Hospital, Memphis, TN; 2CCTR, Nationwide Children’s Hospital, Columbus, OH.

Methods: Using high-resolution genome-wide, array comparative genomic hybridization (aCGH) experiment, using the genomic DNA from 298 RIVUR patients and 600 controls, we evaluated the status of CNVs in pathways involving urinary tract infections. The RIVUR study followed 600 children with vesicoureteral reflux (VUR) and UTIs for two years, and DNA was collected on a subset of patients. We hypothesize that CNVs in pathways involving sterile urinary tract infections (UTIs) may be associated with increased risk for VUR.

Conclusions: Analysis identified a total of 612 common and 2659 rare CNVs differentially present in RIVUR compared to controls. 9 of the top 20 involved common pathways involved in host immune response. Further analysis revealed that these CNVs were present in a subset of patients with disease sequela, and offered potential candidates for novel insights into disease pathogenesis.

Funding: Pharmaceutical Company Support - AbbVie

FR-OR087

Predictors of Progressive Kidney Disease after Definitive Vesicoamniotic Shunting for Lower Urinary Tract Obstruction
Cheryl P. Kaddis, 1 Marissa J. Defreitas, 1 Wacharee Secherunyong, 1 Jayanthi Chandar, 1 Michael Freundlich, 1 Gaston E. Zilleruelo, 1 Carolyn L. Abitbol. 2 Pediatrics/ Pediatric Nephrology, Univ of Miami Miller School of Medicine/Holtz Children’s Hospital, Miami, FL.

Methods: This is a retrospective, cohort study of 17 male infants who survived the fetal intervention to birth. All had patent VAS in place at birth. Patients were followed for one year, or until demise, with serial measures of serum creatinine (SCr) and urine protein profile.

Conclusions: Even with definitive VAS for LUTO, postnatal morbidity and mortality remain high, emphasizing the role of renal dysplasia, in spite of urinary diversion, in postnatal kidney failure. Predictors of infant kidney function in the first year include neonatal Scr at discharge and time to peak SCR, along with neonatal proteinuria.

Funding: NIDDK Support

FR-OR088

Polymorphisms in Antimicrobial Peptide, Ribonuclease 7, Associate with Urinary Tract Infection Risk
Keith Pierce, 1 David S. Hains, 1 Steven Creacy, 1 Andrew L. Schwadener, 1 Brian Becknell, 1 John David Spach. 1 "Innate Immunity Translational Research Center, Children’s Foundation Research Inst at Le Bonheur Children’s Hospital, Memphis, TN; 2YX Genomics, Cordova, TN; 3CCTR, Research Inst at Nationwide Children’s Hospital, Columbus, OH.

Methods: We used quantitative real-time PCR to investigate the prevalence of non-synonymous exonic single-nucleotide polymorphisms (SNPs) in RNASE7 of 444 individuals with urinary tract infections (UTIs) and vesicoureteral reflux (VUR) from the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study. 160 individuals with non-VUR UTIs from the Careful UTI Evaluation (CUTIE) Study, and 482 matched controls.

Conclusions: Additional SNPs in RNASE7 may provide novel insights into modifying factors for susceptibility to both UTIs and VUR.

Funding: NIDDK Support
Recombinant RNase 7 UPEC kill assays demonstrate that wild-type RNase 7 had a MIC of 0.1 ± 3 µM while the RNase 7 variant rs1263872, encoded by an alanine to proline mutation, had an MIC of 0.25-0.5 µM.

Conclusions: Our research suggests these RNASE7 polymorphisms confer a decreased antimicrobial activity and are associated with UTI risk in children.

Funding: NIDDK Support

FR-OR090

Prediction of Progression of Chronic Kidney Disease in Children by Various eGFR Markers in Comparison to Nuclear GFR

Janusz Feber, Razgah Fajr Alldahfiry, Nick Barrowman.

Dept of Pediatrics, Children’s Hospital of Eastern Ontario, Ottawa, ON, Canada; 2Children’s Hospital of Eastern Ontario Research Inst, Ottawa, Canada.

Background: The accuracy of various eGFR formulas in comparison to nuclear GFR has been well documented. It is however unclear which eGFR is best suited for longitudinal follow-up and prediction of progression of chronic kidney disease (CKD). The aim of the study was to analyze the predictive power of various eGFRs obtained during follow-up for the prediction of measured GFR.

Methods: We performed a retrospective analysis of eGFR estimates in children with CKD followed in our institution over the last 8 years. All available results of urea, creatinine, cystatin C and height were used to calculate following eGFRs: Cystatin C eGFR (Pediatric Nephrol 2003;18:981), Schwartz eGFR (JASN 2009;20:629), CKID eGFR (JASN 2009;20:629) and Lyon eGFR (NDT 2014;29:1082). Slopes of each eGFR were constructed by regression analysis in each patient; the intercepts of individual regression lines were then compared to nuclear GFR (nGFR) at the end of follow up. The ratios between predicted eGFR (PeGFR) and measured nGFR were analyzed by linear mixed effects models and intraclass correlation coefficient (ICC).

Results: A total of 366 eGFR values were collected in 23 patients (aged 11.8±5.0 years) with progressive CKD over a median of 400 follow-up days (range= 0 to 2821). There were significant differences among PeGFR/nGFR ratios (linear mixed effect model, p<0.001). In post-hoc Tukey tests, Cystatin C PeGFR was found to be significantly higher than Lyon PeGFR and Schwartz PeGFR (both p<0.01). The agreement between various PeGFR in the prediction of nGFR was modest (ICC=0.57, 95% CI=0.35 to 0.76). The most accurate prediction of the nuclear GFR (PeGFR/nGFR ratio closest to 1) was obtained with CKID PeGFR (mean ± SD ratio = 1.03 ± 0.20) followed by Schwartz PeGFR (0.97±0.23), Lyon PeGFR (0.95±0.23) and Cystatin C PeGFR (1.13±0.27; significantly different from 1.0, p<0.02).

Conclusions: There were significant differences among various eGFR formulas in the prediction of the measured nuclear GFR at the end of follow-up. The most accurate prediction of the nuclear GFR was obtained with the CKID eGFR.

FR-OR091

Long-Term Clinical Outcomes and Risk Factors in Isolated Antenatal Hydronephrosis: A Prospective Cohort Study

Eduardo A. Oliveira, Robert H. Mak.

Pediatrics, UCSD, San Diego, CA; 2Pediatrics, HC-UFMG, Belo Horizonte, MG, Brazil.

Background: Antenatal hydronephrosis (ANH) affects approximately 1-5% of pregnancies. There are few studies on long-term clinical outcomes of infants with ANH. The clinical events of isolated adverse health events (AEH) and the risk factors in a prospective cohort of 447 infants with isolated ANH in a single tertiary center.

Methods: ANH was classified according to the Society Fetal Urology (SFU) grading system into two groups (grades 0-2 vs. 3-4). The primary end-point was time until the occurrence of a composite of incident AHE, including proteinuria, hypertension and chronic kidney disease (CKD).

Results: Median follow-up time was 6.4 years (IQ range, 2.8 – 12.5). During follow-up, urinary tract infections (UTI) occurred in 89 (20%) children. Patients with SFU grades 3-4 had a greater risk of the occurrence of UTI (P < 0.001). Thirteen patients (3%) had recurrent UTI and were independent predictive factors of AHE. Renal parenchyma thickness at birth < 8.7 mm and a baseline creatinine > 0.37 mg/dl were strong predictors of AHE.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline creatinine (mg/dl)</td>
<td>1.27 (1.05 - 1.56)</td>
<td>0.014</td>
</tr>
<tr>
<td>Renal parenchyma thickness at birth (mm)</td>
<td>0.78 (0.62 - 0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td>Recurrent UTI</td>
<td>4.52 (1.49 - 13.6)</td>
<td>0.007</td>
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Conclusions: The lower risk of death for Hispanic Whites vs. white dialysis patients extends to the pediatric age range, but for African Americans there is a reversal with higher mortality rates than their White peers. Lower transplant rates for Hispanics and African Americans also extend across adult and pediatric populations. Future studies are needed to further understand the underlying causes of these contrasting findings in adult and pediatric ESRD patients.

Funding: NIDDK Support
FR-OR093
Antenatal Corticosteroids and the Renin-Angiotensin-Aldosterone System in Adolescents Born Preterm Andrew M. South,1,2 Patricia A. Nixon,1,2 Debra I. Diz,1,4 Gregory B. Russell,1 Beverly Snively1, Hossam A. Shallout,2 James C. Rose, Michael H. O’Shea,1 Lisa K. Washburn1,2.1 Pediatricians, Wake Forest School of Medicine, Winston Salem, NC; 2Hypertension and Vascular Research Center, Wake Forest School of Medicine, Winston Salem, NC; 3Health and Exercise Science, Wake Forest Univ, Winston Salem, NC; 4Surgery, Wake Forest School of Medicine, Winston Salem, NC; 5Biostatistical Sciences, Wake Forest School of Medicine, Winston Salem, NC; 6Obstetrics and Gynecology, Wake Forest School of Medicine, Winston Salem, NC; 7Pediatrics, Univ of North Carolina School of Medicine, Chapel Hill, NC.

Background: Antenatal corticosteroid (ANCS) treatment hastens fetal lung maturity and improves survival of premature infants, but the long-term effects of ANCS are not well described. Animal studies suggest ANCS increases the risk of cardiovascular disease through programmed changes in the renin-angiotensin (Ang)-aldosterone system (RAAS). We hypothesized that ANCS exposure alters the RAAS in adolescents born prematurely.

Methods: A cohort of 173 adolescents born prematurely was evaluated at age 14 years, of whom 92 were exposed to ANCS. We measured plasma and urine Ang II and Ang I(1-7) and calculated Ang II/Ang I(1-7) ratios. We used general linear regression models to estimate the difference in the RAAS between the ANCS-exposed and unexposed groups, adjusting for confounding variables.

Results: In unadjusted analyses, and after adjustment for sex, race, and maternal hypertension, ANCS exposure was associated with increased urinary Ang II/Ang I(1-7) [adjusted estimate 0.27 (95% CI 0.03, 0.5), p = 0.03], increased plasma Ang I(1-7) [0.66 (0.26, 1.07), p = 0.002], and decreased plasma Ang II/Ang I(1-7) [-0.48 (-0.91, -0.06), p = 0.03].

Conclusions: These alterations indicate an imbalance in the RAAS, promoting the actions of Ang II at the expense of Ang I(1-7), which over time may increase the risk of renal inflammation and fibrosis and ultimately hypertension and renal disease.

Funding: Other NIH Support - Program project grant P01 HD047584

FR-OR094
Oliguria Is Independently Associated with Increased Mortality Risk amongst Critically Ill Children with Acute Kidney Injury Ahmad Kaddourah,1,2 Rajjit K. Basu,2 Stuart Goldstein,2 Scott M. Sutherland,2 1Sidra Medical and Research Center, Doha, Qatar; 2Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 3Dept of Pediatrics at Stanford Univ, Stanford, CA.

Background: Acute kidney injury (AKI) is associated with poor outcomes in critically ill children (CIC). While the KDIGO serum creatinine (SCr) AKI criteria have been widely applied, the urine output (UOP) criteria have not been studied. The impact of disregarding UOP criteria and effect of meeting both criteria remains unknown. We hypothesize the mortality rates in CIC meeting one but not both criteria (Cr UOP/SCr) and effect of meeting both criteria remains unknown. We hypothesize the mortality risk associated with meeting both criteria exceeds that of meeting either alone.

Methods: We queried the database for AWARE, a prospective international multicenter study designed to assess AKI outcomes in CIC. We compared 28-mortality rates in CIC with Stage 2/3 AKI based upon whether they met both sets of criteria (SCR/UOP), SCR alone (SCR/UOP), or UOP alone (SCR/UOP).

Results: SCR and UOP data for 3318 CIC were available. 136(4.1%) deaths were reported. We observed poor agreement between SCR and UOP criteria to diagnose Stage 2/3 AKI (κ statistic 0.17, 95% CI:0.12-0.22). Kaplan-Meier survival analysis (figure 1) revealed that the mortality risk of the SCR/UOP group exceeded all other groups (adjusted OR=20.9 [95% CI:11.7–35.6], p<0.001).

Conclusions: Application of the UOP criteria identified a cohort of CIC with AKI undiagnosed by SCR criteria. Notably, this cohort had similar mortality to those with SCR diagnosed AKI. Additionally, we used identified a new AKI risk classification in CIC with a greater mortality risk. These findings underscore the importance of this definitional aspect and highlight the benefit of applying both KDIGO criteria in CIC.

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

Underlines represents presenting author.

FR-OR095
Loss of Serine Protease Hepsin Results in Defective Uromodulin Processing and Increased Activity of NKCC2 Eric Olinger,1 Luca Rampoldi,2 Ron Korstanje,2 Olivier Devyust.1 1Inst of Physiology, Univ of Zurich, Zurich, Switzerland; 2San Raffaele Scientific Inst, Milan, Italy; 3The Jackson Laboratory, Bar Harbor.

Background: Uromodulin, the most abundant protein in healthy urine, is a zona pellucida (ZP)-type protein exclusively produced in the thick ascending limb (TAL), where it modulates NaCl handling by regulating the Na+, K+ 2Cl- cotransporter NKCC2. The release and proper polymerization of uromodulin in urine was recently demonstrated to depend on a C-terminal proteolytic cleavage mediated by the serine protease hepsin (HPN). The functional consequences of defective HPN and uromodulin mis cleavage are unknown.

Methods: We investigated an ENU mouse line harboring a splice site mutation in Hpn, which is predicted to reduce the transcription rate. Furthermore, we performed a knockdown of HPN using lentiviral shRNA in primary mouse TAL cells.

Results: We confirmed the predicted lack of HPN expression in the kidneys of HPN-null mice. In the urine of these mice, we detected a dramatic decrease of mature uromodulin excretion and evidence of mis cleaved, polymerization-in competent uromodulin isoforms. SHRNA-mediated knockdown of HPN in polarized primary mouse TAL cells led to a strong decrease in apical secretion of uromodulin as well as in the amount and size of uromodulin polymers. In parallel with reduced urinary excretion, uromodulin massively accumulated both at the apical membrane and in the cytosol of TAL cells in HPN-ENU mice. These mice showed an exaggerated natriuretic response after furosemide and a better adaptation to 24h water deprivation, suggesting a hyperactivation of the TAL segment. This was supported by an increase in core and phosphorylated forms of NCC in HPN-ENU mice, in absence of adaptations in the distal convoluted tubule.

Conclusions: These data expand the physiological role of HPN in vivo and in primary TAL cells, which endogenously express uromodulin and HPN. The loss of HPN results in intracellular and apical membrane accumulation of uromodulin and a specific activation of the TAL, suggesting that membrane-bound uromodulin activates NKCC2. They give new insights into the regulation of uromodulin processing and its role in the TAL.

Funding: Government Support - Non-U.S.

FR-OR096
Plasma K+ Dependent Regulation of NaCl Cotransporter in Native Distal Convoluted Tubules Involves SPAK/OSR1 and Calcineurin David Penton Ribas,1 Jan Czogalla,1 Agnieszka Wengi,1 Nina Himmerkus,2 Dominique Loffing-Cuén,1 Olivier Staub,1 Markus Blich,2 Frank Schweda,2 Johannes Loffing,1 1Inst of Anatomy, Univ of Zurich, Zurich, Switzerland; 2Inst of Physiology, Univ of Kiel, Kiel, Germany; 3Inst of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; 4Inst of Physiology, Univ of Regensburg, Regensburg, Germany.

Background: A high dietary potassium (K+) intake causes a rapid dephosphorylation and hence inactivation of the thiazide-sensitive NaCl cotransporter (NCC) in the renal distal convoluted tubule (DCT). Based on experiments in heterologous expression systems and in mice, it has been proposed that changes in plasma K+ concentrations ([K+]p) modulate NCC phosphorylation via changes in intracellular Cl- concentrations that control the activity of the WNK/SPAK kinase pathway.

Methods: We used isolated perfused mouse kidneys, isolated perfused DCTs, and mouse kidney slice preparations to test the physiological relevance of this model on native DCT cells in vivo.

Results: We demonstrate that changes in extracellular [K+]p ([K+]p rapidly (<30 min) modulate NCC phosphorylation by direct effects on the DCT, with the most prominent changes occurring around physiological variations of plasma [K+]. The inhibition of cellular K+ fluxes by removing extracellular Cl- or by blocking Cl- channels with DIDS abolished NCC phosphorylation in response to low [K+]p, but did not blunt NCC dephosphorylation in response to high [K+]p. Moreover, NCC dephosphorylation under low [Cl-]p, and high [K+]p was independent from any significant changes in the phosphorylation status of SPAK. However, under these conditions, inhibition of protein phosphatase 1 by tacrolimus diminished [K+]p induced dephosphorylation of NCC. Inhibition of protein phosphatases 1, 2A and 4 by calyculin A did not interfere with the response to [K+]p, but increased NCC phosphorylation in general.

Conclusions: In the native DCT, changes in [K+]p directly and rapidly control NCC phosphorylation by CI dependent and independent pathways that involve both SPAK and calcineurin.

Funding: Government Support - Non-U.S.

FR-OR097
Calcineurin Rapidly Dephosphorylates Sodium-Chloride Cotransporter in Response to High Potassium Intake Wakana Shoda, Naohiro Nomura, Fumiaiki Ando, Yutaro Mori, Takayasu Mori, Eisei Sohara, Tatemitsu Rai, Shinichi Uchida. 1Dept of Nephrology, Tokyo Medical and Dental Univ, Bunkyo, Tokyo, Japan.

Background: Dietary potassium (K+) intake is well known for reducing blood pressure and mortality. Moreover, the sodium-chloride cotransporter (NCC) plays an important role in blood pressure regulation and urinary K+ excretion in response to K+ intake. In previous studies, it has been reported that NCC is activated by the Wnt with no lysine kinase (WNK) - Ste 20-related proline (SPAK) cascade in a low-K+ diet. However, the mechanism
of NCC regulation with high K+ intake is still unclear. A previous study showed rapid dephosphorylation of NCC induced by acute K+ load, suggesting the involvement of phosphotases. Protein phosphatase (PP1) and PP2B (calcineurin) have been reported to dephosphorylate NCC. To identify the mechanism involved in the regulation of NCC with K+ intake, we focused on rapid decrease of NCC phosphorylation during acute K+ load.

**Methods:** We used adult C57BL/6 mice, which were fed with a 1.7% K+ solution by gavage. The renal tubular (pro)renin receptor (PRR) has been shown to modulate water balance, blood pressure and Na+ homeostasis. We recently reported that inducible nephrin wide deletion of the PRR results in Na+ wasting, reduced epithelial Na+ channel (ENaC) expression in the kidney and attenuated hypertensive response to angiotensin-II (Ang-II) infusion.

**Background:** The renal tubular (pro)renin receptor (PRR) has been shown to modulate water balance, blood pressure and Na+ homeostasis. We recently reported that inducible nephrin wide deletion of the PRR results in Na+ wasting, reduced epithelial Na+ channel (ENaC) expression in the kidney and attenuated hypertensive response to angiotensin-II (Ang-II) infusion.

**Conclusions:** Our data show that KS-WNK1-Δ11 is a powerful activator of NCC. The mechanism may mean type-II WNK1-Δ11, which forms KS-WNK1-Δ11 autophosphorylation and activation that in turn promotes NCC N-Terminal phosphorylation by the WNK-SPAK-OSR1 pathway. Given the high expression of KS-WNK1-Δ11 in DCT, these observations may provide a mechanism to explain why the up-regulated NCC in PHAIi remains active despite the salt sensitive, low renin hypertension and hyperkalemia, expected to respond to CaSR via CaSR/CaSR/AQP2 signaling.

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

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**Regulation of WNK4-SPAK-NCC Pathway by the Calcium Sensing Receptor**

**Silviana Baza-Valenti,** Lorena Leonor Rojas, Maria Castañeda-Buono, Alejandro Rodríguez-Gama, Norma Hilda Vázquez, Luz Gracelia Cervantes-Perez, Jonatan Barrera-Chimal, Paola De los Heros, Gerardo Gamba.

**Molecular Physiology Unit, INCMNSZ-IBB-UNAM, Pharmacology, INICH, Faculty of Medicine, UNAM, Mexico City, Mexico.

**Background:** Extracellular calcium induces salt reabsorption in the TAL through the basolateral Calcium Sensing Receptor (CaSR) inducing hypercalciuria. CaSR is also expressed in the apical membrane of the DCT, where we hypothesize plays a role in activating NCC via WNK4-SPAK pathway to prevent salt loss and further decrease the calcium reabsorption.

**Methods:** NCC activity (thiazide-sensitive 2Na+ uptake) and the effect of the type I CaSR agonist galanin were analyzed in X. laevis oocytes in the absence or presence of CaSR and/or CaSR/CaSR/AQP2. Expression and phosphorylation of SPAK were assessed in HEK-293 cells co-transfected with WNK4 + wild type or mutant CaSR harboring the activating mutation E227K, in the presence or absence of the type 2 agonist R-568. Lastly, the WNK4-SPAK-NCC pathway was also studied by western blot analysis in kidneys of 12 mice administered with R-568 at 30 mg/kg or vehicle.

**Results:** In osmotically increased NCC activity by five-fold when co-expressed with WNK4 and CaSR (p<0.001). Absence of either WNK4 or CaSR precluded this effect. In R-568-stimulated HEK-293 cells, SPAK phosphorylation increased in a dose and time dependent manner only if both CaSR and WNK4 were present. Furthermore, co-transfection with the CaSR activating mutation, CaSR-E227K, phosphorylates SPAK in basal conditions (p<0.05). Interestingly, CaSR-E227K markedly increased WNK4-protein expression (almost two-fold, p<0.0001), a condition not observed with a WNK4 harboring PHAIi mutation, suggesting a Kelch-dependent mechanism. Finally, R-568 administration to wild-type mice showed increased NCC phosphorylation and increased WNK4 and SPAK protein expression (five-fold p<0.05).

**Conclusions:** We hypothesize that activation of CaSR can increase the activity of NCC via WNK4-SPAK pathway. It is possible that activation of CaSR by calcium in the apical membrane of DCT increases salt reabsorption via NCC to prevent salt loss and further decrease calcium reabsorption in this nephron segment.

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

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**Regulation of Ion and Proton Transport along the Distal Nephron**

**Cary Ankita L.,* Eduardo R. Areaga,** Lorena Leonor Rojas, María Castañeda-Buono, Alejandro Rodríguez-Gama, Norma Hilda Vázquez, Luz Gracelia Cervantes-Perez, Jonatan Barrera-Chimal, Paola De los Heros, Gerardo Gamba.

**Molecular Physiology Unit, INCMNSZ-IBB-UNAM, Mexico City, Mexico; INSEERM 970, Paris, France; ‘Oregon Health & Science Univ, Portland.

**Background:** The observation that the enri deepened NCC isomorph lacking exon 11 (L-WNK1Δ11) is an activator of NCC (Hypertension, 2014) and that WNK4 can have a dual effect on NCC, which depends on the intracellular Ca2+ concentration (JASN, 2015) have changed our working model of NCC regulation by WNK4. We thus revisited the effect of KS-WNK1-Δ11 isoform on NCC and WNK4 activity.

**Methods:** NCC activity was assayed in Xenopus oocytes by measuring the thiazide-sensitive 2Na+ uptake and the N-terminal phosphorylation by Western blot, two days after microinjection with NCC RNA alone or together human L-WNK1-Δ11, KS-WNK1-Δ11 and/or WNK4. WNK4-S335 phosphorylation was taken as a surrogate of activity. Antibodies used were against -proteins, WNK4, CaSR, SPAK, OSR1, WNK-1 or WNK-3, WNK5.

**Results:** KS-WNK1-Δ11 induced a dramatic activation of NCC by 3 fold (N=30, p<0.001) that was accompanied by increased SPAK/OSR1 phosphorylation as well as NCC surface expression and phosphorylation. The effect of L-WNK1-Δ11 and KS-WNK1-Δ11 on WNK4 was additive. The effect of L-WNK1-Δ11, but not that of KS-WNK1-Δ11 on NCC was precluded by coinjection with WNK4. The presence of KS-WNK1-Δ11 increased WNK4 phosphorylation at S335 by 7.5 fold (N=6, p=0.01), despite no change in intracellular Ca2+ concentration. KS-WNK1-Δ11 and WNK4 interaction was confirmed by immunoprecipitation. Increased WNK4-S335 phosphorylation in the presence of KS- WNK1-Δ11 was only seen in the immunoprecipitated fraction and was not observed with the KS-WNK1-Δ11 IQ mutant that lacks interaction with WNK4.

**Conclusions:** Our data show that KS-WNK1-Δ11 is a powerful activator of NCC. The mechanism may mean type-II WNK1-Δ11, which forms KS-WNK1-Δ11 autophosphorylation and activation that in turn promotes NCC N-Terminal phosphorylation by the WNK-SPAK-OSR1 pathway. Given the high expression of KS-WNK1-Δ11 in DCT, these observations may provide a mechanism to explain why the up-regulated NCC in PHAIi remains active despite the salt sensitive, low renin hypertensive and hyperkalemia, expected to inhibit the kinase.

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

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**A Cysteine-Rich Motif Regulates KS-WNK1 Protein Localization and Abundance**


**Univ of Pittsburgh; 'Univ of Lassanse.

**Background:** KS-WNK1 coordinates tubular NaCl and K+ transport through the concerted action of two major gene products: a ubiquitously expressed full-length "Long" isoform with intact serine-threonine kinase activity (L-WNK1), and an N-terminally truncated kinase-defective "Kidney Specific" isoform (KS-WNK1) that is highly expressed in the DCT. KS-WNK1 is transcribed from an intronic promoter that replaces the first four exons of L-WNK1 with a short unique exon, termed exon 4a. In the DCT, WNK signaling complexes form discrete puncta of unknown function. The marked expression of KS-WNK1 in DCT suggests that it may play a role in the formation of these complexes.

**Methods:** KS-WNK1 isoform localization in kidney was assessed by immunostaining and light microscopy. The role of specific residues in KS-WNK1 trafficking and stability was determined by gRNA mutagenesis, cDNA transfection into 293 and MDCK cells, confocal microscopy, cell fractionation, and cell culture assays.

**Results:** In the human and rodent DCT, C-terminal pan-WNK1 antibodies recognized a punctate signal that differed strikingly from a diffuse localization pattern in other nephron segments where KS-WNK1 expression is low. In cultured kidney epithelia, KS-WNK1 colocalized with WNK4 and was distributed diffusely throughout the cytoplasm. Mutagenesis studies revealed that KS-WNK1 puncta formation was dependent on a cysteine-rich motif harbored in exon 4a. Mutation of this signature to serines shifted KS-WNK1 to the basolateral membrane, rendering the protein unstable due to enhanced sensitivity to its cognate E3 ubiquitin ligase, the KLHL3/3UL3 complex. In coexpression studies, L-WNK1 redistributed into KS-WNK1 puncta, indicating that KS-WNK1 may act as a scaffold that sequesters WNK complexes in the DCT.

**Conclusions:** These results suggest that exon 4a acts as a cap to protect KS-WNK1 from disposal, and that the cysteines in exon 4a are necessary for its assembly into discrete structures that participate in DCT physiology. We propose that the punctate localization of WNK1 kinetics in the DCT may reflect a KS-WNK1 dependent signaling response during oxidative or potassium stress.

**Funding:** NIDDK Support, VA Support

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

Underline represents presenting author.


**FR-OR102**

**Prorenin Receptor/ATP6AP2 Is Required for V-ATPase Assembly and Function but Not for the Renin-Angiotensin System** Matias Simons, 1 Magda Cannata Serio, 1 Virginie Hauser, 1 Francesco Trepiccione, 1 Michael Schwake, 1 Dominique Eladrai. 1

**Background:** The proton pump vacuolar (V)-ATPase acidifies intracellular organelles and is crucial for cellular processes. The multisubunit complex is divided into the proton pore (V0 sector) and the ATP hydrolysis domain (V1 sector). Apart from the V1 and V0 subunits, there are two accessory subunits, ATP6AP1 and ATP6AP2. While ATP6AP1 seems to participate in V0 assembly, ATP6AP2 has been proposed to mediate the endoplasmic reticulum (ER) to Golgi transport and is crucial for many cellular processes. The multisubunit complex is divided into the proton pore (V0 sector) and the ATP hydrolysis domain (V1 sector). Apart from the V1 and V0 subunits, there are two accessory subunits, ATP6AP1 and ATP6AP2. While ATP6AP1 seems to participate in V0 assembly, ATP6AP2 has been proposed to mediate the endoplasmic reticulum (ER) to Golgi transport and is crucial for many cellular processes.

**Methods:** This study aimed at characterizing ATP6AP2 functions in the kidney by combining phenotypic characterization in mouse and Drosophila models with interaction proteomics in cultured human cells. Using an inducible conditional deletion of ATP6AP2 in the tubular nephron of the mouse, we recently showed that acid-base regulation was decreased due to impaired V0 subunit protein expression and activity in the intercalated cells of the collecting duct. By contrast, renal ER stress was not affected.

**Conclusions:** Taken together, our results demonstrate that ATP6AP2 interacts with ATP6AP1 in the ER to control ER homeostasis. Together with the in vivo analysis, our data argue for a main role of ATP6AP2 in V-ATPase assembly and function and against a role in the renin-angiotensin system.

**Funding:** NIDDK Support

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**FR-OR103**

**Recombinant ApoL1 Confers pH-Dependent Anion Permeability to Phospholipid Vesicles** John C. Edwards, Internal Medicine, Saint Louis Univ, Saint Louis, MO.

**Background:** Variants in ApoL1 confer increased risk of certain types of chronic kidney disease in people of African ancestry. ApoL1 has been reported to function as an ion channel but reports on the nature of this activity are rare. The mechanism is not clear.

**Methods:** Recombinant N-terminal His-tagged ApoL1 was expressed in bacteria and purified. N- and C-terminal affinity and gel filtration using methods of Thompson (PNAS 112: 2894 (2015)). Ion permeability was assessed using vesicle-based, voltage dependent CI and K efflux assays employing ion selective electrodes. Single channel properties were investigated using the Tip-Dip lipid bilayer approach with ApoL1 added to the bath solution. Presence of a single channel was probed using intrinsic tryptophan fluorescence.

**Results:** The purification method yields large amounts of very highly purified His-tagged ApoL1 which is active in a trypsinogen killing assay. Direct addition of ApoL1 to pre-formed phospholipid vesicles yields robust CI selective permeability that supports voltage-driven chloride transport. The activity shows a strong dependence on pH at which proton pump membranes interact, with a sharp drop in activity as pH is raised above 6.5. Activity is linearly dependent on mass of protein, and shows strong dependence on lipid composition of the vesicles, requiring the presence of negatively charged phospholipids. We measured vascular reactivity in iliac arteries with wire myographs; these data are presented as mean arterial pressure (MAP) in wild-type (WT, n=3), TLR4−/− (n=3), and TLR4−/− or TLR4+/− (n=3, +5) in an animal model, and the affinity of the peptide to the receptor mediating these effects was identified. The plasma concentration in humans was quantified in CKD patients and controls.

**Results:** The amino acid sequence of the endogenous cofactor of Ang II is important for the development of salt hypertension. Chromatographic fractions with vasodilatory properties were fractionated to homogeneity. The peptide was isolated from bovine adrenal glands chromatographically. The vasodilatory short-term and long-term effects were confirmed in vivo. The plasma concentration of VIF was significantly increased in CKD patients compared to controls.

**Conclusions:** VIF is a novel vasoregulatory peptide which modulates the vasocostrictive effects of Ang II by acting on the AT2 receptor. It is likely that this increase in VIF may serve as a counter-regulatory effect to defend against hypertension. Understanding the mechanisms of this novel peptide may help us to understand the pathophysiology of renal and heart failure and may form a basis for the development of new strategies for the prevention and treatment of cardiovascular disease in these patients.

**Funding:** Government Support - N.I.H.
Sodium on the Podium: The Kidney in Hypertension

ORAL Abstracts

FR-OR107
Renal-Specific Dendritic Cell Depletion Causes Hypertension via Reduced Sodium Chloride Cotransporter Expression
Brandi M. Wynn,1,2 Gillian Grace Hecht,2 Trinity Kronk,1 Henriecie Jacobien van Elst,2 Robert S. Hoover,3 1Dept of Physiology, Emory Univ, Atlanta, GA; 2Dept of Medicine, Renal Div, Emory Univ Atlanta, GA; 3Veteran’s Administration Research Service, Atlanta, GA; 4Atlanta VA Medical Center, Atlanta, GA.

Background: During hypertension, dendritic cells (DCs) have been shown to act as immune cells and secrete cytokines, such as IL-6. Recently, DCs were found to form an intricate network within the renal cortex and especially along the distal nephron. Additionally, during AngII-mediated hypertension, a subset of DCs route to the kidney. Studies have shown that loss of renal-specific DCs (rDCs) reduce glomerulonephritis and play an important role in the progression of hypertension. We hypothesize that rDCs modulate blood pressure (BP) and sodium transporter expression.

Methods: Tail-cuff measurements were performed in rDC-depleted and WT mice. rdc loss contributed to a decreased systolic blood pressure (94±17mmHg vs. 130±10mmHg ±10mmHg wt, n=5 vs. 5). To determine a mechanism, protein expression of phospho-NCC (pNCC) and total NCC, along with IL-6 was determined. rDC-depleted mice had a decreased expression of total NCC (48% decrease), with no changes in pNCC or IL-6. There were no differences in urinary sodium excretion at baseline.

Results: Tail-cuff measurements were performed in rDC-depleted mice and WT (C57Bl/6). Renal-specific loss of DCs contributed to a decreased systolic blood pressure (94±17mmHg vs. 130±10mmHg wt, n=5 vs. p=0.05). To determine a mechanism, protein expression of phospho-NCC (pNCC) and total NCC, along with IL-6 was determined. rDC-depleted mice had a lower expression of total NCC (48% decrease), with no changes in pNCC. In addition, no detectable changes in IL-6 were observed.

Conclusions: These data suggest that baseline BP is modulated by resident innate immune cells specific to the kidney. Our data also demonstrate that rDC-depleted mice have reduced expression of the distal nephron sodium transporter, NCC, which may be contributing to this phenotype. In addition, we observed no differences in IL-6, a predominate cytokine secreted by DCs. Together, our data demonstrate that rDCs contribute to reduced NCC expression and hypertension.

Funding: Other NIH Support - 2T32DK7656-21, VA Support

FR-OR108
Atrial Natriuretic Peptide Knockout Exacerbates Hypertension in Dahl Salt-Sensitive Rat
Darja Ilitovskaya, Gregory Blas, Vladislav Levchenko, Alison J. Kriegel, Alexander Staruschenko. Physiology, Medical College of Wisconsin, Milwaukee, WI.

Background: Atrial Natriuretic Peptide (ANP) encoded by the Nppa gene is an osmoregulatory hormone known to promote salt excretion and therefore lower blood pressure. Nppa knockout mice were shown to exert a salt-sensitive (SS) phenotype; furthermore, Nppa was identified as one of causative genes at a GWAS locus relevant to blood pressure (BP) control. The current project was designed to study the effects of ANP deficiency under the condition of SS hypertension using the Nppa KO developed on the Dahl SS rat background.

Methods: A combination of in vivo (chronic BP monitoring and GFR measurement in conscious unrestrained animals), electrophysiological (single channel patch-clamp analysis of the freshly isolated split-open CCD), molecular and biochemical approaches and echocardiography were used here to characterize the role of ANP in the development of SS hypertension in Dahl SS rats.

Results: Nppa KO rat is viable; there was no difference observed in the body weight or kidney to body weight ratio of the 8 week old Nppa KO animals compared to wild type SS rat. However, heart weight is significantly higher in Nppa KO rat. Echocardiography revealed a striking hypertrophy of the right ventricle, and an increase in right ventricle wall thickness and left ventricle septal wall thickness in Nppa KO rats. Furthermore, Nppa KO rats have lower urine output compared to wild type SS rats, and show decreased GFR even when fed a normal salt diet. BP measurements indicate the Nppa KO rats exhibit exacerbated salt-sensitivity compared to wild type SS controls (mean arterial pressure after 21 days of a 4% NaCl diet was 183 ± 9 in Nppa KO and 144 ± 4 mmHg in SS control group). Additionally, electrophysiological analysis demonstrated that Nppa KO animals have higher Epithelial Sodium Channel (ENaC) activity in the distal nephron (CNT/CCD) compared to wild type rats.

Conclusions: ANP plays a critical role in the development of SS hypertension. Knock out of Nppa is SS rats results in significant abnormalities in heart and kidney function.

Funding: NIDDK Support, Other NIH Support - NHLBI, Private Foundation Support

FR-OR109
Slc26a11 Plays an Important Role in Salt Reabsorption in the Kidney Collecting Duct: Impact on Furosemide Diuresis and Salt/DOCA Hypertension
Jie Xu,1 Sharon L. Barone,1,2 Marybeth Brooks,1,2 Saeed Alshahrani,1 Kamyar Zahedi,1 Maryancho Soleimani.1,2 1Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; Research Services, Veterans Affairs Medical Center, Cincinnati, OH.

Background: The identity and role of trans-cellular chloride reabsorbing pathways in medullary collecting ducts are poorly understood. We have localized Slc26a11 to the apical membrane of A-intercalated cells in the CCD, OMD and IMCD. Functional studies in cultured cells and oocytes indicate that Slc26a11 can function as a Cl/HCO3 exchanger, chloride conductive pathway and electrogenic NaCl co-transporter. Expression of Slc26a11 in mice increases response to furosemide treatment or salt loading, raising the possibility that it is important in salt reabsorption in the setting of enhanced delivery of salt to the collecting duct.

Methods: To ascertain the role of Slc26a11 in the kidney, kidney specific Slc26a11-KO mice were generated by crossing floxed-Slc26a11 mice with Cadherin promoter-driven Cre recombinase transgenic mice.

Results: Immunofluorescence microscopy, northern and western blot analyses showed more than 90% reduction in the expression of Slc26a11 in the kidneys of KO mice. These mice exhibited significant salt wasting in response to furosemide (sodium excretion of 0.44 ± 0.05 vs. 0.18±0.06, n=5 vs. n=6, p<0.01). Based on the evidence that Slc26a11 is present in the two genotypes (0.18 ± 0.02 mmoles/day in WT and KO mice). Slc26a11 KO mice exhibited complete abolition of high salt/DOCA-induced hypertension vs WT mice when animals were placed on a high salt diet for 10 days and injected with a DOCA (systolic blood pressure was 98 mm Hg in KBAT KO vs. 145 mm Hg in WT mice, as measured by computerized tail cuff method (n = 5, p<0.01). Pendrin KO mice were used for comparison and showed a significant protection against salt/DOCA-induced hypertension.

Conclusions: We conclude that Slc26a11 plays an important role in salt reabsorption along the length of the collecting ducts during increased delivery of salt and is essential for the generation of salt/DOCA hypertension. Slc26a11 KO could be a novel target for diuretic therapy in fluid overloaded states and in aldosterone-induced hypertension.

Funding: VA Support

FR-OR110
MIR-204 Protects the Kidney against Hypertensive Injury
Yuan Cheng,1,2,3,4 Dandan Wang,5 Baorui Huang,1,2 Maria Angeles Baker,3 Kristie Us,4 Yongcheng Zhang,1 Lijun Dong,1 Aron M. Geurs,2 Neiansong Wang,1,2 Sheldon S. Miller,1 Yongcheng He,1,2 Mingyu Liang,4 Nephrology, The First Affiliated Hospital of Shenzhen Univ and Shenzhen Second People’s Hospital, Shenzhen, Guangdong, China; 2The Center for Nephrology and Urology at Shenzhen Univ/Shenzhen Univ Health Science Center, Shenzhen Univ, Shenzhen, Guangdong, China; 3Nephrology and Rheumatology, Shanghai Jiaotong Univ Affiliated Sixth People’s Hospital, Shanghai, China; 4Center of Systems Molecular Medicine, Dept of Physiology, Medical College of Wisconsin, Milwaukee, WI; 5Section of Epithelial and Retinal Physiology and Disease, National Eye Inst, National Insts of Health, Bethesda, MD.

Background: Hypertension is the second leading cause of end-stage renal disease. The role of microRNA (miRNA) in hypertensive renal injury remains largely unknown.

Methods: Small RNA deep sequencing was performed to examine miRNA profiles in hypertensive nephrosclerosis patients and Dahl salt-sensitive rats. The functional role of a selected miRNA and the miRNA involved were investigated in a rat model and a human cell model.

Results: MIR-204-5p abundance was significantly lower in kidneys of hypertensive nephrosclerosis patients and Dahl salt-sensitive rats. Administration of anti-miR-204-5p in salt-insensitive SS.13/13 rats decreased detectable miR-204-5p in the kidneys and significantly exacerbated the thickening of interlobular artery and renal interstitial fibrosis without influencing salt-induced increases of blood pressure. Knockdown of mir-204-5p led to up-regulation of protein tyrosine phosphatase SHP2 and increased phosphorylation of signal transducer and activator of transcription 3 in the rat kidneys. The role of mir-204-5p was further examined in a mouse model of hypertensive renal injury induced by uninephrectomy, angiotensin II, and a high-salt diet. MIR-204 gene knockout significantly exacerbated albuminuria, renal interstitial fibrosis, and thickening of interlobular artery in this model despite an attenuation of hypertension.

Conclusions: These findings in patients, rat and mouse models indicate a new mechanism in hypertensive renal injury in which endogenous miR-204 protects the kidney against hypertension.

Funding: Other NIH Support - National Institutes of Health grants HL121233, HL082798-01A1, HL125409, and GM066730; Government Support - Non-U.S.
**FR-OR113**  
**The Effect of Mycophenolate Mofetil versus Cyclosporin as a Combination Therapy to Low Dose Corticosteroid in High Risk Patients with Idiopathic Membranous Nephropathy: A Multicenter Randomized Trial**  
**Hi-Young Choi,1 Dong Ki Kim,1 Yang Wook Kim,1 Tae-Hyun Yoo,4 Jung Pyo Lee,2 Hyun Chul Chung,2 Kyu-Hyang Cho,2 Won Suk An,4 Duk Hyun Lee,2 Hee-Yeon Jung,1 Jung-Hee Cho,1 Chan-Duck Kim,1 Yong-Lim Kim,1 Sun-Hee Park.1 1Kyungpook National Univ; 2Seoul National Univ; 3Inje Univ; 4Yonsei Univ; Ulsan Univ; Yeungnam Univ; Dong-A Univ; Fatima Hospital, Daegu.

**Background:** The effect of mycophenolate mofetil (MMF) versus cyclosporin (CsA) combined with low-dose prednisolone was evaluated in patients with idiopathic membranous nephropathy (MGN) in a multicenter randomized trial (NCT01282073).  
**Methods:** Biopsy-proven idiopathic MGN patients with severe proteinuria (> 8 g/day, n=39) were randomly assigned to MMF or CSa group combined with low dose prednisolone, respectively and followed up for 48 weeks. Complete or partial remission rate of proteinuria as well as eGFR at 48 weeks were compared between the two groups.  
**Results:** Proteinuria at baseline and 48 weeks were 8.9 ± 5.9 and 2.1 ± 3.1 g/day in the MMF vs. 8.4 ± 3.5 and 3.2 ± 5.7 g/day in the CSA group. Cumulative incidences of complete or partial remission of proteinuria at 48 weeks were 76.1% in MMF and 66.7% in CSA group, a difference of 9.4% (95% CI -0.18 to 0.38) that did not exceed the predefined 20% margin.

**FR-OR112**  
**Detection of THSD7A Antibodies Is a Valuable Tool for the Differential Diagnosis of Membranous Nephropathy.** Elion Hoxha,1 Laurence H. Beck,2 Thorsten Wiech,1 Nicola M. Tomas,1 Christian Probst,3 Catherine Meyer-Schewinger,1 Gunther Zahnner,1 Phillip Rolf Stahl,3 Ulf Panzer,3 Sigrid Harendza,1 Udo Helmchen,1 David J. Salant,2 Rolf A. Stahl.1 1III. Medizinische Klinik, UKE-Hamburg, Hamburg, Germany; 2Boston Univ School of Medicine, Boston, MA; 3Inst für Pathologie, UKE-Hamburg, Hamburg, Germany; 4EUROIMMUN AG, Lübeck, Germany.

**Background:** Thrombospondin type-1 Domain-Containing 7A (THSD7A) is a target antigen in membranous nephropathy (MN) in addition to the major antigen Phospholipase A, Receptor 1 (PLA-R1). The prevalence of THSD7A antibody (THSD7A-Ab) positive patients is unknown and it is unclear whether differences occur in the clinical presentation between patients positive for PLA-R1-Ab or THSD7A-Ab.

**Methods:** We screened sera of 1276 patients with MN from three cohorts by Western blot and an indirect immunofluorescence test (IFT) for THSD7A-Ab or THSD7A Ab. Follow-up data over at least 12 months were available for 10 THSD7A-Ab positive patients.

**Results:** The IFT had a 92% sensitivity and 100% specificity compared to Western blot. The prevalence of THSD7A-associated MN in a prospective cohort of 345 consecutive patients with newly diagnosed MN was 2.6%, while the majority of patients was female. 40 of 1276 patients were identified to have a THSD7A-associated MN, in eight of them a malignant tumor was diagnosed within a median time of 3 months from diagnosis of MN. In one patient with THSD7A-associated MN and metastases of an endometrial carcinoma, immunohistochemistry demonstrated THSD7A expression on the metastatic cells and within follicular dendritic cells of the metastasis-infiltrated lymph node. Complete remission of proteinuria was observed in only those 4 patients in whom THSD7A-Ab disappeared from the circulation. Five patients had a partial remission of proteinuria, THSD7A-Ab became negative in one and remained positive in four patients. One patient had no remission of proteinuria and THSD7A-Ab persisted.

**Conclusions:** The IFT allows a sensitive and specific measurement of THSD7A-Ab in patients with MN. Patients with THSD7A-associated MN differ in their clinical characteristics from patients with PLA-R1-associated MN. Intensive screening for malignant tumors is warranted in patients with THSD7A-associated MN.

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

**FR-OR111**  
**MicroRNA-132 Regulates Renin Release via Targeting Cox-2 in the Macula Densa.** Roel Bijlkerk,1 Wendy Stam,1 Sharon Van Gelderen,1 Ton J. Rablink,2 Anton Jan Van Zonneveld.1 1Internal Medicine (Section Nephrology), Leiden Univ Medical Center, Leiden, Netherlands; 2Einthoven Laboratory for Experimental Vascular Medicine, Leiden Univ Medical Center, Leiden, Netherlands.

**Background:** Renin synthesis and release from the juxtaglomerular apparatus is the rate-limiting step in the activation of the renin–angiotensin system, which is central to the regulatory role for microRNA-miR-132 function. Mice were housed in metabolic cages and sacrificed 1 day after i.v. injection of the antagonists or scrambled controls.

**Methods:** We used miR-reporter constructs to validate Cox-2 repression by microRNA-132 (miR-132) and generated antagons to silence miR-132 function. Mice were housed in metabolic cages and sacrificed 1 day after i.v. injection of the antagonists or scrambled controls.

**Results:** We identified miR-132, using in situ hybridization, to be strongly expressed in the macula densa and found miR-132 to be directly target Cox-2 in vitro. In vivo silencing of miR-132 resulted in increased PGE2 and subsequent renin production. Blocking PGE2 synthesis using the selective Cox-2 inhibitor Celecoxib abrogated the miR-132-antagonist induced increase in renin, further supporting a regulatory role for miR-132 in the Cox-2/PGE2 dependent release of renin. Previously, we found that silencing miR-132 resulted in acute diuresis by inhibiting hypothalamic AVP production, resulting in hypovolemia and increased plasma osmolality. To exclude secondary effects on PGE2 and renin production caused by this, we administered ddA VP which reversed these miR-132 mediated diuretic effects, and demonstrated that PGE2 and renin levels remained elevated independent of miR-132-antagonist induced diuresis.

**Conclusions:** Taken together, we demonstrated an essential posttranscriptional regulatory role for miR-132 in the synthesis and release of renin through Cox-2 mediated PGE2 synthesis in the macula densa.

**FR-OR114**  
**Permeable Glycoprotein Expression on Pathogenic IL-17/IFN-γ Double-Positive Th17 Cells Is Responsible for Steroid Resistance in Minimal Change Disease.** Narayan Prasad,1 Akhilesh Jaiswal,1 Vikas Agarwal,2 Raj K. Sharma.1 1Nephrology, SGPGIMS, Lucknow, UP, India; 2Immunology, SGPGIMS, Lucknow, India.

**Background:** Th17 cells and cytokine IL-17 are involved in many autoimmune diseases. Recently, IL-17/IFN-γ double-positive Th17 cell, called pathogenic Th17 cells were found to be associated with multiple autoimmune and inflammatory diseases. P-glycoprotein (P-gp, an efflux pump) positive Th17 cells are refractory to glucocorticoids. P-gp on lymphocytes excretes out steroid and prevents its action. We conducted this study with hypothesis that P-gp expressing Th17 and IFN-γ are one of key pharmacokinetic and pharmacodynamic modulator responsible for steroid resistance in nephrotic Syndrome(NS). As it has not been studied in NS, we studied the frequency of P-gp expressing pathogenic Th17 cells in steroid sensitive (SSNS) and steroid resistant (SRNS) patients.

**Methods:** We analysed the frequency of pathogenic IL-17/IFN-γ double-positive Th17 in patients with idiopathic membranous nephropathy (MGN) combined with low dose corticosteroid, the effect of MMF was comparable to CSA in patients with idiopathic MGN with similar adverse effects including gastrointestinal symptoms.

**Funding:** Pharmaceutical Company Support - Hanmi Pharmaceutical, Seoul, Korea

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

61A
FR-OR115
Angiopoietin-Like-4 and Minimal Change Disease
Gabriel M. Cara-Fuentes,1 Alfonso Segarra,2 Cecilia Sanchez,3 Heiman Wang,2 Miguel A. Lasnapa,3 Richard J. Johnson,1 Eduardo H. Garin,1 1Univ of Florida; 2Hospital Vall d'Hebron; 3Univ of Colorado.

Background: Minimal change disease (MCD) is considered a podocytopathy. It has been hypothesized that in MCD podocyte Angiopoietin-like-4 (Angplt4) lacks sialic acid, and when bound to the glomerular basement membrane (GBM) proteolyses, decreases GBM anionic charge allowing albumin to cross the capillary wall barrier into the urinary space. Objective: To evaluate the role of Angplt4 as a biomarker and/or mediator of proteinuria in MCD.

Methods: 60, 52 and 52 patients with MCD, FSGS and MN respectively and 18 control subjects were included. Urinary and serum Angplt4 were measured by Eisa. pI of Angplt4 in urine of MCD in relapse was determined by 2D electrophoresis. Frozen tissue sections were stained for Angplt4. Statistical analysis using Kruskal-Wallis, Mann-Whitney U test and Spearman correlation.

Results: Urinary Angplt4 was increased in patients with massive proteinuria regardless of the type of glomerular disease compared to controls. No correlation was observed between proteinuria and urinary Angplt4 in MCD patients in relapse. Serum Angplt4 was higher in normal controls compared to MCD, FSGS and MN patients in relapse. Glomerular Angplt4 expression, by immunofluorescence (IF), was absent in MCD patients in relapse. Angplt4 detected in urine in MCD had a pI of 5.4.

Conclusions: 1) Serum and urinary excretion of Angplt4 were not specific for MCD patients, and there was no correlation of urinary Angplt4 with proteinuria in MCD patients. 2) Angplt4 detected in urine in MCD is likely freely filtered circulating Angplt4 given its pM, 3) absence glomerular staining by IF in MCD patients in relapse. 3) Urinary Angplt4 in MCD in relapse is not cationic. In summary, our data do not support a role of Angplt4 as marker and/or mediator of proteinuria in MCD. Increased urinary Angplt4 is likely the result, rather than the cause, of a leaky glomerular filtration barrier.

Funding: Other NIH Support - N01DK008764

FR-OR117
A Clinical Outcome Assessment of Proteinuria in Patients with Focal Segmental Glomerulosclerosis
Jonathan P. Troost,1 Howard Trachtman,2 Cathie Spino,1 Radko Komers,3 Sarah E. Tuller,3 Patrick H. Nachman,4 Matthias Kretzler,1 Debbie S. Gipsen.1 1Univ of MI; 2New York Univ; 3Retrophin; 4Univ of NC at Chapel Hill.

Background: Proteinuria is used as an indicator of disease activity in FSGS, but its use as an end point for clinical trials is not universally accepted. The goal of this study is to examine the strength of the relationship between proteinuria and renal survival in patients with FSGS.

Methods: Data from 118 FSGS patients from the Nephrotic Syndrome Study Network (NEPTUNE) and 109 patients from the completed NIH sponsored FSGS Clinical Trial (FSGS-CT) were used for this discovery and replication analysis, respectively. Central measurements of urine protein: creatinine ratio (UP:C g/g) and serum creatinine were used and eGFR was calculated. Kaplan-Meier methods and log-rank tests were used to estimate the effect of proteinuria on subsequent ESRD or 40% reduction in eGFR. Proteinuria was measured by conventional definitions of complete (UP:C<0.3), CR) and partial remission (50% reduction in UP:C and UP:C<3.5, PR). ROC analyses were performed to determine other important thresholds of proteinuria.

Results: In NEPTUNE and the CT, 40 and 47 patients progressed to ESRD or 40% reduction in eGFR, respectively. In NEPTUNE, reaching a CR, but not necessarily a PR, was associated with a decreased risk of disease progression (hazard ratio (HR) relative to no remission: CR=0.1, p<0.01; PR=1.0, p=0.90). ROC analyses identified a modified PR definition of UP:C 0.3-1.5 associated with a lower likelihood of progression to ESRD or 40% reduction in eGFR in NEPTUNE (HR=0.3 p<0.01), which was replicated in the FSGS-CT (HR=0.4, p=0.03).

Conclusions: Reaching either CR or a modified definition of PR, was associated with better long-term outcomes in patients with FSGS. From a regulatory perspective, this may help improve the feasibility of conducting clinical trials by using proteinuria as an endpoint.

Funding: NIDDK Support, Pharmaceutical Company Support - Retrophin (San Diego, CA, USA)

FR-OR116
Oxidized Low-Density Lipoprotein and Microparticle Tissue Factor Activity
The Leaky Membrane: Nephrotic Syndrome
Jonathan P. Troost,1 Howard Trachtman,2 Cathie Spino,1 Radko Komers,3 Sarah E. Tuller,3 Patrick H. Nachman,4 Matthias Kretzler,1 Debbie S. Gipsen.1 1Univ of MI; 2New York Univ; 3Retrophin; 4Univ of NC at Chapel Hill.

Background: In a NEPTUNE participant sample with overt NS, serum albumin and proteinuria were associated with a 1.3 fold increase in risk in NS, an expected relationship limited by our sample size. Future work will examine if oxLDL directly correlates with mpTFa and increased VTE risk in NS, an expected relationship limited by our sample size.

Funding: NIDDK Support, Private Foundation Support

FR-OR118
Congophilic Fibrillary Glomerulonephritis: Clinicopathologic and Prognostic Characteristics
MARIAM P. ALEXANDER,1 SURENDA DASARI,1 JULIE A. VANA,1 GLEN S. MARKOWITZ,2 VANESA BIBILONI,3 AIVIV HEVER,3 NAVIN VERMA,4 JULIE RIPEL,4 BHARGAVI DEGAPUDI,5 LYNN D. CORNELL,1 MARY E. FIDLER,1 SAMAR M. SAID,1 SANJEET SETHI,1 LOREN PAULA HERRERAZA HERNANDEZ,2 NELSON LEUNG,2 PAUL J. KURTIN,1 SANHIT NAST,1 MAYO CLINIC, ROCHESTER, MN; COLUMBIA Univ, New York, NY; Brigham and Women's Hospital, Boston, MA; Kaiser Permanente, Los Angeles, CA; Hershey Medical center, PA; 1L'Hotel-Dieu de Quebec, Quebec, Canada; 2Atlantic Care, NJ.

Background: Historically Congo red (CR) positivity has dichotomized organized glomerular deposits into amyloid and non-amyloid diseases. Fibrillary glomerulonephritis (FGN) is traditionally defined by CR negative randomly-oriented fibrils. We report the first series of Congophilic FGN (CFGN), defining its clinicopathologic and prognostic characteristics.

Methods: We identified 9 cases of CFGN from our archives from 2014-16. Histologic, clinical and outcome data were evaluated. Mass spectrometry (MS) was performed in all cases and on control samples (9 AL amyloidosis, 5 non-CFGN).

Results: Mean age was 59 yrs, 5 were female. Mean 24 h proteinuria and S. creatinine were 5.9 g and 1.5 mg/dl. 75% had hematuria. 7 of the cases were referred for amyloid typing by MS. 2 pts had hep C, 2 had cirrhosis, and only 1 had monoclonal gammopathy. No pt had extrarenal amyloidosis. LM showed mesangial GN (N=6) or MPGN (N=3). All pts had Congo red positive deposits with mesangial and GBM amyloid. 1 pt had extrarenal amyloidosis. LM showed mesangial GN (N=6) or MPGN (N=3). All pts had Congo red positive deposits with mesangial and GBM amyloid.

Conclusions: Reaching either CR or a modified definition of PR, was associated with better long-term outcomes in patients with FSGS. From a regulatory perspective, this may help improve the feasibility of conducting clinical trials by using proteinuria as an endpoint. Further work will examine if oxLDL directly correlates with mpTFa and increased VTE risk in NS, an expected relationship limited by our sample size.

Funding: NIDDK Support, Private Foundation Support
FR-OR119

Molecular Diagnostics for Glomerular Diseases in Routine Formalin-Fixed Paraffin-Embedded Native Kidney Biopsies
KristaLle Watson,1 Benjamin Alexander Adam,1 Neesh I. Panna,1 Ainslie M. Hildebrand,2 Michael Mengel,1 1Dept of Laboratory Medicine and Pathology, Univ of Alberta, Edmonton, AB, Canada; 2Div of Nephrology, Univ of Alberta, Edmonton, AB, Canada.

Background: Molecular diagnostics can potentially improve the classification and staging of native kidney diseases. The nanoString nCounter gene expression platform can use formalin-fixed paraffin-embedded (FFPE) tissue, representing a potential method for routine molecular diagnostics in renal pathology. We aimed to assess gene expression quantification in the diagnostics and staging in glomerulonephritis (GN) in FFPE native kidney biopsies.

Methods: A literature-derived gene set for renal injury was generated (54 genes related to nephrons, endothelium, and inflammation). RNA was isolated from 386 FFPE native kidney biopsies (275 crescentic GN, 82 non-crescentic immune complex GN, 29 non-crescentic non-proliferative disease). Gene expression was quantified with nanoString and correlated with histology, and clinical indices at biopsy and 1-year follow-up.

Results: Gene set expression was higher in cases with crescentic GN than non-crescentic GN (p<0.001). Gene set expression correlated with interstitial fibrosis and tubular atrophy (r=0.34, p<0.001). Expression of ncounter transcripts correlated with the proportion of crescentic glomeruli (r=-0.39, p=0.001). Expression of ncounter transcripts was higher in patients with crescentic GN and recovery in renal function 1 year post biopsy versus those with stable or deteriorating serum creatinine (p<0.002).

Conclusions: The nanoString platform allows for robust gene expression quantification from FFPE native kidney biopsies. High expression of ncounter genes is associated with functional recovery after crescentic GN. Molecular biopsy assessment has the potential to provide additional diagnostic and prognostic information in renal pathology.

Funding: Clinical Revenue Support

FR-OR120

Identification of Shared Molecular Targets across Glomerular Disease: Case Study in ANCA-Associated Vasculitis and Nephrotic Syndrome (NS)
Sean Eddy,1 Viji Nair,1 Hemang Parikh,1 Laura H. Mariani,1 Felix H. Eichinger,1 Huateng Huang,1 Wenjun Ju,1 Casey S. Greene,1 Peter C. Grayson,4 Jeffrey P. Krischer,1 Peter A. Merkel,1 Matthias Kretzler,1 1Div of Nephrology, Univ of Michigan, Ann Arbor, MI; 2NEPTUNE Consortium; 3Univ of South Florida, Tampa, FL; 4Vasculitis Clinical Research Consortium; 5Univ of Pennsylvania, Philadelphia, PA; 6Vasculitis Translational Research Program, NIAMS, NIH, Bethesda, MD.

Background: Clinical trials in rare diseases typically test therapeutic efficacy in one disease defined by a particular clinical phenotype. An unbiased analysis of kidney diseases suggests many rare kidney diseases share common molecular profiles (Martini et al., 2014). To expand on these findings, we explored shared transcriptional responses in patients with AAV and NS to identify common targetable disease mechanisms.

Methods: Transcriptomic profiles were generated from renal biopsies from NS (MCD, FSGS and Membranous Nephropathy, n=126) from the NEPTUNE cohort and the European Renal DNA Bank (ERBD, n=61), and from AAV (Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)) from the ERBD cohort (n=80) and living donors (n=37) on Affymetrix U133 and ST2.1 platforms. Functional networks were assessed for cross-cutting disease mechanisms, upstream regulators and potential therapeutic targets shared between both diseases.

Results: 5%-25% of expressed transcripts were differentially regulated compared to living donor (FDR<0.05, shared directionality of change) in both NS and AAV in glomerular and tubulointerstitial compartments and replicated across expression platforms. Functional analysis identified conserved, therapeutically targetable transcriptional networks in the glomeruli from NS and AAV patients including activation of Tce kinase, IL-8 signaling, TNF, IFNG, TGFB1, and NFkappaB, while alpha catenin and LXR/RXR signaling were suppressed. A causal analysis approach predicted increase TFN pathway activity across diseases.

Conclusions: AAV and NS, two rare kidney diseases, share common intra-renal transcriptional profiles that can be readily mined to identify shared molecular targets. Shared molecular targets can be leveraged for drug development and repurposing efforts.

Funding: Other NIH Support - NCATS

FR-OR121

ANCA Autoantigen Expression in Combination with ANCA Titer May Be More Useful to Assess Disease Activity Than Either Alone
Jia Jing Yang,1 Caroline J. Poulton,1 Susan L. Hogan,1 Yichun Hu,1 Meghan A. Jobson,1 Candace Henderson,1 Britta E. Jones,7 J. Charles Jennette,7 Ronald J. Falk,1 Dominic J. Ciavatta,2 William Franklin Pendergraft,1 1Medicine, UNC-CH; 2Pathology, UNC-CH; 3Genetics, UNC-CH, Chapel Hill, NC.

Background: We demonstrated aberrant up-regulation of autoantigenic genes in mature neutrophils and monocytes from patients with ANCA disease (JASN 2004, 15:2103-14). Here, we compared the utility of PRTN3 and MPO mRNA and ANCA titers to predict disease activity.

Methods: A total of 969 leukocyte RNA samples from 122 ANCA-patients were collected serially every 3 months over the past 6 years compared to 169 healthy controls. Transcriptomic profiles of PRTN3 and MPO gene transcripts were determined by Q-PCR and expressed as relative levels to standard curve. Active disease was defined as a Birmingham Vasculitis Activity Score (BVAS) ≥ 5 with clinical and/or laboratory evidence of disease activity; remission as a BVAS<0 and no evidence of active disease. Fisher’s exact test was used in this study.

Results: In samples with active disease (n=106), 60% and 67% of samples had significantly increased PRTN3 (385±846, p<0.0001) and MPO (995±1900, p<0.0001) mRNA, respectively compared to healthy donors (PRTN3:16±33; MPO:57±57). Only 65% and 9% of remission samples (n=94) had increased PRTN3 and MPO mRNA, respectively.

Conclusions: The combination of ANCA titer and ANCA autoantigen expression may be more useful to assess disease activity than either alone. Both expression of autoantigenic genes and antibodies are involved in the pathogenesis of ANCA disease.

Funding: NIDDK Support

FR-OR122

Serum Klotho Levels Are Associated with Renal Function Recovery in Patients with Septic Acute Kidney Injury Undergoing Continuous Renal Replacement Therapy
Sandeep Min Park,1 Hyoungnae Kim,1 Young Eun Kwon,2 Min-Uk Cha,1 Yoon Kyung Kee,1 Tae-Hyun Yoo,1 1Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; 2Div of Nephrology, Dept of Internal Medicine, Myongji Hospital, Seonam Univ College of Medicine, Goyang, Korea.

Background: This study aimed to elucidate the role of klotho as a biomarker in septic acute kidney injury (AKI) patients requiring continuous renal replacement therapy (CRRT).

Methods: This is a post hoc analysis of HICORES study (HIgh-volume Continuous REnal replacement therapy in patients with Septic AKI, NCT 0191905) conducted from January 2011 to August 2014 at two tertiary hospitals in Korea. A total of 165 septic AKI patients undergoing CRRT were eligible and serum klotho level at CRRT initiation was measured by ELISA. The patients were divided into high and low klotho groups based on the median value of klotho (244pg/ml). Primary outcome was CRRT weaning rate at 28 day and secondary outcomes were the proportion of intensive care unit (ICU) discharge at 28 day and all-cause mortality rate.

Results: Male was 110 (66.7%) and the mean age was 62.2 years. High klotho group was younger and showed significantly lower norepinephrine requirement, C-reactive protein, and log transformed interleukin (IL)-1β and IL-10 levels compared to low klotho group. Multiple Cox regression analysis revealed that the CRRT weaning rate at 28 day was significantly higher in high klotho group (hazard ratio [HR] 1.634; 95% confidence interval [CI] 1.004–2.659, P=0.048) compared to that in low klotho group. In addition, high klotho group showed more ICU discharges at 28 day (HR 2.959, 95% CI 1.149–5.864, P=0.002) than low klotho group after adjusting confounding factors. Meanwhile, the difference in all-cause mortality rate did not reach statistical significance between the two klotho groups (HR 0.709, 95% CI 0.480–1.049, P=0.085).

Conclusions: Present study suggests that baseline serum klotho might be a potential biomarker predicting renal function recovery in patient with septic AKI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
FR-OR123

Preoperative Plasma Monocyte Chemotactic Protein-1 Is Associated with Postoperative AKI and Long-Term Mortality after Cardiac Surgery: A Multicenter Prospective Cohort Study. Dennis G. Molenda,1 Selin Isguzen,1 Eric McArthur,2 Heather Thiesen Philbrook,3 Amit X. Garg,2 Michael Shlipak,4 Peter Kavask,4 Steven G. Coca,4 Chirag R. Parikh.1 1Yale School of Medicine; 2Icahn School of Medicine; 3McMaster Univ; 4Univ of California.

Background: Monocyte chemotactic protein-1 (MCP-1) is upregulated in ischemia-reperfusion injury and is a promising biomarker of inflammation in cardiac surgery. We evaluated the association of perioperative MCP-1 levels in patients undergoing cardiac surgery with AKI and mortality.

Methods: We measured pre- and postoperative plasma MCP-1 levels in TRIBE-AKI, a prospective, multicenter, observational cohort of patients undergoing cardiac surgery. Short-term outcomes were in-hospital AKI or severe AKI, and long-term outcome was all-cause mortality.

Results: Of the 972 participants in the study, 329 (34%) developed AKI and 45 (5%) developed severe AKI. Of the 957 patients alive at hospital discharge, 103 (11%) participants died during median follow-up of 2.9 (2.2-3.5) years. In fully adjusted analyses, patients with preoperative MCP-1 levels in the highest tertile (>196 pg/ml) had an increased risk of AKI as compared with the lowest tertile (>147 pg/ml; OR, 1.43 [95% CI, 1.00-1.99]); the association appeared similar but was not significant for the outcome of severe AKI [OR, 1.48 (0.62-3.54)]. As compared with patients with preoperative MCP-1 in the lowest tertile, those in the highest tertile had higher mortality risk [HR, 1.63 (1.23-2.16); P<0.001]. Postoperative MCP-1 concentrations were not associated with AKI or mortality.

Conclusions: Preoperative plasma MCP-1 level is associated with increased risk of AKI and long-term mortality after cardiac surgery. MCP-1 could be used as a biomarker to identify high-risk patients to enrich clinical trials for AKI prevention in the setting of cardiac surgery.

FR-OR124

Prediction of Acute Kidney Injury (AKI) and Clinical Outcomes Using a Combination of Routine Clinical Information and Novel Urinary Biomarkers: The Dublin Acute bioMarkEr Group Evaluation (DAMAGE) Study. Patrick T. Murray,1 Marie C. Galligan,1 Valerie Jean Logan,1 Siobhan Elizabeth Mc Kenna,1 Alistair Nichol,1 Peter P. Doran,1 Blaithin A. McMahon.1 1School of Medicine, Univ College Dublin, Dublin, Ireland; 2Div of Nephrology, Johns Hopkins Univ School of Medicine, Baltimore, MD.

Background: Implementation of novel AKI biomarkers in practice has been hampered by a failure to integrate into routine clinical decision making, which involves standard clinical information, including demographics, acute and chronic illness information, and markers of kidney function (urine output, BUN, creatinine).

Methods: The DAMAGE Study is a prospective multicenter observational study investigating the utility of urinary biomarkers for diagnosis and prognosis of AKI in critically ill patients admitted to intensive care units in Dublin, Ireland. Clinical information and urine were collected on admission and daily for 7d. Urine biomarkers analysed were NGAL, n-GST, z-GST, KIM-1, L-FABP, Cystatin-C, creatinine, and albumin. ROC curves were constructed from logistic regression models that predicted AKI (by KDIGO) and adverse clinical outcomes (progression to death or RRT) in combination with APACHE II score, gender, admission serum creatinine, urea and urine output.

Results: The study enrolled 736 patients. 242 (37.4%) developed AKI within 7 days of ICU admission. 208 (31.6%) progressed to death or dialysis within 30d. A panel of admission biomarkers significantly improved prediction of AKI developing within 7d of admission (AUC; 95% CI: 0.77,0.72-0.82) over clinical covariates alone (0.73;0.68-0.79; P=0.029). Similarly, the admission values of Albumin and NGAL improved prediction of early AKI, developing within 48h (0.77;0.73-0.81), compared to clinical covariates alone (0.75;0.71-0.79; P=0.03). Finally, the addition of this biomarker pair improved prediction of 30d adverse clinical outcomes - RRT or death – (0.82; 0.78-0.86) when compared to clinical covariates alone (0.79; 0.75-0.83; P=0.0004).

Conclusions: Combined use of novel urinary AKI biomarkers with knowledge of patient clinical covariates and admission to the ICU significantly improved the prediction of AKI and 30d adverse clinical outcomes.

Funding: Pharmaceutical Company Support - Abbott Labs; Argutus/EKF Diagnostics, Government Support - Non-U.S.

FR-OR125

Saliva Urea Nitrogen Dipstick: A Simple Tool to Detect and Stratify Risk of Renal Disease in Low Resource Settings. Vivianne Calhe-Calhe,Silva.1 Rhys David Russell Evans,2,3 Jochen G. Raimann,1 Ulla Hemmla,2 Alisson Craik,3 Mwaywathu Prince Miekateka,2 Fergus Hamilton,1 Zuze Madalitso Kawale,1 Gavin Dreyer,6 Nathan W. Levin,1 Peter Kotanko,2 Roberto Pecoits-Filho,1 1Pontificia Univ Católica do Paraná, Brazil; 2College of Medicine, Malawi; 3Queen Elizabeth Central Hospital, Malawi; 4Bart’s Health, United Kingdom; 5Renal Research Inst; 6Royal Free Hospital, United Kingdom; 7Icahn School of Medicine at Mount Sinai.

Background: Simple and non-expensive tools for the diagnosis of renal disease, in particular acute kidney injury (AKI), are lacking. We evaluated the diagnostic performance of a salivary urea nitrogen (SUN) dipstick and its ability to predict outcomes in a low-resource setting in Africa.

Methods: Adult patients presenting to general medicine at QECH, Blantyre, Malawi, were screened for kidney disease with serum creatinine (sCR) and SUN on admission. Patients with renal impairment were followed-up for up to 7 days. SUN level greater than 14 mg/dL was the threshold to diagnose renal disease. Cox proportional hazard models were constructed to evaluate the predictors of death.

Results: 742 patients with SUN data were studied (40.9±17.3 years, 56.1% male). We diagnosed 146 patients with renal disease [114 AKI, 26 AKD (AKI without AKI, 6 CKD)] according to KDIGO aCR based criteria. The SUN performance to diagnose renal disease was good [AUC 0.83 (95% CI 0.79 to 0.87)]. SUN levels > 14 mg/dL was the optimal threshold (sensitivity 72%; specificity 87%). Out of 702 patients with complete outcome data, 104 died during hospitalization. Elevated SUN was an independent predictor of all cause mortality (Figure 1; HR=2.43 [95% CI 1.63 to 3.62]).

Figure 1: Kaplan-Meier curve survival analysis of all-cause mortality stratified by SUN results.

Conclusions: SUN showed good diagnostic performance to detect renal disease. SUN was an independent predictor of mortality in this population. Our data suggest that SUN may be used to diagnose kidney disease, particularly in limited health care settings.

Funding: Private Foundation Support
FR-OR126
Fluid Overload in Critically Ill Patients Is Predicted Using Single and Sequential Urinary Biomarker Measurements Erin K. Stenson,1 Shina Menon,1 Stuart Goldstein,2 Rajit K. Basu1 1Pediatric Critical Care, Cincinnati Children’s Hospital; 2Pediatric Nephrology, Seattle Children’s Hospital; 1Center for Acute Care Nephrology, Cincinnati Children’s Hospital.

Background: Fluid overload (FO) is independently associated with worsened outcomes in critically ill patients. Although urinary biomarkers have been studied in multiple populations for prediction of acute kidney injury (AKI), prediction of fluid overload has not been reported. Further, the predictive performance of biomarkers as they change over time has not been explored.

Methods: We leveraged data from a single-center, prospective study of children admitted to the intensive care unit (ICU). The primary outcome for this analysis was the development of >20% FO (derived by net fluid balance and weight) at any time from ICU admission to Day 7. Predictor variables were assessed at least 3 times during the first 36 hours of admission (urinary neutrophil gelatinase associated lipocalin (uNGAL), serum creatinine (SCr), and urine output (UOP)).

Results: 173 pts (51% male, median age 7.7 years) were included. Peak FO >20% occurred in 45 pts (26%) (Median 4 days). uNGAL was elevated over 200 in 52 pts (30%). uNGAL was persistently >200 in 115 pts (66%), intermittently elevated (spiked over 200, and then down trending) in 29 (17%) and persistently <200 (at least 3 values over 200) in 29 (17%). Compared to UOP or SCr measurements, uNGAL levels demonstrated a significant association for prediction of FO >20%. Persistently increased uNGAL strengthened this association (compared to persistently low uNGAL).

Conclusions: Our data suggest that >20% FO can be predicted. Single and sequential urinary biomarkers assessed early in ICU admission are predictive of FO while creatinine and urine output are not. These findings are clinically relevant as fluid accumulation is associated (compared to persistently low uNGAL).

FR-OR127
Urinary Neutrophil Gelatinase-Associated Lipocalin Predicts Non Response to Therapy with Albumin and Terlipressin in Patients with Hepatorenal Syndrome Rafael Oliveira Ximenes,1 Alberto Queiroz Farias,1 Claudia Helo,3 1Gastroenterology, Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil; 2Nephrology, Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil; 3LIM 12, Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil.

Background: Current predictors of response to hepatorenal syndrome (HRS) treatment have limited accuracy, leading to administration of ineffective therapy. The aim of the study was to evaluate the utility of urinary neutrophil gelatinase-associated lipocalin (uNGAL) as a predictor of non response to albumin and terlipressin treatment in patients with HRS.

Methods: Prospective study conducted at a tertiary care unit between June 2013 and November 2015. Inclusion criteria: a) cirrhosis; b) age > 18 years; c) HRS diagnosis according to International Club of Ascites criteria; d) informed consent. Exclusion criteria: a) severe systemic comorbidities; b) shock; c) chronic kidney disease; d) intrinsic nephropathy; e) nephrotoxic drug use; f) previous dialysis; g) liver transplantation recipient. uNGAL was determined in the first day of treatment.

Results: Forty-nine patients (75% male, median age 59 years) were included. 24 (49%) did not respond to treatment. Median uNGAL levels were 728.8µg/L in non-responders, and 182.9 µg/L in responders (p=0.02).

Conclusions: uNGAL had an AUC of 0.69 to predict non response to combined treatment, with the optimal cut-off value of 214.4µg/L (sensitivity 0.83, specificity 0.56, positive predictive value 0.65 and negative predictive value 0.78).

Conclusions: uNGAL is a useful predictor of unresponsiveness to treatment with albumin and terlipressin in patients who fulfill HRS diagnosis criteria.

Funding: Government Support - Non-U.S.

FR-OR129
Haemodialysis for Acute Kidney Injury Results in Myocardial Stunning Huda Mahmoud,1,2 Christopher W. McIntyre,1 Nicholas M. Selby,1 1Dept of Renal Medicine, Derby Royal Hospital, United Kingdom; 2Centre for Kidney Research and Innovation, Univ of Nottingham, United Kingdom; 3Schulich School of Medicine and Dentistry, Canada.

Background: The circulatory stress of chronic haemodialysis (HD) results in repetitive subclinical myocardial ischaemia (myocardial stunning) contributing to adverse patient outcomes. Currently it is unknown if this process occurs during renal replacement therapy (RRT) for acute kidney injury (AKI). Acute RRT differs in both its delivery and because patients do not display the circulatory changes of chronic uremia. We aimed to determine if acute RRT is capable of inducing myocardial stunning.

Methods: 12 patients requiring RRT for AKI participated. Serial echocardiography was performed before, during and after a single RRT session and images analysed off-line using speckle-tracking software. Myocardial stunning was defined as >2 new left ventricular (LV) regional wall motion abnormalities (RWMAs) during dialysis; global longitudinal strain (GLS) assessed LV contractility. Blood pressure (BP) and systemic haemodynamics were measured continuously.

Results: 10 patients were included in the analysis; 2 were excluded due to poor image quality. All 10 patients demonstrated dialysis-induced stunning (>2 new RWMAs), with partial recovery seen at 30min post dialysis. The median number of affected LV segments was 5 (IQR 4-6). GLS significantly declined from a pre-dialysis level of -17.8±3.7% (within normal range) to below the normal range during dialysis (-15.4±2.7%, p<0.05), remaining low at 30min post-dialysis to -14.7±7.3%, p=0.005. There were associations between number of stunned segments and dialysis ultrafiltration volume (r=0.79, p=0.006). 2 patients died at 150 and 153 days post discharge (both left HD dependent). One patient remains HD dependent.

Conclusions: HD induced myocardial stunning occurs during acute RRT in combination with reductions in LV contractility. This suggests that the process is driven by HD related factors (as opposed to patient phenotype) and opens up the possibility of therapeutic HD based interventions. Further study is required to determine whether dialysis induced stunning contributes to the very poor outcomes that are well recognised in this patient group.

Funding: Private Foundation Support
Conclusion: Palliative care is not consistently utilized in patients with AKI, despite its many benefits to critically ill patients. More research is needed to determine reasons for patient and hospital differences in palliative care utilization, as well as to develop palliative care programs targeted at patients with AKI.

SA-OR001

The End-Stage Renal Disease Prospective Payment System Had Little Effect on Home Dialysis Usage in the United States

Eugene Lin,1 Xingxing S. Cheng,1 Kuo-Kai Chin,1 Taliah Zubair,2 Glenn Matthew Chertow,1 Eran Bendavid,2 Jay Bhattacharya.1 1Internal Medicine - Nephrology, Stanford Univ; 2Centers for Health Policy and Primary Care and Outcomes Research, Stanford Univ; Stanford Univ.

Background: Home dialysis modalities (peritoneal dialysis and home hemodialysis) are touted as a way to help reduce the high cost of End-Stage Renal Disease (ESRD) in the United States. The Prospective Payment System (PPS) for ESRD, implemented by Centers for Medicare & Medicaid Services (CMS), in January, 2011, introduced financial incentives to increase home dialysis use.

Methods: In this study, we estimated the effect of the PPS on home dialysis use in adults who initiated dialysis between January 1, 2007 and August 31, 2012. We compared the estimated effect of the PPS in patients with a high incentive to use home dialysis (those with Medicare as primary insurer) with patients with a low incentive to use home dialysis (those with another primary insurer). Using a difference-in-differences method, we compared the estimated effect of the PPS in patients with Medicare as primary insurer versus those without.

Results: On average, home dialysis use increased over time in the pre-PPS era. Home dialysis use increased at a faster rate after the PPS, and by the end of the study period, the introduction of the PPS was associated with an increase in home modality use by 0.8% (CI: 0.3, 1.2). An increase in home dialysis use was observed in both subgroups: 1.0% (CI: 0.5, 1.6%) in the Medicare as primary population and 0.4% (CI: -0.1, 1.6%) in the Medicare as secondary population. The estimated effect size was not statistically different between the two groups (p = 0.2).

Conclusions: Although the PPS was associated with an increase in home dialysis use in the United States, this increase was small relative to the baseline temporal trend, suggesting that the financial incentives for home dialysis instituted by CMS within the PPS were insufficient to yield major changes in practice.

Funding: NIDDK Support
**SA-OR003**

**Variability in Peritoneal Dialysis Patients’ Training: The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)**

Ania Elizabeth Figueiredo,1,4 Juhui Zhao,2 Brian Bieber,2 Helen Hurst,3,4 Francesca Tentori,2,4 Pontificia Univ Catolica do Rio Grande do Sul, Porto Alegre, Brazil; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3Manchester Royal Infirmary, Manchester, United Kingdom; 4On Behalf of the PDOPPS Patient Training and Education Workgroup, Ann Arbor, MI.

**Background:** Controversy exists regarding optimal training practices for PD patients. This study provides important information on international variability in PD training practices across countries participating in PDOPPS.

**Methods:** Launched in 2013, the PDOPPS is a prospective cohort study of PD practices and outcomes ongoing in Australia, Canada, Japan, New Zealand, Thailand, the United Kingdom (UK) and the United States (US). Data on typical training practices were reported by nurse study coordinators at each facility.

**Results:** At the time of submission, data were available from 138 facilities in Australia, Canada, Japan, UK, and the US. Training practices varied internationally and were dramatically different in Japan. Japan had the greatest proportion of facilities providing training greater than one week. Home only training was unique to the UK. Across all countries, the majority of facilities provided individualized training by a specific nurse, two weeks after catheter implantation, for 16 to 30 hours, and an oral and practical demonstration of technical procedure as a final assessment of comprehension.

**Table: PD training practices by PDOPPS country**

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of facilities</th>
<th>When training occurs</th>
<th>1 week after PD catheter insertion</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>13</td>
<td>8%</td>
<td>30%</td>
<td>31%</td>
</tr>
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<td>20</td>
<td>5%</td>
<td>27%</td>
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<td>11%</td>
</tr>
<tr>
<td>UK</td>
<td>19</td>
<td>62%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>US</td>
<td>61</td>
<td>65%</td>
<td>7%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**Conclusions:** Large variation exists in PD training practices across PDOPPS countries. As the study proceeds, and accuces follow-up time, patient-level training practices, and, will be reported in the future, the PDOPPS will provide unique information regarding the association of specific training practices and outcomes, thus contributing to fill this knowledge gap.

**SA-OR005**

**The Inhibition of CTGF Ameliorates Peritoneal Fibrosis through the Suppression of Fibroblast/Myofibroblast Accumulation**

Miki Nakamura,1 Norihiko Sakai,2 Konneth E. Lipson,3 Taito Miyake,1 Yasutaka Kamikawa,1 Akihiro Sagara,2 Shinji Kitajima,1 Tadashi Toyama,3 Akinori Hara,2 Yasunori Iwata,2 Miho Shimizu,2 Kengo Furuichi,4 Takashi Wada,5 Department of Nephrology and Laboratory Medicine, Kanazawa Univ, Kanazawa, Japan; 4Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan; 5FibroGen, Inc., San Francisco, CA.

**Background:** Peritoneal fibrosis is a severe complication of peritoneal dialysis, but the mechanisms driving it remain to be fully determined. Connective tissue growth factor (CTGF) has been shown to regulate fibroblast activity such as proliferation and myofibroblast differentiation. We therefore examined if the inhibition of CTGF has anti-fibrotic effects on the peritoneal fibrosis.

**Methods:** Peritoneal fibroblasts were induced by intraperitoneal injection of chlorhexidine gluconate (CG) in type I pro-collagen promoter-driven green fluorescent protein (GFP) mice to identify fibroblasts. The neutralizing anti-CTGF antibody (FG-3019) was used to inhibit CTGF functions.

**Results:** CG-induced increases in peritoneal thickness, type I pro-collagen mRNA expression and hydroxyproline content were significantly attenuated in FG-3019-treated mice (n=7). In addition, CG challenges induced a marked peritoneal accumulation of G£F fibroblasts that was significantly reduced by FG-3019. To specifically identify proliferating fibroblasts, dual immunostainings of peritoneal sections were performed using anti-fibronectin cell nuclear antigen (PCNA) antibody and anti-GFP antibody. The number of proliferating fibroblasts (PCNA GFP) in the peritoneum after CG challenges was significantly suppressed by FG-3019 (n=5). Peritoneal accumulation of a-smooth muscle actin myofibroblasts was also reduced in FG-3019-treated mice. Moreover, peritoneal CTGF expression was detected in peritoneal mesothelial cells and fibroblasts, and the levels of peritoneal CTGF expression were significantly suppressed in FG-3019-treated mice compared with those in control antibody-treated mice (n=6).

**Conclusions:** Our results suggest that the inhibition of CTGF by FG-3019 might be a novel treatment for peritoneal fibrosis through the regulation of fibroblast/myofibroblast accumulation.

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

**SA-OR006**

**Connective Tissue Growth Factor Is Correlated with Lymphangiogenesis in Peritoneal Fibrosis**

Hiroshi Kinashi,1,2 Trt Q. Nguyen,3 Roel Goldschmeding,1 Yasuhiko Ito,1,2 Pathology, Univ Medical Center Utrecht, Utrecht, Netherlands; 3Nephrology and Renal Replacement Therapy, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

**Background:** Lymphangiogenesis develops during PD peritoneal fibrosis. CTGF is a growth factor that induces the formation of new lymphatic vessels, which may contribute to lymphangiogenesis. Experiments were performed to determine whether CTGF is associated with lymphangiogenesis in peritoneal fibrosis.

**Methods:** Messenger RNA (mRNA) for CTGF, lymphatic markers (lymphatic endothelial hyaluronan receptor-1 [LYVE-1] and podoplanin), and vascular endothelial growth factor-C (VEGF-C), a major lymphangiogenic factor, in human peritoneal biopsies (N=56) was analyzed by quantitative real-time polymerase chain reaction. CTGF and VEGF-C mRNA were assessed in human peritoneal mesothelial cells (HPMC) (N=21) treated with transforming growth factor-β1 (TGF-β1). Immunohistochemistry (IHC) for CTGF, LYVE-1, and VEGF-C in a rat chlorhexidine gluconate (CG) induced-PF model was performed.

**Results:** CTGF mRNA positively correlated with LYVE-1 (R=0.638, P<0.001), podoplanin (R=0.592, P<0.001), and VEGF-C (R=0.670, P<0.001) mRNA in human peritoneal biopsies. We cultured HPMC derived from 21 patients with variable peritoneal membrane transport. CTGF and VEGF-C mRNA expression were increased by TGF-β1 (5 ng/ml) treatment. We then cultured HPMC with VEGF-C mRNA increment at 12 (R=0.722, P<0.001) and 24 (R=0.532, P<0.01) hours after TGF-β1 treatment. IHC analysis indicated that the expression of CTGF (P<0.01), LYVE-1-positive lymphatic vessels (P<0.001), and VEGF-C (P<0.01) were increased in the rat diaphragm compared with controls. Moreover, CTGF expression positively correlated with expression of LYVE-1-positive lymphatic vessels (R=0.775, P<0.05) and VEGF-C (R=0.952, P<0.001) in the CG model. There was also a positive correlation between expression of VEGF-C and LYVE-1 in the CG model (r=0.704, P<0.05)

**Conclusions:** Our results suggest a close relationship between CTGF and PF-related lymphangiogenesis.
SA-OR007
The PD Membrane Microvasculature in Uremia and PD - Findings from the International Pediatric PD Biobank
Maria Bartosova,1 Bett Schaefer,1 Stephan Machter-Goeppinger,1 Peter Sinn,2 Uwe Querfeld,3 Ariane Zoloszycz,3 Gema Ariceta,3 Yok-Chin Yap,3 Philipp Romero,1 Franz S. Schaefer,1 Bradley Warday,1 Claus P. Schmitt,4 1Center for Pediatric and Adolescent Medicine, Univ of Heidelberg, Germany; 2Dept of Pathology, Univ of Heidelberg, Germany; 3Dept of Pediatric Surgery, Univ of Heidelberg, Germany; 4Univ of Charité, Germany; 5Univ Hospital Hautepierre, France; 6Univ Hospital Vall d’Hebron, Spain; 7Hospital Kuala Lumpur, Malaysia; 8The Children’s Mercy Hospital.

Background: Based on modelling and experimental findings, peritoneal microvascularity primarily defines PD membrane transport function, respective human data is scant. Methods: 30 centers collected 322 peritoneal and 256 omental specimens from 106 healthy individuals (0-16 yrs), 114 patients at time of PD catheter insertion and 112 on PD (0.1-20 yrs), 91 treated with low GDP fluid. Aperio® and Nanozoomer/NDP Systems® were used for automated analyses.

Results: Peritoneal peritoneal vessel density depends on age, with highest blood capillary density / endothelial exchange area in infancy and lowest values with 7-12 yrs. Lymphatic vessel density is low, but again highest in infants. Omental blood capillary density correlates with peritoneal capillary density, lymphatic vessels are few. Uremia reduces omental blood vessel density by 51%, Ang-2 protein by 78%, ACTG1 by 34%. The submesothelial three vessel layer structures dissipates with low GDP PD, blood vessel density increases 2-3 fold, as do TGF-β/PSMAD, miR21, VEGF, ASMA pos. fibroblasts and CD45/CD68+ macrophages. Mild lumen narrowing develops in 51% of blood vessels, lymphatic vessel density remains low. Similar changes develop with high GDP PD, while EMT and profibrotic CD90 fibroblast subpopulations are more prominent. D/P creatinine ratios correlate with peritoneal vessel density (r=0.33, p<0.05), but not with lymphatic vessel density or submesothelial thickness; vessel density with PD duration and peritonitis numbers >0.260/20, p=0.0005).

Conclusions: Peritoneal blood vessel density defines peritoneal solute transport. Despite low GDP fluid usage, progressive blood capillarisation develops with time on PD, while lymphatic vessel density and vasculopathy remain low.

Funding: Government Support - Non-U.S.

SA-OR008
Cholecalciferol Supplementation to Correct Hypovitaminosis D in Peritoneal Dialysis Patients Increases FGF23 but Not Other Osteogenic Proteins: A Randomized Clinical Trial
Juan Carlos Ramirez-Sandeval, Mauricio Arvizu-Hernandez, Barbara Vazquez-Cantu, Cristina Cruz, Enrique Gómez, Ricardo Correa-Rotter. Ins Nac de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Background: Very low levels of 25-hydroxyvitamin D (250HD) are common in peritoneal dialysis(PD) patients, and normalization has been advocated as potentially beneficial. The safety, efficacy, and effects of 250HD correction on osteogenic biomarkers in this population remains uncertain.

Methods: We conducted a double-blind, placebo-controlled, randomized clinical trial to assess the effects of cholecalciferol supplementation on osteogenic biomarkers (osteoprotegerin, intact fibroblast growth factor-23 [iFGF23], osteocalcin, osteopontin, iPTH) in PD patients with 250HD<20 ng/mL. 56 patients were randomized to 16 wks. of cholecalciferol (4,800 IU daily) or placebo (25).

Results: Baseline characteristics were similar between groups. Mean±SD serum 250HD increased from 10.5±3.6 ng/ml at baseline to 26.1±4.5 ng/ml in the cholecalciferol group and did not significantly change in the placebo group (11.9±4.1 ng/ml to 13.2±4.5 ng/ml). A larger proportion of the cholecalciferol supplemented subjects had an increase >30% in iFGF23 compared with placebo (95% vs 9%; p<0.0001). Extremely high iFGF23 levels (>30000 pg/ml) were observed in 74% of patients receiving cholecalciferol at 16 wks.

The observed changes in iFGF23 were not confounded by concurrent and sustained changes in iPTH or residual renal function, serum P or iPTH levels. No difference was observed between arms in osteoprotegerin, osteocalcin, osteopontin, Ca, P, iPTH, IL-6, phosphate binder use or calcitriol dose.

Conclusions: Cholecalciferol supplementation increases serum 250HD levels in patients on PD with levels<20 ng/mL, yet it induces an exponential increase of iFGF23 in most PD patients, which may be a major concern and contraindication for this manoeuver.

SA-OR009
Peritoneal Dialysis-Related Infection Rates and Outcomes: Early Results from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)
Jeffrey Perl,1 Junhui Zhao,2 Brian Bieber,2 Ronald L. Pisoni,1 Beth M. Piraino,3-5 Yasukiko Ito,6,4 David W. Johnson,5,4 1Univ of Toronto, Toronto, ON, Canada; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3Univ of Pittsburgh, Pittsburgh, PA; 4Nagoya Univ Graduate School of Medicine, Nagoya, Japan; 5Univ of Queensland, Brisbane, Australia; 6On Behalf of the PDOPPS Infection Prevention and Management Workshop, Ann Arbor, MI.

Background: Peritoneal dialysis (PD)-related infections are a major source of morbidity for PD patients. We describe preliminary peritonitis rates and outcomes among PDOPPS participants.

Methods: PDOPPS is an international prospective cohort study of PD treatment outcomes in Australia/New Zealand (ANZ), Canada, Japan, Thailand, the UK and the USA. Data was collected on peritonitis episodes, and outcomes from countries with ≥100 patient-years of follow-up.

Results: Peritonitis rates were comparable across countries with the exception of Japan which had a slightly higher peritonitis rate. Wide variation was seen in facility peritonitis rates in each country. Organism-specific information revealed: the proportion of fungal peritonitis was highest in ANZ (7%), lowest in Japan (0%), the proportion of peritonitis due to pseudomonas species was highest in Japan (7%) and ANZ (7%), and peritonitis due to CNST was lowest in Japan (13%), but culture-negative peritonitis was highest (34%). Peritonitis associated with a hospitalization was highest in Japan. The proportion of peritonitis episodes necessitating PD catheter removal was similar across countries.

Conclusions: Peritonitis rates vary widely across facilities. Country-specific differences need confirmation with extended follow-up. Variation in the characteristics and details regarding peritonitis episodes may guide the regional development of peritonitis prevention strategies.

SA-OR010
Morbid Obesity and Time to Transfer to Hemodialysis among Incident Peritoneal Dialysis Patients
Yoshitsugu Ohi,1 Amanda R. Tortorici,1 Connie Rhee,1 Elani Streve,1 Daniel L. Giffen,2 Rajnish Mehrotra,3 Kamyar Kalantar-Zadeh,1 UC Irvine; 2Univ of Wash.

Background: The prevalence of obesity is increasing among dialysis patients in the USA and may be associated with higher risk of peritoneal dialysis (PD) modality interruption and transfer to hemodialysis (HD). It is noteworthy the survival advantages of obesity in dialysis patients (obesity paradox).

Methods: In a national cohort of incident dialysis patients in the USA (2007–2011), we identified 15,112 patients who started PD as their 1st or 2nd dialysis modality and who had...
data on body mass index (BMI) during the first 91 days. The association of BMI categories and the association of morbid obesity (BMI ≥35 kg/m²) with transfer to hemodialysis (HD) were examined in competing risk regression models incorporating the competing risk for death and kidney transplantation. Hierarchical adjustments were employed using case-mix variables and clinically relevant laboratory variables.

Conclusions: There was a higher likelihood of transfer to HD across higher BMI (P trend < 0.001). BMI categories above 30 kg/m² were significantly associated with shorter time to transfer to HD. These associations were robust against any adjustment models (left panel). Overall the risk associated with morbid obesity (BMI ≥35 kg/m²) was high (subhazard ratio 1.32 [95% CI, 1.21–1.45]) in the case-mix adjusted model. The risk of morbid obesity was pronounced among male or taller (height > 1.75 m) patients (P trend < 0.05) but was consistently observed across all subgroups (right panel).

Conclusions: Obesity and morbid obesity are incrementally associated with a higher risk for PD patients to transfer to HD. It makes imperative to identify interventions that would prolong patient time on PD in patients who are obese and morbidly obese.

**Funding:** NIDDK Support

### SA-OR011

**33-Induced Innate Lymphoid Cells and Alternatively Activated Macrophages That Reduce Kidney Ischaemia-Reperfusion Injury**

**Qi Cao,** 1 **Yiping Wang,** 2 **Zhiqiang Zhang,** 1 **Ruifeng Wang,** 3 **Vincent W.S. Lee,** 1 **Guoping Zheng,** 1 **Yun Min Wang,** 2 **Stephen I. Alexander,** 1 **David C. Harris,** 1 1Centre for Transplant and Renal Research, Westmead Inst for Medical Research, The Univ of Sydney, Sydney, NSW, Australia; 2Children's Hospital at Westmead, Sydney, NSW, Australia.

**Background:** IL-33 is an important immune regulator which can promote Th2 dependent immunity, inflammation, and tissue repair in several important immune-mediated disorders. In the current study, we sought to determine whether IL-33 is an important regulator in renal ischaemia-reperfusion injury (IRI).

**Methods:** Renal IRI was induced in C57BL/6 mice by bilateral renal pedicle occlusion for 30 minutes. IL-33 was given by 5 consecutive daily injections starting at day 5 before IRI surgery. Separately, adoptive transfer of type 2 innate lymphoid cells into mice with IRI was used to assess their in vivo functions.

**Results:** IL-33 significantly improved kidney functional and structural injury in IRI mice, with lower serum creatinine and less tubular cell injury. The possible mechanisms underlying the protective effect of IL-33 were examined. IL-33 increased the levels of IL-4, IL-5 and IL-13 in serum and kidney and promoted induction of alternatively activated (M2) macrophages in kidney. Moreover, the number of NK cells and neutrophils was significantly reduced in IRI mice treated with IL-33. Of note, IL-33 increased the number of type 2 innate lymphoid cells (ILC2) and regulatory T cells (Tregs) in kidney. The depletion of ILC2 or Tregs by using CD90 or CD25 antibodies in vivo demonstrated that the protective effect of IL-33 in IRI is dependent on ILC2 cells, but not Tregs. Adoptive transfer of ILC2 not only reduced kidney injury of IRI mice but also induced M2 macrophages in kidney.

**Conclusions:** In conclusion, IL-33 elicits ILC2 and Tregs, regulates macrophage phenotype in kidney and prevents kidney IRI. ILC2 is primarily responsible for IL-33's protective effect in IRI.

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

### SA-OR012

**Tubular Cell Endocycle-Related Hypertrophy and Renal Progenitor Mitosis Drive Kidney Function Recovery after AKI but Cannot Avoid Persistent Tubular Cell Loss**

**Elena Lazzeri,** 1 **Maria Lucia Angelotti,** 1 **Anna Julie Peetsd,** 1 **Duccio Lombardi,** 1 **Francesca Becherucci,** 1 **Hans J. Anders,** 1 **Laura Lasagni,** 1 **Paola Romagnani.** 1

1Excellence Centre DENOTHE, Univ of Florence, Italy; 2Division of Nephrology, Klinikum der LMU München, Germany.

**Background:** Acute kidney injury (AKI) is considered largely reversible based on an intrinsic regenerative capacity of tubules. As AKI can be followed by chronic kidney disease (CKD), we questioned this concept and hypothesized that tubular cell division is limited and other mechanisms account for kidney function recovery.

**Methods:** To this aim, we developed four conditional transgenic mouse models: 1. Pax8:rtTA;TetO:Cre;R26.Confetti (Pax8/Confetti) to track all tubular cells; 2. Pax2: rtTA; TetO:Cre;R26.Confetti (Pax2/Confetti) to track putative tubular progenitors; 3. Pax8: rtTA;U:U:t:Cre;R26:Fucci2 (Pax8/Fucci2) and 4. Pax2:rtTA;rtTA;Cre;R26:Fucci2 (Pax2/Fucci2) to identify cell-cycle phase of Pax8+ and Pax2+ cells. Doxycycline administration followed 1 week washout showed the reporter expression to track Pax2+ and Pax8+ progenies in healthy mice and after 30' of unilateral ischemia/reperfusion injury (IRI).

**Results:** To quantify irreversible cell loss we induced IRI in Pax8/Confetti mice where all tubular cells are tracked. Kidney function recovered, but 35% of total tubular cells were irreversibly injured and endoreduplication but not true cell division is strongly indicated by cell-cycle markers immunostaining. Simultaneous cell-cycle phase and DNA content assessment using Pax8/Fucci2 mice and flow cytometry revealed endoreduplication-related tubular cell hypertrophy as the predominant response and showed that cell-cycle recovery occurred at endoreduplication but not true cell division. In contrast, Pax2/Confetti mice showed that Pax2+ tubular progenitors enriched by higher survival and clonogenic capacity after IRI. Consistently, Pax2/Fucci2 mice demonstrated that Pax2+ tubular progenitors continued mitosis while Pax8+ cells endoreduplicated.

**Conclusions:** These results disprove common knowledge about the mechanisms of AKI recovery, 2. identify tubular cell hypertrophy related to endoreduplication cycles as a critical response to AKI 3. explain the high incidence of CKD after an AKI episode.

**Funding:** NIDDK Support

### SA-OR014

**Fibroblast-Specific Integrin-Linked Kinase Signaling Is Required for Kidney Protection and Repair after AKI**

**Haiyan Fu,** 1 **Dong Zhou,** 2 **Youhua Liu,** 1

1Dept of Pathology, Univ of Pittsburgh School of Medicine, Pittsburgh, PA; 2Children's Hospital at Westmead, Sydney, NSW, Australia.

**Background:** Integrin-linked kinase (ILK) signaling plays a critical role in regulating cell proliferation, differentiation, matrix production and tissue homeostasis. Activation of ILK has been linked to the pathogenesis of tubular epithelial-mesenchymal transition (EMT) and kidney fibrosis. Whether ILK plays any role in the repair or progression after AKI is unknown.

**Methods:** To study this, we generated conditional knockout mice in which the ILK gene was specifically depleted in kidney fibroblasts (FC-ILK-/-) by mating ILK-floxed mice with Gli1-Cre transgenic mice. Sex- and age-matched control and FC-ILK-/- mice were subjected to ischemia/reperfusion injury (IRI).

**Results:** Mice with fibroblast-specific deletion of ILK (FC-ILK-/-) were phenotypically normal with no appreciable defects in kidney morphological and function. Following AKI induced by IRI, FC-ILK-/- mice developed more severe kidney injury, comparing to the WT mice. FC-ILK-/- mice had higher serum creatinine level and more severe morphological injury. In addition, ablation of ILK in interstitial fibroblasts promoted chemokine expression and renal infiltration of inflammatory cells after IRI. Consistently, apoptosis was more prevalent in the kidneys of the FC-ILK-/- mice, which was accompanied by increased renal expression of soluble Fas, and Fas-associated protein with death domain (FADD). Notably, the ability of fibroblasts activation and proliferation was largely abolished in the FC-ILK-/- mice, with downregulation of PDGFR-β, PCNA and increased P53 expression.

**Conclusions:** These results suggest that endogenous ILK in fibroblasts is pivotal for proper fibroblasts activation in response to acute injury. Such response from healthy fibroblasts is crucial for tubular cell survival, repair and regeneration after AKI.

**Funding:** NIDDK Support
SA-OR015

Background: In response to kidney injury renin lineage cells (RLC) can give rise to different glomerular cell types such as mesangial cells (MC) or podocytes. Endothelial cells (EC) represent a major glomerular cell type frequently undergoing primary or secondary injury during kidney disease. Up to now it is unknown if RLC can or not differentiate into EC. Thus, we investigated the role of RLC in endothelial regeneration.

Methods: We used a triple transgenic lacZ reporter mouse which allows specific detection and fate mapping of RLC via X-Gal staining. LacZ labeling of RLC in healthy adult mice was induced by doxycyclin/lanapril treatment. Left sided EC injury (ECl) was caused by renal-arterial administration of concanavalin A (conA)/anti-conA. Kidneys were harvested on day 0 (healthy control), 1, 7 and 28.

Results: ECl evaluation using CD31 densitometry showed significant decrease of positive staining area at day 1 and subsequent recovery to HC levels at day 7 (HC 11.7 ± 1.7% d1: 6.7 ± 0.3% d7: 13.7 ± 1.5%). Accordingly AFOG staining revealed glomerular fibrin thrombi at d1. In conjunction with endothelial damage we detected pronounced MC injury by PAS staining, which could be verified by αS integrin densitometry (HC 16.5 ± 1.7% d1: 6.2 ± 1.5% d7: 13.9 ± 1.0%). Whereas Xa-Gal staining was restricted to the juxtaglomerular apparatus (JGA) in healthy controls, 15.6 ± 0.8 % of glomeruli showed migration of RLC from the JGA into the glomerular tuft at d7. Immunohistological analysis revealed that these intraglomerular RLC show a transdifferentiation to mesangial phenotype expressing αS-integrin, Ng2 and GATA3, but do not co-localize with EC (CD31, ERG) or podocytes (WT-1, syntapodin). These findings could preliminarily be confirmed using fluorescent renin lineage mice.

Conclusions: In our model of renal ECl, RLC are recruited from the JGA to the glomerular tuft upon severe injury. These RLC do not show involvement in regeneration of damaged renal endothelium. Rather, recruitment of RLC seems to be specific for the repair of concomitantly injured mesangium.

SA-OR016
Exosomal Transfer of micro-RNA-486-5p Protects against Ischemia-Reperfusion Kidney Injury  Kevin D. Burns, Joe A. Zimpelmann, Alex Gutzol, William A. Knoll, Dylan Burger, David Allan, Jose L. Vinas. Medicine, KRC, OHRI, Univ of Ottawa, Ottawa, ON, Canada.

Background: Exosomes derived from cord blood endothelial colony forming cells (ECFCs) reduce ischemia/reperfusion (IR) kidney injury in immune-incompetent mice. ECFC exosomes are enriched in micro-RNA (miR)-486-5p, which we showed can be transferred to cultured endothelial cells. We studied the role of miR-486-5p transfer in protection against IR kidney injury in vivo, and assessed phosphatase and tensin homolog (PTEN) as a potential target.

Methods: Immuno-competent mice with IR kidney injury were injected with ECFC exosomes (20 µg i.v.) at reperfusion. Some mice received exosomes derived from ECFCs that were transfected with antagoniR to miR-486-5p. After 24 h, mice were sacrificed, plasma was collected, and kidneys were analyzed by real-time PCR, immunoblots, histologic injury, and proliferation analysis. In cultured endothelial vein (HEV) cells, a luciferase reporter assay assessed targeting of PTEN by miR-486-5p, and silencing RNA determined the role of PTEN in apoptotic response by hypoxia.

Results: In mice with IR, exosomes increased kidney miR-486-5p levels, decreased PTEN, and increased phosphorylation of pro-survival Akt. These effects were blocked in mice receiving exosomes from antagoniR-transfected ECFCs. ECFC exosomes potently protected against IR kidney injury, determined by plasma creatinine and BUN, histologic injury, and apoptosis assays (plasma Cr. 117±26 µM (IR) vs 9±4 µM (IR + exosomes), P<0.01, n=5 mice). By contrast, the protective effects were not observed with exosomes derived from antagoniR-transfected ECFCs. In cultured HEV cells transfected with a luciferase reporter, miR-486-5p directly targeted the 3’-untranslated region of PTEN. Knockdown of PTEN in HEV cells inhibited hypoxia-induced apoptosis, to levels observed with exosome treatment (n=3).

Conclusions: In response to IR injury, administration of ECFC exosomes causes transfer of miR-486-5p, which mediates protective effects on kidney function, histology and apoptosis. In endothelial cells, PTEN is directly targeted by miR-486-5p, which blocks apoptosis. Exosomes enriched in miR-486-5p could represent a viable strategy to protect against acute kidney injury.

Funding: Private Foundation Support, Clinical Revenue Support

SA-OR017
Proximal Tubule-Derived Amphiregulin and TNFα Crosstalk Promotes Progressive Fibrotic Kidney Disease  Eirini Kefalogianni,1 Vaishali Krishnadas,1 Muthu Laksmhi Muthu,1 Helmut G. Rennke,2 Benjamin D. Humphreys,3 Joseph V. Bonventre,2 Andreas Herrlich.2 1Nephrology, Washington Univ School of Medicine, St. Louis, MO; 2Renal, Brigham and Women’s Hospital, Boston, MA.

Background: Using global and proximal tubule (PT)-specific knockout, we previously showed in ischemic and obstructive kidney injury mouse models that the metalloproteinase ADAM17 is a key regulator of fibrosis via cleavage-activation of its substrates, epidermal growth factor receptor (EGFR) ligands and TNFα. However, apart from PT, injury also induces ADAM17 upregulation in the interstitial compartment. We thus now examined the effect of stromal- or myeloid lineage-specific knockout of ADAM17 on injury-induced kidney fibrosis in vivo. Further, we studied pro-fibrotic and pro-inflammatory effects of specific PT-released ADAM17 substrates in vitro. Finally, we investigated activation of the EGFR/TNFα pathways with potential pro-fibrotic and pro-inflammatory cytokine expression in PT cells in vivo. This effect is strongly potentiated by TNFα. This newly identified EGFR-TNFα pathway cross-talk partially depends on ADAM17-dependent AREG cleavage. Finally, both EGFR and TNFα pathways are activated in human AKI and CKD samples, and ADAM17 and AREG protein expression are very strongly correlated with pro-fibrotic markers in CKD biopsies.

Conclusions: ADAM17 substrates released from injured PT and their cross-talk, in particular of AREG and TNFα, exert ADAM17’s pro-fibrotic role. Activation of ADAM17 pathways highly correlates with injury and fibrosis in human kidney samples.

Funding: NIDDK Support

SA-OR018
Eliminating the Cellular Mechanisms of a Pro-Regenerative Drug Using the EGFR and the Hippo Pathway in Acute Kidney Injury  Eugene Berndine Burgess,1,23 Muthu Lakshmi, Michael Burns,1,2 Bernd Mekhlafi, Michael Burns,1,2 G. E. Burns,1,2,3 Jacqui A. Hentze,1,2,3 Michael Heimrich,1,2,3 1Dept of Developmental Biology, Univ of Pittsburgh, Pittsburgh, PA; 2Department of Medical and Pathology, Univ of Auckland, Auckland, New Zealand.

Background: Acute kidney injury (AKI) often progresses to chronic kidney disease and end stage renal disease due to inefficient renal tubular epithelial cell (RTEC) proliferation. Therefore, drugs that can enhance proliferation in post-AKI setting are urgently in need. We identified a small molecule, methyl-4-phenylbutanoate (m4PTB), an HDAC inhibitor, which increases RTEC proliferation in zebrafish and rodent models of AKI. However, the mechanisms driving proliferation are not known. Here, we show that m4PTB enhances epithelial-to-mesenchymal transition, a hallmark of dedifferentiating cells. The dedifferentiating cells provide the source of RTEC proliferation, thereby enhancing post-AKI AKI repair.

Methods: We injected gentamicin in larval zebrafish to induce a nephrotoxic model of AKI. We utilized immunohistochemistry to visualize expression of E-cadherin and Vimentin, markers of epithelial and mesenchymal cells, respectively. We stained tubules with Pdx2, and PCNA, markers for renal progenitors and proliferation, respectively. Finally, we stained tubules with kidney injury molecule-1 (KIM-1) to quantify changes in injury level after m4PTB treatment.

Results: m4PTB treatment increased expression of mesenchymal marker and decreased epithelial marker in injured RTECs. Injury stimulated Pux2 reactivation in RTECs, further increasing with m4PTB. Pux2 expression colocalized with Vimentin, suggesting that m4PTB increases the embryonic gene simultaneously undergo dedifferentiation. To investigate whether the dedifferentiating cells provide the source of proliferation, we stained tubules with Pdx2 and PCNA; m4PTB increased the number of double positive cells, demonstrating of which many colocalized. Finally, we show that m4PTB lowers KIM-1 expression, thereby reducing tubular injury.

Conclusions: Our work demonstrates that m4PTB promotes dedifferentiation of RTECs to increase proliferation and reduce injury level. This mechanism of dedifferentiation and proliferation enhances regenerative responses post-AKI.

Funding: Other NIH Support - 2R01DK096043; 2R01HD053287

SA-OR019
Interaction of the EGFR Receptor and the Hippo Pathway in Acute Kidney Injury  Jianchun Chen, Raymond C. Harris. Medicine, Vanderbilt Univ, Nashville, TN.

Background: Activation of both EGFR and the Hippo signaling pathway can control cell proliferation, apoptosis and differentiation. Our previous studies have shown that activation of EGFR in renal proximal tubule epithelial cells plays a critical role in renal functional and structural recovery from ischemia-reperfusion injury (IRI), and wildtype mice were subjected to IRI followed by administration with vehicle or verteporfin, an inhibitor of YAP-TEAD activation.

Methods: Renal proximal tubule cell-specific EGFR receptor knockout mice (EGFR<sup><sup>-/-</sup></sup>) or the wildtype littermates (WT) were subjected to ischemia-reperfusion injury (IRI), and wildtype mice were subjected to IRI followed by administration with vehicle or verteporfin, an inhibitor of YAP-TEAD activation.

Results: In response to IRI, renal YAP expression and nuclear localization were markedly increased within 6 hours and persisted for at least 3 weeks after IRI. YAP activation was dramatically inhibited in EGFR<sup><sup>-/-</sup></sup> mice. Administration of verteporfin significantly delayed renal functional and structural recovery from IRI. The BUN of vehicle-treated mice returned to basal levels (19.65 ± 1.44 mg/dl) at 7 days after IR, but remained elevated in verteporfin treated mice (43.33 ± 6.01 mg/dl, P<0.01, n=5). There was eesnoe presence of tubular dilation and epithelial metaplasia and cast formation.
in verteporfin-treated mice. We also found that upregulation of cyclin D expression and phosphorylation of pRb protein (Rb) 24 h after IRI were dramatically blunted in EGFR1/2 mice or in the mice given verteporfin.

**Conclusions:** This study demonstrates that EGFR-dependent YAP upregulation plays an important role in renal functional and structural recovery in response to acute kidney injury. The decreases in cyclin D and Rb phosphorylation suggest that YAP activation is important for cell cycle activation and epithelial regeneration following AKI.

**Funding:** NIDDK Support, VA Support

SA-OR020

**Kidney Injury Molecule-1 (KIM-1) Interacts with the Dynein Light Chain Tctex-1 to Mediate Efferocytosis**

Lakshaman Gunaratnam,1 Ola Ziyad Ismail,1 Xizhong Zhang.1 1Matthias Mailing Centre for Translational Transplant Studies, Lawson Health Research Inst, London, ON, Canada; 2Medicine, Western Univ, London, ON, Canada.

**Background:** After tissue injury, the phagocytic clearance of apoptotic cells, or efferocytosis, attenuates inflammation and enables tissue repair. KIM-1 is an efferocytosis receptor specifically upregulated on proximal tubular epithelial cells during acute kidney injury (AKI). We previously showed that, after renal ischemia-reperfusion injury, mice deficient in KIM-1 have impaired efferocytosis, with greater tissue damage, renal dysfunction and death, compared to wild-type mice.

**Methods:** To uncover the phagocytic signalling pathway downstream of KIM-1, we utilized a yeast two-hybrid screening system and identified a potential KIM-1-interacting protein, the 14-kDa dynein light chain protein, Tctex-1. Tctex-1 is a component of the dynein microtubule motor complex involved in linking dynein to its cargo as an adaptor protein. It also plays dynein-independent roles in diverse cellular functions. Thus, we hypothesized that Tctex-1 is a required for KIM-1-mediated engulfment of apoptotic cells.

**Results:** First, we confirmed the direct interaction between Tctex-1 and KIM-1 using co-immunoprecipitation, GST-Tctex-1 pull-down assay and immunofluorescence staining. When we stimulated KIM-1-expressing cells with apoptotic cells, the interaction between KIM-1 and Tctex-1 was found to increase during the later stages of the efferocytosis process. Knockdown of endogenous Tctex-1 expression with siRNA significantly inhibited efferocytosis by KIM-1-expressing cells. To test if Tctex-1 inhibition effects caused by Tctex-1 knockdown was related to impaired cargo binding for dynein transport (i.e. dynein-dependent), we utilized transgenic Tctex-1-/- mice that were reported Chronin-94 with glutamic acid (194E) to mimic the phosphorylated form that cannot bind dynein. Surprisingly, the phospho-mimic Tctex-1-194E displayed decreased binding to KIM-1, but did not influence KIM-1-mediated uptake of apoptotic cells.

**Conclusions:** Our studies have uncovered a novel role for Tctex-1 in efferocytosis, which is crucial to tissue repair following AKI.

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

SA-OR021

**New Insights into the Function of Dendritic Cell Subsets in Glomerulonephritis Using Multi-Photon Imaging**

Sebastian Bracheller,1 Saravanan Raju,1 Michael William Johnson,1 Bernd H. Zinselmeyer,1 Jeffrey H. Miner,2 Kenneth M. Murphy,1 Andrey S. Shaw.1 1Dept of Pathology and Immunology, Washington Univ School of Medicine, St. Louis, MO; 2Div of Nephrology, Washington Univ School of Medicine, St. Louis, MO; 3Genentech, South San Francisco, CA.

**Background:** Glomerulonephritis (GN) is a major cause for end stage renal disease. The immunological mechanisms are not completely understood. Studies using CD11c as a marker for dendritic cells (DC) have identified DCs as key players in a mouse model of GN (NTN). How to discriminate macrophages and dendritic cells in various tissues is a matter of ongoing debate. Recently, new markers allow the definition of subsets of macrophages and dendritic cells in the kidney.

**Methods:** Here we used multiphoton imaging of isolated kidney slices from three different fluorescent reporter mice (CD11c-YFP, ZBTB46-GFP for all classical DCs and SNX22-GFP for the CD103+ DC subpopulation) to analyze structure, migration and distribution of dendritic cells under healthy conditions and after NTN treatment. To determine the function of specialized DC subsets, we depleted the general classical DC lineage using zbtb46-DTR bone marrow chimera and the CD103+ subset by using BATF3-knockout mice before inducing NTN.

**Results:** CD11c-YFP-positive cells formed a continuous network with long cell processes, and with many cells in this population also expressing the macrophage markers F4/80 and CD64. In contrast, ZBTB46-GFP-positive and SNX22-GFP-positive DCs have a lower expression of these markers, exhibited shorter processes, higher maturity and were found clustered around blood vessels. Depletion of ZBTB46+ DCs caused an attenuation of NTN, preventing tissue damage in the late stage, whereas depletion of only the CD103+ subset aggravated NTN with rapid crescent formation and excessive neutrophil invasion.

**Conclusions:** Here we provide evidence that CD11c-YFP identifies a mixed population of macrophages and dendritic cells. ZBTB46-depletion studies showed that the dendritic cells in toto have a proinflammatory effect, whereas the CD103+ subset represents an anti-inflammatory population, possibly balancing the immune response generated by their CD11b+ counterparts.

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

SA-OR022

**FcRIV Is Important in the Pathogenesis of Anti-MPO Induced Crescentic Glomerulonephritis**

Hong Xiao, Peiqi Hu, Cheng Wan, Ronald J. Falk, J. Charles Jennette. Pathology and Laboratory Medicine, Univ of North Carolina, Chapel Hill, NC.

**Background:** Anti-myeloperoxidase (anti-MPO) IgG causes crescentic glomerulonephritis (CGN) in mice that mimics human anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis in patients. Our prior studies have shown that knock down of activating Fcγ receptors (FcγRA) decreases disease in anti-MPO CGN, but that KO of activating receptors FcγRI and FcγRIII does not prevent disease. In this study, we investigated the role of the activating receptor FcγRIV in anti-MPO induced CGN in vivo, as well as the effect of blocking anti-FcγRIV antibodies on neutrophil activation by anti-MPO IgG in vitro.

**Methods:** B6 mice with KO of FcγRIV (FcγRIV KO) and wild type (WT) B6 mice were injected i.v. with 50µg/body weight anti-MPO IgG. Circulating anti-MPO IgG was determined by ELISA. Urine abnormalities were monitored, and mice were sacrificed at day 6 and kidney tissue obtained for pathologic examination. In vitro neutrophil activation by anti-MPO was measured by flow cytometry.

**Results:** At day 6, B6 WT and FcγRIV KO mice that received anti-MPO IgG showed similar levels of circulating of anti-MPO. All WT B6 mice developed hematuria and CGN (mean 12% glomeruli with crescents). In contrast, FcγRIV KO mice had normal urine and less CGN with mean 2% crescents (p<0.001). Neutrophils deficient in FcγRIV/- or treated with anti-FcγRIV blocking antibodies had less in vitro activation by anti-MPO than neutrophils from wild type mice as measured by respiratory burst.

**Conclusions:** 1) Absence of the FcγRIV greatly diminishes anti-MPO induced CGN in vivo, and in vitro neutrophil activation, indicating the engagement of FcγRIV by anti-MPO IgG plays an important role in the pathogenesis of anti-MPO induced CGN. 2) Inhibitory effects of anti-FcγRIV antibody on anti-MPO induced activation of neutrophils suggests that blocking FcγRIV engagement by ANCA may have a therapeutic role in ANCA disease.

**Funding:** NIDDK Support

SA-OR023

**CD11b Activation Protects against Lupus Nephritis by Suppressing TLR-Dependent IFN Responses via AKT-FOXO3A**

Sama Khan,1 Mohd Hafeez Faridi,1 Shehryar K. Khaliqindia,1 David J. Cimbaluk,1 Vineet Gupta.1 1Rush Univ Medical School; 2NIAMS, NIH.

**Background:** Genetic variations in the ITGAM gene (coding for CD11b) produce defective CD11b and associate with a risk for systemic lupus erythematosus (SLE, lupus) and lupus nephritis. Elevated level of IFN in circulation is a heritable risk factor for SLE and promotes the immune dysregulation characteristic of this disease. Whether variations in CD11b are linked to high IFN I and whether CD11b activation could be a therapeutic strategy is not known and is explored here.

**Methods:** We measured serum IFN I activity in 171 SLE patients and determined their ITGAM genotype to test for a direct link between ITGAM SNPs and the IFN I pathway. Given that ITGAM SNPs result in functionally deficient CD11b, we tested whether partial CD11b activation with small molecule agonist, leukadherin, would increase basal IFN I in vitro and whether mice that develop IFN 1-dependent multi-organ lupus similar to human lupus with renal injury.

**Results:** We show that three ITGAM variants significantly associate with the elevated levels of IFN I in lupus, suggesting a direct link between reduced CD11b activity and elevated inflammation in patients. Partial CD11b activation with LA1 reduced IFN I responses and protected lupus-prone MRL/lpr mice from kidney injury. LA1-treated mice had reduced proteinuria, IgG renal cell deposition, and glomerular damage as compared to controls. CD11b activation reduced TLR-dependent pro-inflammatory signaling in leukocytes and suppressed IFN I signaling, via an AKT-FOXO3A-IRF7 pathway. TLR-stimulated macrophages from CD11b SNP carriers showed increased basal expression of IRF7 and IFNB, as well as increased nuclear exclusion of FOXP3, which was suppressed by LA1.

**Conclusions:** LA1 suppresses TLR-stimulated overproduction of cytokines in vivo, which have been directly linked to exacerbation of lupus nephritis. These findings suggest that pharmacological CD11b activation should be explored as a potential novel therapeutic target in SLE, particularly in patients identified as carriers of specific genetic polymorphisms.

**Funding:** Other NIH Support - R01DK084195, R01DK106512 and R21CA176055

SA-OR024

**Endothelial NF-κB Blockade Abrogates Anti-MPO Antibody-Induced Glomerulonephritis**

Mira Choj,1 Adrian Schreiber,1 Claudia Eulenberg-Gustavus,2 Claus Scheidereit,1 Jan A.A.M. Kamps,3 Ralph Kettlitz.1 1Nephrology, Experimental and Clinical Research Center, Berlin; 2Department of Internal Medicine, Rush Univ Medical School, Berlin, Germany; 3Dept of Pathology and Medical Biology, Univ Medical Center Groningen, Groningen, Netherlands.

**Background:** ANCA vasculitis is a highly inflammatory condition where ANCA-activated neutrophils interact with endothelium resulting in necrotizing vasculitis. We tested the hypothesis that endothelial NF-κB mediates necrotizing crescentic glomerulonephritis (NCGN) and can be therapeutically targeted.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: P65 siRNA was formulated in liposomes conjugated with anti-E-selectin antibody. Animals were infected with M. tuberculosis infected with intravenous injection of dose TNFα to upregulate E-selectin on EC, followed by SOS siRNA or control compound. Anti-MPO antibodies and LPS were injected 48h later for disease induction. After 7 days urine analysis was done by dipsticks, albuminuria. Glomerular crescents and necrosis were assessed in hematoxylin and eosin stained kidneys, and monoclonal factor was stained in the kidney were measured by flow cytometry. NF-κB activity was quantified in nuclear extracts using electrophoretic mobility shift assays using EMSA and by RT-PCR for TNFα mRNA.

Results: Retrospective analysis of kidneys from murine GN revealed that p30/p65 NFκB expression was upregulated in affected kidneys, resulted in increased NF-κB gene transcription, correlated with crescent formation, and possibly involved the endothelial compartment. ANCA-stimulated primed neutrophils activated endothelial NF-κB in neutrophil-endothelial cell co-cultures. This resulted in increased transcription and protein production of NFκB-dependent genes, and promoted neutrophil adhesion to an endothelial monolayer. We used a passive anti-MPO antibody transfer model for GN and treated mice with p65 siRNA. Active treatment significantly reduced urine abnormalities, myeloid cell influx into the kidneys, and glomerular necrosis and crescent formation. Finally, increased phospho-p65 staining in glomeruli with active lesions indicates that NF-κB is also activated in patients with ANCA-associated NCGN.

Conclusions: We suggest that endothelial NF-κB contributes to NCGN and provides a therapeutic target.

SA-OR025
Transcriptome Analysis of CD4-Lymphocytes Specifically Deleted of NEMO or IKKβ in an Experimental Model of Rapid Progressive Glomerulonephritis
Frederik Thaiss,1 Melian Chen,2 Jiabin Guo,3 Gunther Zahnert4, Malik Aliw3, Linlin Guo.1 1Nephrology, Univ Hospital, Hamburg, Germany; 2HPI, Univ Medical Center, Hamburg, Germany.

Background: Experimental nephrotic nephritis (NTN) is a model for T-cell mediated human rapid progressive glomerulonephritis. T-cell stimulation leads to activation of transcriptional factors, such as NF-kappa B. Recently we published the role of a specific IKK2 (β)-inhibitor in this model. We therefore now examined T-cell specific ablation of IKK2 or NEMO.

Methods: T-cell specific ablation of IKK2 or NEMO was achieved through deletion of IKK2 or NEMO in T-cells isolated from the spleen under control of the CD4ε promoter. NTN-sensitivity was injected and function, histology and kidney chemokines determined during a 10-days period. T cells, Th1, Th17 and Treg infiltration into the kidney were analyzed by FACS. CD4+ NFκc4 αrε cε αrε T cε lε lε αrε aε αrε were used as controls. Transcriptome analysis was performed of CD4+ T cells isolated from spleens before and after NTN induction.

Results: Nephritic CD4εcIKK2/2L and CD4εcNEMO/LLE mice had an increase in albumin/creatinine ratio at day 3 and increased glomerular crescents at day 10. Although the percentage of CD+ T cells infiltrating kidneys was not different between the groups examined further analysis showed significantly reduced Thregs but a significant increase in Th1- and Th17-T cells in CD4εcIKK2/2L and CD4εcNEMO/LLE animals. As a spleen-kidney axis has been described recently next transcriptome analysis of CD4+ splenocytes was performed. Volcano plot revealed 97 genes differentially down- and 120 genes up-regulated in CD4+ splenocytes of nephritic mice. The results of DIRE analysis showed IKK2 and NEMO dependent differential transcription factors activation.

Conclusions: Our data demonstrate that ablation of IKK2 or NEMO specifically in CD4+ T-cells significantly increased Th1 and Th17 cells infiltrating kidneys after NTN. We have identified a key gene pattern in CD4+ T-cell differentiation that were differentially expressed between IKK2 and NEMO deficient CD4+ T-cells. Better understanding the role of IKK2 and NEMO in T-cell regulation will help to recognize the role of IKK2- and NEMO- kinase inhibitors in patients with glomerulonephritis.

Funding: Government Support - Non-U.S.

SA-OR026
Therapeutic Induction of Antigen Specific Tolerance in MPO-ANCA GN Using MPO-Conjugated Apoptotic Splenocytes

Background: Loss of tolerance to myeloperoxidase (MPO) results in MPO-ANCA associated nephropathy. MPO-coated renal glomerular basement membrane (GBM) is critical to the development of glomerular endothelial cell injury and necrosis, and MPO-ANCA – GBM activated T-cell mediated injury to GBM Ig. As a spleen–kidney axis has been described recently next transcriptome analysis of CD4+ splenocytes was performed. Volcano plot revealed 97 genes differentially down- and 120 genes up-regulated in CD4+ splenocytes of nephritic mice. The results of DIRE analysis showed IKK2 and NEMO dependent differential transcription factors activation.

Methods: We generated the following experimental groups of FcgRIIB−/− female mice: TL7/0: wild type, TL7/7/IRF5−/− mice, TL7/7/IRF5−/− mice, TL7/7/FcgRIIB−/− mice, TL7/7/FcgRIIB−/− mice. Mice were analyzed at the age of 8 months. Experimental groups were compared for disease manifestations including autoantibody production, serum IgG levels, and kidney disease severity.

Results: We found that TL7/7 deficiency reduces disease severity and that TL7/7 is required not only for the production of autoantibodies against DNA-containing autoantigens but also for autoantibodies against double-stranded DNA. FcgRIIB−/− mice deficient in both TL7 and IRF5 developed less disease than mice deficient in TL7 alone, with lower titers of anti-DNA autoantibodies, lower levels of the pathogenic IgG isotypes, and less severe renal disease.

Conclusions: We have identified TL7-dependent and TL7-independent roles for IRF5 in the development of lupus nephritis and lupus nephritis. FcgRIIB−/− mice deficient in both TL7 and IRF5 developed less disease than mice deficient in TL7 alone, with lower titers of anti-nuclear autoantibodies, lower levels of the pathogenic IgG isotypes, and less severe renal disease. This suggests that therapies targeting IRF5 may offer some additional benefit compared to therapies targeting only TL7 for the treatment of lupus and lupus nephritis.

Funding: Other NIH Support - ST32DK007053, Research Training in Nephrology T32 Grant
SA-OR029

Treatment with the Natural VEGF Inhibitor Soluble Flt-1 Reduces Renal Complications, Endothelial Activation and Inflammation in Long-Term Type 1 Diabetic Mice

Pascal Bus, Marion Scharpfenecker, Jan A. Bruijn, Hans J. Baedel. Pathology, LUMC, Leiden, Zuid-Holland, Netherlands.

Background: It has been shown that VEGF-A is involved in diabetic nephropathy (DN). Animal models for diabetic nephropathy have shown that glomerular VEGF-A levels are increased, and that reducing VEGF-A is beneficial in preventing renal complications. Besides VEGF-A, VEGF-B is involved in endothelial activation and macrophage migration. The aim of the current study was therefore to investigate if treatment with the natural VEGF-A inhibitor sFlt-1 reduces inflammation and endothelial activation.

Methods: Diabetes was induced in C57BL/6 mice with injection of streptozotocin. After five weeks of diabetes mice were transfected with a sFlt-1 construct via electroporation. 15 weeks after the induction of diabetes mice were sacrificed. Collection of urine and blood was performed at baseline, and subsequently every other week. Albuminuria was measured using Rocket Electrophoresis. Kidneys were sectioned and stained for PAS, collagen IV, fibronectin, vWF, EGF, tnf-α, Iba-1, tfn-α, p-ERK, v-ATPase, p-ERK, and quantified using ImageJ. One-way ANOVA was performed to measure differences between groups. Differences with a probability level (p) < 0.05 were considered statistically significant.

Results: Diabetic mice transfected with sFlt-1 had lower urine albumin/creatinine ratios compared to mice with diabetes alone and reduced glomerular damage (p<0.001). In addition, vcam-1 and icam-1 (p<0.001), the number of glomerular macrophages (p<0.01) and glomerular tnf-α expression (p<0.001), were reduced to basal levels in sFlt-1 treated diabetic mice compared to control diabetic mice.

Conclusions: Our results show that inhibiting VEGF-A levels by sFlt-1 has beneficial effects on inflammation, besides the effect on renal function and morphology. These effects could be attributed to a decreased number of glomerular macrophages, potentially due to the inhibitory effect of sFlt-1 on macrophage migration and by reducing endothelial activation.

SA-OR030

Absence of the Endogenous A2B Adenosine Receptor Increases Severity of Immune–Associated Inflammation

Gabriela E. Garcia,1 Luan D. Truong,2 Kelley S. Brodsky,1 Holger Eltschig,3 Richard J. Johnson.1 1Medicine, Univ of Colorado Denver, Aurora, CO; 2Pathology, The Methodist Hospital, Houston, TX; 3Anesthesiology, Univ of Colorado Denver, Aurora, CO.

Background: Adenosine functions as a signaling molecule through the activation of four adenosine receptors. During conditions in which adenosine levels are elevated such as hypoxia, ischemia or inflammation A2B adenosine receptor (A2BAR) increases ischemia tolerance and attenuates acute inflammation.

Methods: Using an A2B AR knockout reportere gene-knock-in, we investigated the role of A2BAR in kidney injury in the cytokine-dependent anti-glomerular basement membrane glomerulonephritis (anti-GBM GN).

Results: We found that A2BAR is slightly expressed in the vascular pole and that in nephritic kidneys A2BAR expression is highly induced in the vascular pole and also in glomeruli and arteries. Mice with less kidney injury expressed less A2BAR. In contrast, higher expression of A2BAR expression was observed with more kidney injury, suggesting that increased A2BAR is a counter-regulatory response to inflammation. Importantly, nephritic kidneys from A2BAR knockout mice showed more severe kidney injury compared with those in Wild type (WT) animals. Glomerular proliferation, crescent formation, tubulointerstitial injury and inflammatory cell infiltration were significantly higher in A2BAR knockout mice compared to WT mice. A2BAR promoter contains a binding site for the transcription factor hypoxia-inducible factor (HIF)-1 that increases A2BAR expression. To investigate if HIF-1 is induced in GN and could be responsible for A2BAR upregulation, we used a HIF-1α reporter mouse (OUD-Luc) and found that HIF-1α is induced in nephritic kidneys as early as day 3 after induction of the disease. Next, to determine if endothelial A2BAR mediates kidney injury in GN, we compared mice with deletion of A2BAR in endothelial cells with controls. Mice with endothelial-specific A2BAR deficiency showed increased in disease susceptibility. Moreover, use of an A2BAR antagonist significantly attenuated GN.

Conclusions: These findings suggest that A2BAR is a natural mechanism of inhibition of inflammation and protection from tissue damage.

Funding: NIDDK Support

SA-OR031

eGFR, Albuminuria, and Future Risk of Peripheral Artery Disease: The Chronic Kidney Disease Prognosis Consortium


Background: Peripheral artery disease (PAD) is one of the most common cardiovascular outcomes in patients on dialysis. However, the full spectrum associations of eGFR and albuminuria with future PAD risk are yet to be investigated.

Methods: We studied 784,342 participants without a history of PAD from 13 cohorts. Cox models were used to quantify the associations of eGFR and urine albumin-to-creatinine ratio (ACR) with incident PAD (composite of hospitalizations with PAD diagnosis, intermittent claudication, leg revascularization, and leg amputation) beyond potential confounders such as diabetes. We also evaluated whether eGFR and ACR improve PAD risk prediction.

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

SA-OR032

ESRD and Mortality after Medical Therapy Compared with Percutaneous and Surgical Coronary Revascularization in Individuals with CKD at Low, Medium, or High Cardiovascular Risk

David M. Charytan,1 Tanya Natwick,2 Craig Soli,3 Shuling Li,3 Charles A. Herzog.3 Brigham & Women’s Hospital, Boston; 3Chronic Disease Research Group, MMRF, Minneapolis.

Background: Prior analyses suggest that medical therapy (MT) is inferior to percutaneous (PCI) or surgical coronary revascularization (CABG) for the treatment of coronary disease in individuals with CKD, but did not assess ESRD risks and may be confounded by definition of MT as the absence of revascularization as well as failure to stratify by baseline cardiovascular (CV) risk.

Methods: CV risk groups were defined in the 2007-2012 Medicare 20% sample. Low risk: angiography or stress testing without prior CV disease (CVD); Medium risk: stress test or angiography with prior CVD; High risk: admission for acute coronary syndrome (ACS). CKD and ESRD were defined by diagnostic codes, and PCI and CABG as procedures within 60 days of risk group entry. MT was defined as use of new CV medications.

Results: For low risk pts 1000 had PCI, 571 CABG, and 6848 MT. For medium risk 1751 PCI, 718 CABG and 9670 MT. For high risk 4542 PCI, 1481 CABG and 8287 MT. Mortality and CV outcomes increased across risk groups, consistent with excellent discrimination of our metric. Cumulative probability of ESRD was similar with CABG and MT in the low risk group, but was worse with CABG in medium and high risk groups. Notably, ESRD probability was similar with PCI and MT in all groups (figure 1). Mortality rates per hundred patient years were lowest with MT in the low risk group—PCI 9.1, CABG 9.9, MT 8.1—and medium risk—PCI 13.5, CABG 13.0, MT 13.2, but was markedly better with CABG or PCI in high risk patients—PCI 18.4, CABG 13.1, MT 33.5.

Results: There were 19,574 PAD cases over a median follow-up of 3.4-14.9 years across cohorts. Both low eGFR and high ACR were associated with PAD risk independently of each other and known PAD risk factors (Figure). Of note, the association of ACR appeared to be more evident with leg amputation than overall PAD. Both eGFR and ACR improved PAD risk discrimination beyond known risk factors (Ae-statistic: 0.013 [95% CI: 0.011-0.015] and 0.008 [0.006-0.010], respectively). Risk discrimination for leg amputation was improved with ACR (Ae-statistic: 0.037 [0.024-0.050]) but not necessarily with eGFR (0.012 [0.001-0.025]).

Conclusions: Both low eGFR and high ACR were independently associated with future PAD risk and significantly improved its prediction. ACR was particularly relevant to leg amputation, even independently of diabetes. These results suggest the usefulness of CKD measures to identify patients who are at high risk of PAD and may benefit from PAD examination, monitoring, and prevention.

Funding: NIDDK Support

SA-OR033

Adjusted for age, sex, race, smoking, diabetes, systolic blood pressure, antihypertensives, drugs, total and high-density lipoprotein cholesterol, history of coronary disease, stroke, and heart failure, and each CVQ measure.

Funding: NIDDK Support
SA-OR034

The Incidence of Atrial Fibrillation by Chronic Kidney Disease Stage and Proteinuria

Amber O. Molnar,1 Anan Bader Eddean,2 Robin Ducharme,3 Amit X. Garg,2 Ziv Harel,1 Megan K. McCallum,4 Jeffrey Perl,4 Ron Wald,4 Manish M. Sood,2,3 Nephrology, McMaster Univ, Hamilton, ON, Canada; 2Nephrology, Univ of Ottawa, Ottawa, ON, Canada; 3Epidemiology, Ottawa Hospital Research Inst, Ottawa, ON, Canada; 4Nephrology, St. Michael’s Hospital, Univ of Toronto, Toronto, ON, Canada; 1Inst for Clinical Evaluative Sciences, Ottawa, ON, Canada; 4Medicine and Epidemiology, Western Univ, London, ON, Canada.

Background: Prior studies examining the association of CKD with incident atrial fibrillation (AF) are limited by heterogeneous definitions of CKD. Many studies define CKD as a dichotomous outcome and most fail to include albuminuria, which is an important component of new staging systems for CKD.

Methods: In this retrospective cohort study (2002-2015), we grouped 736,666 adults ≥40 years of age with no prior history of AF by eGFR (≥90, 60 to <90, 45 to <60, 30 to <45, 15 to <30, or <15 mL/min per 1.73 m²) and urine albumin-to-creatinine ratio (ACR >300, 30-300 or <30 mg/g) to examine the incidence of new onset AF. Cox models were used to estimate the hazard ratios (HR) for AF. Patients were censored upon death, dialysis or end of follow up.

Results: Median follow up 6 years. 45,499 (6.2%) patients developed AF, 62,243 (8.4%) died and 6,667 (0.9%) patients required dialysis. The incidence rate of AF increased more than 40 fold across declining eGFR and increasing ACR groupings (eGFR >90/ACR <30: 3.29 per 1000 person-years; eGFR <15/ACR >300: 137.3 per 1000 person-years).

In adjusted models using the eGFR >90 and ACR <30 grouping as the referent, patients with an eGFR of ≥90 mL/min per 1.73 m² had adjusted HR’s for AF of 2.4 (95% CI, 2.2-2.6) for the lowest ACR group and 5.5 (95% CI, 4.5-6.7) for the highest ACR group. Patients with an eGFR >90/ACR >300 had an adjusted HR of incident AF of 3.9 (95% CI, 2.9-5.4), higher than the adjusted HR of 2.6 (95% CI, 1.7-3.9) for patients with an eGFR <15/ACR >30. Urine ACR altered the association of eGFR with incident AF (p<0.001).

Conclusions: This study shows that declining eGFR and increasing ACR independently increase the risk of AF. Strategies for the prevention of AF should consider CKD, defined by both eGFR and urine ACR, as a risk factor for AF.

Funding: Government Support - Non-U.S.

SA-OR035

CKD Modifies the Association of Brain Natriuretic Peptide (BNP) and High Sensitivity-Troponin T (TnT) with CV Events and Death

L. Perc Greggs,1,2 Xilong Li,1 Beverley Adams-Huet,1 James Delemos,1 Susan Hedayati.1 UT Southwestern,2 Dallas, TX, TX.

Background: Few data exist assessing associations of traditional cardiac biomarkers and outcomes in non-diabetes CKD patients. We evaluated whether associations between BNP, NT-proBNP and TnT with CV death and CV events were modified by CKD in 3,303 asymptomatic Dallas Heart Study participants followed for 10 years.

Methods: Cox proportion hazards assessed associations between biomarkers and all cause death and CV death/event, adjusted for age, sex, race, diabetes, hypertension, smoking, total and HDL cholesterol. Effect modification of CKD (eGFR<60 mL/min/1.73 m²) on the association of these biomarkers with CV death and CV events was assessed using interaction p<.1.

Results: The cohort was 50% Blacks, 31% Caucasians, 17% Hispanics, and 2% other races. Compared to 3,014 non-CKD, 299 CKD patients were older with a higher percentage of Blacks and diabetics. Proportions with stages 1, 2, 3, and 4 decreased with higher eGFR. Overall, 11% died and 6% had CV death/event vs. 42% and 29% of CKD patients, p<.0001 for both. The interaction between BNP and CKD on death was significant so that the aHR was intensified and significant in CKD but not significant in the non-CKD group. CKD also modified associations of BNP and TnT with CV death/event, with stronger associations in CKD (Table).

Conclusions: These results show: BNP, NT-proBNP, and TnT provide independent prognostic information in early stage CKD, with stronger associations for BNP and TnT in CKD than non-CKD. Future studies should investigate whether these biomarkers differentially add to the prognostic ability of traditional CV risk factors in asymptomatic CKD patients.

Funding: Other NIH Support - NHLBI

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

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SA-OR036

The Association between Rate of Change in Albuminuria and Clinical Outcomes Min Jun,1 2 Matthew T. James,1 Braden J. Manns,1 Marcello Tonelli,1 Jianguo Zhang,1 Vladko Perkovic,2 Brenda Hemmelgarn,1 3Univ of Calgary, Canada; 4George Inst for Global Health, Australia.

Background: Change in albuminuria may have important prognostic utility in determining the future risk of outcomes. We sought to assess the association between change in urine albumin-creatinine ratio (UACR) and the risk of acute myocardial infarction (AMI), end-stage renal disease (ESRD), and all-cause death.

Methods: We identified 170,515 adults (age ≥18 years) in Alberta, Canada, who had ≥2 outpatient UACR measurements (1-2 years apart) within a 2-year period between May 1, 2003 and March 31, 2012. Rate of change in UACR (during a 2-year period; mg/mmol/year) was defined based on 3 groups: 1) decrease (≥-4.6 decrease; 5th percentile of change), 2) stable (-4.6 to 6.1), 3) increase (≥6.1 increase; 95th percentile of change). Follow-up for outcome (AMI, ESRD, and all-cause death) ascertainment commenced at the last UACR measurement during the 2-year period (defined as baseline). We used adjusted Cox regression models to estimate the hazard ratio for each outcome, adjusting for sociodemographic information, baseline GFR and UACR, and comorbidities at baseline.

Results: Over the outcome ascertainment period, 4100 (2.4%) AMI events, 849 (0.5%) ESRD events, and 14450 (8.5%) deaths occurred. Compared with stable UACR, increase in UACR was associated with 56%, 72%, and 50% higher risk of AMI, ESRD, and death, respectively.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>UACR Change</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>Decrease</td>
<td>1.08 (0.95-1.23)</td>
</tr>
<tr>
<td></td>
<td>Stable (Ref)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Increase</td>
<td>1.56 (1.11-1.84)</td>
</tr>
<tr>
<td>ESRD</td>
<td>Decrease</td>
<td>1.32 (1.24-1.41)</td>
</tr>
<tr>
<td></td>
<td>Stable (Ref)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Increase</td>
<td>1.50 (1.40-1.61)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>Decrease</td>
<td>1.00 (1.00-1.00)</td>
</tr>
<tr>
<td></td>
<td>Stable (Ref)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Increase</td>
<td>1.50 (1.42-1.58)</td>
</tr>
</tbody>
</table>

However, decrease in UACR was also associated with greater risk for ESRD and all-cause death, resulting in a U-shaped relationship between UACR change and these outcomes.

Conclusions: Change in UACR over time is associated with future risk of clinically important outcomes. However, given the observed U-shaped relationship between albuminuria change and outcomes, its utility as a prognostic tool among high-risk patient groups requires further assessment.

SA-OR037

Adverse Events in Advanced Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Study Morgan Grams,1 Wei Yang,1 Casey Rebolhol,2 Xue Wang,2 Anna C. Porter,2 Lesley Inker,2 Edward J. Horwitz,2 James H. Sondheimer,3 L. Lee Hamm,3 Jianguo Zhang,4 Matthew R. Weir,2 Bernard G. Jaar,1 Tarig Shah,2 Lawrence J. Appel,1 Chi-Yuan Hsu,2 Johns Hopkins Univ; 4CRIC Study, Univ of Pennsylvania.

Background: People with advanced chronic kidney disease (CKD) are at risk for the development of end-stage renal disease (ESRD), but also many other adverse outcomes, including cardiovascular disease (CVD) events and death. Determination of risk factors that explain the variability in prognosis and timing of these adverse outcomes can aid patient counseling and medical decision-making.

Methods: We followed 1,798 participants with eGFR <60 ml/min/1.73 m2 in the Chronic Renal Insufficiency Cohort (CRIC) study for a median of 5.5 years, evaluating risks of ESRD, CVD (congestive heart failure, stroke, myocardial infarction, peripheral artery disease), and death.

Results: Baseline age of the cohort was 60 years; 46% were women, and 46% were African American. While 52.3% of participants progressed to ESRD during follow-up, the path by which this occurred varied by baseline patient characteristics. For example, the predicted 1-year probabilities for a 60-year old white woman with eGFR 30 ml/min/1.73 m2, 1.8 grams/day of proteinuria, and no diabetes or CVD (risk characteristics similar to the average participant), were 3.3%, 4.1%, and 0.3%, for first developing CVD, ESRD, and death, respectively. For a 40-year-old African-American man with similar characteristics but higher systolic blood pressure, the corresponding 1-year probabilities were 2.4%, 13.2%, and 0.1%. For all participants, the development of ESRD or CVD increased the risk of subsequent mortality, with no differences by patient race or body mass index.

Conclusions: More frequent laboratory testing during the 2 years prior to RRT initiation is associated with lower post-ESRD all-cause and CV mortality.

Funding: NIDDK Support, VA Support.

SA-OR038

Association of the Frequency of Pre-ESRD Medical Care with Post-ESRD All-Cause and CV Mortality Csaba P. Kovacs,1 2 Jun Ling Lu,1 No H. Zhu,1 Molnar,2 Keiichi Sumida,2 Praveen Kumar Potukuchi,2 Elani Streja,3 Kamyar Kalantar-Zadeh,3 1Univ of Tennessee Health Science Center, Memphis, TN; 2Univ of California, Irvine, CA; 3VA Medical Center, Memphis, TN.

Background: Some studies found that receiving Nephrology care in the pre-ESRD period is associated with improved outcomes in dialysis patients. Less is known about the association between the frequency of pre-ESRD laboratory testing and post-ESRD mortality in incident ESRD patients.

Methods: We examined 23,089 US veterans who initiated RRT between 10/2007-09/2011, and had outpatient laboratory tests performed during the last two years prior to RRT (prelude). The association of the frequency of the combined measurement of serum creatinine, potassium and hemoglobin with post-ESRD all-cause mortality and cardiovascular (CV) mortality was examined in Cox proportional hazard regression models adjusted for socio-demographics, comorbidities, BP variability, and CV medication adherence.

Results: The mean age (SD) was 66.2 (13.3) years, and the mean estimated GFR (SD) was 46.8 (23.9) ml/min/1.73m2 entering the 2-year prelude period. 32.3% of the cohort had the lab test trio performed between once-a-year to once every two years; 9.3% had no lab test trio measured during prelude, and 8.9% had the trio measured more often than every other month. Over a 2.5-year median follow-up period, 15,303 (66.3%) patients died (mortality rate: 260/1000 patient years; 95% CI: 256-264). More frequent lab testing was associated with lower post-ESRD mortality (Figure). The adjusted hazard ratio (95%CI) associated with lab testing done more than once every other month compared to once every 6-12 month was 0.66 (0.62-0.71). Associations were similar for CV mortality (Figure).

Conclusions: With replication in additional cohorts, these results can help guide personalized approaches for managing patients with advanced CKD.

Funding: NIDDK Support
surveys (1999-2010). We also examined whether diabetics with eGFR > 60 and ACR < 30 compared to diabetics with eGFR < 60 and ACR ≥ 30 have 7 risk of cardiovascular (CV) or renal events using data from NHLBI funded ACCORD Study. CV outcome was a composite of CV death, MI, CHF or stroke. Kidney outcome was a composite of 50% drop in eGFR, dialysis or serum creat >3.5 mg/dl.

Results: Prevalence of eGFR < 60 in DM has dramatically increased; in this population, nearly 60% have urinary ACR < 30 (fig).

Conclusion:* The very high prevalence of GFR < 60 in type 2 diabetics may suggest the end stage of kidney disease.

SA-OR041
Generation and Analysis of KLHL3 Knockout Mice  Emi Sasaki, Koichiro Susa, Takayasu Mori, Kiyoshi Isobe, Yuya Araki, Yuichi Inoue, Tatetsuki Rui, Shinich Uchida, Eisei Sohara. Nephrology, Tokyo Medical and Dental Univ, Bunkyo, Tokyo, Japan.

Background: Mutations in with-no-lysine kinase 1 (WNK1), WNK4, Kelch-like 3 (KLHL3) and Cullin 3 (CUL3) genes are reported to cause PHAII. Recently, we generated KLHL3−/− mice and demonstrated that mutant KLHL3 resulted in defective degradations of WNK4 and WNK4, leading to PHAII, indicating that KLHL3/CUL3 ubiquitin ligase complex interacts and degrades WNK kinases. However, pathophysiologic roles of KLHL3 other than PHAII are still unclear.

Methods: To answer these questions, we generated two KLHL3−/− mice lines; conventional KLHL3−/− mice and KLHL3−/− mice that express β-gal under endogenous KLHL3 promoter in this study. Using these mice, we sought to determine the tissue distribution of KLHL3 and its role in regulating WNK protein level in each tissue.

Results: At first, we investigated the tissue distribution of KLHL3 using β-gal expression. Immunoblot of β-gal showed the strong expression in brain and kidney, and the lower expressions in eye, testis, lung, and pancreas. Strong β-gal staining was observed in hypothalamus and distal tubules in brain and kidney, respectively. Next, we investigated the protein levels of WNK1, WNK3 and WNK4 in the whole tissues of KLHL3−/− and KLHL3−/− mice where KLHL3 expression was detected. In the brain and other tissues showing the lower expression levels of KLHL3, expression levels of WNK1, WNK3 and WNK4 were not increased in KLHL3−/− and KLHL3−/− mice. However, only in kidney, WNK1 and WNK4 were significantly increased in KLHL3−/− mice, but not in KLHL3−/− mice. KLHL3−/− mice also showed KLHL3-like phenotypes, but without PHAII.

Conclusions: Our data clearly showed that the WNK protein levels in KLHL3-expressing tissues might not be governed only by KLHL3. Lack of PHAII phenotypes in KLHL3−/− mice clearly showed the heterogeneous deletion of KLHL3 was not enough to cause PHAII in the kidney, indicating that PHAII phenotypes in KLHL3−/− heterozygous mice we previously observed are caused by the dominant-negative effect of R528H KLHL3 mutant. Dimer formation of wild-type and R526H KLHL3, which we could demonstrate, would explain the dominant-negative effect of this mutant.

Funding: Government Support - Non-U.S.

SA-OR042
KLHL3-Knockin Mice Featuring Pseudohypoaldosteronism Type II Do Not Correct the Phenotype of WNK4-Null Mice  Chien-Ming Lin,1 Chih-Ien Cheng,2 Sung-Sen Yang,3 Shi-Hua P. Lin.3 Dept of Pediatrics, Tri-State Service General Hospital, National Defense Medical Center, Taipei, Taiwan; 2Graduate Inst of Medical Sciences, National Defense Medical Center, Taipei, Taiwan; 3Div of Nephrology, Dept of Medicine, Tri-State Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Background: Enhanced SPAK/OSR1 would explain the dominant-negative effect of this mutant.

Funding: NIDDK Support

SA-OR040
Glucose Targets for Renal, Mortality, and Cardiovascular Outcomes: A Meta-Analysis of Randomized Trials  Marcellina Russo,1 Valeria M. Saglimbene,1,2 Suetonia Palmer,1 Salvatore De Cosimo,1 Antonio Pacilli,1 Jonathan C. Craig,3 Giovanni F. Strippoli,1,5,6 1Diaverum Medical Scientific Office; 2Amedeo Avogadro Univ of Eastern Piedmont; 3Univ of Otago Christchurch; 4Scientific Inst CSS; 5Univ of Sydney; 6Univ of Bari.

Background: Blood pressure lowering and glucose control are used to reduce diabetes-associated disability including end-stage kidney disease. However, the benefits and harms of tight glycemic control on renal outcomes among patients with kidney disease are uncertain. We summarize the evidence in randomized clinical trials (RCTs) of intensive versus standard glycemic control for preventing the onset and progression of kidney disease among adults with diabetes.

Methods: A Cochrane systematic review with meta-analysis was conducted including trials in which adults with type 1 or 2 diabetes with and without kidney disease were randomly allocated to tight or less stringent blood glucose targets. Treatment effects were estimated using random-effects meta-analysis. Risks of bias were adjudicated using Cochrane methods.

Results: Eleven studies involving 29,140 patients were eligible. Trial follow up was 56.7 months on average. In moderate to high quality evidence, a tight glucose target conferred uncertain risks of serum creatinine doubling (relative risk (RR) 0.84, CI 0.59-1.18), ESKD (RR 0.88, CI 0.70-1.11), all-cause mortality (RR 0.99, CI 0.86 to 1.13), cardiovascular mortality (RR 1.19, CI 0.73-1.92), and sudden death (RR 0.82, CI 0.82-2.57). Tighter glycemic control reduced risks of nonfatal myocardial infarction (RR 0.82, CI 0.69-0.99), and onset (RR 0.85, CI 0.70-0.94) and progression of microalbuminuria (RR 0.50, CI 0.36-0.69).

Conclusions: Tight glycemic control for treatment of diabetes provided uncertain risks of ESKD, death and major cardiovascular events compared with less stringent glycemic control, while lowering risks of myocardial infarction and onset and progression of microalbuminuria. The long-term clinical benefit of glycemic management on microalbuminuria is uncertain until sufficiently powered RCTs evaluate hard renal outcomes.

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

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that ubiquitinates proteins, targeting them for degradation. The mechanism by which deletion of exon 9 (CUL3 Δ403-459) leads to the disease is unknown, but an important feature in CRL activity is cycling between neddylated (active) and unneddylated (inactive) states. The COP9 signalosome (CSN) deneddylates CRLs utilizing the catalytically active subunit JAB1. It has been reported that the cullin 1 CSN-binding region contains the 4HB and α/β domain, that is essential for Hsp70 activation, and that in cells over expressing Hsp40, NKCC2 stability and maturation are improved. Mutation of the lower affinity for the CSN, results in over activation of CUL3 leading to degradation of KLHL3 and a greater WNK abundance.

Funding: NIDDK Support, Other NIH Support - T32 DK007864

SA-OR044
Roles of Cytoplasmic Hsp40 and Hsp70 Molecular Chaperones in NCC2 Stability and Function
Mireille Basset-Fabre,1 Sylvie Derenzetti,2 Bodo H. Beck,3 Martin Köhnbacht,4 Kamel Laghnani,5 CRc, INSERM-U1138, UPMC, CNRS, ERLK22, Paris, France; 1Univ of Cologne, Cologne, Germany; 2Philipps Univ Marburg, Marburg, Germany.

Background: We recently showed that MAGE-D2 mutations causes polyhydramnios with prematurity and a severe but transient form of antenatal Bartter’s syndrome associated with inappropriate expression of the sodium–chloride transporters NKCC2 and NCC and plasma Na and vasopressin (AVP) were measured in mice on Day 1 of the HS diet.

Results: On day 1 of the HS diet, Hkα1 mice had three times greater Na retention (p<0.01) compared to WT and markedly impaired diuresis (50% lower fluid intake vs. WT, p<0.001) with higher urine osmolality. Hematocrit and plasma Na and AVP were significantly greater in Hkα1−/− than WT on the HS diet. During the entire period of HS feeding, Na retention in Hkα1−/− was greater than WT (days 1, 2, 4, p<0.05).

Conclusions: These results suggest an important role for the Hkα1 subunit in the regulation of purinergic signaling in the CD. Hkα1 is physiologically important in the acute regulation of Na balance, affects the diuretic response to a high NaCl diet, and is part of a previously undiscovered element in Na regulation in the CD.

Funding: VA Support

SA-OR047
A Missense Mutation in the Extracellular Domain of α-ENaC Causes Liddle Syndrome
Ewoot J. Hoorn,1 Laurent Schild,2 1Erasmus Medical Center; 2Univ de Lausanne.

Background: Liddle syndrome or pseudohypokalemia is an autosomal dominant form of hypokalemic hypertension that has been linked to mutations in the SCNN1B or SCNN1G gene, encoding the β- or γ-subunit of the epithelial sodium channel (ENaC). Here, we describe one generation of a family with Liddle syndrome due to a novel mutation in SCNN1A and functionally characterize the α-ENaC mutation.

Results: The proband (63-y.o. man) was referred because of unexplained hypertension (since age 26), hypokalemia, metabolic alkalosis, and suppressed plasma renin and aldosterone. Previous genetic testing had not identified mutations in SCNN1B or SCNN1G. Because of a positive family history for hypertension, whole-exome sequencing was performed and revealed a novel mutation in the aminolide-sensitive domain of α-ENaC. This missense mutation was identified in a highly conserved region of the extracellular domain of α-ENaC. Family analysis (5 siblings) identified one affected sister (hypertension, no hypokalemia) and showed that suppressed plasma renin and aldosterone completely segregated with siblings with or without the mutation. Hypertension did not segregate because three other siblings also had (primary) hypertension. Open exome analysis did not identify additional causes of genetic hypertension in the family. A “triamterene test” was performed (adapted from the thiourea test) showing a 2-fold greater natriuresis and 100% suppression of urinary aldosterone excretion in the αENaC blocker in the two affected siblings than in healthy volunteers. Daily treatment with triamterene quickly normalized blood pressure and serum potassium in the affected siblings. Functional analysis of ENaC carrying the missense mutation in oocytes confirmed a channel gain-of-function (12-fold increase in Na' current), predominantly due to an increase in intrinsic activity of the channel.

Conclusions: We report the first mutation in the extracellular domain of α-ENaC causing Liddle syndrome. The mild phenotype correlates with the function studies. This mutation may be present in other unrecognized cases of hypertension with suppressed renin and aldosterone, and also provides novel insight in regulation of ENaC activity.

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

SA-OR046
High Na Diet Causes Increased Na Retention and Impaired Diuresis in Hkα1 H.K-ATPase Knockout Mice
Charles S. Wingo,1 James D. Stockand,1 Elena V. Mironova,1 I. Jeannette Lynch,2 Jonathan M. Berman,3 Michelle L. Gumz,3 1UT HSC, San Antonio, TX; 2NF/ SV HHS, Gainesville, FL; 3UF Dept of Medicine, Gainesville, FL.

Background: Parinergic regulation of the epithelial Na channel (ENaC) is an important mechanism that regulates external Na balance. Loss of this regulation contributes to salt-sensitivity and has been implicated in mineralocorticoid escape. ENaC activity is inversely related to dietary Na intake, in part, due to inhibitory purinergic signaling in the collecting duct (CD), with increasing Na intake stimulating luminal ATP secretion. We previously showed that Na reabsorption in CD of Hkα1, H.K-ATPase null (Hkα1−/−) mice was benzamil-insensitive, and ENaC activity in Hkα1−/− mice was uncoupled from Na intake. ENaC activity on a 2.0% Na (HS) diet was greater in the Hkα1−/− versus wild-type (WT), and dietary Na did not normally modulate ENaC activity in the Hkα1−/−. Purinergic signaling of ENaC was abnormal in Hkα1−/−, with markedly reduced urinary ATP that did not increase in response to the HS diet. ENaC activity in the Hkα1−/− responded normally to exogenous ATP, suggesting a pre-receptor defect. The present studies tested the contribution of this uncoupling at the whole animal level.

Methods: Total Na balance was measured in Hkα1−/− and WT mice placed in metabolic cages and fed a normal Na diet for 7 days followed by HS for 7 days. Blood hematocrit and plasma Na and vasopressin (AVP) were measured in mice on Day 1 of the HS diet.

Results: On day 1 of the HS diet, Hkα1−/− mice had three times greater Na retention (p<0.01) compared to WT and markedly impaired diuresis (50% lower fluid intake vs. WT, p<0.001) with higher urine osmolality. Hematocrit and plasma Na and AVP were significantly greater in Hkα1−/− than WT on the HS diet. During the entire period of HS feeding, Na retention in Hkα1−/− was greater than WT (days 1, 2, 4, p<0.05).

Conclusions: These results suggest an important role for the Hkα1 subunit in the regulation of purinergic signaling in the CD. Hkα1 is physiologically important in the acute regulation of Na balance, affects the diuretic response to a high NaCl diet, and is part of a previously undiscovered element in Na regulation in the CD.

Funding: Support - Non-U.S.
Results: Acidosis induced expression of cathelicidin (2.8 fold ± 0.48, n=4), neutrophil gelatinase-associated lipocalin (NGAL) (6 fold ± 2.1, n=4), and rabbit defensin neutrophil peptide 5 (NP-5) mRNA (1.76 fold ± 0.42, n=6) in the CCDS micro-dissected from rabbit kidney; there was also a large increase in NP-5 mRNA (5.8 fold ± 1.1, n=6) in proximal tubule (PST). Growth was attenuated in acidic urine compared to normal. Antibody mediated induction of cathelicidin activity promoted UPEC growth attenuated in acidotic urine. Conventional qRT-PCR from 4 pairs of Dolichos biflorus agglutinin (DBA)-selected kidney CDs showed that metabolic acidosis induced cytolytic mRNA expression for IL-1β, TNFα, and IL-6, 2-4 fold. Rabbit cytokine/chemokine/peptide PCR array from one pair of DBA- selected kidney CDs showed induction of chemokines CXCL18 (IL-18 receptor) and monocyte necrosis factor receptor superfamily member 11b (TNFRSF11b), and LOC100354804, a permeability factor 2-like gene, 3-7 fold by acidosis.

Conclusions: Metabolic acidosis, possibly via activation of HIF-1α, induces expression and function of innate immune defense peptides as well as pro-inflammatory cytokine/chemokine expression in renal tubules.

Funding: NIDDK Support

SA-OR051
Kruppel-Like Factor 4 Is a Key Mediator of Renal Endothelial Injury in Antibody Mediated Rejection
Chelsea C. Estrada, Edward P. Nord, Sandeep K. Mallipattna.
Medicine/Nephrology, Stony Brook Medicine, Stony Brook, NY.

Background: Yearly mortality for patients with end-stage renal disease on dialysis is 5-times higher than their counterparts who are transplanted, however sustained graft survival is impeded by antibody-mediated rejection (ABMR) with the renal endothelium as the target. Mechanisms that mediate endothelial injury in ABMR are unknown. Endothelial Endothelial-associated transcripts (ENDATs), reflecting activation and injury were recently incorporated into diagnostic criteria for ABMR, and Krüppel-Like Factor (KLF4), a zinc-finger transcription factor, exhibited the highest expression by microarray in biopsies from ABMR compared to T-cell rejection (TCR). KLF4 is known to have anti-inflammatory and anti-fibrotic effects on endothelial cells and the cardiovascular system but its actions in the renal endothelium have not been delineated.

Methods: Immunofluorescence (IF) for KLF4 and isletin B4 (endothelial marker) was performed in human and mouse control kidneys. Wild-type mice were injected with lipopolysaccharide (LPS) 10 μg/μl IP or buffer and sacrificed 48 hours. Human umbilical vein cells (HUVECs) were incubated with LPS or the endothelial specific lectin, concanavalin A (20 μg/ml, 30 minutes) followed by anti-concanavalin A, (200 μg, 6 hours). Results: We demonstrated KLF4 has high baseline expression in all renal endothelial cells by IF. We observed a 4-fold increase in KLF4 by rt-PCR in HUVECs treated with LPS, 1 and 10 μg/ml for 8 hours. Similarly, wild-type mice treated with LPS had a 3-fold increase in endothelial-specific expression of KLF4 as compared to controls by IF and rt-PCR. Both LPS groups exhibited an increase in the adhesion molecules VCAM-1 and ICAM-1, confirming endothelial injury. Subsequently, in a model of antibody mediated endothelial injury, HUVECs incubated with concanavalin A followed by anti-concanavalin A, also demonstrated significant induction of KLF4. Finally, kidney biopsies from patients with ABMR demonstrated a significant increase in endothelial-specific expression of KLF4 compared to healthy donors, TCR, and non-rejecting acute kidney injury by IF.

Conclusions: Our data suggests that KLF4 is a key mediator of endothelial injury in ABMR.

Funding: Private Foundation Support

SA-OR052
Differences in Inflammation and Fibrosis in Deceased and Living Renal Donors Determine Long-Term Renal Function
Monserrat M. Diaz Encarnacion, Elena Guillen-Gomez, Irene Silva, Iara Karilha Dasilva, Yolanda Arce, Jose Ballarin. Fundacio Puigvert.

Background: It is known that living donor (LD) transplants present better outcome than deceased ones (DD). Renal fibrosis and tubular atrophy (IF/TA) is the best predictor of renal function and it could be induce by chronic inflammation. The aim of this study is to analyze the influence of donors in renal outcome.

Methods: Pre-implantational (basal) and 4 months biopsy were analyzed by Remuzzi and Banff scores, respectively. Inflammation and fibrosis markers were quantified by qPCR and immunohistochemistry. The aim of this study was to determine the prevalence of donors in renal outcome.

Results: Our results show that basal inflammation measured by CD68 positive cells (24 mo, p=0.006 and 5 yr, p=0.05) and Remuzzi score (24 mo, p=0.003; 5 yr, p=0.0468) correlated with medium- and long-term renal function in DD, whereas we did not found it in LD. At 4 months, Banff‘05 inflammation (24 mo, p=0.010 and 5 yr, p=0.0233) and inflammatory and fibrosis markers in DD correlated with medium- and long-term renal function (IL-1β, 24 mo, p=0.017 and 5 yr, p=0.0005; ICAM-1, 24 mo, p=0.0473 and 5 yr, p=0.0007; MCP-1, 24 mo, p=0.0212 and 5 yr, p=0.0011 and TNFα, 24 mo, p=0.0274 and 5 yr, p=0.0202; TGF-β1, 24 mo, p=0.0026 and 5 yr, p=0.0001; fibronectin, 5 yr, p=0.0007). On the other hand, in LD, 4 months fibrosis but not inflammation, correlated with renal function only at 24 months, but none of the markers studied by qPCR did it. Moreover, basal inflammation and fibrosis (A-M-basal) correlated with medium- and long-term renal function (MCP1, p=0.0003; TNFα, p=0.0241; IL-1β, p=0.0102 and ICAM-1, p=0.0026; TGF-β1, p=0.0210; fibronectin, p=0.0258).

Conclusions: In conclusion, early and sustained inflammation in DD are predictors of 3-5 year graft outcome and could be essential in dissimilarities between DD and LD renal function.

Funding: Government Support - Non-U.S.
SA-OR053
Loss of Regulatory Anti-Angiogenic Protease Activated Receptor-1 (PAR-1) Antibodies Associate with the Development of Metastatic Cancer Post Renal Transplantation and Patient Death
Rusun Catur,1 Robert Peter Carroll,2 Angelika Kasch,1 Aurellie Philippe,1 Duska Dragun.1 1Clinic for Nephrology and Critical Care Medicine, Charité, Berlin, Germany; 2Centre for Experimental Transplantation, Royal Adelaide Hospital, Adelaide, Australia.

Background: VEGF is crucial for neoangiogenesis in tumors. The GPCR Protease-activated receptor 1 (PAR-1) is closely involved in VEGF regulation. We hypothesized that autoimmune GPCR targeting process may disturb VEGF induced angiogenesis in vitro we found that PAR-1 is a novel activating autoantibody target. We then assessed the presence of PAR-1 autoantibodies in 20 Kidney Transplant Recipients (KTR) with and 29 KTR without metastatic cancer.

Methods: Human microvascular endothelial cells (HMEC-1) were stimulated with IgG isolated from sera of kidney transplant recipients (KTRs-IgG). regulation of VEGF was studied by promoter deletion assay. qRT-PCR, western blot, EMSA and cFOS knockdown. VEGF secretion was determined by ELISA. Tube formation on matrigel served to study endothelial neoangiogenic response. All 40 patients had sera for assessment of PARab and at the time of transplantation and 2014.

Results: PARab levels were lower at the time of transplant in KTR who developed metastatic cancer after transplant compared to those who did not level. Levels were also different at the time of cancer diagnosis compared to those who had not developed cancer when assessed in 2014.

Conclusions: Specific transcriptional and epigenome signatures provide evidence for molecular changes detectable in donor kidneys prior to transplantation and immediately following kidney transplantation independently of IRI and predict post-transplant outcomes. These signatures and pathways drive molecular events leading to impaired graft function and represent potential nodes for therapeutic intervention.

Funding: Pharmaceutical Company Support - GlaxoSmithKline

SA-OR055
Compartment Modulation Abrogated Ischemia/Reperfusion Induced Inflammaging by Inhibiting Senescence-Associated Secretory Phenotype (SASP) in Tubular Epithelial Cells (TEC) Rossana Castellano,1 Rossana Catarina,1 Angela Carla,1 Alessandra Sbati,2 Chiara Devilla,2 Margherita Gigante,1 Simona Simone,1 Paola Pontrelli,1 Giuseppe Grandalduino,1 Loreto Gesualdo.1 1Univ di Bari; 2Univ of Foggia.

Background: Renal senescence is associated to the development of a subclinical, low-grade inflammatory state called inflammaging, as first described in diabetic nephropathy. This process is associated with the diminished regenerative potential of TEC. However, the role of cellular senescence and its modulation in I/R injury is not known.

Methods: Ten pigs were treated with C1-Inhibitor (C1-Inh, 500U/kg, 5 min before reperfusion) (T24 C1-INH). Biopsies were analyzed for markers of SASP (SA-βGal, p16INK4a, p21WAF1 and IL-6) by IHC. In addition, TEC were exposed to C5a and then analyzed after culture in normal medium (24h, 48h) for SA-βGal, p53, NOD-4L, MCP-1 and CTGF by WB and qPCR.

Results: I/R injury induced tubular senescence by increasing SA-βGal, p21 and nuclear p65 expression (T24C1-12:1:2 vs T0:3.7±0.84 p=0.05) typical of SASP. p16INK4a mRNA transcription was significantly increased from 5.4 to 51.5 (p<0.05). Pigs treated with C1-INH efficiently antagonized SASP by restoring p16 (T24 C1-INH 4.93±0.92 vs T24 CTRL, p=0.21), p1-6 expression and SA-βGal at basal level (p<0.05). In accordance, short stimulation of TEC with C5a (3h) induced senescence in vitro by up-regulating SA-βGal (2%/SAS-βGal+) vs baseline 0.8% (p<0.05). SASP were characterized by increase in p53 protein (WB: p53: C5a 24h: 1.4±0.8 vs basal 0.7±0.24, p<0.05) as sign of stable cell cycle arrest and up-regulation of p65 NF-κB subunit (p<0.05). Finally, NOX-3 protein levels significantly increased after C5a stimulation indicating the activation of oxidative stress pathway.

Conclusions: Renal I/R can induce TEC senescence by promoting the development of C1-INH might be a therapeutic approach to prevent graft senescence in renal transplantation.

SA-OR056
Natural Killer Cells in Renal Transplant Rejection and Ischemia/Reperfusion Injury Andri Lassiter,1 Todd D. Merchen,1 Daniel Kleven,2 Ryan P. Jajosy,2 Matthew Winn,2 N. Stanley Nahman,1 Youli Wang.1 1Surgery, Augusta Univ, Augusta, GA; 2Pathology, Augusta Univ; Medicine, Augusta Univ.

Background: The role of natural killer (NK) cells in induction and prevention of cellular damage relies on the balance of activating and inhibitory receptor signaling. NKP46 is a natural cytotoxicity receptor; its activation in NK cells disrupts this balance, leading to a cytotoxic phenotype. To date, the mechanism by which innate immunity contributes to kidney damage in solid organ transplant rejection remains elusive. Herein, we investigate the role of NKP46-positive NK cells in organ dysfunction using porcine models of renal ischemia and transplantation.

Methods: We performed allogeneic kidney transplantation (n=10) or auto-transplantation (n=4). Pairs of pigs were operated on simultaneously with left kidneys exchanged or reimplanted for allotransplantation and autotransplantation, respectively. All pigs underwent rapid nephrectomy prior to closure and transplant nephrectomy upon sacrifice at 72 hours. No immunosuppression was used. Renal function was determined using WGBS.

Results: Increased NKP46 expression and NKP46-positive NK cells was observed in organs that developed delayed graft function or completely lost function. Increased NKP46 expression, increased cytokine release, and increased NKP46-positive NK cells was observed in organs that developed delayed graft function or completely lost function. Increased NKP46 expression, increased cytokine release, and increased NKP46-positive NK cells was observed in organs that developed delayed graft function or completely lost function. Increased NKP46 expression, increased cytokine release, and increased NKP46-positive NK cells was observed in organs that developed delayed graft function or completely lost function.

Conclusions: The dramatic increase in NKP46-positive cells observed in damaged renal allografts suggests that NK cells play a role in renal allograft injury and subsequent dysfunction. Thus, inhibition of NK cell infiltration of the allograft may improve transplant outcomes.

Funding: Pharmaceutical Company Support - Mallinckrodt Pharmaceuticals
SA-OR057
Prediction of Genome-Wide Donor-Specific Minor Histocompatibility
Antigens (mHA) Based on Genotyping of Donor and Recipient Pairs
Roman Reinelt-Schwaighofer, Alexander Kainz, Rainer Oberbauer. Nephrology and
Dialysis, Medical Univ of Vienna, Vienna, Austria.

Background: Two random individuals differ by millions of genetic variants that include
several thousands of protein polymorphisms based on single nucleotide polymorphisms
(SNP) as well as complete gene losses caused by “loss of function” (LoF) variants. We have
established a workflow to identify genome wide genetic incompatibility based on genotyping
data from donor and recipient pairs. A complete gene loss in the recipient (compound LoF
variant affecting both alleles) with at least one functioning copy in the donor represents a
plausible target for an alloimmune response.

Methods: We have genotyped 400 donor / recipient pairs using the iGeneTRAiN transplant
array V1.0 based on Affymetrix Axiom technology that contains 750k genomic
markers, including 10k specific markers for LoF variants. Following imputation we are
able to cover almost 80 million different genetic markers for each individual. We then used
gene expression data from kidney biopsy samples to verify if the identified proteins are
expressed in transplanted kidneys.

Results: We created a candidate gene set containing more than 100 proteins with
predicted homogenous gene loss. Based on the gene expression data from transplant kidney
biopsies we verified that almost 70% of these proteins are transcribed in transplanted kidneys.

Conclusions: Using genomic tools new and donor-specific mHAs can be predicted
on a genome-wide level.

SA-OR058
Angiotensin Receptor Antibodies Are Associated with Hypertension and
Proteinuria in the Setting of Ischemia-Reperfusion Injury
Gaurav Gupta, Siddhartha S. Ghosh, Todd W. Gehr, Irfan Ahmed Moinuddin, Dhiren Kumar,
Anne L. King, Pam Kimball. Nephrology, Virginia Commonwealth Univ,
Richmond, VA.

Background: Angogenic antibodies against the angiotensin II type I receptor (AT1R-Ab)
have been linked with acute and chronic vascular kidney transplant rejection. Preliminary
data has also linked AT1R-Ab with proteinuric conditions including focal segmental glomerulosclerosis and transplant glomerulopathy. In this study we investigated the effects of
AT1R-Ab in an ischemia-reperfusion injury (IRI) model.

Methods: AT1R-Ab obtained from transplant patient serum was purified. IRI was
induced in Sprague dawley rats by clamping the left renal pedicle for 45 minutes followed by
reperfusion. Control animals underwent sham surgery. Alzet pumps containing AT1R-
Ab (AT1R group) or human IgG (IgG group) were placed in 5 animals each with IRI. The
pump was programmed to deliver 1g/kg antibody per day for 7 days. We also investigated the effect of AT1R-Ab on TGF-β secretion in a human proximal tubular (PT) cell line.

Results: Six hours after surgery, serum creatinine (SCr) in AT1R group (1.4±0.09 mg/
dl) was higher than in IgG group (0.78±0.1 mg/dl) and they were both higher than in controls
(0.4±0.1 mg/dl; p<0.01). By 7 days the SCr in IgG group dropped to normal (0.38±0.08mg/
dl) but SCr in AT1R (0.9±0.1mg/dl) remained higher than in controls (0.32±0.09 mg/
dl; p<0.01). Mean arterial pressure (MAP) of IgG group after 4 and 7 days was similar
to controls at 73±12 and 71±14 mm Hg, respectively. The MAP in AT1R group after 4
days was 74±17 mm Hg but SCr in AT1R remained higher than in controls (0.78± 0.1 mg/dl)
and they were both higher than in controls (0.32±0.09 mg/dl; p<0.01). Finally, PT cells treated with either 75 ng of AT1R-Ab, or Angiotensin II (10М) significantly
increased production of TGF-β. This effect was abated by losartan (10−6M).

Conclusions: These preliminary data suggest that AT1R-Ab is associated with worsened
kidney function, hypertension and proteinuria in rats subjected to ischemia-reperfusion
injury. In addition, AT1R-Ab seems to be associated with formation of pro-fibrotic TGF-β.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
and animal models that often capture only a few aspects of disease. Here we overcome this limitation by developing a multi-molecular non-invasive humanized readout of DN based on urinary peptides.

**Methods:** The urinary peptideome of the two most frequently used models of type 2 diabetic (T2D) DN, the BBTransgenic/db/db mice and the uniphenotyped db/db mice on a C57BLKS background (unNOD-KI), treated or not with enalapril, was analyzed using capillary electrophoresis coupled to mass spectrometry.

**Results:** The disease-modified urinary peptides of the two T2D DN mouse models were identified and compared with previously validated urinary peptide markers of DN in humans to generate a classifier composed of 21 ortholog peptides. This classifier predicted the response to disease and treatment with inhibitors of the renin-angiotensin system (RASIs) in mice. The humanized classifier was significantly correlated with glomerular lesions. Using a human T2D validation cohort consisting of 207 patients, the classifier also distinguished between patients with and without DN, and response to RASIs.

**Conclusions:** Our approach demonstrates that a combination of multiple molecular features similar in both human and animal disease could provide a step change in translational drug discovery research in T2D-DN nephropathy.

**SA-OR062**

**Linking Renal Structure to Molecular Function for Outcome Prediction in Diabetic Kidney Disease**

**Viji Nair, Jennifer L. Harder, Wenjun Ju, Carine Boustany, Kevin V. Lemley, Robert G. Nelson, Matthias Kretzler.**

**UM, NIH, Children's Hospital Los Angeles; University of Erlangen; Boehringer Ingelheim.**

**Background:** Genome wide transcriptional profiling identifies active regulatory and transcriptional networks in kidney disease. Integrating structural changes with molecular profiles identifies functionally relevant correlations of early structural damage that predict subsequent disease progression.

**Methods:** Gene expression profiling and quantitative morphometric analysis was performed on protocol kidney biopsies from 49 type 2 diabetic Pima Indians with pre-symptomatic to early DN symptomatology. Experimental groups were generated and associated with morphometric and long term clinical outcomes using Weighted Gene Coexpression Network Analysis. Urinary protein Epidermal Growth Factor (uEGF) levels were assessed for their correlation with the cortical interstitial fractional volume (VvInt) and GFR.

**Results:** Several structural parameters were associated with molecular profiles. The degree of tubulointerstitial damage, assessed by measurement of VvInt, showed a strong association with molecular signatures and was linked to long term clinical outcomes. Evidence for maturational and cell-cell matrix interaction pathways was found in the transcripts that correlated positively with VvInt and enrichment for metabolic pathways, turnover of amino acids, sugars and lipids in those that correlated negatively. A subset of VvInt associated transcripts correlated with GFR and ACR measured ~10 years after biopsy, including EGF. uEGF showed strong positive correlation with intrarenal EGF transcript and negative correlation with VvInt. uEGF was strongly associated with GFR levels and was assessed for its correlation with the cortical interstitial fractional volume (VvInt) and GFR.

**Conclusions:** Cortical interstitial fractional volume-associated gene expression in pre-symptomatic to early DN was associated with ACR/GFR progression. 81% of these transcripts were also associated in a diabetic European cohort with more advanced DN.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Boehringer Ingelheim

**SA-OR063**

**Inactivation of Placental Growth Factor Is Associated with Perirenal Inflammation and Renal Impairment**

**Yaeni Kim, Ji Hee Lim, Min Young Kim, Eun Nim Kim, Yu Ah Hong, Sun Ryong Choi, Hoon Suk Park, Seon Deok Hwang, Yong-Soo Kim, Cheol Whee Park.**

**Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.**

**Background:** An excess of adipose tissue displays impaired angiogenesis that can lead to local hypoxia and apoptosis, resulting in chronic inflammation. Placental growth factor (PIGF) is a multifunctional growth factor that has favorable in vitro interaction with TGFβ and eNOS.

**Methods:** We investigated the role of PIGF in adipose tissue–related angiogenesis in perirenal inflammation and functional deterioration.

**Results:** Male wild-type, PIGF-deficient (PIGF KO), and PIGF transgenic mice (PIGF TG) were fed regular chow. Mice were sacrificed at 13th and 32nd weeks to compare biochemical parameters, relevant molecular expressions and phenotypes of perirenal fat and the kidney at each distinct time point.

**Results:** PIGF KO mice developed features of metabolic syndrome at week 32; body weight and systolic blood pressure significantly increased with concurrent increases in serum insulin level and AUC of IGTT. While perirenal fat of 13 week old PIGF KO mice showed decreased number and increased size of adipocytes with no significant difference in F4/80 positive cells as compared to the others, 32 week old PIGF KO mice revealed increased number of F4/80 positive cells. Vessel density of perirenal fat was decreased with corresponding increase in HIF-1α expression in PIGF KO mice. 32 week old PIGF KO mice showed unfavorable renal phenotypical changes as compared to PIGF TG and controls while these changes were insignificant in those at week 13.

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

**Underline represents presenting author.**

**SA-OR064**

**miR-221-Containing Exosomes from Vascular Endothelial Cells Promote Mesangial Hyper trophy in Diabetic Nephropathy**

**Ji Sun, Junwei Yang.**

**Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.**

**Background:** Diabetic nephropathy (DN) is a major microvascular complication of diabetes that is structurally characterized by extracellular matrix (ECM) accumulation in glomeruli. Hyperglycemia-induced mesangial cell injury has been proved to play a key role in ECM expansion, but the mechanism under this progression has not been fully elucidated. Recently, exosome-associated microRNA transferring represent a newly identified mechanism of intercellular communication. Therefore, we hypothesize that miRNA expression in endothelium-derived exosomes may be critical in the crosstalk between mesangial cell injury and surrounding endothelium under DN condition.

**Methods:** Exosomes were isolated from endothelial cell cultures using exosome isolation reagent and characterized by electron microscopy. The uptake of exosomes by the mesangial cells was assessed by flow cytometry and fluorescence microscopy. The abundance of miR-221 was measured by real-time quantitative PCR in serum, urine and kidney tissues of diabetic mice. Adeno-associated virus (AAV)-mediated miRNA inhibitor was used to explore the role of miR-221 in vivo by tail vein injection.

**Results:** Hyperglycemia upregulates miR-221 expression in cultured HMECs and in glomeruli from db/db type 2 diabetic mice. Incubation cultured mesangial cells with miR-221-containing exosomes can significantly downregulate matrix metalloproteinase 9 (MMP-9) expression by targeting transcription factor Ets-1. Then, we evaluated the efficacy of AAV-mediated inhibitor of miR-221 in db/db mice. AAV-anti-miR-221 reduced levels of miR-221 in kidneys of both normal and db/db mice. Inhibition of miR-221 in diabetic mice significantly increased Ets-1/1MMP9 expression and promoted ECM degradation.

**Conclusions:** In summary, our study provides the first evidence that endothelial cells can promote mesangial hypertrophy by releasing miR-221-containing exosomes, which may create a “pro-hypertrophic” microenvironment and further be delivered to mesangial cells to inhibit ECM degradation by targeting Ets-1/1MMP9 pathway. More importantly, we found that inhibition of miR-221 might be an effective therapy for diabetic nephropathy.

**Funding:** Government Support - Non U.S.**
**SA-OR066**

**CCR2 Expression in Podocytes Mediates Diabetic Renal Injury**

**Hammam You**, Ting Gao, Timothy K. Cooper, Sarah K. Bronson, William Brian Reeves, Alaas A. Awad. 1Medicine, Pennsylvania State Univ College of Medicine, Hershey, PA; 2Comparative Medicine, Pennsylvania State Univ College of Medicine, Hershey, PA; 3Cellular and Molecular Physiology, Pennsylvania State Univ College of Medicine, Hershey, PA.

**Background:** Inflammation is a central pathophysiologic mechanism that contributes to diabetes mellitus and diabetic nephropathy (DN). Recently, we showed that macrophages directly contribute to diabetic renal injury, and that pharmacological blockade or genetic deficiency of CCR2 confers kidney protection in DN. However, the direct role of CCR2 in kidney-derived cells such as podocytes in DN remains unclear. Here, we report that CCR2 in podocytes regulates renal injury in vivo and in vitro.

**Methods:** We developed a transgenic mouse expressing CCR2 specifically in podocytes (Tg(HPK2-Ccr2)) in a nephropathy prone Ccr2 deficient (Ccr2−/−) background, with heterozygous Ccr2−/− littermate controls. Type 1 diabetes was induced by multiple low doses of streptozotocin (STZ) to induce <50% diabetic nephropathy. 

**Results:** As expected, absence of CCR2 conferred kidney protection after 9 weeks of diabetes as evidenced by significantly reduced albuminuria (p<0.05), blood urea nitrogen (BUN) (p<0.05), histopathologic changes, and kidney fibronectin (p<0.01) and type-1 collagen expression (p<0.05) compared to diabetic Ccr2−/− littermate controls. In contrast, diabetic Ccr2+/− mice with podocyte-specific CCR2 expression displayed significantly increased albuminuria (p<0.05), BUN (p<0.05), histopathologic changes, and kidney fibronectin (p<0.05) and type-1 collagen (p<0.05) expression compared to diabetic Ccr2−/− after 9 weeks of diabetes. Of interest, there was no increase in kidney macrophage recruitment or inflammatory cytokine levels in diabetic Ccr2+/− mice with podocyte-specific CCR2 expression.

**Conclusions:** These findings support a direct role for CCR2 expression in podocytes to mediate diabetic renal injury independent of monocyte/macrophage recruitment. Targeting the CCR2 signaling cascade in podocytes could be a novel therapeutic approach for treatment of DN.

**Funding:** NIDDK Support

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**SA-OR067**

**Effect of Janus Kinase 2 on Kidney Serum Amyloid A in a Mouse Model of Diabetic Kidney Disease**

**Rick L. Meek,** Brad Dieter, Robert J. Anderberg, Sheryl K. Conoy, Hongyu Zhang, Frank C. Brosius, Matthias Kretzler, Katherine R. Tuttle, Providence Sacred Heart Medical Center, Providence Health Care, Spokane, WA; Internal Medicine, Univ of Washington, Seattle, WA.

**Background:** Inflammation is a central pathophysiologic mechanism that contributes to diabetes mellitus and diabetic nephropathy (DN). Recent studies have shown that JAK2 signaling and expression of the pro-inflammatory cytokine, IL-6, is upregulated in murine DN models. In this study we sought to determine the role of JAK2 in the development of DN using a mouse model of diabetes.

**Methods:** Male C57BL/6 mice were randomized into 3 groups: normal control, diabetes control, and diabetes + JAK2 inhibitor. Mice were fed with a diabetic diet (40% calories from fat) for 8 weeks and then randomized to the 3 groups. Mice were treated for 6 weeks with vehicle or a JAK2 inhibitor. Serum was collected from all mice and quantified for total and fibrinogen bound amyloid A. Renal histopathology was performed on all mice.

**Results:** JAK2 inhibition significantly decreased serum amyloid A in diabetic mice compared to the diabetes control group (p<0.05). Renal histopathology in the JAK2 inhibitor group showed a reduction in tubular casts and mesangial matrix expansion.

**Conclusions:** Inhibition of JAK2 significantly decreases serum amyloid A in a murine model of diabetes. This decrease may be due to reduced inflammation and/or reduced production of amyloid A.

**Funding:** NIDDK support

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**SA-OR068**

**Telomerase Deficiency Increases Glomerular Endothelial Cell Senescence in Diabetic Nephropathy**

**Huihong Cheng,** Xiaofeng Fan, William E. Lawson, Paisit Paueksakon, Raymond C. Harris. 1Medicine, Vanderbilt Univ School of Medicine, Nashville, TN; 2Pathology, Microbiology and Immunology, Vanderbilt Univ School of Medicine, Nashville, TN.

**Background:** Aging is a risk factor for Diabetic Nephropathy (DN), and shorter telomere length (TL) has been observed in patients with diabetes mellitus. Both telomerase reverse transcriptase (Tet1) and telomerase RNA (Tert) are essential to maintain telomere length.

**Methods:** To investigate the mechanism of telomerase dependent vulnerability to DN, we used telomerase deficient mice in fourth generation TerC and TerT KO mice and measured their TL and senescence in kidneys, compared with wild type (Wt) and used primary cultured glomerular endothelial cells (GECs) for in vitro studies.

**Results:** TL was significantly shorter in kidneys from TerC and TerT KO mice compared with Wt. STZ injection reduced TL in Wt, and further decreased it in TerC and TerT KO mice. After 26 weeks of diabetes, TerC and TerT KO mice had greater decrease in expression of SIRT1 and increased P53 and P16. Similarly SIRT activity was profoundly diminished in TerC/TKO mice compared to Wt. TerC/TKO mice had increased senescence as evidenced by increased annular and GIM thickness and glomerular filtration rate (GFR). Senescence was predominately detected in endothelial cells. Primary GECs from TerC KO mice proliferated slower. After incubation for 96 hours in high glucose (HG, 30 mM), GECs exhibited cellular senescence, with a marked increase in cells with TerC deletion. Telomerase deficient mice had increased senescence in normal glomeruli. Treatment with a mammalian osmolality control, HG decreased SIRT 1 expression and activity, especially in GECs from TerC KO mice, with up-regulation of P16 and P53, especially acetylated P53. The SIRT1 activator, SIRT1720, partially counteracted these alterations.

**Conclusions:** Inhibition of SIRT1 pathway contributes to telomerase deficiency-dependent susceptibility to DN progression and GEC’s senescence. Telomere shortening of aging may be a predisposing factor for development of diabetic nephropathy.

**Funding:** NIDDK Support, VA Support

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**SA-OR069**

**Roles of Hedgehog Interacting Protein in Diabetic Nephropathy**

**Xin-Ping Zhao,** Shiao-Ying Chang, Min-Chun Liao, Chao-Sheng Lo, Isabelle Chenier, Stephan Troyanova, Julie R. Ingelfinger, John S.D. Chan, Shao-Ling Zhang. 1CRCHUM, Univ of Montreal, Montreal, QC, Canada; 2Res. Ctr., L’Hôpital du Sacré-Cœur de Montréal, Univ of Montreal, Montreal, QC, Canada; 3Pediatric Nephrol Unit, Mass. Gen. Hosp., Boston, MA.

**Background:** We previously reported that high glucose (HG) stimulates Hedgehog Interacting Protein (Hhip) gene expression, impairing nephropathy. Whether Hhip contributes to the pathophysiology of diabetic nephropathy (DN) is unknown. Here we examined potential mechanisms of hyperglycemia induced renal Hhip gene expression, leading to endotelial to mesenchymal transition (EndoMT) related renal fibrosis. We asked if urinary soluble Hhip (sHhip) might be a marker of DN onset and/or progression.

**Methods:** We examined the role of renal Hhip expression in diabetic murine models—T1DM (Akita mice) and T2DM (db/db mice), as well as in kidney biopsies from T1DM and T2DM patients cf. to non-diabetic patients. We determined HG-mediated renal Hhip cleavage/shedding and HG-regulated renal Hhip expression at both transcriptional and translational levels in vivo and in vitro and measured HG-induced sHhip expression.

**Results:** Hhip expression in renal cells (glomerular endothelial cells, podocytes and glomerular and tubular epithelial cells) was significantly elevated in both murine diabetes models and diabetic patients. Urinary sHhip/Creatinine (Cr) ratio positively correlated with the time-course of diabetes in our murine models. Hyperglycemia activated ADAM 17, which subsequently cleaved shed Hhip, contributing to urinary sHhip formation. In mouse endotelial cells (mECs) in vitro, H2O2 and angiotensin II (Ang II) directly up-regulated Hhip gene expression. HG and recombinant Hhip (rHhip) stimulated mouse Hhip and TGFβ1 promoter activity dose-dependently; recombinant TGFβ1 (TGFβ1) had no impact on Hhip promoter activity, suggesting that Hhip acts upstream of TGFβ1 signaling. In sum, enhanced Hhip, via TGFβ1 receptors targets TGFβ1-Smad2/3 cascades, promoting endotelial to mesenchymal transition (EndoMT), associated with renal fibrosis. We found that sHhip and Hhip mRNA expression increased in murine DN models and human diabetic kidney biopsies. Urinary sHhip/Cr ratio may indicate onset and/or progression.

**Funding:** Government Support - Non-U.S.
membrane compared to empty vector-transduced podocytes. Furthermore, time series In-Cell Western experiments also revealed quicker turnover of nephrin in the plasma membrane in PASCIN2 overexpressing cells.

**Conclusions:** PASCIN2 is upregulated in glomeruli in diabetes, and in vitro experiments revealed that PASCIN2 enhances nephrin trafficking. This suggests that increased PASCIN2 expression associates with gain of glomerular permeability and proteinuria. Further studies are needed to define the molecular mechanisms by which PASCIN2 regulates nephrin trafficking and whether increased expression of PASCIN2 helps in preventing or accelerates loss of renal function.

**Funding:** Private Foundation Support

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**SA-OR071**

**Policystin 1 Regulates WNT/TAZ, a Non-Canonical WNT and Hippo Signaling Target**

**Nikolay P. Greisko,** David Merrick, Kavita Mistry, Michael J. Captain, Cellular and Molecular Physiology, Yale Univ, New Haven, CT; University of Pennsylvania.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in the PKD1 and PKD2 genes, which encode PC1 and PC2, respectively. PC1 is a 460kD multi-spanning membrane protein that undergoes multiple proteolytic cleavages, at least two of which release C-terminal fragments. One of these fragments includes the last 200 amino acids of PC1 (PC1-CCTP200) and possesses a functional nuclear localization sequence (NLS) that drives its nuclear accumulation. Nuclear PC1-CCTP200 regulates several transcriptional pathways.

**Methods:** One of the top hits in a screen for transcription factors and co-regulators whose activities are modulated by PC1-CCTP200 was TAZ (also known as WTW1), which is a transcriptional co-regulator of normal signaling cascades, including the Hippo pathway.

**Results:** We found that TAZ protein expression in the nephron is localized to the basolateral compartment of S3 segment epithelial cells and to the principal cells of the collecting duct. Interestingly, it has previously been shown that TAZ deficient mice develop severe renal cysts. Moreover, we find that exogenous expression of an active form of TAZ in PC1-CCTP200 prevents them from forming cyst-like structures in the 3D Matrigel culture. Expression of the active form of TAZ also corrects the curly tail phenotype that is seen in PKD1a/b morphant zebra fish. We find that PC1 interacts with TAZ, and furthermore that PC1 expression upregulates TAZ abundance at the mRNA and protein levels. TAZ abundance, Inhibit and activity have been shown to be upregulated through the non-canonical Wnt signalling. A recent study demonstrates that PC1 can serve as a receptor for Wnt ligands. We find that HEK293 cells that express PC1 and PC2 respond to treatment with recombinant Wnt5a protein by increasing the abundance of TAZ mRNA as compared to wild type HEK293 cells.

**Conclusions:** Taken together, our data suggest that PC1 may participate in a novel signalling pathway that links detection of non-canonical Wnt ligands to the positive regulation of TAZ, a multifaceted signalling molecule whose abundance is sufficient to induce renal cystic disease.

**Funding:** NIDDK Support

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**SA-OR072**

**Policystin-1 Regulates EZH2 Expression through the cAMP/PKA/CREB Pathway and EZH2 Inhibition Delays ADPKD Progression**

**Na Qi, Ming Wu, Changlin Mci. Dept of Nephrology, Shanghai Changzheng Hospital, Second Military Medical Univ, Kidney Inst, Shanghai, China.

**Background:** Enhancer of zeste homolog 2 (EZH2) plays important roles in tumor formation and growth, however it is not known whether EZH2 promotes cyst expansion in autosomal dominant polycystic kidney diseases (ADPKD). The aim of this study is to determine the effect and mechanism of EZH2 inhibition in ADPKD.

**Methods:** Pkd1- and Pkd2- mice were treated with 30 mg/kg/day EZH2 specific inhibitor GSK126 or vehicle from day15 to day 35 by IP injection. ADPKD Pkd1-/-Maffs (immortalized and primary) presented decreased maximum respiration and increased extracellular acidification rates as compared to controls, suggesting a switch from mitochondrial oxidation to glycolysis. Analysis suggested that Pkd1-/- cells have glucose anaerobiosis. We applied metabolic deprivation to Pkd1-/- and Pkd2-/- MEFs. Pkd1-/- cells were more sensitive to glucose deprivation. Deprivation of both glucose and glutamine resulted in a more dramatic effect on Pkd1-/- cells than Pkd2-/- suggesting that mutant cells are addicted to glucose and glutamine.

**Conclusions:** A major metabolic rewiring is identified in PKD unexpectedly similar to cancer. Defective TCA cycle and mitochondrial activity likely drive “Warburg effect” in PKD which is accompanied by glucose anaerobiosis, again showing similarities with cancerous cells. Thus metabolic alterations are a hallmark of PKD. Further analysis is required to understand why transformation is not a feature of this disease.

**Funding:** Pharmaceutical Company Support - Sanofi-Geniezyme

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**SA-OR073**

**Global Profiling in Polycystic Kidney Disease Reveals a Metabolic Rewiring Reminiscent of Cancer**

**Christine Di Meo,1 Roberto Pogliarini,2 Silvia Raineri,1 Ioan Vi Meo,1 Marco Chiaravalli,1 Valeria Tiranti,4 Diego Di Bernardo,1 Alessandra Boletta,1 DGCB, San Raffaele Scientific Inst, Milan; 2Univ Vita-Salute San Raffaele, Italy; 3TIGEM, Pozzuolo, Italy; 4IRCCS Foundation Neurological Inst, Italy.

**Background:** We and others have previously uncovered metabolic alterations in ADPKD and in the jck mouse model of PKD. These data is also confirmed by western blot analysis of kidney/total body weight ratio, blood levels of glucose and other metabolic markers. ADPKD cells were more sensitive to glucose deprivation. Deprivation of both glucose and glutamine resulted in a more dramatic effect on Pkd1-/- cells than Pkd2-/- suggesting that mutant cells are addicted to glucose and glutamine.

**Results:** 550 metabolites were named. An unsupervised statistical analysis (PCA) revealed a clear separation between mutant and control kidneys with a significant upregulation of 196 and downregulation of 292 metabolites (total 488). Alterations include defective glycolysis, fatty acids biosynthesis, β-oxidation and TCA cycle. The last suggested a mitochondrial defect. To test this, oxygen consumption rates were measured in a 96 wells SeaHorse. Pkd1-/- MEFs (immortalized and primary) presented decreased maximum respiration and increased extracellular acidification rates as compared to controls, suggesting a switch from mitochondrial oxidation to glycolysis. Analysis suggested that Pkd1-/- cells have glucose anaerobiosis. We applied metabolic deprivation to Pkd1-/- and Pkd2-/- MEFs. Pkd1-/- cells were more sensitive to glucose deprivation. Deprivation of both glucose and glutamine resulted in a more dramatic effect on Pkd1-/- cells than Pkd2-/- suggesting that mutant cells are addicted to glucose and glutamine.

**Conclusions:** A major metabolic rewiring is identified in PKD unexpectedly similar to cancer. Defective TCA cycle and mitochondrial activity likely drive “Warburg effect” in PKD which is accompanied by glucose anaerobiosis, again showing similarities with cancerous cells. Thus metabolic alterations are a hallmark of PKD. Further analysis is required to understand why transformation is not a feature of this disease.

**Funding:** Government Support - Sanofi-Geniezyme

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**SA-OR074**

**Inhibition of CaMKII Reduces ER Stress, Oxidative Damage, Improves Mitochondrial Integrity, and Attenuates Polycystic Kidney Disease**

**Nikolya Bukanov,1 Christina M. Bracken,1 Philippe Beauverger,1 Olivier Duclos,2 Ryan J. Russo,1 Kelly A. Rogers,1 Herve Hussov,1 Thomas A. Natali,1 Steven R. Ledbetter,2 Philip Janiak,2 Oxana Besknova.1 Rare Diseases, Novo Nordisk, R&D Ctr, Copenhagen, Denmark; 3Cardiovascular Research, Sanofi, Chilly-Mazarin, France; 4Mitobridge Inc., Cambridge, MA.

**Background:** Polycystic kidney diseases (PKDs) comprise a large family of cilia-associated genetic diseases characterized by formation and progressive growth of renal cysts, eventually leading to end-stage renal disease. Despite recent advances in understanding of PKD pathogenesis, the exact mechanisms of cystogenesis are not completely understood. We show a new role for calcium/calmodulin-dependent protein kinase II (CaMKII) as a pathobiological mediator of oxidative damage, maladaptive ER stress response and mitochondrial dysfunction in progression of cystic kidney disease.

**Methods:** Western blot analysis of kidney tissue was used for assessment of integral mitochondrial membrane proteins and proteins responsible for oxidative damage, mitochondrial-related apoptotic pathway, and ER stress response. Mitochondrial membrane potential was assessed by MitoTracker and flow cytometry analysis of JC-1 dye uptake; mitochondrial antioxidant gene expression was evaluated with PCR. Efficacy of CaMKII small molecule inhibitor in jck mice was measured by kidney to body weight ratio, blood urea nitrogen, and cystic volume.

**Results:** Here we show that that CaMKII is activated in renal cystic epithelia in human ADPKD and in the jck mouse model of PKD. These data is also confirmed by western blot analysis of normal and human ADPKD and jck kidney lysates. Pharmacological blockade of CaMKII by a novel and selective small-molecule inhibitor significantly attenuates PKD in jck mice, reducing cystic disease endpoints, namely K/BW ratio, cystic volume and BUN levels. Mechanistic analyses show that treated kidneys are characterized by decreased unfolded-protein response, oxidative stress and restoration of mitochondrial membrane potential and integrity.

**Conclusions:** Taken together, our data show that inhibition of CaMKII may be a viable therapeutic approach for the treatment of PKD.

**Funding:** Pharmaceutical Company Support - Sanofi-Geniezyme

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**SA-OR075**

**Re-expression of Polycystin-1 in Polycystic Kidneys Antagonizes Cyst Progression and Prolongs Survival**

**Stephen C. Parnell,4 Archana Ramam, Timothy A. Fields. Kidney Inst, Univ of KS Medical Center.

**Background:** Mutations in the PKD1 gene disrupt the function or cause decreased amounts of its protein product, polycystin-1 (PC1), and are responsible for most cases of autosomal dominant polycystic kidney disease (PKD). However, after cysts have initiated it is not clear whether ongoing PC1 deficiency is necessary for cyst progression, or whether re-expression of PC1 in cystic kidneys will halt or reverse cyst growth.

**Methods:** To determine the effects of PC1 re-expression in cystic kidneys, we engineered an inducible functional allele of mouse Pk1, Pk1iRosa26. In the absence of

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

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Cre, Pkd1^{del4/−} is a non-functional allele. However, Cre-mediated recombination produces a re-arranged allele. Pkd1^{−/−} expressing functional PCK1, Pkd1^{d4/d4} mice were mated to mice with hypomorphic Pkd1^{+} alleles (Pkd1^{d1} or Pkd1^{d2}) and ubiquitously expressed ROSA26-CreERT2. PCK1 re-expression was induced in week 1-old cystic mice by tamoxifen injection, thereby converting the non-functional Pkd1^{−/−} allele to the functional Pkd1^{d1/−} allele, and the effects on cystic kidney disease were determined.

**Results:** Pkd1^{d1/−} and Pkd1^{d4/d4} pups survived embryogenesis but displayed early cystic kidney disease, with death of Pkd1^{d4/d4} pups occurring at 3-4 weeks. Control Pkd1^{−/−} mice were normal. Two weeks of PCK1 re-expression improved cystic kidney disease, increased survival of old pups, with a decrease in kidney weight to body weight (KW/BW) and an improved cystic index compared to pups that did not re-express PCK1. A single cysic mouse was sacrificed at 11 weeks following re-expression of PCK1. While this mouse exhibited prominent cystic kidney disease, its KW/BW was less than that of 1-week-old Pkd1^{−/−} mice. Moreover, there was significant preservation of normal parenchyma, and evidence of cystic epithelial cell apoptosis.

**Conclusions:** These results suggest that re-expression of PCK1 provides a significant benefit to cystic mice, and further suggests that rescue of PCK1 function (e.g., chaperone-mediated therapy for PCK1 mutations that result in misfolded and/or mis-localized PCK1, or small molecule molecules that stimulate polycystin-2 channel activity for PKD1 loss-of-function mutations) may be an ideal therapeutic approach for PKD.

**Fundings:** Other U.S. Government Support, Private Foundation Support

**SA-OR076**

**Loss of Cilia Does Not Inhibit Pkd1-dependent Cyst Growth in the Liver**

Rachel Gallagher,1 Sorin V. Fedeles,1 Matteus Krappitz,1 Ming Ma,1 Stefano Somolo,1,2 Internal Medicine, Yale School of Medicine, New Haven, CT; 1Dept of Genetics, Yale School of Medicine, New Haven, CT.

**Background:** Loss of polycystin in ADPKD and complete removal of cilia by inactivation of intraflagellar transport-related proteins both give rise to cysts in the kidney and liver. Recently it has been shown that inactivation of both polycystin and cilia completely abolishes cystic kidney disease in the ARPKD mouse model (Kif3a). Genetic interaction between Pkd1 and Kif3a in mouse models (Pkd1^{−/−}/Pkd1^{d4/d4} and Pkd1^{−/−}/Pkd1^{d4/d4} Kif3a^{−/−}) gives rise to cysts in the liver. Interestingly, membrane bound CSF1R is essential for liver cyst formation in ADPKD, with loss of CSF1R resulting in a non-cystic phenotype in a Pkd1^{−/−} genetic background.

**Methods:** The animals models used in this study are Pkd1^{d4/d4}, Kif3a^{−/−} allele and ERT2/CBCre. All animals were used in this study were induced with Tamoxifen at postnatal day 28 for 5 days and then aged to 17 weeks. The livers and kidneys were examined for disease progression.

**Results:** At the start of cilia inactivation, the Pkd1^{d4/d4} livers show mild bile duct proliferation. At 17 weeks, the body weights of the Kif3a^{−/−}/UbcCre were higher than the Pkd1^{d4/d4} animals [33.39 ± 5.592 g compared to 25.98 ± 2.584 g]. It has been well documented that loss of cilia results in increased body weight. The body weight of the double knockout were similar to the Kif3a single knockout at 30.44 ± 1.304 g. No significant difference was detected in kidney weights across all genotypes. The liver cystic disease in the ARPKD mouse model Pkd1^{d4/d4} to determine if the CCA4 pathway plays a role in cyst progression in ARPKD.

**Conclusions:** Taken together our data demonstrate that loss of cilia in an ARPKD mouse model is not sufficient to slow disease progression. These data suggest that the cyst formation in the liver due to loss of Pkd1 is not dependent on the presence of intact cilia.

**Funding:** NIDDK Support

**SA-OR077**

**Primary Cilia Regulate Intestinal Macrophage Proliferation and Polarization in an Acute Kidney Injury Model of Polycystic Kidney Disease**

Cheng Ji,1 Jack Song,1 Kurt Zimmerman,1 Michal Mugar,1 Bradley K. Yoder.1 Cell Developmental, and Integrative Biology, Univ of Alabama at Birmingham, Birmingham, AL; 1Div of Nephrology, Univ of Alabama at Birmingham, Birmingham, AL.

**Background:** The mechanism responsible for renal cyst formation often involves defects in primary cilia regulated proteins including intraflagellar transport proteins (e.g., IFT88) or polycystins. Induction of cilia loss in adult mice leads to slow and focal cyst formation; however, rapid cyst formation can be initiated in mice by ischemic reperfusion (IR) injury. Over the last two decades, studies have demonstrated that inflammatory cells, including macrophages, are involved in the pathogenesis of IR injury suggesting a role for inflammation in IR induced cyst formation.

**Methods:** To better define the role of macrophages populations prior to and during cyst formation, we studied effects of IR injury in adult induced Ift88^{−/−} (Ift88^{−/−}/CAGG-CreERT2; Pkd1^{−/−}CAGG-CreERT2) vs. Pkd1^{−/−}CAGG-CreERT2; H2B-tdTomato mice.

**Results:** Following the primary cyst formation, cyst growth began ~14 days following IR and gradually progressed to post-injury day 28. Throughout the time course, there is a persistent increase in the level of pro-inflammatory and pro-fibrotic cytokines including MCP-1, IL-6, TNF-α, A-1, IL-1β, and TGF-β in the injured cilia mutant mice. We also observed significantly higher number of interstitial resident macrophages at post-injury day 7 (prior to cyst initiation). Compared to controls, resident macrophage subtypes (F4/80^+^, CD11b^+^,CD11c^+^) and their proliferation was increased in the cilia mutant mice. Interestingly, membrane bound CSF-1, which is a cytokine responsible for resident macrophage proliferation, was overexpressed in proximal tubule epithelial cells isolated from cilia mutant mice suggesting that cilia on epithelial cells may regulate resident macrophage proliferation and kidney repair after injury.

**Conclusions:** In conclusion, defects in communication between cilia containing epithelial cells and resident macrophages through upregulated CSF-1 results in persistent resident macrophage proliferation that contributes to initiation and progression of polycystic kidney diseases.

**Funding:** NIDDK Support

**SA-OR078**

**Tubule-Expressed Mcp-1 Promotes Macrophage Homing and Cyst Growth in Polycystic Kidney Disease (PKD)**

Marcelo Ferreira Cassini, Armaud Marlier, Elizabeth Y. Chen, Lonnette Digs, Kyoung Pyo Kang, Tinkia Anita Montgomery, Ming Ma, Stefan Somolo, Lloyd G. Cantley. Internal Medicine, Yale School of Medicine, New Haven, CT.

**Background:** Macrophages accumulate around cysts in models of polycystic kidney disease, and macrophage depletion with clodronate has been shown to slow cyst growth. Macrophage chemotractant protein-1 (MCP-1) is highly expressed in orthologous mouse model (ADPKD) and by polycystin-1 null renal tubular cells in culture, leading us to hypothesize that loss of tubular cell PCK1 leads to over-expression of MCP1 and promotes MCP1 receptor (CCR2) dependent macrophage homing and cyst growth.

**Methods:** Mcp1^{−/−}/Pkd1^{d4/d4}/Pax8TetOnCre mice (termed DKO) were generated and immunosuppressed 6 weeks of age with doxycycline to simultaneously knock-out tubular cell MCP-1 and PCK1 expression and compared to Pkd1^{−/−}/Pax8TetOnCre mice (SKO) induced at the same age. Some SKO mice were given daily IP injections of the CCR2-antagonist INCB33434 for 6 weeks beginning at the completion of doxycycline induction. Kidneys were analyzed at 12 weeks of age.

**Results:** DKO mice demonstrated significantly reduced Mcp1 expression, macrophage numbers, kidney weight/body weight, cystic index, and BUN at 12 weeks of age (table 1) with improved survival at 18 weeks (94% vs. 50%).

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

**SA-OR079**

**Investigating the Role of T Cells in Autosomal Dominant Polycystic Kidney Disease Progression**

Emily K. Kleezko, Kenneth H. Marsh, Michel Chonchol, Raphael A. Nemenoff, Katharina Hopp. Univ of Colorado Denver - AMC.

**Background:** While ADPKD is the most common monogenic renal disease, no treatment exists to slow its progression. Much research has focused on alterations in epithelial cell signaling, but little is known about the role of the microenvironment in disease progression. Specifically, the role of T lymphocytes in ADPKD is unknown.

**Methods:** We used flow cytometry and immunofluorescence to identify distinct immune cell populations in mouse models of ADPKD. We used the slower progressing Pkd1^{−/−} p.S327T (RC) model in the C57Bl/6,129S6, and Balb/c strain, which show increasing disease severity, respectively, and the rapidly progressive Pkd1^{−/−} model in the C57Bl/6 strain.

**Results:** We observed a significant increase in immune cells in all ADPKD mice compared to respective wildtype mice. In the Pkd1^{−/−} model at P20, this increase was primarily mediated by macrophages, while in 9-month-old Pkd1^{−/−} mice, the increase was driven by T lymphocytes (CD4 and CD8 T cells), which accumulated around cystic lesions. Importantly, the increase in T cell populations correlated with severity of disease. We also observed higher numbers of T regulatory cells (T_{reg}) in the Pkd1^{−/−} model, which generally are immunosuppressive. In a preliminary experiment, antibody depletion of CD8^+ cells from 1-3 months in C57Bl/6 Pkd1^{−/−} mice, resulted in a significant increase in %kidney weight/body weight compared to IgG-control, suggesting a protective role for CD8 cells in ADPKD progression. Furthermore, Pkd1^{−/−} CD8 and epithelial cells expressed more PD1 and PD-L1 respectively, indicating activation of an immune checkpoint, leading to inhibition of CD8 function. Targeting this pathway has shown great promise as a cancer therapeutic, and antibodies against PD1 and PD-L1 have been approved by the FDA for multiple cancers.

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Conclusions: Together, these data indicate that T cells are upregulated in ADPKD and likely play an important role in slowly progressive cystogenesis. Here, CD8 cells may play an important protective role, which could be disrupted by checkpoint activation, hence leading to more rapidly progressive disease. Targeting T cells may represent a novel therapeutic approach to inhibit ADPKD progression.
Funding: Other NIH Support - T32

SA-OR080

New In Vitro Model for the Study of Phenotypes Associated with Polycystic Kidney Disease: “Pseudonephrons” and “Pseudovessels”

Background: Polycystic kidney disease (PKD) is a group of genetic disorders that cause renal failure and are originated by abnormal tubular morphology by the presence of multiple cysts along the nephron. PKD is associated with other extrarenal manifestations (hepatic and pancreatic cysts, aneurysms...). Up to the moment, in vitro studies of PKD are based on 2 dimensional (2D) culture or 3 dimensional (3D) collagen culture. An in vitro culture model that mimic the shape or the arrangement of cells, cell-to-cell junctions or extracellular matrix environment (ECM) applying a fluid shear stress (FSS) is essential to replicate more accurately the in vivo conditions.

Methods: We have developed a 4 dimensional (4D) culture where flow is the fourth dimension. This model is based on creation of channels embedded in collagen by 3D bioprinting of filaments of gelatin (within or without cells). This gelatin is a temporary material that leaves a hollow channel inside collagen where cells can grow. This technique allow us replicated pseudonephrons and pseudo-blood vessels to monitor different mechanisms related to cell flow sensing and orientation/organization. We have designed a device where can apply a flow through these channels. We were able to print in a tube different renal segment cell type, identifying phenotypical specific characteristics like cell density. Different strategy was applied for endothelial and epithelial cells, and extended to immortalized conditional primary cells derived from PKd mouse models, allowing us to induce the inactivating of pkd genes.

Conclusions: This new 4D model of collagen channels will allow to study molecular mechanisms of endothelial and epithelial in PKD. In vitro culture model will be a powerful tool to study the effects on phenotypical specific characteristics like cell density, cell-to-cell junctions or extracellular matrix environment (ECM) applying a fluid shear stress (FSS) is essential to replicate more accurately the in vivo conditions.
Funding: Government Support - Non-U.S.

SA-OR081

Cross Talk between Myostatin and BMP Signaling Regulates Muscle and Bone Mass in CKD

Background: metabolic defects in CKD include losses of muscle and bone but if and how these defects are linked. We have found that muscle of CKD mice expresses myostatin to cause muscle wasting and now we examine if myostatin-induced intracellular signaling interacts with bone morphogenetic protein (BMP) signaling, regulates muscle and bone mass.

Methods: CKD mice with BUN >80 mg/dL were treated with an antimyostatin peptibody. We monitored body weight, bone mass, mineral density and muscle strength. Cell signaling pathways were assessed in C2C12 myoblasts and MC3T3 osteoblasts.

Results: mice with CKD had increased myostatin expression but decreased muscle mass and reduced mineral density. When the peptibody blocked myostatin in mice with CKD, both body weight and bone mineral density (g/cm²) were 18% higher vs. CKD mice treated with PBS. Skeletal muscle mass was increased 15-32% and blood glucose decreased was as glucose tolerance. There were no changes in fat mass vs. control, CKD mice. Muscle grip strength of myostatin-blocked, CKD mice were 21% higher vs CKD mice treated with PBS. The changes were independent of serum PTH levels. To explain how myostatin changes both muscle and bone, we examined tissue lysates and found that the peptibody decreased p-Smad2/3, pSmad3 and increased p-Smad1/5, 8, pTβR, and p-Akt and in both tissues of mice with CKD. We hypothesized that myostatin could influence bone responses by changing BMP signaling. It was tested in both C2C12 myoblasts or MC3T3 osteoblasts when myostatin production was blocked using a siRNA to myostatin. In the absence of myostatin, both osteoblasts and myoblasts exhibited increased p-Smad1/5, p-TβR, p-Akt plus the differentiation of both osteoblasts and myoblasts. Likewise, treatment of myoblasts with recombinant BMP7 produced increase in p-Smad1/5, pTβR and p-Akt.

Conclusions: Our results indicate that in CKD mice, myostatin exibits cross talk with BMP to regulate intracellular signaling, indicating differentiation of myoblasts and osteoblasts. The result is reduced muscle and bone mass. Anti-myostatin peptibody may be a potent therapeutic strategy for improving muscle and bone growth in CKD.
Funding: NIDDK Support

SA-OR082

A Ligand of the Activin Receptor Type IIA Mediates Osteostat Stimulation of Bone Remodeling in Diabetic Mice with CKD

Background: Dysregulation of skeletal remodeling is a component of renal osteodystrophy. We have reported that activin receptor signaling is differentially affected in various tissues in CKD, and here, using a ligand trap for the activin receptor type II A (RAP-011), we demonstrate that inhibition of skeletal activin receptor signaling has efficacy in the CKD-MBD osteodystrophy.

Methods: CKD, with 70% reduction in GFR, was induced at 14 weeks of age in the ldr−/− high fat model of atherosclerotic vascular calcification and diabetes. CKD mice, with hyperphosphatemia, hyperparathyroidism, and elevated activin A, were treated with RAP-011 10mg/kg (n=20) or vehicle (Veh, n=19), injected SC twice weekly beginning at 22 weeks of age until euthanasia at 28 weeks and study by skeletal histomorphometry, real-time, mechanical testing, and gene expression in bone cell cultures.

Results: Results were compared to sham operated ldr−/− high fat fed mice (Sham, n=16). Sham mice had a low-turnover osteodystrophy and skeletal frailty that was converted by CKD to a higher turnover bone remodelling state with increases in osteoclast and osteoblast numbers and enhanced PTH and P1NP levels. 192±5.80 30.9±1.75 4.36±0.46 1.02±0.20 0.27±0.11 23.3±1.27 75.1±5.72

In conclusion, the calcimimetic AMG641 increases bone turnover in CKD-Bone and Vascular Disorders.

Funding: NIDDK Support, Pharmaceutical Company Support - Celgene

SA-OR083

In Ureemic Rats, the Calcimimetic Maintains Bone Turnover in a Parathyroid Hormone-Independent Manner

Methods: Rats on a 0.9%P, 0.6 %Ca diet were divided in four groups: Sham: 5/6Nx; 5/6Nx+Ptx+PTH (5/6Nx rats underwent parathyroidectomy and received constant infusion of PTH and vehicle) and 5/6Nx+Ptx+PTH+AMG641. After 28 days, euthanized and blood and bone were collected. Mineralization was assessed by double-calcine labeling. Results were compared to sham operated 5/6Nx+Ptx.

Results: Bone volume fraction in renal bone turnover was augmented as compared with sham. In 5/6Nx+Ptx+PTH rats, AMG641 increased bone cells activity , while bone volume was similar vs vehicle. Moreover, bone formation rate was slight but not significantly higher in rats on AMG641 than vehicle.

Conclusions: In conclusion, the calcimimetic AMG641 increases bone turnover in uremic rats with clamped PTH. These results are in agreement with in vitro studies that demonstrate a bone anabolic effect of CaSR activation.

Funding: NIDDK Support, Pharmaceutical Company Support - Celgene

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The response to MET is initiated through OGR1, a specific osteoblastic proton receptor, which has been shown to increase intracellular Ca. To further understand the intracellular signaling events involved in the osteoblastic response to MET, we utilized primary osteoblasts to study potentially important gene expression pathways, including IFRD1, interferon-related developmental regulator 1. MET1 regulates the Wnt/β-catenin signaling pathway, as well as MET induced stimulation of FGF23 is inhibited by treatment with 50 µM 2-APB, which blocks intracellular Ca signaling or by treatment with 1 µM NS398, which blocks cyclooxygenase 2, both integral steps in MET stimulation of bone resorption. Comparable inhibition of MET-induced IFRD1 was also observed after incubation of osteoblasts with 2-APB or NS398. C-reactive protein, a marker of inflammation, was stimulated by MET and may be important in the mechanism of MET-induced bone resorption as well as MET-induced stimulation of FGF23 production. These results suggest that the Wnt/β-catenin pathway could be a therapeutic target to decrease MET-induced bone loss.

Funding: Private Foundation Support

SA-OR085

The Association between Skeletal Muscle Mass Surrogates and the Risk of Bone Fracture in Patients Undergoing Hemodialysis: The Q-Cohort Study

Shunsuke Yamada, 1 Masatomo Taniguchi, 3 Masanori Tokumoto, 2 Narihito Tatsutomo, 1 Hideki N. Hirakata, 1 Takanari Kitaizono, 1 Kazuhiko Tsuurnya, 1 Dept of Medicine and Medical Science, Kyushu Univ, Fukuoka, Japan; 2 Dept of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; 3 Fukuoka Renal Clinic, Fukuoka, Japan.

Background: CKD is an independent risk factor for bone fracture. There is a close interplay between bone and skeletal muscle. It still remains unknown whether lower skeletal muscle mass increases the risk of bone fracture in hemodialysis (HD) patients.

Methods: The present study was an prospective, observational study consisting of 3030 patients undergoing HD. As surrogates of skeletal muscle mass, we used both serum creatinine (Cr) and Cr index. Cr index was calculated using age, sex, serum Cr level, and Kt/V for urea. The association between baseline creatinine (Cr) index or serum Cr level was examined. Patients were stratified by sex-specific quartiles based on serum Cr or Cr index. Cox proportional hazard model was used for analyses.

Results: During the median observational period of 3.9 years, 140 patients developed bone fracture. In the multivariable analysis, the risk of bone fracture was significantly higher in the lowest Cr index quartile (Q1) compared to the highest Cr index quartile (Q4) as the reference value in both male and female patients (multivariable-adjusted hazard ratio [95% confidence intervals]: men; Q1, 6.26 [1.87-23.66]; Q2, 4.33 [1.49-14.62]; Q3, 1.68 [0.45-6.22]; Q4, 1; women; Q1, 4.25 [1.45-13.77]; Q2, 3.00 [1.19-8.23]; Q3, 1.92 [0.81-4.93]; Q4, 1; P=0.007 for trend). Similarly, lower serum Cr level was associated with the increased risk of bone fracture in both men and women. Effects of sex-specific stratification on the correlation between Cr index and serum Cr level was not observed across baseline characteristics.

Conclusions: Lower skeletal muscle mass surrogates were associated with the increased risk of bone fracture in HD patients. Further studies are required to know whether maintaining skeletal muscle mass prevents bone fracture in HD population.

SA-OR086

Progression of Medial Arterial Calcification in End-Stage Renal Disease W. Charles O’Neill, 1 Shamila Manzoor, 1 Syed Mustafa Ahmed. 1 Renal Div, Emory Univ, Atlanta, GA.

Background: Medial arterial calcification is an important lesion in end-stage renal disease (ESRD) but little is known about its progression and the effect of different treatments on this process. Previous studies quantify it and demonstrate rates but do not reverse calcification. These results indicate that hemodialysis or related vascular calcification and that calcification persists when normal renal function is restored.

Funding: Clinical Revenue Support

SA-OR087

Small Vessel and Soft Tissue History in End-Stage Renal Disease: Specificity of Diagnostic Criteria for Calciphylaxis

Carla L. Ellis, 1 W. Charles O’Neill, 2 Peter Mustafa, 2 John D. Humphreys, 3

1 Pathology and Laboratory Medicine, Emory Univ, Atlanta, GA; 2 Renal Div, Dept of Medicine, Emory Univ, Atlanta, GA.

Background: Calciphylaxis (calcific uremic arteriolopathy) is a rare disease characterized by skin ulceration and tissue necrosis presumably resulting from vascular calcification that typically occurs in end-stage renal disease (ESRD). Histologic criteria include intimal hyperthropy, medial calcification, and/or thrombosis of small arteries, and extraskeletal (soft tissue) calcification, but their specificity is unknown. These features were examined in tissue from the margins of amputations performed in ESRD patients.

Methods: 26 amputations above (11) and below (15) the knee in 21 ESRD patients were identified from pathology records for 2014-2015. Sections from the margins were retrieved and both H & E and von Kossa stains were prepared and reviewed by a single pathologist. Chart review was performed by a single nephrologist.

Results: None of the patients had a clinical presentation suggestive of calciphylaxis. Average age was 63.7 years (range 43-83), 16 (76%) were male, 14 (67%) had diabetes, and 5 (24%) were treated with warfarin. Bulky, large vessel calcifications were identified in 24/26 (92%) of specimens, consistent with peripheral arterial disease (PAD). However, 8/26 (31%) also showed dermal/epidermal arterial calcification, and 11/26 (42%) showed extraskeletal soft tissue calcification. Intimal hyperplasia and small vessel thrombosis were observed in 3 and 4 cases respectively (12 and 15%). Arterial calcification and thrombosis were observed in 3 and 5 of the 13 patients with diabetes mellitus but only 1 and none of the 8 patients without diabetes. There was no association with warfarin use.

Conclusions: Histopathologic findings historically associated with calciphylaxis on skin biopsies can also be seen in viable tissue from unaffected ESRD patients. While the results are not necessarily applicable to patients without PAD, they do indicate that histologic findings ascribed to calciphylaxis can be seen in the absence of clinical manifestations, particularly in diabetics. This calls into question the specificity of the histologic diagnosis of calciphylaxis.

SA-OR088

Gli1+ Adventitial MSC Are Vascular Smooth Muscle Cell Progenitors and Key Drivers of Vascular Calcification in CKD

Rafael Kramann, 1,2 Janewit Wongboonsin, 3 Nadine Kaesler, 1 Christoph Kuppe, 1 Benjamin D. Humphreys, 3 Div of Nephrology, RWTH, Aachen, Germany; 2 Div of Nephrology, Washington Univ, St. Louis.

Background: We recently demonstrated that Gli1 expression defines perivascular mesenchymal stem cells (MSCs). A role for adventitial MSCs in vascular injury, repair and calcification has been hypothesized but the absence of a specific in vivo marker for MSCs has prevented progress.

Methods: We used genetic lineage analysis to trace the fate of Gli1+ cells in GlireuserdTdtomato mice subjected to femoral artery injury. Transgenic GlireuserdTdtomato;ApoEKO and GlireuserdTdtomato;iDTR,ApoEKO mice subjected to subtotal nephrectomy or sham surgery followed by western diet versus standard chow were used for fate tracing and ablation experiments during vascular calcification.

Results: We demonstrate that FACS isolated adventitial Gli1+ cells are MSC that can differentiate into mature VSMCs in vitro. Single cell qPCR of adventitial Gli1+ cells indicates a heterogeneous population that gradually loses expression of progenitor markers and acquires expression of VSMC markers. In vivo genetic fate tracing experiments demonstrate that adventitial Gli1+ MSC migrate into the vascular media to become mature VSMCs during aging. Following acute injury to the femoral artery >50% of VSMCs in media are Gli1+. Gli1+ adventitial MSCs are key drivers of vascular calcification.

Conclusions: Adventitial Gli1+ MSC are progenitors of VSMCs during aging and acute arterial injury repair. However, in CKD with vascular calcification Gli1+ cells are the key progenitors of CVCs in media and intima. They represent an important and novel therapeutic target.

Funding: NIDDK Support
SA-OR089
Coronary Calcification and Mortality in Patients with Advanced Chronic Kidney Disease: A 10-Year Follow-Up  
Marta Cano Megias,1 María Perez Fernandez,1 Gabriel De Arriba,2 Diego Rodriguez Payol,1 Concepcion Alvarez Sanz,1 Patricia De Sequera,1 Hanane Bourach,1 'Nephrology, Hospital Univ Principe de Asturias, Alcalá de Henares, Madrid, Spain; 'Nephrology, Hospital Univ de Guadalajara, Guadalajara, Spain; 'Nephrology, Hospital Univ Infantia Leonor, Madrid, Spain; 'Radiology, Hospital Univ Principe de Asturias, Alcalá de Henares, Madrid, Spain.

Background: Haemodialysis and advanced CKD patients have a higher prevalence of coronary calcification (CC) than general population. Previous studies have suggested a potential predictive value of CC on mortality, regardless of traditional cardiovascular (CV) risk factors. However, this mortality predictive ability is not well defined in long-term follow-up in CKD population.

Methods: A 10-year prospective longitudinal study was conducted in 137 CKD patients (stage IV-V and dialysis). A non-enhanced multi-slice coronary computed tomography was performed at baseline. CC was assessed with the Agatston method. Patients were stratified according to their coronary calcium score (CCS): CCS≤400, n=53; and CCS>400, n=84. Patients were followed for median 88 months (30-111), all-cause and CV mortality were recorded.

Results: The median age was 66 years. The median CCS was 600 (70-1794). The overall mortality rate was 58% (40% to CV events). Patients with severe calcification (CCS>400) showed higher total and CV mortality than those with lower calcification (CCS<400); 75% vs. 30% and 34.5% vs. 5.6% respectively (p<0.001). Patients with CCS≥400, were older, have a previous history of type 2 DM and cardiac events, and lower serum albumin levels. In a multivariate Cox model, severe CCS (≥400) was a significant predictor of total mortality in haemodialysis patients (HR 4.12; 95%CI 1.83 to 9.3,p=0.001), whereas it reached significance in the CV mortality in the whole serie (HR 5.01; 95%CI 1.28 to 19.59,p=0.02). The Kaplan-Meier curves of total and CV mortalities were statistical different according to CCS (p<0.001).

Conclusions: During 10-years follow-up period mortality rate was higher among patients with severe coronary calcifications, especially CV mortality. Coronary calcifications might be a proper marker to estimate cardiovascular risk in CKD patients.

SA-OR090
Assessment of Arterial Calcification, Vascular Inflammation, Bone Mineral Density and Metabolism Using Fluorodeoxyglucose-PET/CT in Patients on Maintenance Dialysis: Focused on Relationship with PTH Level  
Young-Joo Kwon,1 Jeim Kim, Gang Jee Ko, Yoonkyung Song. 'Div of Nephrology, Korea Univ; Seoul, Republic of Korea.

Background: Aims of our study are to find factors associated with, and relationships between, aortic and coronary vascular calcification, vascular inflammation, vertebral bone mineral density(VBMD) and bone metabolism in patients on maintenance dialysis with FDG-PET/CT, focused on the relationships with PTH level. Furthermore, we tried to assess simple X-ray methods in predicting vascular calcification scores.

Methods: Thirty patients on hemodialysis (HD, n=15) or peritoneal dialysis (PD, n=15) were enrolled (both >6month). Calcification scores of thoracic (TCS), abdominal (ACS), total aorta (TACS), coronary arteries (CCS) were assessed by Agatston method. In a multivariate Cox model, severe CCS (≥400) was a significant predictor of total mortality in haemodialysis patients (HR 4.12; 95%CI 1.83 to 9.3,p=0.001), whereas it reached significance in the CV mortality in the whole serie (HR 5.01; 95%CI 1.28 to 19.59,p=0.02). The Kaplan-Meier curves of total and CV mortalities were statistical different according to CCS (p<0.001).

Conclusions: During 10-years follow-up period mortality rate was higher among patients with severe coronary calcifications, especially CV mortality. Coronary calcifications might be a proper marker to estimate cardiovascular risk in CKD patients.

SA-OR091
Modeling Podocyte Development with Human Kidney Organoids Derived from Pluripotent Stem Cells  
Yong Kyun Kim,1 Ramila E. Gulieva,1 Stefan Czernecki,1 Nelly M. Cruz,1 Laura V. Islas,1 Craig R. Brooks,1 Benjamin S. Freedman.1 'Div of Nephrology, Kidney Research Inst, and Inst for Stem Cell and Regenerative Medicine, Dept of Medicine, Univ of Washington, Seattle, WA; 'Renal Div, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

Background: Podocytes derived from human pluripotent stem cells (hPSC-podocytes) have recently been generated in kidney organoids, with great potential for modeling complex development and regeneration. We investigated the structure and function of hPSC-podocytes, compared to developing mammalian podocytes.

Methods: hPSC-podos in kidney organoids were analyzed by confocal intramembrane fluorescence and transmission electron microscopy. CRISPR/Cas9 was applied to hPSCs to knock out podocalyxin, a heavily sialylated podocyte glycoprotein. Kidney sections from wild-type or Pods−/− mice were also examined.

Results: Localization of nephrin, podocin, synaptopodin, podocalyxin, and WT1 in kidney organoids closely resembled developing capillary loop stage podocytes in vivo. Ultrastructurally, hPSC-podos formed basement membrane junctional domains containing slit diaphragm components. The apicolateral membranes of hPSC-podocytes were covered with microvillus and podocalyxin, and did not form junctions. Genetic knockout of podocalyxin resulted in ablation of apicolateral microvilli and failure of junctional components to migrate basally. These features precisely phenocopied developing mammalian podocytes in wild-type and Pods−/− mice.

Conclusions: hPSC-podocytes in vitro correspond to capillary loop stage podocytes in vivo. Podocalyxin-mediated microvillus formation regulates podocyte cell spacing and junctional migration in mouse and man. The capacity of hPSC-podocytes to reveal and recapitulate developmental mechanisms makes them a powerful new tool for kidney disease modeling and regeneration. (Supported by Northwest Kidney Centers).

Funding: NIDDK Support, Other NIH Support - Supported by an unrestricted gift from Northwest Kidney Centers to Kidney Research Institute

SA-OR092
Localized mRNA Translation Mediated by Staufen 1 is a Novel Mechanism Regulating Cytoskeletal Reorganization in Response to Podocyte Injury  
Valerie A. Schumacher,1 Jessica J. Harris,1 Astrid Weins,2 Britta George,3 Benjamin D. Humphreys,3 Shuang Yang,1,6 'Urology, Boston Children's Hospital, Boston, MA; 'Pathology, Brigham and Women's Hospital, Boston, MA; 'Renal-Electrolyte and Hypertension Div, Univ of Pennsylvania, Philadelphia, PA; 'Medizinische Klinik und Poliklinik D, Universitätsklinikum Münster, Muenster, Germany; 'Renal Div, Washington Univ School of Medicine, St. Louis, MO; 'Medical College of Nankai Univ, Tianjin, China.

Background: Podocytes sometimes recover from foot process effacement indicating that there is an intrinsic plasticity inherent in foot processes in vivo. Moreover, Staufen2 focuses on the role of localized mRNA translation as a mechanism to dynamically regulate reorganization of the actin cytoskeleton in foot processes and modulate podocyte cell-matrix adhesion, thereby maintaining the glomerular filtration barrier during injury.

Methods: A cell biological and gene targeting approach was used to study the role of local mRNA translation in podocytes.

Results: We show that the RNA-binding protein Staufen2, previously demonstrated to mediate RNA transport and localized translation in neurons, is expressed in podocytes and localizes to focal adhesions in vivo. Moreover, our study focuses on the role of localized mRNA translation as a mechanism to dynamically regulate reorganization of the actin cytoskeleton in foot processes and modulate podocyte cell-matrix adhesion, thereby maintaining the glomerular filtration barrier during injury.
podocytes affects actb mRNA localization and Dock3 mRNA stability and results in cell detachment and impaired establishment of actin stress fibers upon recovery from injury. Lastly, we generated Staurosporine (Staurosporine) and Staurosporine double knockout (DKO) mice; these mice had normal baseline kidney function but DKO mice developed massive proteinuria and foot process effacement in response to Adriamycin, far greater than observed in control, or Staurosporine and Staurosporine single knockouts.

Conclusions: Localized mRNA translation mediated by Staurosporine represents a novel mechanism to regulate cytoskeletal reorganization and cell-matrix adhesion in response to podocyte injury. Funding: NIDDK Support, Private Foundation Support

SA-OR093
Novel Mat of Contractile Actin Filaments Formed at the Base of Podocytes during the Process of Foot Process Effacement
Hani Salehian, Jeffrey H. Miner, Andrey S. Shav.

Background: Because the diffusion limit of light microscopy restricts the resolution of structures smaller than 200 nm such as podocyte foot processes and imaging the podocyte cytoskeleton is challenging. Traditional tissue preparation methods don’t preserve the actin cytoskeleton enough, further restricting our ability to view changes after podocyte injury. We developed a new method of cytoskeletal preservation that allowed us to image actin and actin-associated molecules in kidney glomeruli. 2D and 3D superresolution imaging enabled us to study the architecture of the podocyte in normal and diseased states.

Methods: Two superresolution methods, STORM and Airyscan, were used to study the changes in podocyte cytoskeleton during foot process effacement in healthy and injured mouse glomeruli. Antibodies used are: synaptophysin (synpo), α-actinin-4 (α-actin), myosin IIα (myb2), nephrin, podocin.

Results: Synpo and Actn4 stained the center of healthy podocyte foot processes, while nephrin and podocin labeled between the foot processes. In injured podocytes, slit diaphragm proteins moved apically inside the effaced foot processes. While synpo and Actn4 clusters did not change upon injury, there was robust staining of myb2 at the base of the podocytes. Myb2 stained in alternating stripes with synpo and Actn4, suggesting the formation of contractile actin fibers during podocyte foot process effacement. 3D superresolution imaging confirmed that myb2 is part of sarcomere-like structures near the GBM in different injury models. In contrast, normal podocytes show myb2 staining only in primary podocyte processes. En face views of effaced foot processes showed that myb2, intertwined with synpo, covered the entire effaced area.

Conclusions: Using a new way of imaging the actin cytoskeleton, we visualized podocyte-specific focal adhesion and demonstrated in healthy and diseased podocytes in vivo the formation of contractile actin cables are present in primary processes, while the actin filaments in the podocyte foot processes in healthy and diseased conditions. In the normal podocyte, podocin is involved in establishing the actomyosin system in podocytes affecting their ability to respond to podocyte injury and to withstand the enormous transcapillary filtration forces driving glomerular filtration. The involvement of podocyte-specific focal adhesions in podocyte function and podocyte injury is an important finding for understanding podocyte function in health and disease.

Funding: NIDDK Support, Private Foundation Support

SA-OR094
Dynamics and Importance of Slit Diaphragm Molecules in Adulthood
Florian Grahammer, Corinne Antignac, Alessia Foroni, Tobias B. Huber.

1Dept of Medicine IV, Univ Hospital Freiburg, Freiburg, Germany; 2Laboratory of Inherited Kidney Diseases, Neph-Enfants Malades Hospital, Paris, France; 3Peggy and Harold Katz Family Drug Discovery Center and Div of Nephrology and Hypertension, Univ of Miami Miller School of Medicine, Miami, FL, Germany; 4Dept of Internal Medicine, Div of Nephrology, Washington Univ School of Medicine, St. Louis, MO.

Background: Little is known on the inherent dynamics of the slit diaphragm proteins nephrin, podocin and nephe lin. While constitutive deletion of any of these genes results in increased proteinuria, renal failure and absence of podocytes in vivo.

Methods: 5 week old, inducible Nphs2*NEFTA8rtTA*TeTOCre mice were crossed with Δpod−/− mice to assess the role of KLF15 in FSGS murine model. CRISPR/CAS9 genome edited immortalized mouse models for EPB41L5 and CORO2B. Genetic deletion of EPB41L5 in vivo resulted in severe proteinuria, detachment of podocytes and development of FSGS. By binding and recruiting the RhoGEF ARGHEF18 to the leading edge EPB41L5 directly controls actomyosin contractility and subsequent maturation of focal adhesions. Furthermore, these effects were mediated in an ECM-dependent manner. Surprisingly, deletion of CORO2B in vivo prevented podocyte damage in two different stress models, via modulating focal adhesion disassembly.

Conclusions: Collectively, these observations support a novel concept of podocyte intrinsic balancing of FA turnover to maintain the integrity of the kidney filtration barrier.

Funding: NIDDK Support, Private Foundation Support

SA-OR095
Mechanical Overload May Lead to Podocyte Damage by Increasing Podocyte GAPD [Ca2+] through TRPC6 Channels and P2Y2 Receptors
Georgia Gyarmati, Ildiko Toma, Janos Peti-Peteri.

Background: TRPC6 channels are known to be one of the important Ca2+ influx pathways. The effect of extracellular nucleotides by the activation of TRPC6 by P2Y2 receptors on podocyte [Ca2+] has also been reported. However, the mechanical mechanism behind the overload leading to podocyte injury is still elusive. We aimed to study and quantitatively visualize the dynamic effects of high intra-glomerular capillary pressure, a solely mechanical stimulation on podocyte [Ca2+] and the role of TRPC6 and P2Y2 receptors in mechanosensation.

Methods: Time-lapse high resolution multiphoton microscopy imaging on intact living kidneys and freshly dissected in vitro microperfused glomeruli of wild type (WT), TRPC6 transgenic (TG), TRPC6 knockout (KO), and P2Y2 KO mice was used to directly visualize the changes in podocyte [Ca2+] after acute isolated intra-glomerular capillary pressure elevation. All mice were subjected to high intra-glomerular capillary pressure by intravenous injection of Stau2, which resulted in a 2-fold increase of GMAP3 fluorescence intensity in podocytes in vivo and more than 2-fold in vivo as compared to baseline. Podocyte GMAP3 fluorescence intensity in TRPC6 TG mice increased more than 2-fold in vivo. While Stau2 injection in WT mice resulted in GMAP3 fluorescence intensity increase in podocytes in vivo, and more than 2-fold in vivo as compared to baseline. Podocyte GMAP3 fluorescence intensity in TRPC6 TG mice increased more than 5-fold. In TRPC6 KO and P2Y2 KO mice the effect of acute mechanical overload on podocyte [Ca2+] was significantly reduced, the increase in GMAP3 fluorescence intensity was 1.3-fold and 1.41-fold, respectively.

Conclusions: This study demonstrated direct visual evidence of the effect of high intra-glomerular capillary pressure on podocyte [Ca2+] and the important pathological role of TRPC6 and P2Y2 in the related podocyte injury. Podocyte TRPC6 and P2Y2 are promising therapeutic targets in conditions with high intra-glomerular capillary pressure, such as diabetic and hypertensive nephropathy for the prevention of CKD.

Funding: NIDDK Support

SA-OR096
Dynamic Control of Focal Adhesions in Podocyte Health and Disease
Christoph Schell, Manuel Rogg, Tobias B. Huber.

1Univ Hospital Freiburg, Dept of Pathology, Freiburg, Germany; 2Univ Hospital Freiburg, Internal Medicine, Nephrology, Freiburg, Germany.

Background: Pericyte-like podocytes form the outer layer of the glomerular filter where they have to withstand the enormous transcapillary filtration forces driving glomerular filtration. Dysfunction of podocyte-specific adhesions may result in the glomerular basement membrane is a common hallmark and final pathway in various glomerular diseases. However, little is known about the regulation of podocyte adhesion in response to continuous physical filtration and under disease conditions in vivo.

Methods: We screened for podocyte specific focal adhesions (FA) components employing genetic reporter models in combination with iTAG-based quantitative mass spectrometry. Applying bioinformatic filtering algorithms allowed for the identification of podocyte specific FA components. Super resolution microscopy (STORM) was employed to analyze these adhesins in situ. In vivo characterization was performed in newly generated mouse models for EPB41L5 and CORO2B. CRISPR/CAS9 genome edited immortalized podocyte cell lines as well as primary podocytes were analyzed in vitro using life imaging.

Results: The MS-based FA mapping approach led to the identification of two novel podocyte-specific FA components, the FERM protein EPB41L5 and the WD40 protein CORO2B. Genetic deletion of EPB41L5 in vivo resulted in severe proteinuria, detachment of podocytes and development of FSGS. By binding and recruiting the RhoGEF ARGHEF18 to the leading edge EPB41L5 directly controls actomyosin contractility and subsequent maturation of focal adhesions. Furthermore, these effects were mediated in an ECM-dependent manner. Surprisingly, deletion of CORO2B in vivo prevented podocyte damage in two different stress models, via modulating focal adhesion disassembly.

Conclusions: Collectively, these observations support a novel concept of podocyte intrinsic balancing of FA turnover to maintain the integrity of the kidney filtration barrier.

Funding: NIDDK Support

SA-OR097
The Podocyte-Specific Induction of Krüppel-Like Factor 15 Attenuates Glomerulosclerosis in FSGS
Yingqiao Guo, Zhengli Li, Timothy W. Miller, Monica Patricia Revelo Penafiel, Xianguen Gu, John C. He, Sanjiv K. Mallapu, Marjorie H. Guo, Xiaofang Zhang, John W. Poiesz, 1NYU, New York, NY; 2Univ of Utah, Salt Lake City, UT; 3MSSM, New York, NY; 4Nephrology, Yueyang Hospital of Integrated TCM and Western Medicine, Shanghai, China.

Background: Krüppel-Like Factor 15 (KLF15) is a critical regulator of podocyte differentiation. KLF15 is also required for steroid-induced restoration of podocyte differentiation markers. Podocyte-specific loss of KLF15 exacerbates podocyte injury in proteinuric murine models. Furthermore, the level of KLF15 expression in podocytes correlates with steroid-responsiveness MCD and primary FSGS. We now hypothesize whether the podocyte-specific induction of KLF15 in mice attenuates FSGS.

Methods: Full-length ORF cDNA of KLF15 was cloned into a TREV plasmid. Mice with TREV-KLF15 and Nphp2+/-transgenes (shKLF15) exhibited dyscoxsidase (DOX) induced transgeno-specific KLF15 in vivo. KLF15 transgenic (KFL15) mice were crossed with shKLF15 mice to assess the role of KLF15 in FSGS murine model.

Results: Acute intra-glomerular capillary pressure elevation was induced by obstructing the different mice with laser induced microthrombus in vivo and by a micropipette in vitro. In WT mice GMAP3 fluorescence intensity increased podocytes in vivo and more than 2-fold in vivo as compared to baseline. Podocyte GMAP3 fluorescence intensity in TRPC6 TG mice increased more than 5-fold. In TRPC6 KO and P2Y2 KO mice the effect of acute mechanical overload on podocyte [Ca2+] was significantly reduced, the increase in GMAP3 fluorescence intensity was 1.3-fold and 1.41-fold, respectively.

Conclusions: This study demonstrated direct visual evidence of the effect of high intra-glomerular capillary pressure on podocyte [Ca2+] and the important pathological role of TRPC6 and P2Y2 in the related podocyte injury. Podocyte TRPC6 and P2Y2 are promising therapeutic targets in conditions with high intra-glomerular capillary pressure, such as diabetic and hypertensive nephropathy for the prevention of CKD.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
RESULTS: DOX-treated Tg26;AKLF15 exhibited a significant reduction in albuminuria (40-50%) and glomerulosclerosis (30-50%) as compared to DOX-treated Tg26 mice. In addition, DOX-treated Tg26;AKLF15 exhibited a 50% increase in survival as compared to DOX-treated Tg26 mice at 10 weeks of age. TRANSFAC promoter analysis was performed to identify genes with binding sites for KLFL5. Gene-set enrichment analysis of these genes identified a significant increase in the pathways involved in suppression of Wnt/β-catenin pathway. Finally, a foot process effacement, glomerulosclerosis, serum BUN and creatinine, interstitial inflammation, glomerular epithelial cell proliferation (Claudin1, K67), podocyte differentiation markers (Nephrin, Synaptopodin, Podocin, WT1), kidney fibrosis (αSMA, Colllα1, Fibronectin, Vimentin) as compared to DOX-treated Tg26 mice. In contrast, DOX-treated Tg26;AKLF15 exhibited a reduction in Wnt/β-catenin pathway (C-myc, Left1) compared to DOX-treated Tg26 mice in isolated glomeruli.

Conclusions: Taken together, these data suggest that upregulation of KLFL5 in the podocyte abrogates FSGS, kidney fibrosis, and overall mortality by inhibiting Wnt/β-catenin signaling in HIV-1 transgenic mice.

Funding: NIDDK Support

SA-OR100

APOL1 Risk Alleles (G1, G2) Induced Kidney Disease Development Is Dose Dependent and Reversible Jing Bi Karchin,1 Pazit Beckerman,1 Ae Sco Deok Park,1 Matthew Palmer,1 Jeffrey H. Minner,1 Katalin Susztak,1 1Div of Renal-Electrolyte and Hypertension, Univ of Pennsylvania, Philadelphia, PA; 2Dept of Pathology and Laboratory Medicine, Univ of Pennsylvania, Philadelphia, PA; 3Div of Nephrology, School of Medicine, Washington Univ, St. Louis, MO.

Background: Two coding variants (G1 and G2) in the Apolipoprotein L1 (APOL1) gene increase the risk of developing chronic kidney disease (CKD) by 2-80 fold in African Americans. However, it remains unclear what triggers disease development in 2 risk allele carriers. Endogenous APOL1 expression can be stimulated by inflammatory cytokine interferon γ (IFNγ), which also triggers albuminuria in 2 risk allele subjects. Therefore, we hypothesized that the APOL1-associated kidney disease development depends on risk allele APOL1 expression levels.

Methods: We generated conditional inducible G0, G1 and G2 APOL1 transgenic animals and crossed them with the nephrin rtTA to induce podocyte specific expression. In these animals transgene expression can be controlled by doxycycline. Renal function was evaluated by albumin ELISA and structural changes by light and electron microscopy.

In vitro cytotoxicity was analyzed by propidium iodide and intracellular ATP content.

Results: APOL1 expression levels showed significant variations between the different founder lines. Risk allele APOL1 levels (G1 and G2) strongly correlate with the severity of albuminuria, which was 20 fold higher in mice expressing reference allele (G0). Similarly, glomerulosclerosis was more severe in mice with higher expression of risk allele APOL1. In vitro experiments supported the in vivo results and indicated that risk allele APOL1 causes an increased inflammatory type cell death (pyroptosis) in a doxycycline-dose dependent manner. Furthermore, initial studies indicated that albuminuria development was reversible; upon discontinuation of doxycycline diet, APOL1 expression and albuminuria returned to baseline.

Conclusions: APOL1 risk (G1 or G2) variant levels likely play an important role in disease development. Our results suggest that reducing risk allele APOL1 expression could be a realistic targeting strategy in patients with high-risk genotype.

Funding: Other NIH Support - NIH Clinical Research Training in Kidney Disease Grant Program T32-DK07785

SA-OR109

Excessive Proliferator-Activated Receptor Gamma Coactivator 1α (PGC1α) Expression and Mitochondrial Biogenesis in Podocyte Results in Cell Cycle Entry and Collapsing Glomerulocarcinosis Szu-Yuan Li,1,2 Jihwan Park,1 Chengxiang Qiu,1 Matthew Palmer,1 Katalin Susztak,1 1Medicine, Univ of Pennsylvania, Philadelphia, PA; 2Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; 3Pathology and Laboratory Medicine, Univ of Pennsylvania, Philadelphia, PA.

Background: Mitochondrial genes can result in FSGS. Acquired mitochondrial defects in podocytes have been described in other forms of glomerular disorders. We hypothesized that increasing mitochondrial biogenesis in podocytes would be beneficial. For this, we generated transgenic mice with increased expression of mitochondrial genes with binding sites for PGC1α. Mitochondrial biogenesis and tubule specific expression of PGC1α has been beneficial in acute and chronic kidney injury.

Methods: Gene expression were analyzed in microdissected human glomeruli using Affymetrix gene expression arrays. Podocyte specific inducible PGC1α transgenic mice were created by breeding Nephrin rtTA with tetr-o-PGC1α mice. We have studied PGC1α function in cultured murine podocytes using an adenosine evaluation system.

Results: Glomerular expression of mitochondrial specific genes and PGC1α showed significant positive correlation with kidney function. It was also implicated that mitochondrial content likely decreased with GFR. PGC1α expression was also decreased in diabetic mouse models. Cell type specific inducible expression of PGC1α in podocytes increased mitochondrial number and size, however, animals developed albuminuria. Histologically examined showed glomerular hypercellularity, cellular crescent formation and glomerular sclerosis. Further, podocytes were positive for proliferation marker PCNA, resembling collapsing FSGS. Overexpression of PGC1α in cultured podocytes resulted in an increase in metabolism related gene expression and oxygen consumption rate. Excess PGC1α also caused uncontrolled mitochondrial biogenesis and fusion, accompanied with cell cycle repression.

Conclusions: Decreased podocyte PGC1α expression and mitochondrial content is a consistent feature of chronic glomerular disease. While PGC1α improves podocyte energy metabolism, excessive activation promotes podocyte proliferation and result in glomerulosclerosis, indicating that there is a narrow therapeutic window for PGC1α.

Funding: NIDDK Support

SA-OR099

SGPL1 Mutations Lead to Sphingosine-1-Phosphate Lyase 1 Deficiency with Nephrotic Syndrome, Deficiency of Cellular Immunity, Adrenal Insufficiency, and Ichthyosis in Humans Sgpl1 Mutations Lead to Sphingosine-1-Phosphate Lyase 1 Deficiency with Nephrotic Syndrome, Deficiency of Cellular Immunity, Adrenal Insufficiency, and Ichthyosis in Humans

SGPL1 (sphingosine-1-phosphate lyase) is an intracellular enzyme responsible for the final step in sphingolipid breakdown, converting SIP into ethanolamine phosphate and hexadecenal. SIP functions as a ligand for G protein coupled receptors that mediate autocrine and paracrine signals controlling cell migration and proliferation. Mouse models of SGPL1 deficiency exhibit hyperlipidemia with an increase in lipidogenic hormones and podocytes and were positive for proliferation marker PCNA, resembling collapsing FSGS. Overexpression of SGPL1 in cultured podocytes resulted in an increase in metabolism related gene expression and oxygen consumption rate. Excess SGPL1 also caused uncontrolled mitochondrial biogenesis and fusion, accompanied with cell cycle repression.

Methods: We performed homozygosity mapping (HM) and WES to identify loss

Conclusions: We have identified SGPL1 mutations as a novel cause of human SRNS, acanthosis and adrenal insufficiency. Our findings delineate a new RAC1-mediated molecular pathogenesis of syndromic SRNS that may be amenable to treatment.

Funding: Other NIH Support - R01

SA-OR110

Does Acute Declines in Renal Function during Intensive BP Lowering Associate with Higher Risk of ESRD during Long-Term Follow-Up? Elaine Ku,1 Kirsten L. Johansen,2 Vito M. Campese,2 Jennifer J. Gassman,3 Mirosлав Smorgorzewski,1 Chi-Yuan Hsu1, UCSC, USA; 1AASK.

Background: Intensive blood pressure (BP) lowering frequently leads to acute declines in renal function, which was demonstrated in the recent Systolic Blood Pressure Intervention Trial (SPRINT). The long-term implications of such declines—whether it has been thought to be “hemodynamic/functional” in nature are unclear. We determined whether acute declines in renal function during the first three months of intensive BP lowering in the African American Study of Kidney Disease (AASK) trial (1995-2001) were associated with a higher long-term risk of ESRD.

Methods: The percent decline in renal function (by CKD-EPI equation) in AASK CKD trial participants (N=899) randomized to mean arterial pressure (MAP) target of <92 mm Hg (Strict BP arm) versus 102 mm Hg (Usual BP arm) was determined between time points of randomization and month 3 of the trial (period of intensive BP lowering to achieve MAP goals). Risk of ESRD (ascertained through 2012) was compared among those with a <5%, 5-<20%, versus ≥20% decline in eGFR in adjusted Cox models.

Results: Up to a 20% decline in eGFR during anti-hypertensive therapy intensification in the Strict BP arm was not associated with a statistically significantly higher risk of ESRD during mean follow-up of 14.4 years, compared to the reference group of <5% decline in the Usual BP arm (HR 1.16, 95% CI 0.79-1.69). In contrast, a ≥5% decline in the Usual BP arm and ≥20% decline in Strict BP arm was associated with a higher risk of ESRD.

Conclusions: Acute declines in eGFR up to 20% during intensive BP lowering appears to be safe and is not associated with a higher long-term risk of ESRD. Further studies are needed to confirm the long-term safety of a <20% decline in eGFR during intensive BP lowering.

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

Underline represents presenting author.
SA-OR102
Blood Pressure Parameters and Their Associations with Various Causes of Death in Chronic Kidney Disease
Sankar D. Navaneethan,1 Jesse D. Schold,2 Susana Arrigain,3 Stacey Jolly,4 Matthew F. Blum,5 Wolfgang C. Winkelmayr,5 Joseph V. Nally,5 1Bayor College of Medicine, Houston, TX; 2Cleveland Clinic, Cleveland, OH.

Background: Previous observational studies reported higher risk for death with lower blood pressure levels in CKD. However, recent clinical trial evidence suggest targeting BP <120/80 mm Hg results in better cardiovascular outcomes even among those with CKD. We examined the associations of different BP levels with various causes of death in a CKD population.

Methods: We included 45,433 patients with eGFR 15-59 ml/min/1.73 m² (twice 90 days apart) with underlying hypertension and taking at least one antihypertensive agent. We ascertained overall and cause-specific deaths from State department of health mortality data and classified deaths into three major categories: a) cardiovascular b) malignancy and c) non-cardiovascular/non-malignancy conditions. We fitted Cox models for overall mortality and separate competing risk regression models for each major cause of death categories to evaluate their associations with various BP (<110, 110-129, 120-139, 130-149 and >150 mm Hg) and DBP levels (<50, 50-59, 60-69, 70-79, 80-89, >90 mm Hg) adjusting for relevant covariates.

Results: During a median follow-up of 3.9 years, 13,343 patients died. SBP <110, 110-119 and >150 mm Hg (vs. 130-139) were associated with all-cause mortality and cardiovascular mortality (Table). DBP <50, 50-59 mm Hg (vs. 70-79 mm Hg) were associated with all-cause and non-cardiovascular/non-malignancy related deaths. DBP >90 mm Hg was associated with higher cardiovascular mortality.

Conclusions: Among non-dialysis dependent CKD population, SBP <120 and >150 mm Hg were associated with all-cause cardiovascular deaths, and DBP >60 mm Hg was associated with all-cause and non-cardiovascular/non-malignancy related deaths. Additional studies examining the differential associations with cause-specific death are needed.

Funding: Pharmaceutical Company Support - Development of CCF CKD registry is supported by an unrestricted grant to the Department of Nephrology and Hypertension, Cleveland Clinic from Amgen

SA-OR103
Pre-ESRD Systolic Blood Pressure and Post-ESRD Mortality in Advanced CKD Patients Transiting to Dialysis
Keichi Sumida,1,2 Miklos Zsolt Molnar,3 Praveen Kumar Potukuchi,1 Fridjof Thomas,1 Jun Ling Lu,1 Connie Rhee,1 Elani Streja,3 Kunihiro Yamagata,3 Kamyar Kalantar-Zadeh,3 Csaba P. Kovesdy,1,4 1Univ of Tennessee Health Science Center, Memphis, TN; 2Univ of Tsukuba, Ibaraki, Japan; 3Univ of California, Irvine, CA; 4VA Medical Center, Memphis, TN.

Background: Previous studies of non-dialysis dependent (NDD) CKD patients have shown J-shaped association of systolic blood pressure (SBP) with mortality. However, the association of SBP in late-stage NDD/CKD with post ESRD mortality remains unknown.

Methods: We identified 17,994 US veterans with advanced CKD transitioning to dialysis between 10/2007-9/2011 who had at least 3 outpatient BP measurements within 1 year prior to dialysis initiation. Associations of 1-year averaged pre-ESRD SBP categories (<90, 90-109, ≥110) with all-cause and cause-specific mortality during the 2-year period following dialysis initiation were examined using Cox (for all-cause) and competing risk (for cause-specific mortality) regressions (multivariable adjusted hazard/subhazard ratios).

Results: The mean±SD of SBP was 141±16 mmHg. There was a reverse J-shaped association of SBP with all-cause and CV mortality (Figure). The lowest mortality was associated with SBP of 140-149 mmHg (multivariable adjusted hazard/subhazard ratios [95% CI] for SBP <120 vs. 140-149 mmHg: 1.64 [1.51-1.79] and 2.01 [1.72-2.35] for all-cause and CV mortality, respectively). There was an inverse linear trend of association between SBP and infectious mortality, none of which were statistically significant.

Conclusions: Low SBP in late-stage NDD-CKD are associated with higher post-ESRD all-cause and CV mortality, but not infectious mortality. Further studies are needed to clarify ideal SBP levels among these patients.

Funding: NIDDK Support, VA Support

SA-OR104
Lanosterol Gene Polymorphisms Impact the Decline in Renal Function among Hypertensive Patients: A Follow-Up Study
Simone Fontana,1 Chiara Lanzani,2 Rossella Iatrino,3 Lorena Citerio,4 Marco Simonini,4 Simona Delli Carpini,1 John Hamlyn,5 Elena Broioni,5 Stefano Tentori,5 Paolo Manunta.6 1San Raffaele, Italy; 2Univ Maryland.

Background: Cholesterol is an essential component of mammalian cell membranes and serves as a precursor for bile acids and various steroid hormones. The gene for Lanosterol (LSS), the first committed intermediate in cholesterol biosynthesis, has a missense polymorphism that affects EO biosynthesis in adenocortical cells. Recently, we reported (Hypertension 2016) that the LSS AA genotype is associated with salt-sensitive hypertension. Exposure to increased circulating EO causes glomerular damage, and is a risk factor for acute kidney injury (Cri Care Med 2015). Furthermore, LSS gene is transcribed in discrete nephron sites (JASN 2017). In this report, we explore the importance of LSS in the progression of chronic kidney disease (CKD).

Methods: A cohort of 421 naïve hypertensive patients (female 188, male 233, age 42.7 ± 8.41 years), were enrolled in a follow-up study (5.32 ± 4.37 years) in which BP values were kept at goal with ACEI plus diuretic and, when needed, a Ca2+ channel antagonist. Renal function and other kidney parameters were evaluated every six months.

Results: BP values (SBP/DBP) after 4.6 years of follow-up were at target (LSS AA 138±85 AC 140±86 CC 141±85, respectively). The slope in eGFR (CKD-EPI) was 1.43±0.47 ml/1.73m²/yr in the whole study population. When analysed according to the LSS genotype, the decline in renal function was double in the AA homozygotes (LSS AA -2.35 ± 4.79 ml/1.73m²/yr, p<0.024). The impact of LSS polymorphisms was also reflected in patient renal survival (see Fig. 1).

Conclusions: Our findings further support the role of LSS polymorphisms and circulating EO in the progression of CKD. This metabolic pathway may accelerate the decline in renal function via its effects on glomerular podocyte and tubular components.

SA-OR105
Prevalence of White-Coat (WCH), Masked (MH), and Sustained Hypertension (SH) Using Uniform Definitions across Multiple Cohorts - The International Database of Ambulatory Blood Pressure in Renal Patients (1-DARE) Collaborative Group
Paul E. Dzwon,1 Luca De Nicola,1 Naohiko Fujii,1 Francis B. Gabbai,2 Jennifer J. Gassman,3 Jing He,4 Satoko Iimuro,1 James P. Lash,5 Roberto Minutolo,2 Robert A. Phillips,4 Luis M. Ruijlope,6 Susan P. Steigerwald,7 Raymond R. Townsend,8 Dawei Xie,9 Mahboob Rahman,10 1Univ of Minnesota; 2Italian Cohort; 3AASK Cohort; 4CRTC Cohort.

Background: Differences in ABPM profiles based on ethnicity and geography have been well studied. In addition, differences in definitions have made it hard to compare the prevalence of WCH, MH, and SH across cohorts.

Methods: A database of demographic, clinical, and ambulatory BP (ABP) data from renal patients from AASK, CRIC, Italy, CKD-JAC, and Spain was established. Participants with CKD, either eGFR <60ml/min/1.73m² or proteinuria, were included in this cross-sectional analysis. Cutoffs for controlled clinic and 24h ABP were 140/90 and 130/80mmHg, respectively.

Results: Characteristics of the 9,293 participants are shown in the table. The prevalence of MH was higher in AASK, CRIC, and CKD-JAC (30-38%) compared to the Italian and Spanish cohorts (7-10%) in which WCH was higher.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Covariate | Overall | AASK | CRIC | Italy | CKD-JAC | Spain
--- | --- | --- | --- | --- | --- | ---
N | 9293 | 581 | 1356 | 444 | 107 | 5945
Age | 64.5 (12.3) | 62.1 (11.4) | 63.5 (10.1) | 61.1 (13.9) | 61.2 (11.3) | 65.8 (12.9)
Male (%) | 51.8 | 62.5 | 56.6 | 59.0 | 63.3 | 47.2
eGFR (CKD-Epi) | 46.7 (22.6) | 34.4 (14.8) | 38.3 (15.0) | 38.5 (18.1) | 34.2 (15.9) | 52.5 (23.8)
Proteinuria (% pts) | 35.1 | 48.0 | 49.7 | 71.4 | 40.7 | 26.9
BP category (%) | | | | | | |
- Controlled BP | 23.7 | 38.8 | 46.6 | 21.2 | 37.3 | 15.8
- WCH | 22.0 | 22.0 | 4.4 | 28.6 | 5.1 | 30.1
- MH | 15.1 | 38.2 | 30.5 | 10.1 | 32.8 | 6.7
- SH | 39.2 | 28.7 | 18.3 | 40.1 | 24.4 | 47.3

Conclusions: This international database of ABP in renal patients reveals a large heterogeneity of BP profiles across countries. This project represents an important advance in our ability to study racial/ethnic/geographic variations in ABP profiles. Future analyses will evaluate factors that contribute to elevated ABP, the effect of elevated ABP on adverse cardio-renal outcomes, and whether there are any ethnic or geographic differences in these associations.

Funding: NIDDK Support

SA-OR106
Graded Association between Kidney Function and Postural Blood Pressure Instability
Mark Canney,1,2 Matthew D.J. O’Connell,1 Donal J. Sexton,1,2 Neil O’Leary,1 Rose Anne M. Kenny,1 Mark Alan Little,1 Connal M. O’Seaghdha,1 1The Irish Longitudinal Study on Ageing, Trinity College Dublin; 2Trinity Health Kidney Centre, Trinity College Dublin; 1Nephrology Dept, Beaumont Hospital, Dublin.

Background: Postural blood pressure (BP) instability is a predictor of cognitive dysfunction, falls and mortality. We sought to characterize postural BP behavior across the spectrum of estimated glomerular filtration rate (eGFR) in older adults.

Methods: Cross-sectional analysis of 4204 participants from The Irish Longitudinal Study on Ageing, a representative national cohort of community-dwelling adults aged ≥50yrs. Beat-to-beat BP was measured by finometry during a 2 minute active stand test. The primary predictor was cystatin C eGFR categorized as follows (mL/min/1.73m2): ≤90 (ref); 75-89; 60-74; 45-59; <45. We used multivariable linear regression to model the association between eGFR groups and postural BP behavior, defined as the change from baseline in mean systolic BP (SBP) at 10 second(s) intervals. In a secondary analysis we modeled the association between eGFR groups and postural BP behavior, defined as the change from baseline in mean systolic BP (SBP) at 10 second(s) intervals. In a secondary analysis we modeled the association between eGFR groups and postural BP behavior, defined as the change from baseline in mean systolic BP (SBP) at 10 second(s) intervals.

Results: Mean(sdl) age was 61.6(8.2)yrs, 53% were female and mean(sdl) eGFR was 81.7(17.6)mL/min/1.73m2. We observed a graded association between postural BP instability and cystatin C eGFR. This was evident within 20s of standing and was robust to multivariable adjustment.

At 40% participants with eGFR<45 had a mean SBP deficit of (89% CI, 5) to 11 mmHg vs the reference group. There was no evidence of effect modification by antihypertensive therapy. The association between creatinine eGFR and postural BP behavior was comparably modest.

Conclusions: We report a novel relationship between postural BP instability and eGFR in a large representative sample of older adults using beat-to-beat data. This graded association was marked within the first minute of standing, a time window not captured by conventional BP measurements.

SA-OR107
Intensive Blood Pressure Lowering Will Prevent over 100,000 Deaths Annually
Tisha Joerla M. Tan,1 Adam Bress,2 Richard Cooper,1 Paul Munter,2 Srinidhi Beddu,2 Holly J. Kramer,1 Loyola Univ; 1Univ of Alabama; 2Univ of Utah.

Background: The Systolic Blood Pressure Intervention Trial (SPRINT) trial randomized 9,361 adults aged ≥50 years at high cardiovascular disease (CVD) risk without diabetes or stroke to intensive systolic blood pressure (SBP) lowering (<120 mmHg) or standard SBP lowering (≥140 mmHg). After a median follow up of 3.2 years, all-cause mortality was 27% (95% CI 40%, 10%) lower with intensive SBP lowering. We estimated the potential number of prevented deaths with intensive SBP lowering in the U.S. population meeting SPRINT criteria.

Methods: SPRINT eligibility criteria were applied to the National Health and Nutrition Examination Survey 1999-2006, a representative survey of the U.S. population, linked with the mortality data through December 2011. Eligibility included (1) age ≥50 years with (2) SBP 130-180 mmHg depending on number of antihypertensive classes being taken, and (3) presence of ≥2 CVD risk conditions (history of coronary heart disease, estimated glomerular filtration rate (eGFR) 20 to 59 ml/min/1.73 m2, 10-year Framingham risk score ≥15%, or age ≥75 years). Adults with diabetes, stroke history; >1 g/day proteinuria, heart failure, or eGFR<20 m/l/min/1.73m2 were excluded. Annual mortality rates for adults meeting SPRINT criteria were calculated using Kaplan-Meier methods and the expected reduction in mortality rates with intensive SBP lowering in SPRINT was used to determine the number of potential deaths prevented. Analyses accounted for the complex survey design.

Results: An estimated 18.1 million U.S. adults met SPRINT criteria with 7.4 million taking blood pressure lowering medication. The mean age was 68.6 years and 83.2% and 7.4% were non-Hispanic white and non-Hispanic black, respectively. The annual mortality rate was 2.2% (95% CI 1.9%, 2.5%) and intensive SBP lowering was projected to prevent 107,453 deaths per year (95% CI 45,374, 139,490). Among the estimated 4.1 million adults with eGFR 20-59 ml/min/1.73 m2 meeting SPRINT criteria, the annual mortality rate was 2.9% (95% CI 2.3%, 3.6%) and intensive SBP lowering was projected to prevent 32,145 deaths per year (95% CI 25,493 - 39,903) in this group.

Conclusions: We project intensive SBP lowering could prevent over 100,000 deaths per year of intensive treatment.

SA-OR108
Dose Requirements, Hospitalization, and Mortality Are Similar with Subcutaneous versus Intravenous Erythropoietin Administration
Ambreen Gul,1 R. Schrader,1 D. Miskulin,1,2 S. Paige,1 Antonia Harford,1 Philip Zager,1 1DCI; 2Tufts; 3UNM.

Background: Erythropoietin (EPO) is indicated for the treatment of the anemia of ESRD. Results of the CREATE and CHOIR trials as well as implementation of the bundle payment system led many providers to switch from intravenous (IV) to subcutaneous (SC) EPO administration. A retrospective analysis of hemodialysis (HD) patients enrolled in the CMS Clinical Performance Measures Project from 1997 to 2005 found that IV vs. SC EPO administration was associated with 25% higher doses and an increased risk for the composite outcome of death or cardiovascular hospitalization. However, only 8% of patients received SC EPO. Since then, target hemoglobin (Hgb) values, EPO doses and the percent of patients treated with IV EPO have decreased significantly. Therefore, it is unknown if the alleged advantages of SC over IV are still operative.

Methods: We conducted a retrospective study of 24,957 HD patients treated between 2011 and 2014 at DCI facilities. The majority of SC and IV doses were administered once and thrice weekly, respectively. We used linear mixed models to compute mean weekly EPO doses. High doses, whether IV or SC, were associated with increased risks of hospitalization and mortality. However, there were no differences in hospitalization or mortality risk by route of administration.

Results: From 2011 to 2014, the proportion of patients treated with SC EPO increased from 41% to 69%. For a given achieved Hgb there were no significant differences between SC and IV mean weekly EPO doses. High doses, whether IV or SC, were associated with increased risks of hospitalization and mortality. However, there were no differences in hospitalization or mortality risk by route of administration.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Mean weekly doses of EPO and the risks for hospitalization and mortality were similar for IV and SC EPO administration.

SA-OR109

Mortality among Undocumented Hispanic ESRD Patients with Different Availability to and Access for Dialysis Lilia Cervantes,1 Delpriene S. Tuot,2 Rajeev Raghavan,3 Jeff Zoucha,1 Lena C. Sweeney,3 Chandan Vangala,1 Madelyne L. Hull,1 Mario Andres Camacho,1 Jessica B. Kendrick,1 Neil R. Powe,2 Stuart L. Linas,1 1Univ of Colorado; 2Univ of California, San Francisco; 3Baylor College of Medicine.

Background: Treatment strategies for undocumented end-stage renal disease (ESRD) patients in the U.S. varies between and within states. Most states provide dialysis to undocumented patients only when they present to an emergency department with life-threatening complications. We sought to determine whether the frequency of available treatment and access to AVF/AVG placement yielded mortality differences in three cities.

Methods: We conducted a retrospective cohort study of undocumented Hispanics who initiated hemodialysis January 2007 through July 2014 at three sites with different approaches: Denver Health (DH) (n = 45) in Colorado, Harris Health (HH) (n = 47) in Texas, and Zuckerberg San Francisco General (ZSFG) (n = 119) in California. Standardized mortality ratios (SMR) were calculated using participant gender and age at initiation. Sites were individually and collectively compared to the documented Hispanic population in the U.S. Renal Data System (USRDS). A Kaplan-Meier curve described one, three, and five year survival across cities.

Results: Compared to the USRDS Hispanic population, undocumented Hispanics had greater risk of mortality at three and five years following dialysis initiation (Table). SMRs show patients who received emergent dialysis with either a catheter or AVF/AVG experienced higher rates of mortality compared to counterparts who received routine dialysis with access to AVF/AVG placement. Kaplan-Meier curves were consistent.

Conclusions: Availability of routine dialysis and permanent vascular access for undocumented Hispanics is strongly associated with improved mortality.

Funding: Private Foundation Support

SA-OR110

Anemia and Iron Management over the First 5 Years after Dialysis Start: Results from the DOPPS Angeloo Karaboyas,1 Bruce M. Robinson,2 Yvonne Meier,3 Lisa Lorain,3 Masaaki Inaba,3 Stefan H. Jacobson,3 Raymond C. Vanholder,2 Ronald L. Pisoni,1 1Archer Research Collaborative for Health, Ann Arbor, MI; 2U of Michigan, Ann Arbor; 3Vifor Pharma Ltd, Glattbrugg, Switzerland; 4Keryx Biopharmaceuticals, Boston, MA; 5Osaka City U, Japan; 6Danderyd Hosp, Stockholm, Sweden; 7Univ Hosp, Gent, Belgium.

Background: Hemodialysis (HD) patients are at an especially high risk of adverse events in the period following HD initiation. Optimizing treatment practices before, during, and after this transition is paramount, particularly for anemia management. Hemoglobin (Hgb) levels typically rebound on HD due to substantial ESA and IV iron dosing, but the trajectory of ferritin and TSAT levels after the transition to dialysis has not been well-studied.

Methods: Restricted cubic splines were used to model the mean (SE) of ferritin, TSAT, Hgb, IV iron and ESA dose over the first 5 years of HD using longitudinal data from 6612 patients in phase 5 (2012-2015) of the Dialysis Outcomes and Practice Patterns Study (DOPPS) in Europe (EUR), Japan, and the US.

Results: In the first year after HD initiation, IV iron and ESA doses were higher in the US vs. EUR, but achieved mean Hgb levels were lower in the US. In contrast, iron parameters increased more quickly in the US and remained high, reaching a mean plateau of 900 ng/mL (ferritin) and 32% (TSAT) after 2 years, despite IV iron doses declining to EUR levels. Anemia treatments and measures were generally more stable across HD vintage in Japan.

Conclusions: Regional differences in anemia management are accentuated during the early HD period, when US patients receive the highest IV iron and ESA doses and have larger, sustained increases in ferritin and TSAT levels. Because early HD mortality is high, future investigation is needed including identifying pre-HD practices that can support the use of lower IV iron and ESA doses soon after HD start, and what effect if any this might have on clinical outcomes.

Funding: Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsy, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain. All grants are made to Arbor Research Collaborative for Health and not to Mr. Karaboyas directly

SA-OR111

Improving Interdialytic Weight Gain in Dialysis Patients Chandandeep Takkar,1 Karen D. Burchell,1 Laura Montes,1 Wajej Y. Qinibi,1 1Nephrology, UTHSCSA, San Antonio, TX; 2UHS, San Antonio, TX.

Background: UF Rate (UFR) above 13 ml/Kg/hour (vs 10-13 ml/kg/hour) in hemodialysis (HD) patients is associated with increase in mortality. Moreover, UFR is being considered as a reportable quality measure for HD by the CMS. Aim of our project is to improve interdialytic weight gain (IDWG) to keep UFR <12ml/Kg/hour in at least 65% of HD patients.

Methods: A multidisciplinary team was convened in Sept 2015. Baseline IDWG (average of 13 months) was recorded from 10/2014-9/2015. Goal IDWG was calculated for each patient to keep maximum UFR<12ml/Kg/hour as follows: 12 X Estimated Dry Weight X treatment duration (in hr) – Rinse back. Patients met goal the preceding month if their average IDWG was at/below maximum goal. Volume overload-related admissions, pre and post-dialysis BP and hypotensive episodes during dialysis were recorded. A fishbone diagram was used to identify barriers to goal IDWG and a driver diagram to identify key actionable items. We counseled patients extensively regarding sodium and fluid restriction, adjusted their dialysate sodium (DNSa) prescription according to the 3 month pre dialysis average serum sodium concentration (SNA), in order to reduce the DNSa to SNa gradient. Standardized educational process and material for counseling was also developed. For sustainability, IDWG calculation, maximum goal and monthly average IDWG report was incorporated in EMR.
SA-OR113
Continuous ECG Recording of Cardiac Rhythm Shows That Pre-Hemodialysis (HD) Potassium (K+) Levels Need To Be Tightly Controlled between 4 to 5.5 mEq/L

Methods: A search strategy was developed for searching Medline, PubMed, EMBASE, Cochrane Central and CINAHL databases from inception until July 15, 2015. We included randomized controlled trials that compared high dose IV iron to low dose IV iron in the Cochrane Central and CINAHL databases from inception until July 15, 2015. We included (HR 0.93 [95% C.I. 0.47, 1.84]). No significant statistical heterogeneity was detected.

Results: Seven studies met the criteria for inclusion with five in HD, one in PD, and one in both HD and PD. Four studies reported infections (n=743) and six reported mortality of at least 30 days. Outcomes included infections, hospitalizations, cardiovascular events, and death

Conclusions: A team based approach involving intensive patient counseling and attention to dialysis prescription are effective means to reduce IDWG in dialysis patients.

SA-OR112
Intravenous Iron Dosing and the Risk of Adverse Events in End Stage Renal Disease: A Systematic Review and Meta-Analysis

Ingrid Hougen, Mathieu Bourrier, David Thomas Collister, Thomas W. Ferguson, Paul Komenda, Claudio Rigatto, Navdeep Hougen. Max Rady College of Medicine, Univ of Manitoba, Winnipeg, MB, Canada.

Background: Anemia and relative iron deficiency are common in patients with end stage renal disease (ESRD) and contribute to morbidity and mortality. The optimal intravenous (IV) iron dosing strategy in dialysis patients is unclear with controversy regarding the safety of high versus low dosing. We performed a systematic review and meta-analysis in order to assess the safety of IV iron dosing in adults with ESRD.

Methods: A search strategy was developed for searching Medline, PubMed, EMBASE, Cochrane Central and CINAHL databases from inception until July 15, 2015. We included randomized controlled trials that compared high dose IV iron to low dose IV iron in the adult ESRD population using daprodustat to treat anemia of CKD. Daprodustat can maintain Hgb at target levels for 24w. In the same time frame, daprodustat produced dose produced dose dependent changes in Hgb (g/dL) from baseline after 4w (placebo: -0.72; 4mg: -0.29; 6mg: 0.18; 8mg: 0.40; 10mg: 0.69; 12mg: 0.69). The mean change from baseline in Hgb at 24w for the combined daprodustat group was 0.03 g/dL (control: -0.11 g/dL). Mean hepcidin levels were reduced from baseline at 24w by 20.6% in subjects in the combined daprodustat group (control: 3.6%). The median maximum observed plasma EPO levels in the control group during rEPO therapy were -14-fold higher than the combined daprodustat group (control: 522.9 IU/L; daprodustat: 36.5 IU/L). There was no effect on plasma VEGF for either group. Daprodustat demonstrated an adverse event profile consistent with the HD population; however, the incidence of overall mortality and major cardiovascular events were lower than expected across all treatment arms.

Conclusions: These data inform the Hgb dose response relationship of daprodustat in anemic HD subjects who were switched from a stable dose of rEPO and demonstrate daprodustat can maintain Hgb at target levels for 24w. In the same time frame, daprodustat reduced hepcidin levels, maintained physiologic levels of plasma EPO, and there was no effect on plasma VEGF. These data support future long-term clinical studies in the dialysis population using daprodustat to treat anemia of CKD.

Funding: Pharmaceutical Company Support - Medtronic, Government Support - Non-U.S.

SA-OR114
Daprodustat, a HIF-Prolyl-Hydroxylase Inhibitor, Maintains Hemoglobin Levels over 24 Weeks in Anemic Hemodialysis Subjects Switching from Recombinant Human Erythropoietin


1GlucoSmithKline; 2Roivant Sciences; 3Nossuli Research.

Background: This study was conducted between June 2017 and April 2018 in 216 subjects on hemodialysis (HD) previously receiving a stable dose of recombinant human erythropoietin (rEPO).

Methods: Subjects were randomized to receive daily oral daprodustat 4, 6, 8, 10, 12 mg or control (placebo for 4w, then open-label rEPO as required). After 4w, doses were titrated to a Hgb target of 10-11.5 g/dL.

Results: Mean baseline Hgb was 10.4 g/dL. Switching from rEPO to daprodustat produced dose dependent changes in Hgb (g/dL) from baseline after 4w (placebo: -0.72; 4mg: -0.29; 6mg: 0.18; 8mg: 0.40; 10mg: 0.69; 12mg: 0.69). The mean change from baseline in Hgb at 24w for the combined daprodustat group was 0.03 g/dL (control: -0.11 g/dL). Mean hepcidin levels were reduced from baseline at 24w by 20.6% in subjects in the combined daprodustat group (control: 3.6%). The median maximum observed plasma EPO levels in the control group during rEPO therapy were -14-fold higher than the combined daprodustat group (control: 522.9 IU/L; daprodustat: 36.5 IU/L). There was no effect on plasma VEGF for either group. Daprodustat demonstrated an adverse event profile consistent with the HD population; however, the incidence of overall mortality and major cardiovascular events were lower than expected across all treatment arms.

Conclusions: These data inform the Hgb dose response relationship of daprodustat in anemic HD subjects who were switched from a stable dose of rEPO and demonstrate daprodustat can maintain Hgb at target levels for 24w. In the same time frame, daprodustat reduced hepcidin levels, maintained physiologic levels of plasma EPO, and there was no effect on plasma VEGF. These data support future long-term clinical studies in the dialysis population using daprodustat to treat anemia of CKD.

Funding: Pharmaceutical Company Support - This study was funded by GlucoSmithKline.

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

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93A
SA-ORI15

Effects of Hemodialysis and Dialysate Potassium on Maximum P Wave Duration and P Wave Dispersion  Yi-Lun Zhou. Dept of Nephrology, Tiantan Hospital, Capital Medical Univ.

Background: Atrial fibrillation (AF) is a frequent arrhythmia in hemodialysis (HD) patients and is associated with increased morbidity and mortality. Maximum P-wave duration (Pmax) and P-wave dispersion (Pd) are effective electrocardiographic predictors of AF. This study was designed to evaluate the influence of HD session and dialysate potassium concentration (Kd) on Pmax and Pd.

Methods: 117 chronic HD patients with sinus rhythm and 50 healthy controls were included. Kd 2.5 mmol/L (K2.5) was normally used and then once raised to 3.0 mmol/L (K3.0). Blood samples were drawn and twelve-lead electrocardiograms (ECG) were recorded immediately before and after HD session. Pd was defined as the difference between the maximum and minimum P-wave duration on ECG. Home blood pressure monitoring was performed and home systolic blood pressure (home-SBP)≥150mmHg was defined as uncontrolled hypertension. Left atrial diameter was measured by ultrasonography.

Results: Pmax and Pd were significantly increased in HD patients than healthy controls. Multiple stepwise regression analysis revealed that left atrial enlargement (p<0.001) and uncontrolled home blood pressure (p=0.030) were independent predictors of pre-dialysis Pmax and Pd among HD patients. Pmax significantly increased during both HD sessions compared with predialysis values (121.1±11.6 vs. 105.4±11.6ms, 115.8±10.7 vs. 106.1±11.6ms, respectively, p<0.001) after HD sessions. Furthermore, postdialysis Pmax and Pd were decreased in K3.0 group than K2.5 (115.8±10.7 vs. 121.1±11.6ms, 40.4±9.7ms vs. 46.2±10.3ms, respectively, p<0.001).

Conclusions: Pmax and Pd increase significantly after HD sessions. Raising dialysate potassium concentration can shorten postdialysis Pmax and Pd, and this may help to decrease the incidence of AF among HD patients.

SA-ORI16

A Novel Method of Delivering Bicarbonate-Based Dialysis Fluid: A 4-Stream Approach  Susie Q. Lew,1 Yuk Lun Cheng,2 Todd S. Ing,1,3 Medicine, George Washington Univ, Washington, DC; 1Medicine and ICU, Alice Ho Miu Ling Nethersole Hospital, Hong Kong, China; 2Medicine, Stritch School of Medicine, Loyola Univ Chicago, Maywood, IL.

Background: A conventional 45X, 3-stream method of delivering a bicarbonate-based dialysis fluid (DF) uses an acid concentrate stream (CS), A; a bicarbonate (BC) CS, B; & H2O stream, W. The flow rate ratios (FRR) for A:B:W are: 1:1.72:42.28, respectively (totaling 45 or 45X). By altering the B flow rate, BIC level in the final DF ranges from 20 to 40 mM. Variations beyond these limits leads to excessive reciprocal changes in the DF levels of A ingredients.

Methods: We have devised a 4-stream method to overcome the above range limitation by adding a NaCl CS, C. B & C’s FRR are controlled by an electronic pulley-like mechanism.

Results: The FRR for the 4-streams A:B:C:W are: 1:1.72:1.72:40.56 (45X). Contributions to the final DF are: A: Chlorides of Na (63 mM), K, Ca, & Mg, & glucose; B: 37 mM NaHCO3; C: 37 mM NaCl, and W: H2O. With B & C, when the FRR changes in 1 stream, the other changes by the same magnitude but in the opposite direction. For example, B’s FRR decreases by 0.2 to 1.52 in order to lower the DF NaHCO3 level to 32.7 mM to treat metabolic alkalosis, then C’s FRR will reciprocally increase by 0.2 to 1.92 to raise the DF NaCl level to 41.3 mM. The opposite sequence of events occur if FRR of B increases to treat metabolic acidosis. The 2 fluid volumes responsible for diluting the ingredients derived from A, namely, the sum of the FRR for B & C (3.84) and the FRR for W (40.56) remain unchanged. Hence, the levels of A ingredients in the final DF will remain untouched. Since B & C are isonatric, their reciprocal changes described will not affect the final DF Na level either.

Conclusions: This 4-stream approach allows a wider [BIC] range in the final DF without changing the levels of Na or A ingredients.

SA-ORI17

Real-World Effectiveness of Biosimilar Epoetin α: 2-Year Outcomes in the Monitor-CKD5 Study  Johannes F. Mann,1 Gerard M. London,2 Christian Combe,1 David Goldsmith,3 Philippe Zauuri,4 Frank Dellanna,6 Michael Gorray,1 Nadja Hoebel,5 Karen Macdonald,4 Ivo Abraham,3 Friedrich Alexander Univ Erlangen-Nürnberg, Erlangen, Germany; 1Centre Hospitalier É.H. Manhes, Fleurie-Mérignac, France; 2Centre Hospitalier de Bordeaux, Bordeaux, France; 3Guy’s and St. Thomas’ NHS Foundation Hospital, London, United Kingdom; 4Univ de Grenoble-Alpes, Grenoble, France; 5Dialyseklinikum, Düsseldorf, Germany; 6Sanoe/Hexal AG, Holzkirchen, Germany; 7Matrix45, Tuscon, AZ; 8Univ of Arizona, Tuscon, AZ.

Background: Biosimilar erythropoiesis-stimulating agents (ESAs) are not yet available in the US, but longitudinal evidence on real-world use abroad is growing. MONITOR-CKD5 is a European study examining long-term safety and effectiveness of biosimilar epoetin α (Binoctir®) in hemodialysis (HD) patients (pts).

Methods: Prospective 24-month (24m) pharmacoepidemiological study of 2023 HD pts with renal anemia treated with Binoctir® in 10 European countries. Binoctir® dosing and hemoglobin (Hb) outcomes over 24m are presented.

Results: Mean±SD age was 64.8±14.95y; 59.3% were male. Mean time on HD was 3.8±4.6y. Most had received an ESA previously (82.5%). Primary CKD etiology: diabetic nephropathy (25.4%), chronic glomerulonephritis (20.4%), renal vascular disease (16.4%). At enrollment 73.0% had adequate iron stores, 22.2% had functional and 4.8% absolute deficiency. Over 24m, mean serum ferritin ranged from 466±320 to 581±434ng/mL; supplemental iron was given to 59.7-67.5% and transfusion to 0.3-1.2% of pts. Baseline Hb was 11.1±1.1g/dL, with 68% between 10-12g/dL; mean weekly Binoctir® dose at baseline was 106.5±78.7IU/kg. Mean Hb and Binoctir® dose remained stable over 24m (both p=ns)

Conclusions: In this real-world study Binoctir® maintains stable Hb over 24m, consistent with originator. This is the first 2-year evidence of the effectiveness of Binoctir® in HD.

Funding: Pharmaceutical Company Support - SANDOZ.
Discontinuation of Eculizumab in a Patient with Atypical HUS

Juan Calderon, Anushree C. Shirali. Dept of Nephrology, Yale School of Medicine, New Haven, CT.

Introduction: Since atypical HUS (aHUS) is a disease of disordered serum complement activation, eculizumab has been used successfully in its treatment. While this approach has been beneficial in the acute treatment of aHUS, the optimal duration of therapy remains unknown, particularly in patients with mutations of complement regulatory proteins. We report a case of aHUS in a patient with a membrane cofactor protein (MCP) mutation who was successfully treated with eculizumab and remains without disease recurrence after its discontinuation.

Case Description: A 26-year-old man was diagnosed with aHUS after presenting with influenza, non-bloody diarrhea, hematuria and a serum creatinine (Cr) of 5.1 mg/dL. He had 4%gs of proteinuria, hemolytic anemia and thrombocytopenia. He showed improvement in hematologic parameters with steroids and plasmapheresis but had persistently elevated Cr proteinuria on initiation of eculizumab. His Cr was 1.1 mg/dL with monoproteinuria. Direct sequence analysis revealed that he had a heterozygous MCP missense mutation c.586G>A (G196R). Two years later, in consultation with hematology, eculizumab was stopped. He was being followed with monthly labs. Over the past year, he has shown no evidence of disease recurrence, with stable Cr at 1.1 mg/dL and no significant proteinuria, hematuria or hemolysis.

Discussion: Approximately 60%-70% of aHUS patients have mutations in the genes encoding complement factor (CFH), factor I, MCP, factor B, thrombomodulin or C3. In a study of 10 aHUS patients with different mutations who were taken off eculizumab maintenance, 3 patients had recurrent disease, all of whom had CFH mutations. Immediate improvement was seen with reinitiation of eculizumab. Our patient with a MCP mutation has been recurrence free for a year following discontinuation of eculizumab. The rationale for this approach includes avoiding high drug cost and minimizing risk of meningococcal infection. Further, eculizumab has shown to be effective in drug reactions. Frequent laboratory testing is necessary for early detection of recurrence. Improved understanding of specific genotypes and aHUS recurrence will help tailor therapy individually and maximize benefit while minimizing risk.

TH-PO002

Two Cases of Adult Onset Henoch-Schönlein Purpura with Acute Kidney Injury and Severe Gastrointestinal Manifestations: Successful Treatment with Factor XIII Replacement Therapy

Takeyuki Takamura, Fumihiko Furuya, Kenichiro Kitamura. Third Dept of Internal Medicine, Univ of Yamanashi, Chuo, Yamanashi, Japan.

Introduction: Gastrointestinal involvement occurs in 50-75% of Henoch-Schönlein Purpura (HSP) patients. Several prior studies have identified a correlation between the decreased FXIII activity and the severity of gastrointestinal manifestations or kidney injury in HSP patients.

Case Description: [Case 1] A 48-year-old woman was hospitalized with purpura, gastrointestinal hemorrhage, proteinuria, and macroscopic hematuria. Kidney biopsy revealed granular deposition of IgA and C3 in the mesangial region with crescent formation. She was initially treated with intravenous methylprednisolone pulse therapy followed by prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and oral prednisolone 40mg daily, but her symptoms were not improved.

Discussion: We report 2 cases of HSP with acute kidney injury and severe gastrointestinal manifestations and successfully treated with FXIII replacement therapy. In both cases, immunosuppressive therapy did not improve the kidney or gastrointestinal injury, but FXIII replacement therapy or combination of plasmapheresis and FXIII replacement substantially ameliorated the both injury. These findings strongly suggest the possibility that FXIII plays critical roles in the pathogenesis and the progression of kidney and gastrointestinal injury that are associated with HSP.

TH-PO003

A Case of Nephrotic Syndrome Secondary to Kimura Disease

Divya Raghavan, Mazad A. Khaliqhe, 2Laith Al-Rabah, 3Josephine Abraham. 1Dept of Nephrology, Univ of Utah, Salt Lake City, UT; 2Dept of Pathology, Univ of Utah, Salt Lake City, UT.

Introduction: Kimura disease (KD) is a rare chronic inflammatory disorder typically presenting with head and neck masses, peripheral eosinophilia and elevated serum IgE levels. Histology is unclear and it is usually seen in East Asians. A multitude of renal lesions have been described with KD, including membranous glomerulonephritis (GN), mesangioproliferative GN, minimal change disease (MCD) and IgA nephropathy. We report a case of KD in a Caucasian man who primarily presented with MCD.

Case Description: A 70 year old Caucasian man with a history of diabetes mellitus and recurrent skin lesions (lymphomatoid cutis on biopsies) was admitted to the hospital with complaints of leg swelling and dyspnea on exertion. Physical exam revealed pitting pedal edema and enlarged right post-auricular and right cervical lymph nodes. Labs showed a serum creatinine (SCR) of 2.4 mg/dL (baseline 1.1 mg/dL), eosinophilia (14%), and total protein – creatinine ratio of 8.8 g/g. Kidney biopsy showed MCD. Prednisone 1mg/kg PO QD was started soon after he underwent a CT scan of head, neck, chest, abdomen and pelvis to evaluate for lymphoma as the etiology of MCD. A large infiltrative soft tissue mass involving more than 50% of the examined glomeruli, with no endocapillary hypercellularity. The serologic studies (ANA, pANCA, cANCA, anti-GBM antibodies) were negative. An initial 6-month course of corticosteroid therapy, the NS persisted. In this setting, 500 mg of Rituximab was administered. Subsequent check-ups are shown in table.

Case 1: A 27 year-old male presented with edema, NS (proteinuria of 8 g/day), altered renal function with estimated glomerular filtration rate (eGFR=CKD-EPI) of 63 ml/min and microscopic hematuria. Kidney biopsy revealed IgAN with fibrocellular crescents involving more than 50% of the examined glomeruli, with no endocapillary hypercellularity. In the cases described, Rituximab treatment was associated with a clear improvement of NS. However, after completing the immunosuppressive regimen, the NS relapsed and eGFR decreased to 41 ml/min, so it was decided upon administration of 500 mg of Rituximab. Subsequent check-ups are shown in table.

Discussion: In the cases described, Rituximab treatment was associated with a clear improvement of NS and stabilization of renal function. Still, randomized clinical trials to assess the efficacy of rituximab in IgAN treatment are needed.

TH-PO005

Acute Kidney Injury and Possible Thrombotic Microangiopathy Associated with EGFR Inhibitor Osimertinib

Niha Ibrahim, Antony Joseph Ferrey, Yongen Chang. Nephrology, UC Irvine, Orange, CA.

Introduction: Osimertinib is a small molecule inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase approved to treat non-small cell lung cancer (NSCLC). Here, we report a case of acute kidney injury (AKI) associated with the use of osimertinib.

Case Description: A 68 year female with metastatic NSCLC presented with dyspnea, hypertension and swelling after taking osimertinib for one month. Exam was remarkable for JVD and peripheral edema. Serum creatinine (SCr) was 4.4 mg/dL from baseline 0.89mg/dL. Urine protein creatinine ratio was 3.9 g/g and albumin creatinine ratio was 1905mg/g. Urine sediment revealed many nondysmorphic RBCs but no casts. Echocardiogram showed ejection fraction of 33%. Patient was oliguric and hemodialysis was initiated. Renal biopsy was performed. Light microscopy showed severe acute tubular epithelial cell injury with tubular basement membrane rupture and secondary interstitial inflammation. Both LM and electron microscopy showed extensive glomerular and arteriolar hyalinosis and glomerular basement membrane (GBM) thickening. No endocapillary fibrin thrombi were observed. There was also mild effacement of podocyte foot processes. Given the severity of endotheliosis, the possibility of early TMA was considered. Further laboratory studies showed no thrombocytopenia or evidence of hemolysis. On hospital day 3, patient improved and osimertinib was held. Hg Scr was 2.6, imd. ant. protein and albumin 2.0mg/dL. No dye was injected, surveillance imaging demonstrated stable renal function. No evidence of tumor progression or metastatic disease was identified.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Discussion: In summary, we presented a case of new onset heart failure (HF), AKI and proteinuria in a patient with lupus nephritis. HF is a known adverse effect of omeprazole. Unlike vascular endothelial growth factor (VEGF) receptor inhibitors, EGF inhibitors were not known to be nephrotoxic. To our knowledge, this is the first report of EGF inhibitor associated AKI. Interestingly, renal biopsy not only demonstrated ATN but also features of TMA and podocyte injury. This case expands the current knowledge of the renal effects of tyrosine kinase inhibitors in the era of biologics.

TH-PO006
A Report of 3 Cases of MPGN Type III, Strife and Anders Type: A Definitive Diagnosis by EM-PAM Proposes a Negative Application to C3 Glomerulonephritis Naomi Sato, Yasuyoshi Nakamura, Takashi Takaki, Kensuke Joh, Pathology, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan; Pathology, Tohoku Medical and Pharmaceutical Univ, Sendai, Miyagi, Japan.

Introduction: C3 glomerulopathy is an umbrella term comprising of dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). C3GN is composed of primary membrane proliferative GN (MPGN) type I and type III after differentiation of DDD. Since primary MPGN type III is considered a similar entity to DDD, MPGN III S&A can be a candidate of C3GN. We experienced 3 cases of MPGN III S&A, which were definitely diagnosed by electron microscope with Periodic Acid-Methenamine-Silver stain (EM-PAM) according to the original articles of Strife and Anders. The purpose was to analyze these rare cases and to estimate whether MPGN III S&A can be categorized into C3GN.

Case Description: Patients (pts) were 57 yrs male, 23 yrs male and 20 yrs female, respectively. All pts showed no clinical symptoms of secondary GN. Only one presented C3 hypocomplementemia. Renal biopsy revealed MPGN-like lesion with double contour. Immunoglobulins (heavy and light chains) besides C3 deposition were demonstrated as glomerular peripheral pattern. In EM, all cases showed a large amount of lumpy intramembranous continuous dense deposits in the glomerular basement membrane (GBM) with mesangial interposition, whereby a continuity of lamina rara externa was well preserved. EM-PAM demonstrated a disruption of lamina densa of the GBM, which may relate to immunoglobulins deposition.

Discussion: EM-PAM proposed substantial reasons to diagnose these all cases as MPGN III S&A, which consists of first, a disruption of lamina densa, which can differentiate a diagnosis of DDD without GBM disruption and second, intact lamina rara externa, which can differentiate MPGN type III Burckholder with epimembranous deposits showing destruction of lamina rara externa. The term C3 GN is coined to describe glomerular lesions in which there is glomerular accumulation of C3 with little or no immunoglobulin. So far, all cases showed lumpy intramembranous continuous dense deposits in the glomerular basement membrane (GBM) with mesangial interposition, whereby a continuity of lamina rara externa was well preserved. EM-PAM demonstrated a disruption of lamina densa of the GBM, which may relate to immunoglobulins deposition.

TH-PO007
A Complex Case - Solitary Kidney with Crescentic IgA Nephropathy during Pregnancy Rekha Kambhampati, Daphne Harrington Knicely. Nephrology, Johns Hopkins Univ School of Medicine, Baltimore, MD.

Introduction: IgA nephropathy is the most common glomerular disorder. We present a complex case of successfully treated crescentic IgA nephropathy in a solitary kidney diagnosed in early pregnancy.

Case Description: A 28-year-old Caucasian G1P101 at 14 weeks and 5 days gestation with a past medical history of left donor nephrectomy and gestational hypertension presented with acute kidney injury. Fifteen days prior to admission, her creatinine was 0.95 and 24-hour urine protein was 4448 mg. Five days prior to admission, she developed group A streptococcal infection. On admission, her creatinine rose to 2.4 with gross hematuria. On admission, she was found to be hypertensive with a creatinine of 3.2 and 36 red blood cells per high power field on urinalysis. A renal biopsy revealed 70% crescentic and necrotizing proliferative glomerulonephritis with IgA dominant deposits. She was treated with methylprednisolone 1 gram daily for three days and then transitioned to prednisone 60 mg daily. Her creatinine improved to 1.0-1.1. Her pregnancy was complicated by variable fetal heart decelerations requiring delivery of a live infant at 28 weeks gestation. Post-partum, her prednisone was tapered at monthly intervals. Her creatinine remained stable at 1.5-1.7. Maximum 24-hour urine protein was 14.6 gm and improved to 1 gm. Post-partum, she was started on an ACE inhibitor.

Discussion: There is very little literature on treatment of crescentic necrotizing glomerulonephritis in pregnancy. Current recommendations advise for corticosteroids and cyclophosphamide as initial therapy in non-pregnant individuals. However, given its teratogenic side effects, cyclophosphamide was not a feasible option for our patient. A case report by Komatsu et al. (1994) revealed successful treatment of a patient with crescentic IgA nephropathy diagnosed at 21 weeks gestation with corticosteroids. No literature currently exists regarding treatment of crescentic IgA nephropathy in a solitary kidney during pregnancy. We were able to successfully treat our patient with pulse dose steroids followed by high dose oral steroid therapy for the duration of her pregnancy with favorable post-partum outcomes.

TH-PO008
Proliferative Glomerulonephritis with Masked Monoclonal Deposits Responsive to Myeloma Chemotherapy Anjuman A. Howlader, Amy Nicole Sussman, Erika R. Bracamonte, Samih H. Nass, Bijin Thajudeen.1 Nephrology, Banner Univ of Arizona, Tucson, AZ; 2Pathology, Banner Univ of Arizona Medical Center, Tucson, AZ; 3Pathology, Mayo Clinic, Rochester, MN.

Introduction: MPGN with masked monotypic immunoglobulin(Ig) deposits is a recently described entity. In the absence of an electron microscopy(EM), some of these patients can be misdiagnosed as having post-infectious glomerulonephritis(PIGN).

Case Description: A 48-year-old Hispanic male transferred to our institution with a diagnosis of biopsy-proven PIGN. His lab evaluation: urine 82 RBC/Hpf, urine pro cr 6100 mg/gm, alb cr 5403 mg/gm, BUN 208 mg/dl, serum Cr 4.6 mg/dl. Serum electrolythesis: monoclonal gammopathy(MG) with predominant IgG kappa on immunofixation. Serum free kappa elevated(1246 mg/l) and lambda fraction normal. A repeat kidney biopsy was performed. LM demonstrated diffuse endocapillary proliferative GN. IF was negative except for trace granular staining for C3. EM showed large non-organized intraluminal electron dense deposits. In view of histopathology and MG, IF study on paraffin-digested, paraffin embedded tissue was performed which showed bright (2-3+) staining for IgG kappa.

The findings were consistent with diffuse endocapillary proliferative GN with masked monoclonal IgG kappa deposits. Bone marrow aspiration showed myeloma, treated with revlimid-velcade-dexamethasone. He also received HD support for 3 weeks with subsequent improvement in renal function. The most recent serum Cr and urine pro/cre ratio were 0.8 mg/dl and 300 mg/gm respectively.

Discussion: This case highlights the importance of performing paraffin IF for GN associated with C3 deposits in adults, especially in the presence of MG regardless of the ultrastuctural appearance and location of deposits. It is also recommended when the findings by routine IF do not match either the clinical scenario or EM findings.

TH-PO009
Concomitant Heparin Induced Thrombocytopenia and Hemolytic Uremic Syndrome Sarthak Virmani, Ari B. Gellett.1 Internal Medicine, Univ of Connecticut School of Medicine, Farmington, CT; 2Div of Nephrology, St. Francis Hospital, Hartford, CT.

Introduction: Thrombotic microangiopathy (TMA) with renal failure has a broad differential including TTP, HUS, DIC, APLS and renal sclerodema crisis.

Case Description: A 54 year old female presented with bilateral blurry vision, unilateral leg weakness and altered mental status 11 days after a bio-prosthetic valve repair for critical aortic stenosis. Initial blood work showed hemolytic anemia (Hb 10.7 g/dl, haptoglobin < 6 mg/dl), AKI (Cr 2.4 mg/dl, baseline 0.9 mg/dl) and thrombocytopenia (60,000/mm³). MRI of the brain showed multifocal acute infaracts of the anterior and posterior circulation. ANA titers were found to be 1:160. Plasma exchange (PLEX) therapy was initiated for a clinical diagnosis of TTP while awaiting ADAMTS13 levels. After 5 days of therapy, her initial ADAMTS13 measured 50% activity and her heparin PF4 antibody screen was positive. This effectively ruled out TTP and established a diagnosis of Heparin Induced Thrombocytopenia (HIT). PLEX therapy was then stopped and Argatroban was initiated. Soon after this intervention, her platelet counts, LDH and other hemolysis markers improved. However, progressive renal failure (Cr 5.0 mg/dl) prompted a biopsy which demonstrated thrombotic microangiopathy. This raised a concern for concomitant atypical HUS.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
She received a total of 4 weekly doses of Eculizumab for presumptive diagnosis of atypical HUS. She had significant improvement of her renal function (Cr 1.9 mg/dL). She was continued on anticoagulation. On follow-up, she reports improvement of all her symptoms with improving hemolysis parameters. She will be continued on Eculizumab for 6 months.

**Discussion:** This case not only highlights the need to have a broad differential diagnosis for TMAs and renal failure, but also the complex management of a patient with overlapping syndromes of HIT and HUS.

**TH-PO010**

**Association of Atypical ANCA with Glomerular Disease**


**Div of Nephrology, Univ of Wisconsin SMPH, Madison, WI.**

**Introduction:** Anti neutrophilic cytoplasmic antibodies (ANCA) include a wide range of antibodies directed against cytoplasmic antigens of neutrophils. Indirect Immunofluorescence (IF) is commonly used to identify ANCA with different patterns. Cytoplasmic pattern (cANCA) is mostly caused by proteinase-3 (PR3) whereas perinuclear pattern (pANCA) is mostly caused by Myeloperoxidase (MPO) antibodies. Any pattern other than these two is labeled atypical ANCA (aANCA). Whereas cANCA & pANCA have been associated with small vessel vasculitis in the kidneys, aANCA has not been previously associated with any glomerular pathology.

**Case Description:** We reviewed cases of 7 patients who had aANCA positive on serological testing with negative MPO and PR3 antibodies on ELISA. The details of clinical course and biopsy findings are mentioned in the table included.

**Table:**

<table>
<thead>
<tr>
<th>No.</th>
<th>Global presentation</th>
<th>Initial treatment</th>
<th>Remission</th>
<th>aANCAYellburg</th>
<th>Treatment and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29 year male, SE with flares, eosinuria, crithidia</td>
<td>0.5</td>
<td>0.5</td>
<td>Present</td>
<td>L640</td>
</tr>
<tr>
<td>2</td>
<td>40 year male, hypertension, CEG, hematuria &amp; family history of aortic aneurysm</td>
<td>1.26</td>
<td>0.5</td>
<td>Absent</td>
<td>L130</td>
</tr>
<tr>
<td>3</td>
<td>38 year male, long term smoker, CIE, New onset nephrotic range proteinuria</td>
<td>2.26</td>
<td>0.1</td>
<td>Absent</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>64 year male, All SE-ESS</td>
<td>1.56</td>
<td>0.6</td>
<td>Present</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>70 year male, All SE</td>
<td>2.79</td>
<td>2.35</td>
<td>Present</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>57 year female, Neuromyotonic range proteinuria, deafness</td>
<td>0.6</td>
<td>0.65</td>
<td>Present</td>
<td>L640</td>
</tr>
<tr>
<td>7</td>
<td>48 year male, All SE-ESS</td>
<td>4.58</td>
<td>0.67</td>
<td>Present</td>
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</tbody>
</table>

**Discussion:** As opposed to cANCA and pANCA, target antigens for aANCA have not been identified but have been associated with inflammatory bowel disease, autoimmune hepatitis, primary sclerosing cholangitis, rheumatoid arthritis and certain chronic infections. All seven patients with aANCA showed glomerular damage but no common pattern was identified. A strongly positive antineutrophil (ANA) can lead to cross-reactivity with ANCA and three of our patients had concurrent ANA positivity. Interestingly, three patients were diagnosed with pauci-immune glomerulonephritis despite having a negative MPO and PR3 antibodies. The presence of aANCA in our patients could be due to other antibodies implicated in ANCA negative vasculitis like leukocyte associated membrane protein 2 (LAMP-2) or anti-pantrexin 3 antibodies and might have been the direct pathogenic cause implicated in ANCA negative vasculitis. The presence of aANCA in our patients could be due to other antibodies implicated in ANCA negative vasculitis like leukocyte associated membrane protein 2 (LAMP-2) or anti-pantrexin 3 antibodies and might have been the direct pathogenic cause implicated in ANCA negative vasculitis.

**Conclusion:** All seven patients with aANCA showed glomerular damage but no common pattern was identified. The best of our knowledge, this is the first case describing FSGS-associated MD caused by a m.5538 G>A mutation. The presence of aANCA in our patients could be due to other antibodies implicated in ANCA negative vasculitis like leukocyte associated membrane protein 2 (LAMP-2) or anti-pantrexin 3 antibodies and might have been the direct pathogenic cause implicated in ANCA negative vasculitis.
His CG test was positive for type 1 CG (monoclonal IgM HC). His serum immunofixation (HPA 80, Immunotech Labs, Marseille, France) showed a band at γ and κ, which was supported by Bone marrow biopsy and CT scan of the abdomen, and pellets were negative for malignancy. Renal biopsy showed MGP pattern of glomerular injury with a full-house immunofluorescence pattern and subendothelial deposits with electro-lucent areas inside and subendothelial podocyte foot process effacement. He was treated with pulse dose steroid followed by 4 weekly doses of rituximab 375 mg/m². His renal function improved to a Cr of 1.97 mg/dl and UPCR 0.43/g.

Most cases of CG associated GN are seen in the setting of mixed CG. Type 1 CG is associated with underlying hematologic malignancy is rare. Interestingly our patient had multiple oligoclonal bands of IgG on regular IF but his renal disease was likely caused by IgM HC. This monoclonal IgM HC was detectable only on IF done on serum for testing of CG due to its precipitation at a lower temperature. Data regarding optimal therapy for such a presentation is scarce. A study of 23 patients with type 1 CG treated with rituximab had shown a response rate of 80%, however, one-third had relapse by 12 months. Another case series of 2 patients with type 1 CG, rituximab was associated with treatment failure.

Discussion: Further data is needed to evaluate the efficacy of rituximab monotherapy for type 1 CG associated GN, which was successful in our patient.

TH-PO014

The Importance of Renal Biopsy in the Diagnosis of Fabry Nephropathy Eduardo Tenorio Leite, ¹ Luiz Antonio Magnata Da Fonte Filho, ¹ Jose Edevanilson Gueris, ¹ Ana Paula Gueris, ¹ Luiz A. Mora. ¹ "Nephrology, IMPF, Recife, Brazil; ²Pathology, UNIFESP, Sao Paulo, Brazil.

Introduction: Fabry disease (FD) is caused by mutations in the α-galactosidase A gene (GLA) leading to the progressive accumulation of globotriaosylceramide (GL-3) in various tissues including the kidney, brain and heart. The current challenge is the search for biomarkers that allow early identification of patients with progressive disease, mainly in asymptomatic young people. In this context, the renal biopsy (RB) is gaining importance in the diagnosis of Fabry nephropathy, in the indication and evaluation of the response of enzyme replacement therapy (ERT).

Case Description: A female patient was diagnosed as a carrier of the p.R356W mutation at 14 years old through family screening after her father, (already on hemodialysis) had been diagnosed with FD. At first, the asymptomatic patient rejected the diagnosis and on follow-up at 17 years old, sought medical help. She remained asymptomatic, denied having neuropathic pain, hypohidrosis or anhidrosis or gastrointestinal symptoms. She did not have angiokeratoma. Laboratory tests showed serum creatinine 0.64mg/mL, urinary albumin-creatinine ratio 29 mg/g and normal urinalysis. Normal echocardiography. With the nephropathic history she was coupled with the fact that a cousin had a kidney transplant at age 32 (daughter of a deceased uncle), we opted to do a RB. Light microscopy revealed vacuolization of podocytes, tubules with small and sparse atrophy foci and discreet interstitial fibrosis. Small-size arteries showed discrete fibrous intimal hyperplasia. In electron microscopy, podocytes were observed with large cytoplasm containing inclusions in concentric lamellar (myelin figures) and periodic band (zebra bodies) configuration. In these, there is effacement of foot processes. When evaluated by the renal scoring system for type 1 CG associated GN, which was successful in our patient.

Discussion: RB is of fundamental importance for early therapeutic intervention in FD in order to mitigate or prevent progressive nephropathy and other life threatening complications.

TH-PO015

Novel Treatment of HCV Induced Cryoglobulinemia Glomerulonephritis Saeed Shawk, Sandhya S. Thomas. Nephrology Dept, Baylor College of Medicine, Houston, TX.

Introduction: Current standard treatment of HCV-induced cryoglobulinemia GN (Cryo GN) in severe cases involve plasmapheresis plus steroids with induction immunosuppressive (IS) (ie: cytotoxan), but in era of the antiviral therapy with 90-100% Sustained virologic response, it is unclear if standard therapy remains the best option.

Case Description: 66 year old white man with history of HTN, HLD, history of bladder cancer s/p resection, presented to renal clinic for evaluation of elevated creatinine (Cr) 6.3 mg/dl from his baseline 1mg/dl (4month ago), he was complaining from generalized fatigue, joint pain, no joint swelling, redness, mouth ulceration, skin rash, no fever, no history of NSAID or herbal medication. His physical examination was unremarkable. His medical history of the father, coupled with the fact that a cousin had a kidney transplant, and severe podocyte foot process effacement. He was treated with pulse dose steroid followed by 4 weekly doses of rituximab 375 mg/m². His renal function improved to a Cr of 1.97 mg/dl and UPCR 0.43/g.

Most cases of CG associated GN are seen in the setting of mixed CG. Type 1 CG is associated with underlying hematologic malignancy is rare. Interestingly our patient had multiple oligoclonal bands of IgG on regular IF but his renal disease was likely caused by IgM HC. This monoclonal IgM HC was detectable only on IF done on serum for testing of CG due to its precipitation at a lower temperature. Data regarding optimal therapy for such a presentation is scarce. A study of 23 patients with type 1 CG treated with rituximab had shown a response rate of 80%, however, one-third had relapse by 12 months. Another case series of 2 patients with type 1 CG, rituximab was associated with treatment failure.

Discussion: Further data is needed to evaluate the efficacy of rituximab monotherapy for type 1 CG associated GN, which was successful in our patient.
TH-PO018

Corticotropin Injections (Acthar®) Treatment of Fibrillary Glomerulonephritis with Use of Repository TH-PO018


Mitochondrial Deficiency Nephrotic Syndrome in a Patient with Mitochondrial Trifunctional Protein

We present a case of partial remission in FG with complete resolution of nephrotic syndrome and stabilization of renal function over 26 months of therapy.

Deficiency Nephrotic Syndrome in a Patient with Mitochondrial Trifunctional Protein

We present a patient found to have de novo lambda light chain nephropathy from MM 33 years after his renal transplant. This case highlights the importance of considering de novo pathology in transplant patients presenting with proteinuria.

Case Description: A 66 year-old African American male with a history of hypertension and hypothyroidism was referred to outpatient nephrology consultation in 10/2013 for worsening renal insufficiency over the prior of 2 years. Physical exam was notable for uncontrolled HTN, obesity, and 2+ pitting edema of lower extremities. Elevated creatinine of 2.7mg/dl and nephrotic range proteinuria 5.9g/dm day prompted renal biopsy in 12/2013, which showed advanced fibrillary glomerulonephritis with proliferative features, extensive interstitial scarring, and tubular atrophy. Serological work up was negative for autoimmune disorders, hepatitis C or monoclonal gammopathy. No malignancy was identified. Initially, treatment was deferred due to patient preference, advanced disease, and consideration of adverse effects of IA. Four months later, he was started on Acthar®/ACTH three times weekly in hopes to slow progression to ESRD while avoiding the potentially more severe systemic immunosuppressive effects of alternative cytotoxic agents. Within 8 months he had resolution of nephrotic range proteinuria (from a peak of 8.1g/m/d to 600mg/day). Acthar® was further tapered to 40 units twice weekly and eventually 20 units twice weekly. Creatinine peaked at 3.8mg/dl on 09/2015 but improved to 2.8mg/dl within 8 months and remained stable over subsequent 18 months.

Discussion: FG has no standardised treatment regimen owing to the lack of clinical trials. The use of corticosteroid injections have been seen to mitigate nephritogenic injury in variety of glomeruloneuris. We report a case of partial remission in FG with complete resolution of nephrotic syndrome and stabilization of renal function over 26 months of therapy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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99A
Crescentic Glomerulonephritis Associated with Acquired Angioedema

TH-PO023

allowing restoration of glomerular maintenance.

or KDR, or another anti-endothelial vascular protein that is removed with plasmapheresis

excellent sustained response with resolution of AKI and edema following plasmapheresis.

On EM, the capillary lumen was occluded by endothelial swelling, electron-lucent widening


mechanism of recurrent angioedema in this case remains unclear. We would like to add

made pauci-Immune crescentic glomerulonephritis likely the cause of AA. The exact

compatible chronology, complement level and lack of other possible causes of angioedema

lymphoma, monoclonal gammopathy. Other nonhematologic malignancy, infections, and

swelling. He had similar symptoms in the past over past 2 years which required multiple

methylprednisolone and cyclophosphamide. At 1-month follow up and 6-month follow

necrotizing and crescentic glomerulonephritis, pauci-immune type. Patient was started on

were compatible with diagnosis of acquired angioedema (AA). According to rapid decline

for anti-Glomerular basement membrane (GBM) and proteinase 3 (PR3) ANCA. Serum C3

admission. Vasculitis workup was positive for Myeloperoxidase (MPO) ANCA, negative

of 3.8 mg/dL. Urine analysis was significant for hematuria and proteinuria without casts

Comprehensive metabolic panel revealed Blood urea nitrogen of 49 mg/dL, creatinine

of dominant renal amyloidosis. Patients invariably present

1993—is a form of autosomal dominant renal amyloidosis. Patients invariably present

and uncle’s son) had previously developed ESRD and are deceased. Her father had a

developed proteinuria. Four other members of their family (father, older brother, uncle,

Our asymptomatic patient first

dysregulated alternate complement pathway. Histologically it is rare to have crescents on

Counseling Challenges

for pre-emptive liver transplantation for our patient and her children (while their livers

can be used for domino transplants), or have them wait for a liver-kidney transplant when

which she does not have.

liver transplant now, before she gets sick. Yet, a liver transplant is based on a MELD score,

transplant fail within a few years” and instead advocated that she should pursue a curative

enlarged glomeruli stuffed with amyloid. No extraglomerular amyloid was apparent.

would “develop ESRD and die of amyloidosis” and was terrified that one or both of her

transplants over the next 6 years.

1971 (age 51) that showed “amyloidosis,” which recurred in 2 kidney

and uncle’s son) had previously developed ESRD and are deceased. Her father had a

100A

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TH-PO026

IgA-Dominant Acute Post-Infectious Glomerulonephritis in a Kidney Transplant Recipient

Hassan Alhalabi, Manish Anand, Juan Pablo Arroyo, Timothy E. Thayer, Mark Lusco, Anthony J. Langone, Beatrice P. Concepcion. Vanderbilt Univ Medical Center.

Introduction: IgA-dominant acute post-infectious glomerulonephritis (IgA-APIGN), a morphologic variant of APGN, is a rare disease in which IgA is the dominant immunoglobulin found in glomerular immune deposits. All prior reported cases have been in native kidneys. Here we present the first reported case of IgA-APIGN in a kidney transplant recipient, successfully treated with steroids.

Case Description: A 62/M with ESRD secondary to DM underwent kidney transplantation in 2012 and was maintained on tacrolimus and MMF. He was admitted in 2015 with right foot osteomyelitis and MSSA bacteremia and was treated with antibiotics and BKA. Twelve days after initial presentation, he was readmitted with oligoanuric AKI with a Cr of 8.2 mg/dL (baseline 1.4 mg/dL), low C3 and normal C4, UA 2+ protein, 122 WBCs, 133 RBCs, and urine PCR of 1. Biopsy was performed and LM revealed diffuse global endocapillary hypercellularity with frequent neutrophils and 2/10 glomeruli with fibrinoid necrosis. By IF, IgA was the dominant Ig with stronger C3 staining in a diffuse global granular mesangial and irregular chunky capillary loop pattern. By EM, there were frequent mesangial, scattered subendothelial and rare subepithelial deposits. He was given pulses of methylprednisolone (1.5 g) then prednisone 40 mg daily. Renal function improved rapidly with a discharge Cr of 2.1 mg/dL. Steroids were tapered over 3 months and on last follow-up 5 months after presentation Cr was 1.7 mg/dL, UA 1+ protein, 1 RBC, 18 WBCs, urine PCR 0.3.

Discussion: IgA-APIGN is often associated with a staphylococcal infection and usually presents with AKI, hematuria and proteinuria. Antibiotics are the mainstay of therapy alone. This case suggests a possible causal relationship between SS infection and this disease. Considering steroid dependence with chronic respiratory infections, tend to trigger relapses. She has experienced significant toxicity from her chronic immunosuppression. Considering steroid dependence with chronic glucocorticoid toxicity, and lack of remission with tacrolimus and mycophenolate mofetil, we decided to initiate rituximab treatment. The patient underwent induction with 2 doses of rituximab 375 mg/m², with mycophenolate mofetil as maintenance. The patient has been in remission on less than 20 mg of steroids in the last 6 months and completely off of steroids in the last 6 weeks with no evidence of relapse.

Discussion: We describe a case demonstrating achievement of steroid-free remission using rituximab in a patient with longstanding IgM Nephropathy.

TH-PO027

Tip Variant Focal Segmental Glomerulosclerosis Associated with Strongyloides Stercolaris

Massini Merzkan,1,2 Vivette D. D’Agati,2, Pranisha Gautam-Goyal,2 Kenar D. Jhaveri. 1Nephrology, Hofstra Medical School; 2Pathology, Columbia Univ Medical Center; 3ID, Hofstra Medical School.

Introduction: Although parasitic infections are known to be associated with glomerular lesions, strongyloidiasis-associated glomerulopathy has not been well documented. We report a case of tip variant focal segmental glomerulosclerosis(FSGS) associated with strongyloides stercoralis (SS).

Case Description: A 36 year-old male from Guatemala presented with sudden onset of lower extremity and facial edema. Lab data revealed urinary protein/creatinine ratio of 10.6 g with serum albumin(Ab) 0.4 g/dl and serum creatinine 0.5mg/dl. Past medical history included tip variant FSGS in childhood that had responded to steroids. A repeat kidney biopsy showed tip variant FSGS with marked podocyte effacement. A detailed history revealed that the patient had recently traveled and had suffered episodic abdominal pain and diarrhea with peripheral eosinophilia of 41 % (2.7 kiu). His stools confirmed SS. Conservative management with lisonipril, atorvastatin and diuretics was initiated with no improvement in edema. He was not given steroids. Ivermectin was initiated to treat the parasitic infection. His edema improved one month after ivermectin treatment, and his nephrotic syndrome resolved in 2 months. Changes in proteinuria, Ab and creatinine over time are graphed below.

Discussion: This is the first case report of tip variant FSGS secondary to SS. Given his predilection for podocytopathy, the parasitic infection was likely the precipitating immune stimulus as “second hit”. Surprisingly, the nephrotic syndrome resolved with antihelminthic therapy alone. This case suggests a possible causal relationship between SS infection and FSGS. Even in primary podocytopathies, it is important to consider precipitating infectious triggers that can be specifically treated without resorting to steroid therapy.

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

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TH-PO028

IgM Nephropathy: Achievement of Steroid Free Remission with Rituximab

Fatima Khalid,1 Catherine A. Moore.1 1Nephrology, Univ of Rochester; 2Nephrology, Univ of Rochester.

Introduction: Immunglobulin M (IgM) nephropathy often presents as nephrotic syndrome in childhood which is poorly responsive to steroids. Likelihood of steroid free remission is very low in the long term, and this exposes individuals to long term complications of steroid therapy. Rituximab has been successfully used in cases of steroid resistant/refractory nephrotic syndrome. However, there are only a few case reports of use in IgM nephropathy, all early in the course of disease.

Case Description: We present a case of a 22 year old female with history of nephrotic syndrome, initially diagnosed at age 20 months. Her first biopsy was at age 6 year old, revealed minimal change disease and possible early cyclosporine nephrotoxicity. Immunofluorescence was not performed on this specimen. Subsequent biopsies have revealed mesangial hyper-cellularity with mesangial IgM consistent with IgM nephropathy. Her second biopsy, performed at age 17, revealed 40% global glomerulosclerosis and mild interstitial fibrosis with tubular atrophy. She was steroid-resistant until age 8, and subsequently was steroid dependent. Cyclophosphamide and cyclosporine therapy were used without clear response. This was followed by a trial of tacrolimus and mycophenolate mofetil. She was in complete remission with the above regimen and steroid free for two years. She then relapsed and was steroid dependent again. Infections, particularly upper respiratory infections, tend to trigger relapses. She has experienced significant toxicity from her chronic immunosuppression. Considering steroid dependence with chronic glucocorticoid toxicity, and lack of remission with tacrolimus and mycophenolate mofetil, we decided to initiate rituximab treatment. The patient underwent induction with 2 doses of rituximab 375 mg/m², with mycophenolate mofetil as maintenance. The patient has been in remission on less than 20 mg of steroids in the last 6 months and completely off of steroids in the last 6 weeks with no evidence of relapse.

Discussion: We describe a case demonstrating achievement of steroid-free remission using rituximab in a patient with longstanding IgM Nephropathy.

TH-PO029

Intravenous Heroin Use Associated with AA Amyloidosis

Ariun V. Sharma, Priyanka Govindan, Bryan R. Kestenbaum. Dept of Nephrology, Univ of Washington, Seattle, WA.

Introduction: Secondary (AA) renal amyloidosis is characterized by the deposition of serum amyloid A within the glomerular basement membrane, mesangium, tubules, and blood vessels. Affected patients typically present with nephrotic range proteinuria and rapid loss of kidney function. We and others have observed renal AA amyloidosis among patients who use intravenous (IV) heroin; however, the association of IV drug use and renal AA amyloidosis is incompletely described.

Case Description: We evaluated all biopsy proven cases of renal AA amyloidosis within native kidneys at the University of Washington Medical Center and Harborview Medical Center, in Seattle Washington, from 2005-2015. We extracted medical data via chart review. We used Kaplan-Meier estimation to describe renal and overall survival of affected patients. We identified 43 patients who had biopsy proven renal AA amyloidosis from 2005-2015. Among this group, 42 patients (97%) had chart documentation of IV heroin use with 29 (67%) in use within 6 months prior to biopsy. In addition to IV heroin use, “muscling” and “skin-popping” were also common (83% and 70%, respectfully). Cocaine (72%) use was frequent. Renal co-morbidities included hepatitis C (81%), HIV (9%), and rheumatic disease (5%). At time of biopsy, the mean protein to creatinine ratio was 13.3±8.1 g/g and the mean serum creatinine concentration was 4.0±2.6 mg/dL. Among 39 of the 43 patients who were not receiving dialysis at the time of biopsy, 25 initiated dialysis over a maximum of 6.9 years of follow-up. Overall patient survival at 5 years was 47%.

Discussion: Nearly all patients who have renal AA amyloidosis in Seattle, WA use IV heroin. The marked geographical variation in the association of IV heroin use with AA amyloidosis strongly suggests that specific components of street heroin and/or local patterns of use are a cause of this disease.

Figure. Time to dialysis initiation among 39 patients with AA amyloidosis.
Membranous Nephropathy Related to the Checkpoint Inhibitor Nivolumab

Jonathan T. Lin,1 Morgan A. Schiff,2 Steven Salvator,2 Alexander N. Shoushtari,4 Ilya Glezerman,5 1Div of Nephrology, New York Presbyterian / Weill Cornell, New York, NY; 2Critical Care Service, Memorial Sloan Kettering, New York, NY; 3Pathology and Laboratory Medicine, New York Presbyterian / Weill Cornell, New York, NY; 4Memorial Sloan Kettering, New York, NY; 5Renal Service, Memorial Sloan Kettering, New York, NY.

Introduction: Programmed cell death (PD) inhibitors are novel anti-cancer immunotherapy, and cases of autoimmune nephritis have been described. We report the first case of nephrotic syndrome with membranous nephropathy associated with the IgG4 PD-1 inhibitor nivolumab.

Case Description: A 75-year-old male with metastatic melanoma of unknown primary treated with nivolumab and tolerated weekly infusions with few adverse effects, including mild pruritis and colitis. After his fifth treatment, he noted scrotal and lower extremity edema. Subsequent labs revealed hypoalbuminemia to 1.4 (4.5-2.0) mg/dL with stable creatinine at 1.2 (0.6-1.3) mg/dL. Urine studies were notable for 12 g proteinuria/24 hours, without RBCs, WBCs, or casts on urine microscopy. Serological workup including Anti-Phospholipase-A2-Receptor (PLA2R) antibody testing was negative. Nivolumab infusions were held, and the patient was started empirically on steroids with prednisone 0.5 mg/kg for presumed autoimmune nephritis. A renal biopsy was performed, with electron microscopy revealing scattered subepithelial electron dense deposits with nearly complete podocyte effacement and immunofluorescence revealing predominantly granular IgG capillary wall staining, consistent with membranous nephropathy. PLA2R staining was negative. Imaging one month later showed interval decrease in size of both masses. Repeat spot urine protein-to-creatinine was 4.0, plasma albumin was 1.2 g/dL, and his edema resolved.

Discussion: Membranous nephropathy has been linked to solid malignancies including melanoma, but the timing of nephrotic syndrome in this patient coincided with treatment with PD-1 inhibitor. With awareness of this risk, and additional workup, we hope to elucidate alterations in the immune response and mechanisms of renal injury by therapy with PD-1 inhibitors.

TH-PO030

Spontaneous Clinical Resolution in Dense Deposit Disease

Anna Lane Baldwin, Katherine D. Westreich, Akhil Hegde, Volker Nickeleit, Harsharan Kaur Singh, Gerald A. Hladik. UNC Kidney Center, UNC Hospitals, Chapel Hill, NC.

Introduction: Dense deposit disease (DDD) is often progressive and incurable morbidity. We present two atypical cases of DDD that are somewhat atypical with spontaneous remission of proteinuria and renal dysfunction.

Case Description: Case 1: 24-year-old white woman with acute kidney injury (AKI) and nephrotic syndrome. She had a remote skin infection in the band that resolved. C3 <40 mg/dl and anti-DNAse B titer was elevated at 862 U/mL. Biopsy: DDD, with proliferative GN, C3 deposits, and electron dense deposits (EDD) within the glomerular basement membrane (GBM). C3 nephritic factor (C3NeF) was detected; extensive testing of the complement system, including sequencing of 6 genes with known mutations causing CSGN/ DDD, was normal. Serum creatinine (Scr), C3, and urine protein normalized in 1 month without treatment; microscopic hematuria persists. Case 2: 8-year-old white girl with AKI and nephritis during an upper respiratory infection; anti-streptococcal antibodies were 1+.

Discussion: The two patients under discussion had DDD with self-limited clinical findings. Both had increased C3NeF with relatively limited intramembrane deposits. In Case 2, a second biopsy showed no evidence of chronic kidney injury. The underlying etiology remains undetermined. We speculate that infection, autoimmune, or inflammation-related complement activation may cause transient and rudimentary forms of DDD in patients with elevated C3NeF. Alternatively, these might reflect early clinical expression of DDD. Overall, these cases illustrate that the clinical manifestations may largely resolve with a short course of steroids.

TH-PO032

Membranous Nephropathy in a Patient with Common Variable Immune Deficiency


Introduction: Secondary membranous glomerulonephritis occurs in patients with systemic lupus erythematosus, infections such as hepatitis B and C, and solid tumors. There have been no prior case reports of membranous nephropathy in adult patients with common variable immune deficiency (CVID).

Case Description: A 36-year-old Caucasian woman with CVID on weekly subcutaneous immunoglobulin (IgG) therapy presented with fluid overload. Labs were notable for 8 g/dL proteinuria, albumin 2.0 g/dL, and creatinine of 0.6 mg/dL. She underwent renal biopsy revealing membranous nephropathy (MN) with negative staining for-PLA2R on immunofluorescence. She had initially treated conservatively; within two weeks, she was admitted for worsening lower extremity edema, abdominal pain, and nausea. Her creatinine had risen to 2.0 mg/dL with albumin 1.5 g/dL and urine protein of 6 g/day. Urine protein was 8 g/day, and her albumin was 3.0 g/dL. She subsequently elevated levels of C3NeF with a peak creatinine of 5.8 mg/dL. Serologic test for PLAR antibody was negative. A repeat renal biopsy revealed acute tubular injury in addition to prior findings of PLAR negative membranous nephropathy. She was treated with 6 sessions of hemodialysis, two doses of recombinant tissue plasminogen activator, and a ten day taper. At 2 months after starting treatment, her creatinine had returned to 0.6 mg/dL, urine microalbuminuria and creatinine ratio was 345 mcg/mL and albumin was 3.4 g/dL.

Discussion: The treatment of membranous glomerulonephritis in an immunocompromised patient can be challenging. A previous case report of MN in a child with CVID reported remission of proteinuria with cyclosporine, and here we report successful response to rituximab-based therapy. CVID, a rare disease, may be an even rarer etiology of secondary membranous nephropathy that, nonetheless, appears to respond to immunosuppressive therapy.

TH-PO033

Kidney Disease and Neurologic Deficits from a Rare Collagen Type 4 Mutation

Dominique Dorsamyl, Jeffrey M. Turner. Nephrology, Yale School of Medicine, New Haven, CT.

Introduction: Type 4 collagen is the main component of the basement membrane in the filtration barrier of the glomerulus. Mutations in the genes coding for the six alpha chains lead to various disorders with renal and non-renal manifestations. Mutations in COL4A5 cause Alport syndrome, the most common inherited type 4 collagen disorder. Recently an autosomal dominant disorder termed hereditary angioedema with nephropathy, aneurysms and muscle cramps (HANAC) has been described due to mutations in the COL4A1 gene.

Case Description: Case 1: A 24-year-old African American man with a past medical history of Klinefelter Syndrome and hypertension was transferred from an outside facility with a peak creatinine of 5.8 mg/dL. Serologic test for PLAR antibody was negative. He was discharged home on immunosuppressive therapy. Case 2: A 24-year-old African American man with a past medical history of Klinefelter Syndrome and hypertension was transferred from an outside facility with a peak creatinine of 5.8 mg/dL. Serologic test for PLAR antibody was negative. He was discharged home on immunosuppressive therapy.

Discussion: The treatment of membranous glomerulonephritis in an immunocompromised patient can be challenging. A previous case report of MN in a child with CVID reported remission of proteinuria with cyclosporine, and here we report successful response to rituximab-based therapy. CVID, a rare disease, may be an even rarer etiology of secondary membranous nephropathy that, nonetheless, appears to respond to immunosuppressive therapy.

TH-PO034

Patient with Thrombotic Microangiopathy: Thrombotic Thrombocytopenic Purpura and Atypical Hemolytic Uremic Syndrome at the Same Time

Ahmad Daud, Lauren L. Pacheco, Umbar Ghaffar. Nephrology, UAMS, Little Rock, AR.

Introduction: Thrombotic microangiopathy (TMA) is a pathological process characterized by microangiopathic hemolytic anemia, thrombocytopenia and microvascular occlusion. TMA are classified into 4 major syndromes: Hemolytic uremic syndrome (HUS), Atypical HUS (aHUS), Thrombotic thrombocytopenic purpura (TTP) and other disorders including malignant hypertension. We are reporting a case of a patient presenting with clinical features of a TMA who was diagnosed with both allUS & TTP at the same time.

Case Description: A 24-year-old African American man with a past medical history of Klinefelter Syndrome and hypertension was transferred from an outside facility with the chief complaint of generalized fatigue. Labs showed renal failure, thrombocytopenia, and hemolytic anemia. He underwent workup for TMA which revealed low ADAMTS13 level of 15% with a positive ADAMTS13 inhibitor screen. The ADAMTS13 inhibitor Binding ELISA test was elevated at all low molecular weight (LMW) assays, and a low ADAMTS13 genetic test revealed C679T to be the cause of the ADAMTS13 deficiency, which is strongly associated with the presence of Factor H auto-antibodies and a heterozygous, missense variant in exon 20 of CFH which was recently cited as a mutation associated with aHUS. Patient was started with plasmapheresis and eculizumab, vincristine, cyclophosphamide, and prednisone with resolution of thrombocytopenia and anemia. However, he remained dialysis dependent for his renal failure. Near discharge, his ADAMTS13 level was 31% with a negative inhibitor. He was discharged home on infusions of cyclophosphamide and prednisone and with follow-up appointments for labs and weekly eculizumab.

Discussion: TTP is an uncommon TMA-related disorder that occurs mainly in adults, and is associated with acquired (or rarely genetic) severe deficiency of the cleaving protease for Von Willebrand Factor (vWF), ADAMTS13. aHUS is a rare disease associated with genetic (or acquired) defects of the alternative complement pathway. This patient had low ADAMTS13 levels indicating TTP & complement gene mutations indicating aHUS. The occurrence of both these conditions together is extremely rare, and has not been reported before.
A Case of Glomerular Capillary Endotheliosis due to Multicentric Castleman’s Disease

TH-PO035

Introduction: Glomerular capillary endotheliosis (GE) is the result of severe endothelial cell injury and manifests histologically with endothelial swelling, glomerular hypertrophy, and capillary lumen narrowing. GE has been previously associated with thrombotic microangiopathy and pre-eclampsia. We report a case of severe GE causing acute renal failure in a patient with Multicentric Castleman’s Disease (MCCD).

Case Description: A 59-year-old male presented with anasarca, hypoalbuminemia, and orthostatic hypotension consistent with systemic capillary leak syndrome (SCLS). He developed acute renal failure requiring hemodialysis. Workup was negative for autoimmune disease, infection, or malignancy. A kidney biopsy showed severe glomerular capillary endothelial swelling with acellular closure of capillary loops consistent with GE. Empiric treatment with high dose prednisone led to remission but disease relapsed after steroid withdrawal. He had nephritic urine sediment and 750mg/d proteinuria. A second renal biopsy showed severe GE. Remission was again achieved after 6 months of oral cyclophosphamide and prednisone taper. Maintenance mycophenolate mofetil was given for 3 years without relapse. Therapy was stopped but this time with diffuse lymphopenopathy and a circulating mononuclear IgG-kappa light chain in addition to SCLS and nephritis. A lymph node biopsy was consistent with MCCD. IL-6, CRP, and VEGF levels were markedly elevated. Anti-IL-6 antibody therapy was started and a complete remission was achieved after 2 months of treatment.

Discussion: This is the first report of GE as a manifestation of MCCD. MCCD is a rare, life-threatening lymphoproliferative disease associated with hyperactivation of the immune system causing excessive release of IL-6 and similar cytokines. The hypercytokinemia seen in MCCD is likely responsible for the increased vascular permeability and GE seen in this case. The MCCD should be considered in patients with acute kidney failure or proteinuria. The pathogenesis of severe GE remains unclear. Therapy, with immunosuppression is effective and may prevent life-threatening complications.

Using Steroids for Nephrotic Syndrome in Proliferative Glomerulonephritis with Monoclonal IgG Deposits

TH-PO036

Introduction: Proliferative Glomerulonephritis with Monoclonal IgG Deposits (PGNMID) is a rare disorder associated with monoclonal gamopathy of renal significance (MGRS) that has unique pathological and glomerular histological features from other MGRS disorders. The prognosis and best treatment options remain unknown.

Case Description: A 57-year-old man was found to have nephrotic range proteinuria of 8 grams/24 hours. On exam he had 2+ pitting edema to the knees. Labs showed hemoglobin 12.2 mg/dl, creatinine 1.3 mg/dl, calcium 8.6 mg/dl, and albumin 2.7 mg/dl. Renal biopsy revealed glomerular basement membranes (GBM) with irregular thickening with “tram tracking” and diffuse moderate mesangial expansion. Immunofluorescence showed 3+ granular staining for IgG3, 3+ kappa light chains, 2-3+ C3, and 2-3+ C1q. Electron microscopy showed irregular thickness of the GBM with subendothelial electron dense deposits and podocyte foot process effacement. Uremia and protein urine were nephrotic range. At 50 years of age, skeletal survey was normal with no bone lesions and bone biopsy showed plasma cells less than 5% of total cellularity. He was started on lisinopril and prednisone taper. His 24-hour urine protein was 800 mg at 6 month follow up.

Discussion: We report an uncommon case of PGNMID responding to steroid therapy and renin angiotensin-system (RAS) blockade. PGNMID has been associated with myeloma, chronic lymphocytic leukemia, parvovirus and hepatitis C infection. In a study of 37 PGNMID patients, Nasr et al. suggest PGNMID is not a precursor to hematological malignancies in most patients. However, the best treatment option remains elusive and prognosis typically is poor. Biopsy may show endocapillary proliferation, and the best treatment option remains unknown. Biopsy with RAS blockade may be considered in patients with nephrotic syndrome and positive renin angiotensin-system (RAS) workup.

Characteristics of Genetic and Biomolecular Backgrounds in Patients with LAMB2 Related Nephropathy

TH-PO037

Introduction: Characteristics of Genetic and Biomolecular Backgrounds in Patients with LAMB2 Related Nephropathy (LAMB2) have not been fully described. We aim to present a comprehensive overview of genetic and clinical characteristics in a cohort of patients with LAMB2.

Case Description: A 3 year old boy; developed nephrotic syndrome at 6 mo. Case 2 is a 1yo girl, younger sister of the case 1. She presented nephrotic syndrome at 1 mo. Case 3 is a 2yo boy, exhibited hematuria and non-nephrotic range proteinuria at 1 mo. None of these three patients showed kidney dysfunction, ocular or neurological defects until now. Renal biopsy showed mesangial proliferation, and electron microscopy findings showed thinning and Basket- weave change of the GBM in all cases. As a result of genetic analysis by NGS, novel frameshift mutation: c.225delC and known pathogenic missense mutation: p.Gly69Arg in LAMB2 were detected in case 1 and case 2. In case 3, novel frameshift mutation: c.596-597dupCAG and novel splice-site mutation: c.3797+5G>A in LAMB2 were detected which resulted in whole intron 24 (96bp) insertion between exon 24 and exon 25 at the transcript level. Laminin β2 positive expression on GBM was evaluated by immunohistochemistry in all cases.

Discussion: We detected compound heterozygous mutations in LAMB2 gene in all patients. One family showed missense mutation and another showed in-frame mutation. We proved laminin β2 positive expression in all cases. These results might reflect milder phenotypes for PS in our cases. In conclusion, we clarified the genetic and biomolecular backgrounds for milder phenotypes in our cases with LAMB2 mutations. NGS is a powerful tool to make genetic diagnosis of inherited kidney diseases showing atypical phenotypes.

ANCA Vasculitis Induced Aortitis

TH-PO038

Introduction: ANCA vasculitis primarily affects small vessels; however, large vessel involvement has been reported in literature. We present a case of aortitis caused by ANCA vasculitis.

Case Description: We evaluated a 49 years old man with history of granulomatosis with polyangiitis (GPA), that was diagnosed 15 years ago and was treated with induction therapy (steroids, cyclophosphamide and plasmapheresis) followed by maintenance therapy (azathioprine) for 5 years, in our transplant clinic. He was recently admitted to the hospital for chest pain that had been worsening over the last few days with a chest CT showing an ascending aortic aneurysm that mandated urgent repair. Physical examination during the clinic visit was unremarkable. Pertinent diagnostic data is shown in Figure 1. The patient is currently receiving induction therapy for anti-proteinase 3 (PR3) positive ANCA vasculitis with monthly intravenous cyclophosphamide doses and oral steroids.

Mixed Cryoglobulinemic Glomerulonephritis Associated with Ulcerative Colitis in a Liver Transplant Patient

TH-PO039

Introduction: Mixed Cryoglobulinemic vasculitis is most commonly associated with Hepatitis C infection but rarely reported in chronic autoimmune disorders. We present a patient who developed cryoglobulinemic vasculitis with membranoproliferative glomerulonephritis after ulcerative colitis (UC) flare.

Case Description: 47 year male with ulcerative colitis, primary sclerosing cholangitis s/p liver transplant, CKD III presented with an ulcerative colitis flare which was treated with adalimumab and prednisone with improvement in symptoms. He was also found to have AKI on CKD with new onset nephrotic range proteinuria, hematuria. He also developed venous thrombosis of his legs. Hepatitis B & C panel, HIV, CMV, EBV, ANA and ANCA were negative. LFTs and serum free light chain ratio were normal. C3 was low but C4 was normal. Serum cryoglobulins were negative. Kidney biopsy showed Membranoproliferative glomerulonephritis. Electron microscopy showed electron dense deposits with ultrastructural features of cryoglobulinemic glomerulonephritis. Skin biopsy of the rash was consistent with cryoglobulinemic vasculitis. He developed anuric AKI requiring temporary hemodialysis. He was given rituximab due to severity of his AKI and no improvement with treatment of ulcerative colitis. He subsequently came off dialysis and his GFR improved back to baseline. His urine protein to creatinine ratio improved from 4.81 to 0.73.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Discussion: This case highlights the rare association between ulcerative colitis (UC) and cryoglobulinemia. Studies have shown the presence of autoantibodies to Saccharomyces cerevisiae (ASCa) in patients with UC as well as in those with cryoglobulinemia which could explain the association. Although this is rare, clinicians treating IBD should have a high suspicion for cryoglobulinemic vasculitis especially in patients with vasculitic rash or Raynaud’s phenomenon. Rituximab has been shown to be effective in treating both hepatitis C and non-HCV related cryoglobulinemic vasculitis and should be considered in severe glomerulonephritis with nephritic range proteinuria.

TH-PO040
Rituximab Therapy Worsens Hepatitis C Associated Cryoglobulinemic MPGN Post Kidney Transplant Despite HCV Eradication

Samuel Chakola,1 Nomsa Musenwa,1 Swati Rao,1 Mythili Ghana,1 Duncan B. Johnstone,1 Xu Zeng,2 Serban Constantinescu,1 Avrum Gillespie,1 Crystal A. Gagebeku,1 Iris J. Lee,1 Section of Nephropathy and Transplantation, Temple Univ, Philadelphia, PA; Section of Pathology, Temple Univ, Philadelphia, PA.

Introduction: Chronic Hepatitis C virus infection (HCV) is prevalent in end stage renal disease and kidney transplant recipients (KTR). Polyclonal B-cells stimulation by HCV leads to cytoplasmic and rheumatoid factor (RF) production, manifesting as systemic vasculitis and/or MPGN in KTR. Standard of care is therapy with steroids, Rituximab (RTX), plasmapheresis (PP) and eradication of HCV with anti-viral regimens. We report a case of persistent cryoglobulinemia with vasculitis and MPGN, despite eradication of HCV in a KTR.

Case Description: A 63 year old AA male with HCV on hemodialysis received a cadaveric KT from a HCV positive donor. Proteinuria, HCV, high RF and low complement levels prompted an allograft biopsy which showed cryoglobulinemic MPGN. Therapy was initiated with steroids, PP and RTX (375mg/m2 for 2 doses), with remaining doses of RTX held due to sepsis. Despite rapid resolution of HCV with an IFN-free regimen cryoglobulinemia persisted. Work up for a mononuclear lymphoproliferative disorder was negative. A third dose of RTX was given but the patient subsequently developed gross hematuria, proteinuria, acute kidney injury and a purpuric rash. Allograft biopsy showed progressive MPGN with crescents improved by aggressive PP and steroids. We reasoned that RTX triggered an accelerated vasculitis and MPGN, and therefore opted to give 2 cycles of Bortezomib along with PP and achieved complete clinical remission.

Discussion: RTX is a chimeric molecule possessing a humanized IgG tail, a potential target for IgM with RF activity. The resulting increase in IgG-IgM complex could have precipitated acute vasculitis and organ damage in our patient. In addition, RTX alters B-cell populations by upregulating BAFF receptor on B-cells favoring mature B-cell development, counter-productive to treatment goals. Our case highlights the complications of RTX in HCV cryoglobulinemia and suggests studying the role of bortezomib in resistant cases likely driven by plasma cell dyscrasia.

TH-PO041
Hydralazine-Induced ANCA Vasculitis with Glomerulonephritis and Diffuse Alveolar Hemorrhage

Josef Bautista, Katherine Mikovna Scovorne, Section of Kidney Diseases and Hypertension, Brown Univ - Rhode Island Hospital, Providence, RI.

Introduction: Hydralazine is known to cause drug-induced lupus. However, this entity has very limited renal involvement. In contrast, hydralazine-induced ANCA vasculitis, a rarer pathology, may result in catastrophic renal and pulmonary disease.

Case Description: This is a 71-year-old woman with hypertension who had been on hydralazine 50 mg twice daily for 2.5 years. She presented with hematuria, acute renal failure, hemoptysis and hypoxic respiratory failure. Physical exam was notable for hypertension, coarse lungs sounds and bilateral pitting edema. Serum creatinine was 5.4 mg/dl. Her UA showed 3+ blood and 100mg/dL protein. ANA was 1:1,280, p-ANCA was 1:30, anti-histone antibody was elevated to 2.8, anti-doppel-stranded (ds) DNA antibody was elevated at 155, and C3/C4 were low. Renal ultrasound showed increased echogenicity concerning for medication-induced renal disease. Renal biopsy showed diffuse acute tubular necrosis with RBC casts and active vasculitis in 5 of 23 glomeruli. 10 of 18 glomeruli had fibrocellular crescents. Immunofluorescence was negative for immune complex deposition while electron micrograph showed no deposits in the glomerular basement membrane or mesangium. Hydralazine was discontinued. The patient received stress dose steroids and was started on plasmapheresis. She was also started on rituximab 375mg/m2 weekly for 4 weeks for induction immunosuppression. 1 week after the diagnosis, labs showed improvement in her ANA, anti-histone and myeloperoxidase titers. Her complement levels remained low. After 2 months, she remained dialysis-dependent.

Discussion: This case illustrates an exceedingly rare complication of hydralazine. Hydralazine may alter the expression of MPO and other neutrophilic antigens (e.g. HLA, anti-dsDNA) by inhibiting DNA methyltransferases in the neutrophils. The presence of P-ANCA, positive anti-histone antibodies, and pauci-immunity are consistent with drug-induced ANCA vasculitis rather than with drug-induced lupus or primary vasculitis. Treatment of this condition is similar to that of idiopathic ANCA vasculitis but, in addition, the offending agent must never be reintroduced to the patient.

TH-PO042
Successful Treatment with Spironolactone and Acetazolamide for Severe Metabolic Alkalosis and Hypokalemia Secondary to Ectopic Secretion of a Neuroendocrine Hormone-Secreting Extramammary Small Cell Neuroendocrine Carcinoma of the Rectum

Luis A. Vazquez, William Chastant, Jonathan G. Owen. Nephrol and Hypertension, Louisiana State Univ Health Sciences Center, New Orleans, LA.

Introduction: Metabolic alkalosis is life threatening with reported mortality of 35% with arterial blood pH of 7.55. We present a case of severe metabolic alkalosis and hypokalemia secondary to an ACTH-secreting neuroendocrine tumor.

Case Description: 58 year old man with hypertension and HIV on HAART therapy, presented with limited case reports of Spironolactone and Acetazolamide treatment for this rare complication. He was started on spironolactone 12.5mg daily, for 4 weeks and subsequently doubled his valsartan-HCTZ. Labs showed creatinine 0.6 mg/dl, hypokalemia (2.3 mmol/L) and serum CO2 level of 42mmol/L, prompting admission. Arterial blood gas showed pH 7.57, HCO3 42.8 mmol/l, PCO2 45.8 mmHg. Nephrology consulted after no improvement with a liter of normal saline. 80mg spironolactone was started and acetazolamide 500mg IV started q12 hours for two doses, followed by acetazolamide 500 mg orally q12 hours for 4 doses.

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Underline represents presenting author. 104A
The pH improved to 7.577 at 24 hours, 7.505 at 48 hours, and to 7.442 at 72 hours upon completion of acetazolamide. He was maintained on spironolactone 50mg daily and KC 40mEq orally thrice daily with no return of severe alkalosis or hypokalemia. Creatinine improved to 1.2mg/dL. Cortisol level resulted greater than 110 µg/dL, and ACTH level of 1585 pg/mL. Work-up suggested non-pituitary source, and CT-imaging revealed concern for metastatic involvement of rectum and liver. Biopsy of the rectal mass confirmed extramedullary small cell ACTH-secreting neuroendocrine carcinoma.

Discussion: Severe metabolic alkalosis and hypokalemia secondary to mineralocorticoid effects of cortisol in ACTH-secreting neuroendocrine tumors has been rarely reported. Our case demonstrates the potential severity and a treatment regimen that has not previously been reported in this rare condition.

**TH-PO045**

Novel Treatment: Nephrogenic DI Swupa P. Vantzelulle, Jean M. Francis, Craig E. Gordon. Boston Medical Center, Boston, MA.

Introduction: A patient with lithium-induced nephrogenic diabetes insipidus (NDI) was treated with acetazolamide. This was modeled after a trial in mice.

**Case Description:** 49 year old male with bipolar disorder on chronic lithium therapy, admitted for resection of acoustic schwannoma due to ipsilateral hearing loss. Post-operatively, he was delirious with limited water intake. Lithium was discontinued on day 3 for worsening mental status. Serum sodium ranged from 153mmol/L to 164mmol/L and urine output ranged from 8 to 12L per day. Urine osmolality was 150mmol/kg H2O.

The free water deficit was initially treated with D5W IV without improvement. His mental status continued to deteriorate and his serum sodium remained elevated. DDAVP was administered with no change in the urine osmolality or serum sodium, conferring the diagnosis of complete NDI. Hydrochlorothiazide was started, and 4 days into treatment his urine output had increased to 14L per day. On day 18, acetazolamide started and hydrochlorothiazide stopped. By day 20 of admission there were dramatic improvements; urine output dropped to 3 to 5L per day, urine osmolality increased to 300mosm/kg H2O and serum sodium normalized. The beneficial effects of acetazolamide persisted, but were confounded by recent cessation of lithium and thus the acetazolamide was stopped which led to rise in urine output, to 7L per day. The acetazolamide was resumed on day 34, with marked reduction in polyuria to 1.5-3.5L per day for the duration of admission.

**Discussion:** The most common cause of NDI is chronic lithium use. Traditionally, the therapeutic approach emphasizes reduced sodium intake and thiazide diuretics with or without amiloride. Recent data from animal models of lithium-induced NDI delineate that hydrochlorothiazide reduces polyuria in mice lacking the thiazide-sensitive sodium-chloride co-transporter. This suggests an alternative mechanism of action than previously accepted.

Carbonic anhydrase inhibition was proposed and a trial utilizing mice and collecting duct cells showed that acetazolamide was at least as effective for treatment of NDI. We utilized acetazolamide monotherapy in a patient with severe lithium-induced NDI and to our knowledge this is the first case with successful use of acetazolamide in humans with NDI.

**TH-PO046**

Attempt to Treat Anti-Brush Border Antibody-Mediated Tubulointerstitial Nephritis with Rituximab. Emily Drye, Robert B. Colvin, Ivy A. Rosales, A. Bernard Collins, Katherine Westin Kwon. 1Lakeland Health, Saint Joseph, MI; 2MGH Pathology, Boston, MA.

Introduction: A case of immune complex tubulointerstitial nephritis due to autoantibodies to the proximal tubule brush border was recently described. We describe a second case, identified prior to the onset of end stage renal disease, and the lack of response to therapy with rituximab.

**Case Description:** A 76 year old man was referred to nephrology for evaluation after admission to a rehabilitation hospital for increased fatigue. These symptoms and her disturbance of consciousness became gradually worse to the point where she could not eat. On admission, ketone body levels in urine and blood were markedly elevated and her serum levels of bicarbonate were extremely low at 8.8 mmol/L. However, blood gas analysis revealed a paradoxical normal anion gap 27.7 (15-24) mmol/L and the mildest hypokalemia (3.5-4.0 mmol/L on 20 mmol KCl/day) in the CBS patient. Combination treatments of oral KCl (20-160 mEq daily), amiloride (5-10 mg daily), and MgOx (400-1800 mg daily) improved symptoms and serum K rose to 3.27 mmol/L (2.4-4.1).

Discussion: We describe a case of idiopathic disease in five unrelated adults. 8 mutations were predicted to be pathogenic, of which 7 missense mutations and 1 deletion. Differentiation of BS and GS based on clinical presentations is difficult. Normotension and hypertension are common. Genetic testing is informative.

**TH-PO047**

Inherited Salt-Losing Tubulopathy: A Case Series Zhen Cheng, Jing Lin. 1Nephrology, Jinling Hospital Nanjing Univ, Rochester, MN; 2Nephrology, Zhongshan Hospital Fudan Univ, Rochester, MN; 3Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, MN.

Introduction: Two major syndromes of salt-losing nephropathy are Bartter syndrome (BS) and Gitelman syndrome (GS). We presented a series of GS and BS with unique mutations and some atypical presentations.

**Case Description:** Clinical data were collected through Mayo Clinic Electronic Medical Records with the IRB approval.

Five cases were identified (2010-2015). Average age was 37.2 yr (range: 20-50). BP 113.2±6.5 mmHg (96-140/68-88), common presentations were fatigue/muscle cramps and BUN (2.8±3.3) while on K supplementation. Mutation analysis showed SLC12A3 gene mutations in 4 patients, consistent with GS, and CLCNKB gene mutation in 1, consistent with classic BS (CBS). The SLC12A3 mutations were (1) novel combination of double heterozygous c.1849C>G and c.1964G>A; (2) novel combination of double heterozygous c.537G>A and c.815T>C; (3) homozygous mutations in two positions c.2221G>A and c.791C>G; and, (4) novel combination of heterozygous c.1315G>A and c.1964G>A. The remaining patient had CLCNKB mutation c.508G>A combined with an allelic deletion. Atypical presentations included (1) normotensive and hypertensive in 4 cases, 2 were on treatment; (2) erythrocytosis requiring phlebotomy in 1; (3) reversible hypercalcaemia (11.5 mg/dL) associated with Ca supplementation (1250 mg 2xdaily) and with fixed low urine Ca excretion (65 and 67 mg/24 hr urine before and after serum Ca correction (9.6 mg/dL) by discontinuation of Ca intake; and, (4) the most severe hypokalemia (1.8-2.0 mmol/L). 60 mmol KCl/day was administered to this patient and the mildest hypokalemia (1.5-4.0 mmol/L on 20 mmol KCl/day) in the CBS patient. Combination treatments of oral KCl (20-160 mEq daily), amiloride (5-10 mg daily), and MgOx (400-1800 mg daily) improved symptoms and serum K rose to 3.27 mmol/L (2.4-4.1).

Discussion: We describe unique mutant alleles in five unrelated adults. 8 mutations were predicted to be pathogenic, of which 7 missense mutations and 1 deletion. Differentiation of BS and GS based on clinical presentations is difficult. Normotension and hypertension are common. Genetic testing is informative.

**TH-PO048**

Pseudonormalization of the Serum Anion Gap in a Patient with Ketoadioidosis Caused by Bromvalerylurea Intoxication. Yatsumu Saito, Akiko Soda, Shuichiro Yanamaka, Kyoko Kishida, Yasuyuki Nakada, Takeso Uchiyama, Izumi Yamamoto, Ichiro Ohkido, Takashi Yooko. Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.

Introduction: Although nonsteroidal anti-inflammatory drugs (NSAIDs) containing bromvaleryluriea are prohibited in the United States, such drugs are commonly available over-the-counter in Asian countries. The clinical features of acute intoxication include nausea, vomiting, and disturbed consciousness. Chronic intoxication induces irreversible neurological deficits and cerebellar atrophy. Importantly, the commonly used assays cannot distinguish bromides from chlorides, with the result that serum hyperchloremia may be a key feature of bromvalerylurea intoxication.

**Case Description:** A 50-year-old woman had a history of Neuro-Behçet’s disease from the age of 48 years. She felt nauseous, and vomited repeatedly for 3 weeks prior to admission. Therefore, these symptoms and her disturbance of consciousness became gradually worse to the point where she could not eat. On admission, ketone body levels in urine and blood were markedly elevated and her serum levels of bicarbonate were extremely low at 8.8 mmol/L. However, blood gas analysis revealed a paradoxical normal anion gap 27.7 (15-24) mmol/L and the mildest hypokalemia (3.5-4.0 mmol/L on 20 mmol KCl/day). Furthermore, a magnetic resonance imaging brain scan revealed severe cerebellar vermis atrophy compatible with chronic bromvalerylurea intoxication. A medical interview revealed a history of common use of NSAIDs containing bromvalerylurea. Ultimately, we diagnosed her with acute to chronic bromvalerylurea intoxication. Prohibition of drug use resolved the digestive symptoms quickly, resulting in normalization of chloride levels and the metabolic acidosis. She was discharged, ambulating, 21 days after admission.

Discussion: Bromvalerylurea intoxication is uncommonly encountered in modern practice but has not disappeared; cases are still reported in Asian countries. Our case suggests that pseudohyperchloremia and pseudonormalization of the anion gap in patients with severe acidosis could be key features in the diagnosis of bromvalerylurea intoxication.

**TH-PO049**

Succinylcholine Induced Hyperkalemia in Pregnancy: A Unique Clinical Presentation Maria Theodorou, Jennifer K. Bond, Kavitha Vellanki. Loyola Univ Medical Center, Maywood, IL.

Introduction: Succinylcholine is used as a paralytic for endotracheal intubation, especially when rapid onset and offset of effect is needed. One adverse effect in certain patients is acute onsets hyperkalemia and associated cardiovascular instability. Little is known about such effects in pregnancy. Here we report one such rare case.

**Case Description:** A 31 year-old G1 P1 resident was intubated on 1st day of life while on K supplementation. Maternal controlled asthma presented with severe acute asthma exacerbation. Over 36 hours, she deteriorated despite maximal medical support, requiring emergent intubation for severe hypercapnic respiratory failure with succinylcholine and propofol induction. 7 hours post-intubation, while OR complexes were noted on cardiac STAMP workup a revealed a serum potassium of 9.5 MM/L (Table 1).

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TH-PO051

Hyperphosphatemia, Normal eGFR, and Complete Tubular Phosphate Reabsorption Leading to a Pitiutary Tumor Diagnosis
Jawlant R. Modi, Ghurulakshmi Moorthy, Michael T. Eadon. Medicine, Indiana Univ, Indianapolis, IN.

Introduction: The classic presentation of a pituitary tumor is comprised of hormonal symptoms related to gonadal hormone deficiency or neurological symptoms including diplopia, headache, or visual field defects. However, these tumors may be dormant clinically, be found incidentally on brain imaging, or provide subtle clues which can be easily overlooked.

Case Description: A 49 year old African American woman was seen following hospitalization for sudden-onset hand cramping and facial contracture due to hypokalemia for many years. She presented with hypokalemia induced nephropenic diabetes insipidus. History was notable for hypertension, normal eGFR, fibroids, colonic polyps, wrist fracture and a 15 lb weight loss in 1 year. She complained of diffuse body aches, fatigue, and poor appetite, but denied any nipple discharge, major headaches, or visual symptoms. She no longer menstruated as she had undergone hysterectomy. On lab studies, she had hyperphosphatemia, recurrent hyperphosphatemia, hypomagnesemia, TTKG 65.6, urine K+/Creatinine ratio 20 meq/g; Fractional excretion (FE) of Mg 1.3% and FE-phos 0%. Her adrenal level was low with a normal renin level. The most differential-focusing aspect was the complete tubular reabsorption of phosphate in the setting of hyperphosphatemia and normal eGFR. Her 25-OH and 1,25-OH vitamin D were suppressed. It is known that acromegaly may lead to phosphorus reabsorption. Even though she had no phenotypic features of acromegaly, we checked growth hormone, IGF-1, and IGF-BP3, as well as an MRI brain. Her growth hormone was not suppressed, but the MRI revealed a sellar mass, suspicious for a pituitary macro adenoma. Her endocrine work-up revealed pan-hypopituitarism, except for a prolactin level of 72.4 · elevated, but atypical for a prolactinoma. She was started on hydrocortisone and levothyroxine and will undergo transsphenoidal tumor removal.

Discussion: Since this patient had hyperphosphatemia with normal eGFR and complete tubular reabsorption of phosphate, this case raises the question of whether pituitary hormones (other than IGF-1) contribute to the regulation of FGF-23 and the sodium phosphate co-transporter.

TH-PO052

TB or Not TB. That Is the Question
Mitraie Wardi,1 Angelica Aurora Nunez,2 Dubier MatoS,2 Hasan Joseph Salanach.1 Internal Medicine - Div of General Medicine, TTUHSC Paul L. Foster School of Medicine, El Paso, TX; 1Internal Medicine - Div of Nephrology, TTUHSC Paul L. Foster School of Medicine, El Paso, TX.

Introduction: Mycobacterium wolinskyi, a member of the Mycobacterium smegmatis group of rapidly growing mycobacteria (RGM), is a rare cause of infection in humans. To date, less than 20 cases have been reported, most of which are associated with post-traumatic and post-surgical wound infections. We report a case of M. wolinskyi-induced peritoneal dialysis (PD) catheter exit-site infection, an entity never before reported in the literature.

Case Description: A 46 year old female with a past medical history of end-stage renal disease secondary to lupus nephritis on chronic PD presented for constant abdominal pain of 3 days duration after manual exchanges. Pain was localized in the epigastrium and lower abdomen with no radiation with associated nausea and vomiting. Upon initial evaluation, she was found to be febrile and normotensive. Abdominal examination was significant for a tender abdomen in the lower and epigastric regions with thick purulent discharge easily expressed from the exit site. ACT of the abdomen failed to show infectious changes tracking along the catheter tunnel. Peritoneal fluid analysis was unremarkable. Bacterial and fungal cultures of the purulent discharge were taken and the patient was started on empiric levofloxacin. Initial cultures were negative. The patient with discharged home on topical gentamicin. Upon follow up, the purulent discharge remained. Analysis of exit-site cultures at 168 hours revealed growth of M. wolinskyi. Long-term dual antibiotic therapy was initiated and currently pending follow up.

Discussion: M. wolinskyi was discovered in 1999 using 16sRNA sequencing. Only 19 cases of M. wolinskyi infections in humans have been described, the majority of which are associated with post-orthopedic surgical site infections, although a few cases of post-operative M. wolinskyi bacteremia have been described. It has also been described in one case of PD catheter-related acute peritonitis within 6 months of surgical placement of PD catheter. To our knowledge, this is the first case of M. wolinskyi-induced PD catheter exit-site infection.

TH-PO053

The Tale of a Forgotten Tumor

Introduction: Phaeochromocytoma (PCC) is a rare catecholamine-secreting neuroendocrine tumor that arises from chromaffin cells of the adrenal medulla. Approximately 10% are malignant, often diagnosed as a result of local invasion into surrounding organs or distant metastases. We present a case of an apparently benign PCC that presented 10 years after diagnosis as metastatic disease.

Case Description: A 64 year old Caucasian man was seen by us for hypertension (HTN) and an adrenal mass. 10 years prior to presentation, he was diagnosed with a left adrenal mass while undergoing work up for uncontrolled HTN. He underwent anatomic left adrenalectomy and pathology confirmed PCC. The tumor was 8.3 cm in size with focal areas of hemorrhage and necrosis, but confined to the adrenal gland. His BP normalized.
and he was tapered off of anti-hypertensives a few weeks later. He was then lost to follow up. 3 months ago, he saw his primary care physician for a 40 lbs unintentional weight loss. He was found to be hypertensive & hygroscopic. He denied headache, palpitations or sweating. 24 hour urine studies confirmed elevated (~1,000x normal) metanephrines & normetanephrines. CT revealed a 3.8cm left adrenal mass with focal calcification. PET CT identified multiple areas of bone involvement suggestive of metastatic disease. Biopsy of the sacral mass was attempted, but the blood pressures rose to 240/124. He was started on phenoxybenzamine & labetalol with good response. He is currently being treated with I-131 metaiodobenzylguanidine. Prior MRI and current MIBG are shown.

Discussion: Malignant PCCs are histologically and biochemically similar to benign ones with the only reliable clue to malignancy being local invasion or distant metastases, which may be missed during initial diagnosis. Although benign appearing PCCs are completely excised, we recommend continued follow up of these patients until reliable predictors of malignancy are defined.

TH-PO054
Severe Hypertriglyceridemia and Fasting Ketoacidosis Associated with Clevidipine
Daniel Dudenko,1 Insara Jaffer Satib,1 Robert C. Albright,1 Internal Medicine, Mayo Clinic, Rochester, MN; 2Nephrology, Mayo Clinic, Rochester, MN; 3Nephrology, Mayo Clinic, Rochester, MN.

Introduction: Clevidipine (CLV) is a newer intravenous calcium channel blocker used to treat high blood pressure in acute settings. Although CLV is generally considered safe, clinical experience is limited, especially pertaining to rare adverse effects.

Case Description: Patient is a 60 year-old male with a history of allogeneic cardiac transplantation for ischemic cardiomyopathy, immunosuppressed with mycophenolate mofetil and cyclosporine. He gradually developed progressive metabolic acidosis with bicarbonate 13mmol/L and anion gap 23 (Figure 1). Due to increased work of breathing, he was placed on BiPAP support, with arterial blood gas showing pH 7.37, pCO2 27, and pO2 81. Other labs revealed a lactate 1.0 mmol/L, creatinine 1.0 mg/dL, glucose 121 mg/dL, beta-hydroxybutyrate (BHB) 3.9 mmol/L, and triglycerides (TG) 2000 mg/dL. Due to concern for CLV toxicity, he was transitioned to a nicardipine drip. He was also given IV dextrose with insulin. Within 24 hours, the patient’s acidosis resolved with normal blood sugars, glycosuria, phosphaturia, bicarbonaturia, with venous bicarbonate of 18 mEq/L. Specific aminoaciduria could not be demonstrated. Urinary calcium excretion, serum Vt D and PTH levels were normal. X-rays showed fractures and looser’s zone in many bones. CT KUB showed non obstructing renal calculi and amorphous chunky calcification in renal medulla suggestive of medullary nephrocalcinosis. Patient was treated with potassium, calcium, phosphorus and alcali supplements. Her power returned to normal and she could walk with support.

Discussion: Our patient has features of proximal (p) and distal (d) RTA. The term Type 3 RTA is not in use, but it is an extremely rare autosomal recessive syndrome. Combined dRTA and pRTA is also observed in inherited carbonic anhydrase II deficiency. Patients with pRTA may have high urinary calcium excretion; however, nephrocalcinosis and renal calculi are rare in type 2 but common in type 1 RTA. Stunted growth is a prominent clinical feature in children. Rickets and osteomalacia are never observed unless hypophosphatemia is present as occurs in the Fanconi syndrome. We feel this patient has Type 3 RTA.

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TH-PO055
Coexistence of Proximal and Distal Renal Tubular Acidosis

Introduction: Renal tubular acidosis (RTA) is a group of transport defects in the reabsorption of bicarbonate, the excretion of hydrogen ion (H+), or both, resulting in systemic acidosis and hypokalemia with a normal glomerular filtration rate. Isolated proximal (type 2) or distal (type 1) tubular pathologies are well characterized, a combined pathology leading to type 3 RTA is very rare. We report a case with features of type 1 and type 2 RTA. We wonder if this is a case of type 3 RTA, a term, which is not in use.

Case Description: 20 years old female presented with diarrhea and weakness of all 4 limbs. She had 5 episodes of weakness over past 10 years, and fracture of left shaft of femur. She had growth retardation, left genu valgum, power was 4 in all 4 limbs. She was 1st of 4 siblings of parents, and no family history of similar disease. Clinical diagnosis: renal tubular acidosis with rickets. Investigations: isosthenuria, urine pH 9.0; urine protein creatinine ratio 0.47 mg/mg, normal renal function, hypokalemia, hypercalcaemia, hyperphosphatemia, normal blood sugars, glycosuria, phosphaturia, bicarbonaturia, with venous bicarbonate of 18 mEq/L. Specific aminoaciduria could not be demonstrated. Urinary calcium excretion, serum Vit D and PTH levels were normal. X-rays showed fractures and looser’s zone in many bones. CT KUB showed non obstructing renal calculi and amorphous chunky calcification in renal medulla suggestive of medullary nephrocalcinosis. Patient was treated with potassium, calcium, phosphorus and alcali supplements. Power returned to normal and she could walk with support.

Discussion: Our patient has features of proximal (p) and distal (d) RTA. The term Type 3 RTA is not in use, but it is an extremely rare autosomal recessive syndrome. Combined dRTA and pRTA is also observed in inherited carbonic anhydrase II deficiency. Patients with pRTA may have high urinary calcium excretion; however, nephrocalcinosis and renal calculi are rare in type 2 but common in type 1 RTA. Stunted growth is a prominent clinical feature in children. Rickets and osteomalacia are never observed unless hypophosphatemia is present as occurs in the Fanconi syndrome. We feel this patient has Type 3 RTA.
**Case Description:** A 53 years old female was diagnosed with PBC with elevated alkaline phosphatase (ALP) of 1.320 and high IgM levels (500 mg/dL). Laboratory results at the time of diagnosis:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>Creatinine</td>
<td>3.1 mg/dL</td>
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<tr>
<td>Serum Potassium</td>
<td>3.4 mEq/L</td>
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<tr>
<td>Serum Phosphate</td>
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<td>Serum bicarbonate</td>
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<td>Serum uric acid</td>
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<td>Glycerina</td>
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<tr>
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<tr>
<td>WBC in urine</td>
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<tr>
<td>Protein/creatinine ratio</td>
<td>2.9</td>
</tr>
<tr>
<td>SPEP-abst</td>
<td>UPEP-abst</td>
</tr>
</tbody>
</table>

She underwent kidney biopsy which showed normal Glomeruli. Interstitial edema, marked tubulo-interstitial inflammatory infiltrates and significant fibrosis were present. Renal cortical density of calcium phosphate was also noted with granules noted. Immunoﬂuorescence showed C3 activity in arterioli. EM showed extensive mononuclear inﬁltrate. Proximal and distal RTA and TIN was likely related to PBC in this patient. Patient was started on potassium citrate. Due to significant fibrosis were not given. Later her renal function worsened and the need for dialysis was raised.

**Discussion:** PBC can be associated with TIN and RTA which can be easily missed. Possible mechanisms include autoantibotic T lymphocytes driven by abnormal antigen expression in both hepatocytes and similar antigen expression in renal tubules might be involved leading to T lymphocyte infiltration into the interstitioli. Also, Heat shock proteins cause renal dysfunction in subjects with PBC and early treatment with steroids may prevent further renal damage.

**TH-PO058**

**A Heterozygous Mutation in NPT2c (SLC34A3) Is Associated with Marked Hypercalciuria and Kidney Stones During Infancy**

Marvam Gondal, Olivia Marsenic Coulores, Neera K. Dahl, Clemens Bergwitz. Yale University School of Medicine, New Haven, CT.

**Introduction:** The SLC34A3 gene encodes for the renal sodium-phosphate co-transporter NPT2c. A homozygous or compound heterozygous inactivation results in Hereditary hypophosphatemic rickets with hypercalciuria (HRHR, OMIM#241530). Affected individuals present with hypophosphatemia and hypercalciuria. Heterozygous carriers of SLC34A3 mutations often present with idiopathic hypercalciuria (IH). Here we present the case of a child with multiple kidney stones and hypercalciuria since birth. His father was also found to have marked hypercalciuria.

**Case Description:** The child was born prematurely (29GW), and presented as a new born with hypertension. Renal imaging revealed bilateral kidney stones and nephrocalcinosis. Urine analysis showed calcium stones with calcium excretion of 4 mg/kg/day. His most recent laboratory studies at age 10 years show serum calcium of 9.8 mg/dL, phosphorus 4.9 mg/dL, PTH 12 mg/mL, and 25-OH vitamin D 27 pg/mL. His 24-hr urine calcium is 8.6 mg/kg/day. Prompted by his son’s ﬁndings, the father’s renal stones were investigated. Whole exome sequencing (WES) of the father revealed a left calcified renal cyst and left sided renal mass, found to be renal cell cancer and he underwent partial nephrectomy. Whole exome sequencing (WES) of the father was also found to have marked hypercalciuria.

**Discussion:** Our patient with hypercalciuria, hypophosphatemia and recurrent kidney stones demonstrates the phenotype of SLC34A3 mutations (NPT2c). SLC34A3 is the sodium-coupled phosphate transporter that mediates reabsorption of phosphate in the proximal tubule. Mutations in NPT2c result in marked hypercalciuria and kidney stones. Parental WES revealed a familial WES found that a 53 years old female was diagnosed with PBC with elevated alkaline phosphatase (ALP) of 1.320 and high IgM levels (500 mg/dL). Laboratory results at the time of diagnosis:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>3.1 mg/dL</td>
</tr>
<tr>
<td>Serum Potassium</td>
<td>3.4 mEq/L</td>
</tr>
<tr>
<td>Serum Phosphate</td>
<td>2.6 mg/dL</td>
</tr>
<tr>
<td>Serum bicarbonate</td>
<td>15 mEq/L</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>2.0 mg/dL</td>
</tr>
<tr>
<td>Serum alkaline phosphatase</td>
<td>1.14 mg/dL</td>
</tr>
<tr>
<td>Urine pH</td>
<td>5.5</td>
</tr>
<tr>
<td>Glycerina</td>
<td>1.0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2.8</td>
</tr>
<tr>
<td>Aminoaciduria</td>
<td>1.0</td>
</tr>
<tr>
<td>RBC in urine</td>
<td>6.0 cells/µL</td>
</tr>
<tr>
<td>WBC in urine</td>
<td>6.0 cells/µL</td>
</tr>
<tr>
<td>Protein/creatinine ratio</td>
<td>2.9</td>
</tr>
<tr>
<td>SPEP-abst</td>
<td>UPEP-abst</td>
</tr>
</tbody>
</table>

The second patient was a 54 year old man with bipolar disorder who presented with hypertension. He was also found to have hypophosphatemia and hypercalciuria. Both cases demonstrate the importance of identifying oxalate nephropathy early and treating inﬂammation with glucocorticoids if there are no underlying contraindications.

**TH-PO060**

**Glucocorticoid Therapy for the Treatment of Oxalate Nephropathy**

Dominique Dorsainvil, Bryan Tucker, Randy L. Luciano. Nephrology, Yale School of Medicine, New Haven, CT.

**Introduction:** Oxalate nephropathy is an uncommon form of kidney injury marked by calcium oxalate crystals in kidney tubules leading to acute tubular injury and interstitial inﬂammation. Supportive treatment includes intravenous ﬂuids to flush crystals out of the tubules. However in severe injury, renal replacement therapy may be required. No studies report the use of anti-inﬂammatory medications to treat oxalate induced kidney injury. Here we present two patients who presented with acute kidney injury (AKI) attributed to oxalate nephropathy. Both patients had signiﬁcant acute interstitial inﬂammation resulting in prolonged AKI that improved with glucocorticoids.

**Case Description:** The first patient was a 54 year old man with bipolar disorder who presented with hypertension and normal electrolyte levels. He was also found to have tympanic membrane tenderness. The second patient was a 71 year old gentleman with hypertension, non insulin dependent diabetes mellitus, mild dementia, prior stroke, and CKD stage III presenting with AKI of unknown etiology. Creatinine increased from 1.5 mg/dL to 8.4 mg/dL, all the while receiving intravenous isotonic ﬂuid and antibiotics for a pneumonia. Due to the continued rising creatinine a biopsy was performed and unexpectedly revealed diffuse oxalate crystals with a reactive peri-tubular interstitial inﬂammation. The patient was started on prednisone 60 mg daily. His renal function subsequently improved. In retrospect, it was noted that he ate copious amount of chocolate and peanut butter.

**Discussion:** Both cases demonstrate the importance of identifying oxalate nephropathy early and treating inﬂammation with glucocorticoids if there are no underlying contraindications.
TH-PO062
Combined Liver/Kidney Transplantation in a Patient with Primary Hyperoxaluria Type 2

Introduction: Liver transplantation is an accepted therapy for primary hyperoxaluria type 1 (PH1), but has not been shown to correct the enzyme defect causing PH2. Unlike PH1, the enzyme deficiency in PH2 is found not only in the liver, but also in cells in multiple body organs. To date, the question of whether liver transplantation can provide sufficient correction of the metabolic deficiency in PH2 has remained unanswered. We report a case of a 44-year-old man with PH2 who had successful reduction in plasma oxalate (POx) and urine oxalate (UOx) after combined liver/kidney transplantation.

Case Description: Born with a solitary kidney, the patient’s first symptomatic stone event occurred at the age 6. The next symptomatic nephrolothiasis was at age 37 when he presented with an elevated creatinine and a large obstructing renal stone requiring endoscopic removal. Progressive chronic kidney disease ensued and he underwent a preemptive living donor kidney transplant elsewhere. Allograft dysfunction occurred 6 months post-transplant and a biopsy revealed oxalate nephropathy. Urine studies showing elevated urine glycerate and normal glycolate suggested PH2. Multiple stone events and progressive allograft dysfunction followed. Genetic testing confirmed PH2 with a nonsense mutation in GRHPR (c.139C>T; p.R47X). Creatinine was 4.1 and both UOs (1.51 mmol/24hr) and POx (22.1 umol/L) were markedly elevated. Because of the marked hyperoxaluria, frequency of stone events, and loss of the first renal allograft to oxalate nephropathy, he was listed for combined liver/kidney transplant at our center.

The combined transplant occurred 1 year later at age 44 before dialysis was required. He developed delayed renal allograft function and received hemodialysis daily for the first 9 days post-transplant. By postoperative day 26, creatinine had improved to 1.4 and both POx and UOx had normalized (1.2 umol/L [reference < 1.8 umol/mL] and 0.23 mmol/24 hr [normal 0.11-0.46 mmol/24hr]) respectively.

Discussion: Although GRHPR is expressed throughout the body, this case suggests that a liver transplantation may normalize oxalate generation in PH2. Thus the role of liver transplantation in PH2 merits further study.

TH-PO063
Alternative Chemotherapy Resulting in Pancreatitis, Ketoacidosis and Oxalate Nephropathy
Caroline Johnson, Lindsay Sanders, Ayan Sen, Mira T. Keddis, Leslie F. Thomas. Nephrology, Mayo Clinic Hospital, Phoenix, AZ.

Introduction: Alternative treatments for cancer are used increasingly in the United States. Unintended harms of these novel regimens may be profound but underreported. Here, we describe a non-diabetic patient with solitary kidney who developed pancreatitis, ketoacidosis and oxalate nephropathy quickly following the use of high dose vitamin C and 3-bromopyruvate.

Case Description: A 72 year old man presented with progressive fatigue, nausea, and mid-epigastric pain. Two weeks prior to admission, he initiated an 8-day course of an alternative chemotherapeutic regimen for metastatic bladder cancer consisting of oral vitamin C 2g daily, IV vitamin C 50g daily, and 3-bromopyruvate. CT and alternative chemotherapeutic regimen for metastatic bladder cancer consisting of oral vitamin C 2g daily, IV vitamin C 50g daily, and 3-bromopyruvate.

Discussion: Given the unlikely, but possible transition to SCC, it is prudent to monitor these patients conservatively with invasive treatment reserved for those with ureteral obstruction by stones or other kidney disease. He saw multiple urologists and underwent multiple ureteroscopies some of which showed glistening, soft, acellular debris in the upper ureter. Of pain about 2 years prior to presentation that was recurrent. There was no associated chronic infection or irritant exposure including smoking. Management is largely supportive measures.

We diagnosed KDSM and managed conservatively with adequate hydration and supportive measures.

Discussion: KDSM is a condition in which the urothelium of the urinary tract, which is an uncommon and under-recognized condition that mimics Nephrolithiasis in symptomatology.

Case Description: 66 year old Caucasian male with history of hypertension, hyperlipidemia, osteoarthritis and 16 pack-year smoking was referred to us for evaluation of recurrent right sided flank pain and suspected Nephrolithiasis. He had the first episode of pain about 2 years prior to presentation that was recurrent. There was no associated hematuria, dysuria, fever, chills, urinary hesitancy or incontinence. No family history of stones or other kidney disease. He saw multiple urologists and underwent multiple ureteroscopies some of which showed glstitening, soft, acellular debris in the upper ureter. Last available pathology showed minute fragments of acellular keratin debris. Interestingly, he never had imaging evidence of renal stone, though had mild hydronephrosis one time. During the episodes of flank pain, he can feel ‘something’ sloughing off and traversing through the ureter. Excised material is shown.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Refractory Hungry Bone Syndrome in a Patient with Prior Roux-en-Y Gastric Bypass Surgery Jared Crisafi,1 Natallia Maroz,2,3 Kettering Medical Center; 1Boosnhoft School of Medicine, Wright State Univ; 2Univ of Florida.

Introduction: Hungry bone syndrome (HBS) with hypocalcemia is a known complication following parathyroidectomy (PTX) for hyperparathyroidism with incidence reported up to 20%. Risk factors include volume of resected adenoma, age, azotemia, and elevated alkaline phosphatase. Few cases have attributed prolonged hypocalcemia to prior gastric bypass surgery.

Case Description: A 64 year-old-female with past medical history of chronic kidney disease stage IV (CKD) and Roux-en-Y gastric bypass (RYGB) underwent subtotal PTX for primary hyperparathyroidism. Pathology revealed three hyperplastic glands and an adenoma. PTH was reduced from 1,452.9 pg/ml to 187 pg/ml. She subsequently developed symptomatic hypocalcemia with facial and acral paresthesias secondary to HBS with calcium <5 mg/dl and urine calcium <5mg/dl. During this time she became dialysis dependent. Patient’s symptomatic hypocalcemia was unresponsive to oral therapy necessitating intravenous calcium replacement for 253 days to date.

<table>
<thead>
<tr>
<th>Days post PTX</th>
<th>Calcium mg/dl</th>
<th>Ionized Calcium mmol/L</th>
<th>PTH pg/ml</th>
<th>Therapy (dose/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-10.5</td>
<td>5.7-6.5</td>
<td>1.09-1.3</td>
<td>15-65</td>
<td>Calcium gluconate IV 3-8g three times per day</td>
</tr>
<tr>
<td>Preoperative</td>
<td>7.7</td>
<td>0.90</td>
<td>187.5</td>
<td>Calcium carbonate 5 g</td>
</tr>
<tr>
<td>Day 1</td>
<td>5.7</td>
<td>0.88</td>
<td>49.4</td>
<td>Calcium carbonate 15 g</td>
</tr>
<tr>
<td>Day 30</td>
<td>5.3</td>
<td>0.88</td>
<td>49.4</td>
<td>Calcium carbonate 5 g</td>
</tr>
<tr>
<td>Day 253</td>
<td>6.7</td>
<td>0.96</td>
<td>49.4</td>
<td>Calcium carbonate 5 g</td>
</tr>
</tbody>
</table>

Discussion: This case demonstrates HBS in a patient with prior RYGB lasting 253. The duration of hypocalcemia is unlikely due to CKD given an undetectable urine calcium suggesting minimal renal calcium loss. Additionally, Mittendorf demonstrated HBS in patients with CKD had a mean duration of only 4.7 days. We propose that prior surgical diversion of the duodenum where intestinal calcium is preferentially absorbed resulted in calcium malabsorption which impaired bone mineralization and lead to hypocalcemia refractory to oral calcium. Prior case reports by Petras and by Panazolla have also attributed prolonged HBS to prior gastric bypass. History of bariatric surgery should be considered a risk factor for development of HBS.

Pancreatobiliary Adenocarcinoma Secreting Fibroblast Growth Factor 23 Valerie Suzanne Barto, Mala Sachdeva. Hypertension, Northwell Hofstra School of Medicine, Great Neck, NY.

Introduction: Oncogenic renal phosphate wasting secondary to fibroblast growth factor 23 (FGF23) secretion is a rare paraneoplastic syndrome, causing tumor induced osteomalacia (TIO). The majority of cases reported are benign mesenchymal tumors. Malignant FGF23 secreting tumors have been reported in lung, colon, prostate, ovarian osteosarcoma, multiple myeloma and lymphoma. We report the first case of a malignant pancreaticobiliary tumor secreting FGF23.

Case Description: A 60 year old Amish male with end stage heart disease from familial hypertrophic cardiomyopathy and renal syndrome underwent total ventriculectomy and TAH implantation as a bridge to heart transplantation. Two weeks prior to surgery, amino-terminal pro-BNP (NT-proBNP) level was 1318 pg/ml and serum creatinine (SCR) was 1.8 mg/dl. Nesiritide infusion was started on post-operative Day 2 (POD) after surgery when he failed to respond to intravenous high dose diuretics. Immediately the urine output improved and over the next few days SCR improved to a nadir of 1.2 mg/dl. Blood NT-proBNP level was 349 pg/ml on POD 4. On POD 6 Nesiritide was stopped and again he did not respond to high dose diuretics. Nesiritide was resumed after 24 hours with marked improvement in urine output. Further attempts of weaning off Nesiritide drip were futile and led to worsening of renal function. Unfortunately, he developed acute tubular necrosis (ATN) and had to be started on dialysis. He ultimately succumbed to sepsis before heart transplant could take place.

Discussion: In heart failure, BNP and intracellular cyclic GMP synthesis is upregulated, causing vasodilation, diuresis and inhibition of the renin–aldosterone system. With total ventriculectomy as part of TAH implantation, there is a sudden marked decline in endogenous BNP production. Thereupon, renal function declines and diuretic resistance develops. Low-dose BNP infusions post operatively restores the urine output. This finding suggests that BNP may be a useful marker in patients with congestive heart failure. Literature review showed that Nesiritide can be weaned off once endogenous production of BNP from extra cardiac tissue (e.g., brain) is restored usually between POD 7 to 30. In our case, it could not be stopped even 8 weeks after surgery until patient develop ATN and needed dialysis.

An Atypical Case of Renal Tubular Acidosis Type I Laura Onuchic, Talita R. Sanches, Camila Eleuterio Rodrigues, Antonio C. Seguro, Lucia Andrade. Nephrology, Univ of São Paulo, Brazil.

Introduction: Distal renal tubular acidosis (RTA type I) is characterized by impaired urine distal acidification and can be associated with multiple etiologies, including autoimmune diseases, hereditary disorders and drugs.

Case Description: A 34 y/o male presented with a year history of diffuse weakness, vomiting and a 20-kg weight loss. He denial relevant medical history other than alcohol abuse. Laboratory data at admission revealed: serum creatinine 3.9 mg/dl, BUN 47.2 mg/dl, Na 114 mEq/L, K 1.2 mEq/L, Mg 1.8 mEq/L, iCa 3.9 mg/dl, pH 7.22, bicarbonate 9 mEq/L, CPK 1039 IU/L and urinary pH 7.0. TTKG was 10 and the FEK was 25%, extremely high considering low serum K. CT scan revealed a slightly enlarged pancreas and no renal abnormalities. He was started on intravenous saline 0.9% and electrolyte reposition, presenting no recovery of laboratory abnormalities within the following 5 days. Further on he was started on metimazol based on a TSH of 0.02 mU/L and free T4 level was 1318 pg/ml on POD 4. On POD 6 Nesiritide was stopped and again he did not respond to high dose diuretics. Nesiritide was resumed after 24 hours with marked improvement in urine output. Further attempts of weaning off Nesiritide drip were futile and led to worsening of renal function. Unfortunately, he developed acute tubular necrosis (ATN) and had to be started on dialysis. He ultimately succumbed to sepsis before heart transplant could take place.

Discussion: TIO is characterized by oversecretion of FGF23 by tumor cells causing renal tubular acidosis type I. B-Type natriuretic peptide (BNP) related peptides are mainly produced by ventricular myocytes in response to stretch. Its production is upregulated in cardiac failure. However its exact effect on renal function is poorly understood. Total artificial heart (TAH) implantation provides a unique scenario where the role of BNP in renal physiology is highlighted.

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

110A

B-Type Natriuretic Peptide and Renal Physiology Tarapantre Preet,1 Joseph V. Nally,1 Hernan Rincon-Cho,es,1 'Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH;' 1, '1.'

Introduction: B-Type natriuretic peptide (BNP) related peptides are mainly produced by ventricular myocytes in response to stretch. Its production is upregulated in cardiac failure. However its exact effect on renal function is poorly understood. Total artificial heart (TAH) implantation provides a unique scenario where the role of BNP in renal physiology is highlighted.

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Discussion: In heart failure, BNP and intracellular cyclic GMP synthesis is upregulated, causing vasodilation, diuresis and inhibition of the renin–aldosterone system. With total ventriculectomy as part of TAH implantation, there is a sudden marked decline in endogenous BNP production. Thereupon, renal function declines and diuretic resistance develops. Low-dose BNP infusions post operatively restores the urine output. This finding suggests that BNP may be a useful marker in patients with congestive heart failure. Literature review showed that Nesiritide can be weaned off once endogenous production of BNP from extra cardiac tissue (e.g., brain) is restored usually between POD 7 to 30. In our case, it could not be stopped even 8 weeks after surgery until patient develop ATN and needed dialysis.

Funding: Government Support - Non-U.S.
Effect of Lowering Hemoglobin S Level to Less Than 30 Percent on Renal Physiology and Pathology in Sickle Cell Disease

Introduction: Sickled red blood cells in sickle cell disease (SCD) cause repeated episodes of ischemia and reperfusion in all organs, including the kidney. The most common marker of nephropathy from SCD is albuminuria, occurring in 19% of children age 10 and older and 68% of adults. Red blood cell exchange (RBCE) has been documented to prevent stroke, acute chest syndrome, and recurrent pain crises. Thus we investigated the role of RBCE on renal function in SCD patients.

Case Description: Charts of 81 patients with SCD undergoing monthly prophylactic RBCE were reviewed. Excluded were patients with diabetes (1), advanced chronic kidney disease (1), missing data (12), the deceased (2) and those less than 15 years old (7). Variables included a positive ANA, reduced C3 and C4 levels, and negative HBsAg and anti-HCV. The disease is almost always described in ESRD patients and despite intensive combined management, the prognosis of CUA remains poor. This case of calciphylaxis in a renal transplant patient was reported to emphasize the need to maintain a high degree of suspicion in the renal transplant population even more when other risk factors are present.

Primary hyperparathyroidism (PHP) is a condition in which one or more of the parathyroid glands becomes overactive due to an abnormal regulation by calcium and produce parathyroid hormone (PTH) in excess. The prevalence of PHP is 21% of 100,000 person-year, with hyperfunctioning single adenoma of the parathyroid gland is the most common form. The primary major clinical presentation includes polyyuria, nephrolithiasis, hypercalcemia and rarely nephrocalcinosis and renal tubular acidosis (RTA). A 30 year-old man was admitted in the emergency department with subtle weakness in lower limbs. Laboratory studies revealed normal renal function, serum sodium 142 mEq/L, serum chloride 116 mEq/L and CPK 116 U/L. Venous blood gas analysis showed hyperchloremic metabolic acidosis. Urinalysis with density 1010, pH 6,5 and negative proteinuria and hematuria. He had no known diseases and was not taking any medication. He had a family history of nephrolithiasis. The weakness improved with venous potassium replacement. Subsequent laboratory studies revealed PTH 601 pg/ml, phosphate 1,9 mg/L, calcium 11,7 mg/L, albumin 4,5 mg/dL, 25-hydroxyvitamin D 19,9 ng/mL, thyroid stimulating hormone 2,2 nUI/mL and a 24 hour urine calcium of 449mg. The sestamibi parathyroid scintigraphy showed hyperfunction of the lower left gland. After partial parathyroidectomy (PTX) the patient had resolution of the distal RTA.

The type 1 RTA represents the inability of the distal tubule to acidify the urine. The major acquired causes of distal RTA includes Sjögren syndrome, HIV, hyperparathyroidism, use of amphotericin or lithium and vitamin D intoxication. PHA is a rare cause of distal RTA with 5 previous reports (4 indian and 1 philippine) and in 4 of these, PTX solved the RTA. In our case, PTX also treated the patient.

IgG4-related kidney disease (IgG4-RD) is characterized by tissue lymphoplasmacytic infiltration with IgG4-positive plasma cells and CD4+ T lymphocytes. The role of IgG4 in the pathogenesis of the disease is poorly understood and association with autoimmune or infectious triggers is unclear. We describe here an unusual presentation of IgG4-RD in an HIV-positive patient.
lymphoplasmacytic infiltrate and no significant glomerular abnormalities. Immunostaining showed >100 IgG4-positive cells per HPF and serum IgG4 level was >300 mg/dL. Bone marrow biopsy performed to rule out lymphoma was unremarkable and lymph node biopsy showed an average of 130 IgG4 cells per HPF. Once malignancy was excluded and undetectable HIV viral load confirmed, patient was started on prednisone 0.6 mg/day for IgG4-related tubulointerstitial nephritis. Cr level thereafter improved from 3.1 mg/dL to 2.6 mg/dL over the first 10 days of therapy.

**Discussion:** IgG4-RD is a rare multi-systemic disorder, initially described as a cause of autoimmune pancreatitis. To our knowledge, this is the first report of IgG4-RD in an HIV-positive patient, with its only manifestation being renal dysfuction. HIV is known to target CD4+ T cells and some reports have suggested abnormal IgG4 regulation. Given that many patients are now surviving with a long-term diagnosis of HIV, further investigation may be warranted to determine if IgG4-RD is a more frequent, yet less considered, cause of renal dysfunction in HIV.

**TH-PO075**

Apolipoprotein L1 and Soluble Urokinase Receptor in the Activation of Integrin Avb3 and Incident Kidney Disease

Salim Hayek,1 Kwi Hye Kho,2 David Changli Wei,1 Cheryl Ann Winkler,1 Jeffrey B. Kopp,1 Jochen Reiser.1
1Loyola Univ, Maywood, IL.

**Introduction:** Apolipoprotein L1 (APO1) genetic variants are strongly associated with but only partially explain the increased risk of chronic kidney disease (CKD) in African Americans (AA). Immunologic factors such as HIV may synergistically increase the risk of CKD associated with APO1. Soluble urokinase receptor (suPAR) is a marker of immune activation and a predictor of CKD. Mechanistically, suPAR activates podocyte αvβ3 integrin. An interaction between suPAR and APO1 with regards to kidney disease is however unknown.

**Case Description:** We measured plasma suPAR and characterized APO1 genotype in 825 AA patients (mean age 58±12, male 52%, eGFR<60 in 27%) enrolled in the Emory Cardiovascular Biobank. Follow-up serum creatinine was collected (median measures ~7, median follow-up ~10 years). We characterized the cross-sectional association between suPAR and APO1 genotype and determined the interaction between future eGFR decline, suPAR and APO1 risk alleles. We studied the biochemical interaction between APO1, suPAR, and integrin β3 by co-immunoprecipitation (Co-IP) and surface plasmon resonance (SPR).

Patients with 2 APO1 risk alleles (14%, median suPAR 330 pg/mL) had significantly higher levels of suPAR compared to those with 1 (44%, median suPAR 2770 pg/mL) or 0 (42%, median suPAR 2827 pg/mL) after adjusting for baseline eGFR, age, gender and BMI. In longitudinal analyses, patients with 2 APO1 risk alleles and high suPAR levels had a steeper decline in eGFR compared to those with 1 or no alleles (β=2.96, P=0.04 for three-way interaction). Co-IP data show that APO1 wild type protein binds both suPAR and integrin β3. In SPR analysis, APO1 directly binds suPAR (Kd = 11.71 nm). APO1 binds strongly to integrin αvβ3 (Kd = 2.67 nm) but not α3β1. Interestingly, the binding affinity of APO1 to integrin αvβ3 increased 100-fold upon activation of the integrin.

**Discussion:** A synergistic, eGFR independent relationship between suPAR and APO1 explains the heightened risk for kidney disease in patients with 2 APO1 risk alleles. suPAR mediated integrin αvβ3 activation facilitates a high affinity binding of APO1.

**Funding:** NIDDK Support

**TH-PO076**

Serum Free Kappa/Lambda Ratio in Primary Amyloidosis: Can It Be Abnormally Normal? Arouna Senthilkumar, Saud Rana, Kavitha Vellanki. Loyola Univ, Maywood, IL.

**Introduction:** Free light chain quantification is considered to be highly sensitive for diagnosis of primary renal amyloidosis, reported sensitivity as high as 95 to 100%. Here we report a rare case of Primary renal amyloidosis with normal serum and urine free light chain ratio.

**Case Description:** A 67 year old male with no past medical history was referred for evaluation of worsening lower extremity swelling after negative cardiac work up. He continued to experience fever spikes and intermittent gross hematuria despite broad spectrum antibiotics. Renal ultrasound showed hypovascular solitary nodules, as well as renal atrophy. Here, we describe a patient with IgG4-RKD manifesting as predominantly unilateral renal atrophy.

**Case Description:** A 73-year-old woman with obstructive jaundice was first referred to our hospital 6 years prior. At that time, an elevated serum IgG4 level (378 mg/dL) was found and CE-CT revealed a mass in the pancreatic head. Renal lesions were absent. The patient was diagnosed with autoimmune pancreatitis (AIP) and treated with prednisolone (PSL) 30 mg/day. As her AIP symptoms improved and serum IgG4 level decreased, the PSL dose was gradually tapered to 5 mg/day. Her renal function had been normal (Cr 0.7 mg/dL) for 1 year before the current admission, and CT showed no renal atrophy. During the intervening 12 months her renal function declined (Cr 1.1 mg/dL), and she was admitted to our hospital. A urineysis showed no abnormality, CE-CT revealed marked right renal atrophy and multiple low-density lesions on both kidneys. Serum IgG4 level was elevated (204 mg/dL). A renal biopsy was not performed because of the right renal atrophy and malformation of the left renal vein. Through careful examination, we ruled out vascular diseases and clinically diagnosed IgG4-RKD. PSL dose was increased to 30 mg/day. One month later, her renal function improved, with no obvious change in CE-CT findings. Six months later, PSL dose was tapered to 10 mg/day. Her renal function was stable, and no worsening of renal atrophy was seen.

**Discussion:** Bilateral renal atrophy sometimes occurs in patients with IgG4-RKD. However, this patient presented with predominantly unilateral renal atrophy. Renal lesions are sometimes asymptomatic in patients with IgG4-RKD; therefore, when caring for such patients, careful examination is required if the patients’ renal function declines.

**TH-PO078**

Adenovirus Related Granulomatous Intestinal Nephritis Masquerading as Sarcoïdosis in Renal Transplant Recipient Dilek Yarar,1 Pradeep Vartha,2 Stephen O. Pastan,2 Carla L. Ellis.3 1Nephrology Dept, Emory Univ, Atlanta, GA; 2Transplant Nephrology Dept, Emory Univ, Atlanta, GA; 3Renal Pathology Dept, Emory Univ, Atlanta, GA.

**Introduction:** Granulomatous intestinal nephritis is an uncommon entity in kidney transplant recipients.

**Case Description:** A 42-year-old African-American female with a history of sarcoidosis, and antiretroviral therapy for renal disease presumed secondary to hypertensive nephropathy, received a deceased donor renal transplant in 2012. The immunosuppressive regimen was prednisone, mycophenolate mofetil and belatacept. She was admitted in 2016 with fever, chills, myalgia, gross hematuria and acute kidney injury. The patient’s creatinine was 2.6 on admission with baseline creatinine of 1.2-1.5. Workup showed no growth on urine and blood cultures, serum PCR was negative for BK and CMV viruses. Renal ultrasound showed hydronephrosis, but renal function did not improve with percutaneous nephrostomy. She continued to experience fever spikes and intermittent gross hematuria despite broad spectrum antibiotics. Renal biopsy showed severe granulomatous interstitial nephritis with focal areas of necrosis. Given the history of sarcoidosis, she was started on high dose Prednisone. Serum angiotensin converting enzyme level, vitamin D and calcium were normal. Kidney tissue stained positive for adenovirus in the areas of the granulomas; serum PCR was strongly positive for adenovirus. The patient’s symptoms significantly improved with steroids and supportive care. The infectious disease specialist recommended brincidofovir, which the patient refused due to her clinical improvement. She was discharged home on steroid taper. The hematruia resolved and the creatinine decreased down to baseline.

**Discussion:** We report a case of granulomatous intestinal nephritis affecting a renal transplant secondary to adenovirus infection, a known but uncommon entity.
that can be confused with sarcoidosis. Adenovirus infection should be considered in immunocompromised patients with acute kidney injury, hematuria and granulomatous inflammation on renal biopsy.

**TH-PO079**

Renocerebral Reflex Activates Renin-Angiotensin System and Promotes Renal Damage after Ischemia-Reperfusion Injury

**Methods:** Ischemic AKI in C57BL/6J mice was induced by bilateral clamping of the renal pedicles for 45 minutes. The status of renin-angiotensin system, oxidative stress, and activity of sympathetic nervous were studied in AKI mice with or without various inhibitors.

**Results:** Bilateral ischemia-reperfusion activated the intrarenal and cerebral, but not the circulating, renin-angiotensin system, increased sympathetic activity in the kidney and the cerebral sympathetic regulatory regions, and induced brain inflammation and oxidative stress, and kidney injury. Central blockade of central renin-angiotensin system or oxidative stress by intracerebroventricular losartan or tempol reduced the renal ischemic injury score by 65% or 58%, respectively, and reduction of renal effluent sympathetic signal by intracerebroventricular elonidine decreased the score by 52% (all P<0.05). Remarkably, selective blockade of renal effluent sympathetic signal by capsaicin inhibited the upregulation of the brain renin-angiotensin system, and decreased brain oxidative stress, sympathetic activity and inflammation after ischemia-reperfusion injury. Ischemia-reperfusion-induced renal damage and dysfunction persisted after controlling blood pressure with hydralazine.

**Conclusions:** In conclusion, this study demonstrates that ischemia-reperfusion induces AKI in a mouse model, at least in part, by activation of a renocerebral RAS axis interlinked by renal afferent and effluent sympathetic nerves. This identifies a novel mechanism underlying renocerebral interaction in response to renal ischemia-reperfusion, and thereby could lead to new interventional approaches, such as the use of RAS inhibitors, sympathetic agents or even renal nerve ablation.

**TH-PO080**

The Effect of Circulating Extracellular Vesicles on the Response of the Kidney Proximal Tubule to Injury

**Methods:** To complement our ALI profiling data [1], the circulating miRNA response was compared to kidney injury in a mouse model. miRNA profiles were performed using small RNAseq. MiRNAs of interest were quantified in additional human samples and in mice. In mouse models, miRNA containing circulating EVs were isolated after myocardial infarction (MI) or paracetamol-induced acute liver injury (ALI). Murine kidney primary PT cells were co-cultured with fluorescently-labeled EVs and their uptake was quantified by flow cytometry. PT cells exposed to EVs were injured and their viability was determined.

**Results:** 333 miRNAs increased or decreased more than 1.5 fold after CABG compared with control. miR-22, -30a, -30d, -145, -140, -99b, -99, -1, -133a, -23 were successfully back-translated into mice. EVs from MI and ALI models entered PT cells (control EVs: mean fluorescence intensity/S.D 12,989±8282 a.u.; ALI: 17,689±10782 a.u.; MI: 23,541±26915 a.u.). ALI EVs reduced PT cell injury caused by cisplatin (10µM) (ATP luminescent assay ALI:142,300:17307u; control: 84,373;13861u; n=6; P=0.03). EVs had no effect.

**Conclusions:** Liver and cardiac injury induced significant but distinct changes in circulating miRNA. Only EVs from mice with ALI protected PT cells. EVs represent a potential mechanism of liver to kidney signaling that is amenable to therapeutic modulation.

**TH-PO081**

Long-Acting Albumin-Thioredoxin Fusion Protein Prevents AKI-Associated Acute Lung Injury

**Results:** A pharmacokinetic study of HSA-Trx or Trx in mouse showed that the plasma retention and lung distribution of Trx were markedly increased by fusion with HSA. Renal I/R mice showed not only an increase in BUN and serum creatinine levels, but also an increase in neutrophil infiltration in lung and protein concentration in bronchoalveolar lavage fluid (BAL) compared to sham mice. In contrast, systemic administration of HSA-Trx significantly decreased the number of neutrophils in lung and BALF protein compared with PBS administration. HSA-Trx also suppressed the elevation of plasma IL-6 level, CCL1/CCL2 chemokine and oxidative stress in lung.

**Conclusions:** HSA-Trx has potential for use in the treatment of AKI-induced ALI via its extended effects of modulating oxidative stress and inflammation.
Transcutaneous Measurement of Glomerular Filtration Rate to Assess the Progression from Acute to Chronic Kidney Disease following Bilateral Ischemic Injury in Mice

Jianyong Soranno, Chris Altmann, Sarah Faubel. 114A

Background: We previously reported that insufficiencies of antithrombin III (ATIII), the major anti-coagulation molecule in vivo, exacerbated renal ischemia-reperfusion injury in animal models and possibly humans.

Methods: In the present study, we investigated the relationship between ATIII levels and two additional types of acute kidney injury in patients and examined therapeutic effects of ATIII in animal models.

Results: Patients with low ATIII activity had a higher incidence of acute kidney injury (AKI) following severe acute pancreatitis (SAP). Intravenous injection of ATIII (500μg/kg) before or after the induction of SAP in Sprague-Dawley rats did not attenuate pancreatic injury, but significantly attenuated the elevation of serum creatinine, blood urea nitrogen, and renal histological injury. The beneficial effects of ATIII were accompanied with diminished renal inflammatory response, oxidative stress, and tubular cell apoptosis. Similarly, patients with low ATIII activity showed a higher incidence of contrast induced nephropathy (CIN), and the ATIII treatment significantly attenuated contrast induced AKI and improved renal blood flow in rats. In cultured renal tubular epithelial cells, ATIII attenuated tumor necrosis factor α (TNFα) -stimulated intercellular cell adhesion molecule (ICAM)-1 and monocytie chemotactic protein (MCP)-1 upregulation.

Conclusion: ATIII administration may represent a promising strategy for the prevention and treatment of SAP or contrast-induced AKI.

Funding: NIDDK Support, VA Support

TH-PO088

Pulmonary CD40 Levels Are Increased 24 Hours after Ischemia-Reperfusion Kidney Injury

Mark Hepokoski, Laura E. Crotty Alexander, Prableen Singh. 1

Div of Pulmonary and Critical Care Medicine, Univ of California San Diego, La Jolla, CA; 2Div of Nephrology and Hypertension, Univ of California San Diego, La Jolla, CA.

Background: Pulmonary complications are known to significantly increase the mortality of acute kidney injury (AKI) up to 80%. Multiple mediators of lung injury after AKI have been identified, the majority of which induce damage within 24 hours. The purpose of this study was to identify mediators of lung injury that are present 24 hours after AKI, as this is potentially a more useful time point for interventions.

Methods: Mice were randomized to ischemia-reperfusion (IR) kidney injury via 15 minutes of bilateral renal arterial clamping or sham operation (n=4 for each group). Pulse oximetry measurements were obtained prior to surgery and at harvest. At 24 hours, the pulmonary arteries were perfused with PBS to wash out blood and lung parenchyma was harvested, lysates prepared, and levels of 111 common inflammatory mediators were analyzed (Proteome Profiling kit XL Cytokine Array, R&D Systems).

Results: Only 10 inflammatory mediators showed increased levels at 24 hours in IR mice compared to sham controls. Of these, CD40 had the most robust change with a 5-fold increase. There was no difference in mean pulse oximetry measurements between groups, 96.2% in sham compared to 95.8% in IR.

Conclusion: CD40 is a costimulatory protein known to amplify inflammatory cascades, such as NF-κB, a previously described mediator of lung injury after AKI. We show that IR kidney injury leads to a remarkable increase in pulmonary CD40 expression at 24 hours. CD40 may be a mediator of lung injury in the later phases of AKI, and further research into the role of CD40 in lung injury after AKI is warranted.

Funding: NIDDK Support, VA Support

TH-PO087

Expression of Endomucin, an Endothelial-Specific Sialomucin in Normal and Injured Kidneys

Li Li, Xiaoyao Xiao, Takaharu Ichimura, Hong Shi, Zheng Dong, Seiji Soranno, Chris Altmann, Sarah Faubel.

Norwood VA Hospital, Augusta, GA; 3Georgia Cancer Center, Medical College of Georgia, Augusta Univ, Augusta, GA; 4Charlie Norwood VA Hospital, Augusta, GA; 5Georgia Cancer Center, Medical College of Georgia, Augusta Univ, Augusta, GA.

Background: Endomucin (EMCN) is a membrane bound O-sialoglycoprotein. Recent studies suggest that EMCN is part of endothelial glycosylcan and maintains the anti-adhesive property of normal endothelium. The role of EMCN in kidney injury is unknown.

Methods: We have demonstrated that EMCN is expressed in the proximal tubule, and functional evidence of CDK in a murine model of bilateral ischemia-reperfusion AKI. The utilization of non-invasive iGFR monitoring allows for accurate, serial measurements of kidney function following injury.

Funding: Private Foundation Support

TH-PO086

Mir-219 Is a Pro-Fibrotic MicroRNA That Is Hyper-Methylated and Suppressed in Kidney Injury Associated Fibrosis

Qingwei Wei, Chunjing Guo, Xiaoxiao Xiao, Huidong Shi, Zheng Dong, Chunyan Zheng, Zeyuan Huang, Zhenxing Tan, Xiaojie Cheng, Xiaofeng Zhang. 1

Cellular Biology & Anatomy, Medical College of Georgia, Augusta, GA; 2Georgia Cancer Center, Medical College of Georgia, Augusta, GA; 3Georgia Cancer Center, Medical College of Georgia, Augusta, GA; 4Charles Drew University of Science and Medicine, Los Angeles, CA; 5Memorial Sloan-Kettering Cancer Center, New York, NY; 6Second Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang, China; 7Emory University School of Medicine, Atlanta, GA.

Background: Epigenetic regulation, including DNA methylation, plays important roles in gene expression under various patho-physiological conditions.

Methods: To understand DNA methylation after kidney injury, we analyzed the global DNA methylation change in different mouse kidney injury models.

Results: Interestingly, in addition to protein coding genes, the global analysis revealed the hyper-methylation of mir-219-2 in kidney tissues of 3 days of cisplatin nephrotoxicity, 25 minutes of ischemia with 1 week or 1 month reperfusion, and 1 week of unilateral urinary obstruction (UOU). The hyper-methylation was associated by a significant decrease in mir-219 expression in the injured kidneys. In vitro, 48 - 72 hours of hypoxia also lead to a decrease in mir-219 in BUMPT proximal tubular cells. Overexpression of mir-219 in BUMPT cells enhanced the pro-fibrotic reaction during hypoxia or TGF-β treatment, as shown by significantly higher induction of fibronectin. Though immunoblotting did not show obvious difference of TGF-β signaling pathway activation, GSK-3β phosphorylation was significantly increased by mma-mir-219 overexpression. The KEGG pathway analysis of the predicted mma-mir-219 targets from TargetScan indicated that mma-mir-219 may regulate several important pathways related to renal fibrosis regulation, which include insulin signaling pathway, phosphatidylinositol signaling system, MAPK signaling pathway, and WNT signaling pathway.

Conclusions: These results suggest that intrinsic anti-fibrotic mechanisms are activated in response to kidney injury and fibrosis. DNA hyper-methylation of mir-219 may be one of these anti-fibrotic mechanisms, which is activated to repress mir-219, a pro-fibrotic microRNA.

Funding: NIDDK Support, Private Foundation Support

TH-PO085

Transcutaneous Measurement of Glomerular Filtration Rate to Assess the Progression from Acute to Chronic Kidney Disease following Bilateral Ischemic Injury in Mice

Danielle Soranno, Chris Altmann, Sarah Faubel. Univ of Colorado, Aurora, CO.

Background: AKI is common and predisposes patients to developing CKD. Biomarkers used to estimate kidney function (BUN and Cr) are less accurate than measurement of GFR. The utilization of non-invasive iGFR monitoring allows for accurate, serial measurements of kidney function following injury.

Methods: We have demonstrated that EMCN is expressed in the proximal tubule, and functional evidence of CDK in a murine model of bilateral ischemia-reperfusion AKI. The utilization of non-invasive iGFR monitoring allows for accurate, serial measurements of kidney function following injury.

Funding: Private Foundation Support

TH-PO084

Antithrombin III Protects against AKI following Acute Severe Pancreatitis and Contrast Medium Administration

Feng Wang, Zeyuan Lu, Jianyong Yin, Nian-Song Wang. 1

Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People’s Hospital, Shanghai, China; 2Physiology, Medical College of Wisconsin, Milwaukee, WI.

Background: We previously reported that insufficiencies of antithrombin III (ATIII), the major anti-coagulation molecule in vivo, exacerbated renal ischemia-reperfusion injury in animal models and possibly humans.

Methods: In the present study, we investigated the relationship between ATIII levels and two additional types of acute kidney injury in patients and examined therapeutic effects of ATIII in animal models.

Results: Patients with low ATIII activity presented a higher incidence of acute kidney injury (AKI) following severe acute pancreatitis (SAP). Intravenous injection of ATIII (500μg/kg) before or after the induction of SAP in Sprague-Dawley rats did not attenuate pancreatic injury, but significantly attenuated the elevation of serum creatinine, blood urea nitrogen, and renal histological injury. The beneficial effects of ATIII were accompanied with diminished renal inflammatory response, oxidative stress, and tubular cell apoptosis. Similarly, patients with low ATIII activity showed a higher incidence of contrast induced nephropathy (CIN), and the ATIII treatment significantly attenuated contrast induced AKI and improved renal blood flow in rats. In cultured renal tubular epithelial cells, ATIII attenuated tumor necrosis factor α (TNFα) -stimulated intercellular cell adhesion molecule (1ICAM)-1 and monocytie chemotactic protein (1MCP)-1 upregulation.

Conclusion: ATIII administration may represent a promising strategy for the prevention and treatment of SAP or contrast-induced AKI.

Funding: NIDDK Support, VA Support

TH-PO083

Serial BUN and Cr used to estimate kidney function, demonstrates a persistent elevation in BUN and a mild increase in Cr 28 days after AKI. Serial iGFR used to measure kidney function demonstrates a persistent decrease in GFR 28 days following AKI. Picrosirius Red staining demonstrates the presence of cortical fibrosis 28 days following AKI.

Funding: Private Foundation Support
Methods: We investigated the expression of EMCN and PNAd using immunohistochemistry in both normal and injured kidneys. In male B6 mice, ischemia-reperfusion injury (IRI) was induced by clamping the renal pedicle of both kidneys for 27 min at 37 °C. Aristolochic acid nephropathy (AAN) was induced by a one-time intraperitoneal injection AA (5 mg/kg BW).

Results: EMCN stained glomerular and peritubular capillaries in normal kidney, co-localizing with CD31. In post-ischemic mouse kidneys, EMCN staining became significantly thicker and more intense at 1 day. EMCN continued to co-localize with CD31, but did not overlap with F4/80 (macrophages), Ly6G (neutrophils), KIM-1 (injured tubules), von Willebrand factor (vascular structures) and fibroblast. A similar pattern of EMCN staining was observed at day 2, 4, 7, and 9 post-ischemia. At day 28 post-ischemia, EMCN staining returned to baseline thin capillary morphology as observed in normal kidney. In contrast, there was significant loss of the EMCN staining in the AAN model associated with much more fibrosis at day 21 and 42. EMCN co-localized with CD 31 in AAN model. On the other hand, PNAd was not expressed in the day 2 post-ischemic kidneys. On the other hand, PNAd was not expressed in the day 2 post-ischemic kidneys.

Conclusions: These data suggest that EMCN is expressed in normal and injury kidney. Up-regulation of EMCN expression after ischemic injury suggests that EMCN might serve as a specific marker for activated remodeling endothelium. Loss of EMCN in AAN may facilitate endothelial rarefaction. No PNAd expression in ischemic kidney suggests EMCN bears a specific glycosylation epitope and may serve different function in kidney compared to EMCN in HEVs in lymph node.

Funding: Other NIH Support - T32

TH-PO088
Stromally Derived Endothelial Progenitors Mediate Injury after Acute Kidney Injury
Katherine V. Maringer, Jeffrey S. Isenberg, Sander Sims-Lucas, Pediatric Nephrology, Rangos Research Center Children's Hospital of Pittsburgh, Pittsburgh, PA; 2Vascular Medicine Inst, Univ of Pittsburgh, Pittsburgh, PA.

Background: Acute Kidney Injury (AKI) is an abrupt decrease in renal function leading to renal failure, and contributing to high percentages of morbidity and mortality. The kidney contains a complex and high degree of vascularization making it susceptible to ischemic injury. We have identified a subset of stromally derived endothelium (SDE) that is important for kidney vascular development. We hypothesize that SDE are critical to the kidneys ability to recover from AKI.

Methods: To confirm the importance of SDE: following ischemia reperfusion injury (IRI) we performed lineage tracing, using a TdTomato reporter (permanently labeling all SDE cells) and interrogated the percentage of SDE cells that were present in the IRI and compared to normal kidney. Furthermore, we evaluated the effect of treatment with a conditional deletion of Fkhi (flxed) in the Foxd1kre positive renal stroma (Fkhiflex+) and evaluated the tissue after IRI, focusing on the recovery phase (7 days) post injury.

Results: We determined in control mice following IRI that stromal genes were re-expressed suggesting that the stroma may be undergoing de-differentiation and subsequently driving SDE proliferation. Furthermore, using lineage tracing we found that SDE preferentially increase during the repair phase (7 days) of IRI. To evaluate the role of SDE during IRI we used Fkhik+ animals subjected to IRI and found that mutants had less perfusion and an increase in hypoxia at 7 days. This was coupled with inappropriate continued expression of de-differentiation markers in the proximal tubules, which failed to re-differentiate in the hypoxic environment causing exasperated kidney damage in the mutant animals.

Conclusions: Taken together we determined that SDE are important mediators of vascular perfusion after kidney injury. Furthermore, SDE play a vital role in reestablishing normal oxygen concentrations after AKI to regulate the repair of the de-differentiated proximal tubules.

Funding: NIDDK Support

TH-PO089
Genetic Deletion of Endogenous Proangiogenic Factor Vasohibin-2 Exacerbates Renal Ischemic Reperfusion Injury
Katsuyuki Tanabe, Kana Masuda, Yuka Arata, Hitoshi Sugiyama, Jun Wada. Dept of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ Graduate School of Medicine, Okayama, Japan.

Background: During the progression of acute kidney injury (AKI), dramatic alteration in the expression of vasoregulators including angiogenic-related factors has been reported. Understanding the role of such mediators in AKI may lead to development of novel therapeutic strategies. Vasohibin-2 (VASH2) was originally identified as a proangiogenic factor secreted by bone marrow-derived mononuclear cells and it has been shown to be expressed in various malignant tumor tissues. However, its pathogenic role in kidney injury has not been elucidated yet. In the present study, we examined the effects of lacking VASH2 in I/R mouse model.

Methods: Vasohibin-2 (VASH2) was originally identified as a proangiogenic factor secreted by bone marrow-derived mononuclear cells and it has been shown to be expressed in various malignant tumor tissues. However, its pathogenic role in kidney injury has not been elucidated yet. In the present study, we examined the effects of lacking VASH2 in I/R mouse model.

Results: I/R injury caused marked increase in serum creatinine and blood urea nitrogen in WT mice, and such increase was significantly accelerated in VASH2-/- mice (1.05±0.51 vs 2.20±0.41 mg/dl and 143±26 vs 203±25 mg/dl, respectively). Histologically, renal tubular injury (ATN score) following I/R in VASH2-/- mice was significantly exacerbated compared with WT mice. Likewise, increased oxidative stress associated with the accumulation of malondialdehyde and protein carbonyl was more pronounced in VASH2-/- mice.

Funding: NIDDK Support

TH-PO090
Activated CD47 Dysregulates Metabolic Pathways and Cellular Reprogramming in Acute Kidney Injury
Masuda, Yuka, Katsuyuki Tanabe, Lucas, Jeffrey S. Isenberg, Sander Sims-Lucas, 1Pediatric Nephrology, Rangos Research Center Children's Hospital of Pittsburgh, Pittsburgh, PA; 2Vascular Medicine Inst, Univ of Pittsburgh, Pittsburgh, PA.

Background: acute kidney injury (AKI) is a serious disorder that is identified in 50% of ICU patients. We have previously shown that 1) TSP1-CD47 signaling exacerbates ischemia-reperfusion injury (IR) mediated AKI in mice, 2) in some non-renal tissue beds, absence of CD47 was associated with improved mitochondrial function, and that 3) multiple self-renewal factors including Oct4, Sox2, Ki67 and c-Myc (OSKM) are increased in murine CD47+ primary renal tubules. We hypothesize that AKI-induced TSP1-CD47 signaling dysregulates PTEC metabolism pathways and cellular reprogramming to limit kidney healing.

Methods: To localize TSP1-CD47 signaling, we utilized antibodies bound to magnetic beads to selectively enrich for PTEC and renal arterial endothelial cells as compared to whole kidneys from age/ gender matched CD47+ and wild type (WT) mice. RNA sequencing (RNAseq) was performed with whole kidneys of age/ gender-matched WT and CD47+ mice 24 hours after I/R.

Results: TSP1 and CD47, mRNA levels were increased in WT PTEC and endothelial cells compared to whole kidneys. Conversely, cMyc and Ki67 mRNA expression was decreased in CD47+ TPECs compared to WT+TPECs as was VEGF mRNA. CD47+ arterial endothelial cells in post I/R were characterized by increased phosphorylation of the mTOR pathway as well as of mitochondrial and glycolysis were upregulated in CD47+ kidneys.

Conclusions: TSP1-CD47 signaling is maladaptively upregulated in IR-mediated AKI in a cell type specific fashion, suppresses expression of self-renewal factors OSKM, dysregulates oxidative phosphorylation, and suppresses proliferation of PTEC to limit tubule repair.

Funding: Other NIH Support - P01 HL103455, R01 HL108954, IR01HL112914-01A1, P30-DK079307

TH-PO091
Role of IL-17 in the Induction of Fibrosis and Neutrophil Recruitment in Post AKI Rats Fed on High Salt Diet
Purvi Mehrotra, Jane Androuel Collett, Seth D. Mckinney, Jackson Stevens, David P. Basile. Cellular and Integrative Physiology, Indiana School of Medicine, Indianapolis, IN.

Background: T cells have been implicated in the pathogenesis of acute kidney injury (AKI) as well as its progression to chronic kidney disease (CKD). Previous studies from our laboratory suggest that a specific subset of T helper cells, Th17, characterized by IL-17 secretion, is the predominant subtype activated during AKI to CKD transition. Further, inhibition of T cell activity by mycophenolate mofetil (MMF) or losartan, protected from fibrosis in post AKI rats fed on high salt diet, but the role of Th17 cells in AKI-CKD transition is not clear. We hypothesized that T cell deficient rats, may have reduced cytokine levels leading to decrease fibrosis.

Methods: Ischemia and reperfusion was performed on T cell deficient athymic rats (Foxn1nu/nu) and control heterozygote control euthyamic rats (Foxn1+/+) and allowed to recover for 35 days. AKD progression was hastened by unilateral nephrectomy and high salt diet for an additional 4 weeks. These rats were also treated with MMF or vehicle along with high salt diet.

Results: As expected, I/R and high salt diet increased fibrosis in euthyamic rats (206±0.05%) as indicated by an increase in picoresus red staining, which was reduced by MMF treatment (66%; p<0.05). However, the degree of fibrosis was similar in the athymic rats (246%) as compared to euthyamic controls (206%). Surprisingly, MMF treatment had no effect on AKI induced fibrosis in athymic rats. This may be due to the compensatory role, MMF-inhibitory natural killer (NK) T cells in IL-17 production in athymic rats. Blockade of IL-17 activity using IL-17RC soluble receptor (150ng/day), significantly decreased fibrosis in both euthyamic (66%) and athymic (75%) rats as compared to vehicle treated control. In addition, we also observed a decrease in neutrophil recruitment in IL-17 treated rats as compared to vehicle-treated rats.

Conclusions: Taken together, we conclude that IL-17 cytokine secretion from any source plays a central role in the pathogenesis of fibrosis during AKI to CKD transition.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO092
Adenine Overload Causes Severe AKI Progressing to CKD by Activation of Innate Immunity in Rats and Mice Gizeley C S Moreira,1 Flavia G Machado,2 Clarice K Fujihara,1 Benjamin D. Humphreys,2 Roberto Zatz,2 1 Renal Div, Univ of Sao Paulo, Sao Paulo, SP, Brazil; 2 Div of Nephrology, Washington Univ in St. Louis, St. Louis, MO.

Background: Adenine (ADE) overload is a known model of kidney injury due to precipitation of crystals in the tubular lumen leading to epithelial damage and interstitial expansion. Here we investigated glomerular filtration rate (GFR), the role of innate immunity and tubular damage in both rat and mouse models of tubulointerstitial nephritis.

Methods: Adult male Mannich-Wistar rats were fed with chow containing 0.5% of ADE for 1 week and analyzed and 4 weeks after cessation of ADE. A separate group of mice were fed with 0.25% ADE chow for 10 days and evaluated 4 weeks after ADE cessation. GFR was measured through transcutaneous elimination kinetics of FITC-Sinistram.

Results: At the end of 1 week under ADE overload in rats, innate immunity components such as IL1β, IL6, NLRP3 and TLR4 were upregulated. After 4 and 24 weeks of ADE cessation interstitial tubular crystals could be observed and innate immunity protein expression had fallen back to normal levels, translating a foreign body reaction against ADE crystals in tubulointerstitial compartment. At 24 weeks, glomerulosclerosis and collagen interstitial deposition indicating irreversible tubulointerstitial fibrosis. A similar overall pattern was observed in mice, where ADE induced KIM-1 and NGAL mRNA expression to 620-fold and 3810-fold over control. Four weeks after ADE, their expression fell but remained elevated at 20-fold and 555-fold over control. Fibronectin, collagen Iα1, ASMA and F4/80 mRNA were also induced over the 4 weeks time course. Importantly, acute ADE overload induced chronic GFR (1049±96 μl/min/100 g bw at baseline vs. 330.60 μl/min/100g bw ADE 10d, p<0.05) that made an incomplete recovery 4 weeks after discontinuation of ADE (792±18 μl/min/100 g bw, p=0.05 vs. baseline).

Conclusions: ADE overload causes severe AKI that progresses to CKD in both rats and mice. This is mediated by acute activation of innate immunity. The ADE model is an attractive one to study AKI to CKD transition because it is associated with GFR reduction.

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

TH-PO093
Effects of Acute Coxsackievirus Infection on the Kidneys of Non-Obese Diabetic Mice Debra L. Walter,1 Kelly D. Mccall,1 Karen T. Coschigano,1,2 1Biological Sciences, College of Arts and Sciences, Athens, OH; 2Specialty Medicine, Heritage College of Osteopathic Medicine, Athens, OH; 3Biomedical Sciences, Heritage College of Osteopathic Medicine, Athens, OH; 4The Diabetes Inst at Ohio Univ, Athens, OH.

Background: Enteroviruses, like coxsackievirus, are one of the most common virus genera infecting humans worldwide. Enterovirus infections have been documented to mediate a wide range of infections including direct injury as well as indirect injury through mechanisms such as autoimmune disease. Chronic kidney disease (CKD) can result from each type of damage (direct or indirect), however, little work has been done to differentiate the effects of each type of damage as a cause of CKD. This study, therefore, evaluates acute coxsackievirus infection in the kidneys of non-obese diabetic (NOD) mice that are genetically susceptible to develop autoimmune diseases and can ultimately result in CKD. Characterizing the effects of an acute viral infection in the kidneys of these mice will strengthen our understanding of direct virus-induced injury which can then be used to understand chronic kidney disease with respect to virus infection and autoimmune disease both alone and together.

Methods: In the current study, NOD mice were infected with coxsackievirus at 8 weeks of age and euthanized 3, 7, 10 and 14 days post infection.

Results: Coxsackievirus infection within the kidneys of NOD mice peaked at 3 days and disappeared by 14 days post infection. While morphological evaluation has not yet revealed any significant changes, genes involved in kidney damage and the inflammatory response (e.g. IL-6, TLR3, TNFα, CCL2, and others) were found to be significantly upregulated 3 days post infection.

Conclusions: Characterizing the direct effects of an acute virus infection within the kidneys of these mice will strengthen our understanding of the nature of virus-induced acute kidney injury that may trigger CKD resulting from either virus infection (direct), autoimmune disease (indirect) or both together. Together, these data will help identify how CKD develops in different situations and reveal potential treatment strategies for each causative agent.

Funding: NIDDK Support

TH-PO094
Macrophage Promoted Kidney Repair in the Ischemia-Reperfusion Injury via the Activation of IKKa Xin Wan, Changchun Cuo. Dept of Nephrology, Nanjing First Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Macrophage played a notable role in the renal ischemia-reperfusion injury (IRI). IKKa, a key mediator of NF-kB nonclassical pathway was considered could inhibit the progression of inflammation. The roles and underlying mechanisms of IKKa in macrophage was not clear in kidney IRI.

Methods: To investigate the phenomenon of IKKa in macrophages, we generated a chuk knock mouse (IKKα−/−MlysCre, IKKα−/−) and they were submitted to unilateral renal I/R or sham operation. Histomorphological, immunohistochemical methods were performed to judge the kidney samples.

Results: Compared to WT, KO mouse was smaller (<P<0.05). After IRI, the ratio of left kidney and whole weight was higher in KO mouse than they survived more than WT (Figure 1, 2). KO group showed less SDF-1, IL-10 expression in renal epithelial cells than another group, accompanied with a higher injury score (Figure 3, 4).

Conclusions: The IKKa in macrophage was essential for the restoration of kidney injury.

Funding: Government Support - Non-U.S.

TH-PO095
Splenic Marginal Zone Macrophages Regulate NKT Cell Activation in Acute Kidney Injury Elvira Kurnaeva, Liping Huang, Amandeep Bajwa. Medicine, Univ of VA, Charlottesville, VA.

Background: Marginal zone macrophages (MZM) are present in lymphoid and non-lymphoid organs and regulate innate immune responses. In spleen MZM are arranged around the marginal sinus lining and consist of several subsets: CD169−, CD209− or MARCO−. CD169+ MZMs are involved in thymocyteogenesis, capture blood born particles and target endogenous glycolipids to activate splenic NKT cells. In kidney ischemic reperfusion injury (IRI), NKT cell activation through production of IFNα is crucial in initiating ishemic injury. Depletion of NKT cells or use of NKT KO mice Protects kidneys from injury. We functionally evaluated the role of splenic CD169+ MZM to present endogenous glycolipid to activate NKT cells to initiate injury in kidney IRI.

Methods: Renal injury was assessed by plasma creatinine (Pcr; mg/dl). 8-wk old CD169−/− and CD169+/+ male mice were used for all IRI studies. Mice were injected with 10ng/g of dipheria toxin (DT) one day prior to 24 mins or 26 mins of IRI. For NKT functional studies, o-galactosylceramide (o-GaLaCer, 10µg/mouse), was administered 2 days after CD169-depletion and all samples were collected after 2 hrs.

Results: CD169−/− mice are partially protected compared to WT mice (Pcr; 0.8±0.2 vs 6.0±0.31; 26-mins). However, with sub-threshold clamp time of 24 mins, CD169−/− depleted mice have significantly lower Pcr compared to littermates (2.1±0.5, p<0.0011. Sham and CD169−/− depleted IRI mice had comparable IFNα (P<0.05 vs 0.02±0.01). Additionally, CD169−/− depleted mice have less infiltration of CD11bGr1Ly6Chigh (neutrophils) and CD11bGr1Ly6CGlow (monocyte) in kidney kidneys compared to controls. Additionally, administration of o-GaLaCer to CD169−/− depleted mice results in two times less IRI Protection by splenic NKT cells (NKT−/−, 80±15 vs 14.74±4.103, p<0.0003).

Conclusions: Depletion of CD169+ MZM in CD169−/− DTR mouse induced IFNα production by NKT cells, neutrophil and monocyte infiltration into IRI kidneys. Due to prime location of CD169+ macrophages at the MZ of the spleen, our data further demonstrates that endogenous glycolipid presentation takes place in the spleen to regulate ischemic injury and depletion of CD169+ MZM protects kidneys from IRI.

Funding: NIDDK Support

TH-PO096
Acute Splenic Iron Loading Protects against Ischemic AKI Yovesh M. Scindia, Ewa U. Mandziak, Liping Huang, Saleh Mohammad, Sundararaman Swaminathan. Medicine, Univ of Virginia, Charlottesville, VA.

Background: We have previously demonstrated that hepcidin (Hamp) mitigates renal ischemia reperfusion injury (IRI) by inducing splenic iron retention. In these studies, we observed that renal protection was associated with splenic iron accumulation that far out weighed that in the liver and kidney. We therefore hypothesized that strategically iron overloading the spleen with iron preparations known to be targeted to splenic macrophages may be beneficial in renal IRI.

Methods: Mice, C57Bl/6 (WT), and Hamp−/− mice were injected with saline or 14 mg/kg Ferumoxytol (Feraheme) (i.v.), a FDA approved iron nanoparticle preparation in current use for treating anemia of chronic kidney disease. Twenty-four hours later, mice were subjected to renal IRI (24-26 min). In some experiments, WT mice were injected with Ferumoxytol, 2 h post reperfusion. Outcomes (renal function, injury markers, histopathology and inflammation) were examined after 24-72 h of reperfusion.

Results: Ferumoxytol significantly reduced IRI-induced kidney injury in WT mice as measured by plasma creatinine (WT P<; 2.5±0.32 vs Ferumoxytol−/− IRI; 0.38±0.01 mg/dl, p<0.005), NGAL, acute tubular necrosis score and immune cell infiltration. Ferumoxytol protected hepcidin-deficient (Hamp−/−) mice against renal IRI despite the presence of kidney iron overload. Splenic iron accumulation was a common feature in the protected WT and Hamp−/− mice. In contrast, the spleens of injured mice were depleted. Mice injected with Ferumoxytol after the onset of AKI had significantly lower plasma creatinine, after 72 h of reperfusion (WT P<; 1.2 vs Ferumoxytol+IRI; 0.30 mg/dl, p<0.05). The kidneys of the protected mice had more M2 macrophages and loss neutrophils.

Conclusions: Our results reveal a novel protective effect of Ferumoxytol in renal IRI. Moreover, its actions are independent of hepcidin or kidney iron content. The ability of Ferumoxytol to protect against IRI even when administered after the onset of injury highlights its therapeutic potential. These observations validate our previous studies suggesting the critical importance of splenic iron content for inducing protection in ischemic AKI.

Funding: NIDDK Support
A Novel Mouse Model of Acute Kidney Injury Induced by Hemorrhagic Shock

Lei Wang, Jin Wei, ShaoHui Wang, Jie Zhang, Ruisheng Liu. Molecular Pharmacology and Physiology, Univ of South Florida, Tampa, FL.

**Background:** Current animal models for hemorrhagic shock-induced acute kidney injury (HS-AKI) need extensive surgery and monitoring which are very time consuming. The goal of the present study is to develop an easy and reliable mouse model of HS-AKI.

**Methods:** C57BL/6J mice were implanted with radio-transmitters for mean arterial pressure (MAP) measurement. Hemorrhagic shock was induced by left retro-orbital bleeding of 0.4 ml blood. After 30 min, bilateral pedicels were clamped for 18 min at 36.8-37.0°C. One group of mice were then resuscitated with 0.2 ml of collected blood 2-fold diluted with Lactated Ringer’s solution. Another group was not given resuscitation. The clamps were then released to start the reperfusion. Renal blood flow (RBF) was measured in separate non-survival experiments.

**Results:** Hemorrhagic shock reduced MAP from 77 ± 4 to 35 ± 3 mmHg, which returned to 90% of baseline in 3 hours in the resuscitation group and in 8 hours in the non-resuscitation group. Plasma creatinine levels increased from 0.09 ± 0.01 mg/dl to 1.71 ± 0.08 mg/dl in the resuscitation group and from 0.08 ± 0.01 mg/dl to 2.03 ± 0.12 mg/dl in the non-resuscitation group 24 hr after HS-AKI. GFR was decreased by 69% in the resuscitation group and by 78% in the non-resuscitation group (p<0.05, resuscitation group vs non-resuscitation group, n=6/group). All of the above parameters returned to near baseline at 4 weeks after HS-AKI. Hemorrhagic shock reduced RBF from 0.68 ± 0.13 to 0.24 ± 0.09 ml/min. RBF was returned about 92% of baseline with resuscitation, but remained low in the non-resuscitation group. (p=0.01 resuscitation group vs non-resuscitation group, n=5/group).

**Conclusions:** We propose to generate this HS-AKI mouse model without MAP and RBF monitoring by: 1) retro-orbital bleeding 0.4 ml blood; 2) bilateral pedicels clamping for 18 min at 36.8-37°C; 3) with or without resuscitation of 0.2 ml LR + blood via retro-orbital sinus. This new HS-AKI model is a well-controlled, easy and reliable mouse model, which may facilitate investigators to further investigate and understand the mechanisms of HS-AKI.

**Funding:** NIDDK Support

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Estrogen Receptor Alpha Mediates Female Protection from Renal Ischemia-Reperfusion Injury

David J. Rickard,1,2, Robert S. Geske,1,3, Cathly Simmons,1, Jean-Lois D. Klein,1, Robert Kirkpatrick,1,2, Craig Leach,5, Luke Devey,4,1 Target Sciences, GlaxoSmithKline R&D, Collegeville, PA; 2Pipeline Futures Group, GlaxoSmithKline R&D, Collegeville, PA; 3Platform Technology and Science, GlaxoSmithKline R&D, King of Prussia, PA; 4Heart Failure DPU, GlaxoSmithKline R&D, King of Prussia, PA.

**Background:** In AKI, tubular epithelia respond to ischemia-induced hypoxia and nutrient deprivation with oxidative and metabolic stress, leading to cell death, inflammation and impaired kidney function in severe cases. A possible reason for the failure of several promising therapeutic approaches is poor predictability of preclinical models of renal ischemia. We sought to develop a cellular model of renal tubular ischemia amenable to the identification of potential therapeutic targets and agents. Precision-cut kidney slice cultures were used for comparison with the cell model.

**Methods:** HK-2 proximal tubule and primary human renal epithelial cells subjected to chemically-induced redox, hypoxic, metabolic and fibrotic stresses were analyzed for changes in mitochondrial activity, cell death, as well as expression of genes associated with hypoxia, nephrotoxicity and genes identified from patient samples exhibiting delayed graft function (DGF) after renal transplant (see abstract by Kirkpatrick R, et al).

**Results:** HIF hydroxylase inhibitors (hypoxia mimics) and TGFβ1 (fibrosis) both had little effect on cell death, while ATP and glucose deprivation (metabolic stress) induced apoptosis and hydrogen peroxide (oxidative stress) increased necrosis. Despite differing effects on cell death, metabolic and hypoxic stressors caused time-dependent mitochondrial damage. Consistent with their divergent effects on cell health, each stress treatment produced distinct changes in gene expression. Importantly however, the effect of each stressor in epithelial cell culture correlated poorly with the DGF-induced change for a subset of differentially expressed genes. Moreover, gene expression analysis in cultured cortical slices demonstrated a greater number of hypoxia rather than DGF-mediated changes.

**Conclusions:** The DGF tissue dataset indicates that our in vitro models may require an immune component to better recapitulate the complex pathology of AKI.

**Funding:** Pharmaceutical Company Support - GlaxoSmithKline

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Diff erential Susceptibility to Renal Ischemia-Reperfusion Injury in Heterogeneous Stock Rats

David Charles,1, David Houser,1 Bohan Xing,1 Leah C. Solberg Woods,2 Kevin R. Regner,1 1Nephrology; 2Pediatrics, Medical College of Wisconsin.

**Background:** Renal ischemia-reperfusion injury (IRI) is a common cause of acute kidney injury (AKI). In animal models of AKI, we and others have demonstrated that genetic factors may play a role in modulating the severity of AKI. Heterogeneous stock (HS) rats are outbred from eight inbred founder strains and can be used to fine map genes involved in complex traits. The aim of the present study was to evaluate the range of phenotypes in HS rats and HS founder strains following renal IRI.

**Methods:** Groups of eight week old male outbred Sprague-Dawley (SD), inbred HS founder (ACI, BN, BUF, F344, M520, WKY), and outbred HS rats underwent 30 min bilateral renal ischemia and 24 hrs reperfusion or sham surgery. Renal function was assessed by measurement of serum creatinine (sCr) by LC-MS/MS. Tubular injury (TI) was assessed by histologic analysis in kidney sections and immunoblot analysis of neutrophil gelatinase-associated lipocalin (NGAL) expression.

**Results:** TI scores and sCr did not significantly differ between groups 24 hrs after sham surgery. Following IRI, sCr was 4.1 ± 0.22 mg/dl in SD rats. In comparison to SD rats, sCr was significantly lower in the in the BN and WKY founder strains (see Figure). As expected, sCr in HS rats varied across the range found in the inbred HS founder strains (see Figure). Similar trends in TI scores were found in HS founder strains and HS rats. NGAL expression correlated with sCr (r = 0.7, P < 0.01) and with renal cortex TI scores (r = 0.5, P<0.01) in HS rats.

**Conclusions:** In conclusion, we found that susceptibility to renal IRI varied between HS founders and that HS rats exhibited a high degree of variability in response to renal IRI, with some rats completely protected from AKI. This variability indicates that HS rats can be used to fine-map genetic loci and to uncover the causal genes that alter susceptibility to AKI in HS founder strains.

**Funding:** NIDDK Support

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

**Underline represents presenting author.**

117A
Influence of Gender and Regulatory T Cells on Autistic Acidic Osteoclast Pathway in Mice

Lisa

Method: To study the influence of age and sex on HO-1 expression in response to AKI in aged (4 month) and young (2 month) old male and females. C57BL/6 mice were injected with a single intra-peritoneal injection of Cp (20 mg/kg body weight) or saline as control. 1 and 3 days post injections, the kidneys were processed for western blot analyses. Serum creatinine (SCr) was measured by LC-MS/MS. Data and statistical values indicate mean ± SD. FDR was considered significant at 0.05.

Results: SCr values in aging males (3.6±0.40 mg/dL) and females (3.4±0.44 mg/dL) showed worsening of kidney function as compared to the young males (1.69±0.66 mg/dL) and females (0.61±0.12 mg/dL) p<0.01 and p<0.001 respectively, after 3 days post Cp injection. Western blot analyses of kidney homogenates indicated that young mice had significantly higher HO-1 induction as compared to young females 1 day post Cp injection. Young females and males had significantly higher HO-1 induction as compared to aged females and males, respectively, at 1 day after Cp. 3 days post Cp, in contrast to aging females that showed no expression increase, young males returned to baseline saline control treated levels. The increased HO-1 protein levels persisted in young and aging males 3 days after Cp as compared to saline treated control mice. ATG5, a marker of autophagy, was significantly decreased in aging females compared to young females at 3 days post Cp. Levels of p62 were significantly higher in all the aging mice as compared to their younger counterparts after 1 and 3 days of Cp injection.

Conclusions: These results indicate that age and sex influence renal HO-1 expression and after the autophagy pathway after Cp-induced AKI and may contribute to worse outcomes in this setting.

Funding: VA Support

Protective Effects of Heme Oxygenase-2 in Ischemic Acute Kidney Injury

I. Heme Oxygenase-2 (HO-2) isoform. HO-1 is widely recognized as a protectant against ischemic and nephrotoxic AKI. Our prior studies demonstrate that HO-2 protects against heme protein-induced AKI. The current study examined whether HO-2 is protective in ischemic AKI.

Methods: Bilateral renal ischemia (15 minutes) was imposed on young (18-19 wk) and old (80-85 wk) HO-2+/+ and HO-2−/− mice of either gender. Renal function (BUN and serum creatinine) and relevant gene expression were then assessed.

Results: We observed no significant differences in BUN or serum creatinine in young HO-2+/+ and HO-2−/− mice (either male or female) on days 1 and 2 following ischemic AKI. However, for aged male mice, HO-2 deficiency significantly worsened renal function: BUN on day 1 (73 ± 10 vs 113 ± 6 mg/dl) and day 2 (94 ± 15 vs 186 ± 17 mg/dl); serum creatinine on day 1 (0.9 ± 0.1 vs 1.5 ± 0.2 mg/dl) and day 2 (0.9 ± 0.2 vs 1.9 ± 0.3 mg/dl). No significant differences in function were observed in similarly aged female HO-2+/+ and HO-2−/− mice. In aged male mice, HO-2 deficiency also significantly increased the upregulation of a number of genes at day 2 after ischemia, including proinflammatory genes which contribute to ischemic AKI, such as CCL2 (9.8±1 vs 18.3±1.8 AU) and IL-6 (18.9±1.6 vs 36.8±8.3 AU).

Conclusions: We conclude that the protective effects of HO-2 in ischemic AKI are evident in aged male mice and involve, at least in part, suppression of proinflammatory pathways.

Funding: Private Foundation Support

LPS Binding Protein (LBP) Amplifies TLR-4 Signaling and Pericyte (PC) to Myofibroblast Trans-Differentiation (PMT) in LPS-Induced Acute Kidney Injury (AKI)

Methods: AKI was induced by i.v. LPS infusion in 8 pigs (LPS group). After 3h from LPS infusion, 8 pigs were treated with coupled plasma filtration adsorption (CPFA) to remove LBP. Renal biopsies, performed at 9h from LPS infusion (T9), were analyzed by IHC and IF. PC (PDGFRβ) were studied in vitro and analyzed by FACS, IF and WB. Serum LBP and TGFβ were quantified by ELISA.

Results: In endotoxic pigs, we found the occurrence of acute PMT by reduction of PDGFRβ expression and sNMA increase in peritubular PC (Fig.1A, T9LPS vs CTR). CFAA treatment restored PDGFRβ expression and significantly decreased sNMA PC (Fig.1B). PDGFRβ vs CTR and TGFβ vs CTR PC with reduced serum levels of LBP and TGFβ (p<0.05). LPS and endotoxic sera led to PMT in vitro with Collagen I synthesis and sNMA (p<0.05) reorganization in contractile fibers (Fig.1B-C).

The removal of LBP from septic plasma (p=0.05) maintained Collagen I and sNMA expression (p>0.05) at basal
level. On the contrary, LBP supplementation completely reversed CPFA effects (Fig 1D).

Finally, LPS induced acute PMT by both canonical TGFβ-Smad2/3 dependent and non-canonical TGFβ-β-Smad independent signaling (MAPK), by increased phosphorylation of Smad2/3 and ERK1, respectively (p<0.05).

Conclusions: PC might be pivotal in the generation of renal myofibroblasts by PMT during AKI upon LPS/TLR4 signaling pathways. Removal of LBP might represent a potential novel strategy to hamper the acute development of renal fibrosis.

TH-PO106
Role of Adenosine 1a Receptor Signaling on GFR Early after the Induction of Sepsis
Jonathan Street, Erik H. Koritzinsky, Peter S.T. Yuen, Robert A. Star.
NIDDK, Bethesda, MD.

Background: Sepsis is a common condition with a high mortality and morbidity. Organ dysfunction, including acute kidney injury (AKI), strongly predicts adverse outcomes. Kidney injury is diagnosed by a reduced glomerular filtration rate (GFR). The mechanisms underlying a reduced GFR are poorly characterized and have been proposed, in part, to be an adaptive, protective response limiting the metabolic demand on the kidney tubules. The extent of reabsorption by the tubules can be sensed at the macula densa, and adenosine 1a receptor (A1aR) signaling reduces GFR via tubuloglomerular feedback (TGF). We tested whether TGF contributes to sepsis-AKI using A1aR knockout mice.

Methods: Cecal ligation and puncture (CLP) was used as a model of sepsis in A1aR knockout (KO) and wild type (WT) littermate control mice. GFR was monitored using pressure transducer telemetry devices.

Results: In WT, GFR was stable for the first hour following CLP surgery to induce AKI upon LPS/TLR4 signaling pathways. Removal of LBP might represent a potential novel strategy to hamper the acute development of renal fibrosis.

Conclusions: PC might be pivotal in the generation of renal myofibroblasts by PMT during AKI upon LPS/TLR4 signaling pathways. Removal of LBP might represent a potential novel strategy to hamper the acute development of renal fibrosis.

TH-PO107
A Furosemide Excretion Stress Test (FEST) Predicts Mouse Mortality after Sepsis
NIDDK, Bethesda, MD; VA, Washington, DC.

Background: The furosemide stress test (FST) measures urine production after a furosemide bolus. FST is a sensitive and specific predictor of mortality and a need for renal replacement therapy in the ICU. Furosemide must be actively secreted into the proximal tubule lumen to inhibit NCC2 in the thick ascending limb, causing a diuresis. Tube damage should thus reduce furosemide excretion (FEST) and prevent a subsequent increase in urine volume (FST). As filtration markers have limited predictive value of sepsis mortality in mice, we tested FST and FEST in a murine model of sepsis.

Methods: We developed a sensitive reverse phase HPLC assay for urine furosemide. Male CD-1 mice underwent cecal ligation and puncture (CLP) to induce sepsis. 48 hrs post-CLP 1 mg/kg furosemide was given s.c. and urine was collected for the next 12 hrs to allow for intermittent urination. The mice were monitored every 8 hrs and euthanized if their clinical score exceeded the protocol threshold.

Results: A moderate severity of CLP injury was used; 20 of 32 mice survived to 48 hr and underwent FST/FEST, and 15 mice survived 7 d. Urine production during 12 hr varied from 0.08 to 2.62 ml. Both urine production and the fraction of furosemide recovered in the urine predicted mortality [AUC ROC values of 0.92 (p<0.01) and 0.87 (p<0.05), respectively]. There was a strong correlation between time to event and fraction of furosemide recovered in the urine among mice that died, R²=0.96 (p<0.01).

Conclusions: The furosemide excretion stress test and furosemide stress test strongly predict post-sepsis mortality in mice, allowing for early stratification by severity in future drug studies.

Funding: NIDDK Support

TH-PO108
RIPK3 Is a Mediator of Oxidative Stress, Mitochondrial Dysfunction and Necroptosis in Sepsis-Induced Kidney Injury in Mice
Weill Cornell Medicine, New York City, NY.

Background: Sepsis causes multi organ dysfunction including acute kidney injury (AKI). Recent studies have identified Receptor Interacting Protein Kinase-3 (RIPK3) and Mixed Lineage Kinase domain-like protein (MLKL) as key mediators of necroptosis.

Methods: We sought to investigate the role of RIPK3 in sepsis-induced AKI using cecal ligation and puncture (CLP) sepsis model in mice.

Results: We showed that RIPK3 deficiency (Ripk3–/– mice) significantly decreased intracellular vacuolization and improved brush border in proximal tubular epithelial cells compared to Ripk3+/+ mice at 24 h CLP. Furthermore, proteinuria and lipocalin-2 (both in urine and serum) induced in Ripk3+/+ mice at 6 h CLP were significantly reduced in Ripk3–/– mice. We showed increased expression of p-RIPK3, RIPK3, p-MLKL and NOX4 upon 6h LPS treatment in human proximal tubular epithelial (HK-2) cells. Pharmacological inhibition of RIPK3 and NOX4 significantly reduced lactate dehydrogenase levels as compared to LPS treatment alone in HK-2 cells. Knock down of RIPK3 by specific siRNA in HK-2 cells decreased expression of NOX4/1 but NOX2 as compared to scrambled siRNA-treated cells after LPS treatment. Similarly, kidney tissue lysates of Ripk3–/– mice showed decreased expression of NOX4 and MLKL as compared to Ripk3+/+ mice at 6h CLP. Also, elevated mitochondrial DNA levels in the plasma of Ripk3–/– mice at 6 h CLP were reduced in Ripk3–/– mice. Using transmission electron microscopy, we noted increased swelling of intracellular organelles, rupture of outer mitochondrial membrane and poorly defined mitochondrial cristae in proximal tubular epithelial cells of Ripk3–/– mice compared to Ripk3+/+ mice at 24 h CLP. Using immunohistochemistry, we noted decreased nitrotyrosine staining in tubular epithelial cells in Ripk3–/– mice compared to Ripk3+/+ mice at 6 h CLP. Furthermore, kidney tissue lysates of Ripk3–/– mice showed significantly reduced ROS and MDA levels as compared to Ripk3+/+ mice at 6 h CLP.

Conclusions: Together, our data suggest that RIPK3 acts as mediator of oxidative stress and mitochondrial dysfunction and resultant necroptosis in CLP-induced kidney injury in mice.

TH-PO109
Sphingosine Kinase-2 Inhibitor ABC294640 Attenuates Endotoxin-Induced Acute Kidney Injury
Zhi Zho, Yasodha Krishnasamy, John J. Lemasters, Rick G. Schnellmann, "Medical Univ of South Carolina; "Ralph H. Johnson VA Medical Center.

Background: Sphingosine kinase (SphK) is a phosphatidylinositol kinase that mediates signaling in cells and is regulated by sphingosine-1-phosphate (S1P). The liver secretes S1P into the bloodstream, where it is converted to SphK products including sphingosine which can induce necrosis. We hypothesized that blocking endogenous SphK activity may decrease neutrophil and macrophage recruitment in the renal cortex of endotoxin-induced AKI.

Methods: Male C57BL/6 mice were treated with lipopolysaccharide (LPS, 10 mg/kg, ip), and ABC294640, a specific sphingosine kinase-2 (SK2) inhibitor, or vehicle (10% dimethyl sulfoxide, DMSO, ip) for 24 h. LPS and SK2 inhibition decreased renal injury, suggesting that SK2 mediates endotoxin-induced AKI.

Results: At 24 h after LPS treatment, renal pathological changes were mild. Tubular necrosis was absent, but cast formation and inflammatory cell infiltration occurred. TUNEL-positive cells were not increased, and NGAL expression increased, and serum creatinine increased 2.6 folds, indicating LPS-treated AKI. ABC294640 decreased kidney injury and post-LPS death.

Conclusions: ABC294640 decreases endotoxin-induced AKI through a SphK-dependent mechanism. The SphK-2 inhibitor ABC294640 might be useful for the treatment of sepsis-induced AKI.

Funding: VA Merit Award, VA Biomedical Research and Development Program, NIH (DK59630, HL83483, DK069628, DK080567, TL1-TR000428, KL2TR000434), and Ohio State University.
serum creatinine after LPS treatment. LPS increased Nfkb p65 phosphorylation and TLR4 and ICAM-1 expression, indicating increased inflammatory signaling. Myleoperoxidase, F4/80, and CD4, markers of neutrophils, monocyte/macrophages, and T lymphocytes, respectively, also increased, confirming leukocyte infiltration. ABC294640 decreased these inflammatory responses and inflammatory cell infiltration. In control mice by intravital imaging. TMRM fluorescence, a marker of mitochondrial membrane potential, was bright and punctate in tubular cells, indicating mitochondrial polarization. Depolarization occurred in >60% tubular cells after LPS, indicating mitochondrial dysfunction. Reactive nitrogen species are known to cause mitochondrial dysfunction. iNOS expression increased in the kidney after LPS treatment. ABC294640 blunted iNOS expression and mitochondrial depolarization.

Conclusions: SK2 inhibition by ABC294640 attenuates endothelin-induced AKI, most likely by inhibiting inflammatory responses and prevention of mitochondrial dysfunction. Funding: NIDDK Support

TH-PO110

Protective Role of AMPK in Sepsis-Associated AKI Ying Li, Elanore Hall, Hai Pham, Prabhleen Singh. Medicine, UC San Diego & VASDHS, San Diego, CA.

Background: Sepsis-associated acute kidney injury (s-AKI) significantly contributes to morbidity and mortality in critically ill patients. Effective therapeutic strategies for s-AKI are limited due to incomplete understanding its pathogenesis.

Methods: We performed FITC inulin clearance to examine renal function and other functional and molecular analyses to examine mitochondrial dysfunction in the pathogenesis of sepsis using a model of cecal ligation and puncture (CLP). 24 hours post injury. Mitochondrial function was evaluated in fresh isolated proximal tubules by assessing oxygen consumption rates (OCR) during oxidative phosphorylation with a high-throughput XF96 Seahorse® analyzer. We also evaluated the role of AMPK in mitochondrial function in sAKI.

Results: At 24 hours post-CLP, GFR was significantly reduced in CLP mice (345±19 vs. 155±35 uL/min; p<0.004). AICAR (AMPK activator) treatment 24 hours prior to CLP significantly improved GFR. CLP mice displayed elevated basal OCR rates, and significantly increased maximal respiratory OCR in the presence of uncoupler, FCCP. This was eliminated by pre-treatment with AICAR. AMPK was decreased in CLP kidney, along with decreased fusion proteins (Mfn1 and Mfn2). Expression of an autophagy protein Beclin was decreased while apoptosis protein cleaved caspase 3 was increased. Pre-treatment with AICAR increased AMPK and ATP levels in CLP kidney and increased fusion and autophagy proteins in the CLP kidney.

Conclusions: Our findings indicate cellular stress with decreased AMPK is associated with abnormal regulation of signaling pathways involving autophagy, apoptosis, mitochondrial function and mitochondrial biogenesis, which may play an important role in the pathogenesis of sepsis associated AKI. AMPK and its signaling pathway may serve as novel therapeutic targets in s-AKI.

Funding: NIDDK Support, VA Support

TH-PO111


Background: A common factor in many forms of kidney disease is increase of reactive species of oxygen (ROS) and nitrogen (RNS). Enhanced production of ROS/RNS affects the redox state of molecules such as the alarmin high mobility group box 1 (HMGB1). HMGB1 is released from the kidney following sepsis-induced acute kidney injury (AKI), and can promote repair or damage depending on its redox state. We hypothesized that during sepsis-induced AKI, elevated ROS/RNS cause an imbalance of antioxidants and promote HMGB1 oxidation and its pro-damage effects.

Methods: After injection of either a low or high dose of lipopolysaccharide (LPS) to induce sepsis in mice, kidney samples were fractionated, and the redox of HMGB1 and antioxidant activity were measured. Experiments also measured cytokine release in mice plasma after injection of reduced or oxidized HMGB1. In cell culture experiments, endothelial and proximal tubule cells were treated with LPS and glutathione/thioredoxin inhibitors, with subsequent analysis of HMGB1 redox.

Results: High dose LPS enhanced ROS/RNS and blunted thioredoxin activity in the kidney, while lower dose caused less pronounced ROS/RNS increase and enhanced thioredoxin activity. Glutathione activity paralleled thioredoxin, except when nuclear activity. High LPS dose enhanced HMGB1 oxidation in the cytoplasm, plasma and extracellular matrix (ECM). AICAR (140 mg/kg) increased HMGB1 to healthy levels accompanied by release of anti-inflammatory cytokines, while reduced HMGB1 stimulated release of pro-inflammatory cytokine. In cell culture experiments, glutathione and thioredoxin activity inhibitors augmented HMGB1 oxidation. However, glutathione inhibition diminished the protective effects in proximal tubular cells, while thioredoxin inhibition was more effective in proximal tubular cells.

Conclusions: Low dose LPS upregulated antioxidants, while higher dose enhanced ROS/RNS, increased oxidation of HMGB1, and altered levels of antioxidants which maintained HMGB1 in a reduced state. Release of pro-inflammatory cytokine after injection of oxidized HMGB1 is indicative of the alarmin’s role in inflammation, while reduced HMGB1 promotes reparative processes.

TH-PO112

Real-Time Quantification of Temporal and Cell Specific Oxidative Stress in the Ischemic Kidney Tomoaki Miyazaki, Yun-Wei A. Hsu, Neal A. Paragas. Medicine, Univ of Washington, Seattle, WA.

Background: A key factor in acute kidney injury (AKI) has been oxidative stress (OS) after the ischemic event. A classic model of AKI is renal ischemia and reperfusion (IR) which leads to OS due to hypoxia during ischemia and subsequent generation of reactive oxygen species (ROS) during reperfusion. A major ROS is hydrogen peroxide (H2O2) and excess H2O2 can be injurious, however to date, there has never been a cell-specific, non-invasive, real-time, and longitudinal method to quantitate this H2O2 after an acute kidney injury.

Methods: We created the following mice expressing the luciferase (luc) gene in a cell specific manner: Aquaporin2, HoxB7, Podocin, and E2a. Luc cell-specific reporter mice were injured by 30 min bilateral I/R and H2O2 activity imaged at 3, 6, 12 and 24 hrs after perfusion using an optical imaging system. Using a novel H2O2 sensitive caged-luciferin substrate, that only releases luciferin to react with luciferase in the presence of H2O2, we quantified cell specific changes of H2O2 after I/R.

Results: At 24 hrs after surgery while Podocin-Luc2 showed increased H2O2 activity at 24 hrs. At the peak, E2a-Luc2 mice, the global luciferase expressers, had 10% increase in H2O2-luminescent flux while both Aquaporin2-Luc2 and HoxB7-Luc2 both had 10% increase in H2O2-luminescent flux. Podocin-Luc2 mice had log orders less increase in H2O2-luminescent flux within the 24 hr reperfusion period.

Conclusions: For the first time, we demonstrate the feasibility of quantifying kidney ROS non-invasively and longitudinally in the living animal in a cell-type specific manner. These early data reveal that the cells of the nephron and the collecting duct have logarithmic order differences in ROS generation after AKI. Here we prove that the ability to monitor H2O2 generation non-invasively in a cell-specific manner will permit the identification of cell-types susceptible to OS during an AKI and ultimately lead to mapping the time-course of kidney OS. This is a powerful new system to better understand the pathophysiology of renal disease progression and to test the specificity and efficacy of novel therapeutics.

Funding: NIDDK Support

TH-PO113

Interleukin-(IL)-36 Axis Is Modulated in Mice Acute Kidney Injury Model and Human Urine Hirofumi Nishikawa, Naoki Arima, Tatsuki Matsumoto, Yoshiko Shimamura, Kosuke Inoue, Yoshinori Taniguchi, Taro Horino, Shimpei Fujimoto, Yoshio Terada. Dept of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi Univ, Nankoku, Kochi, Japan.

Background: IL-36 is a newly named cytokine of the IL-1 cytokine family comprising three members, IL-36α, IL-36β and IL-36γ. All three IL-36 isoforms bind to a heterodimeric receptor (IL-36R receptor) and IL-36R (IL36R). IL-36 axis plays roles in inflammation and tissue repair. However, little is known about the role of IL-36 axis in acute kidney injury (AKI) pathogenesis.

Methods: We evaluated the role of IL-36 in renal function in bilateral renal ischemia (28 min)/reperfusion injury (IRI) model using IL-36R knock-out (KO) and wild type (WT) mice. We evaluate the localization of IL-36 in WT mice kidney by confocal microscopy. Plasma was evaluated cytokine (PCR), BUN, IL-6 and kidneys were prepared for histology. Total kidney tissue mRNA was measured by RT-qPCR. The effects of IL-36α on NF-kB and TNF-α expression in WT and IL-36R KO mice were examined in cultured renal tubular cells. In clinical study, we measured urine IL-36α in AKI patients, and immunohistochemical examination of IL-36α in AKI and minimal change renal biopsy sample.

Results: IL-36α was expressed in mainly proximal tubules in WT mice. IL-36R KO mice showed significantly lower PCR (0.41 ± 0.12 versus 1.08 ± 0.21 mg/dl), BUN (65.3 ± 14.8 versus 158 ± 31.5 mg/dl) and IL-6 (2.43 ± 5.7 versus 39.6 ± 7.9 ng/ml) at 24h after IRI compared to WT. Immunohistochemical examination showed mild tubular injury in IL36R KO mice compared to WT mice. IL-36α, IL-36β, and IL-36γ expression were up-regulated at 24h post IRI. IL-36α expressions were observed at neutrophil (74%) and proximal tubules. IL-6 and TNF-α expressions after AKI were lower in IL36R KO mice compared to WT mice. In vitro experiments, up-regulation of NF-kB and Erk activity was observed by IL-36α and WT mice.

Conclusions: These data demonstrate that IL-36 axis plays pathologic roles in AKI induced mice AKI. IL-36α is up-regulated in renal tissue not only mice AKI but also human AKI. These results indicate that IL-36 blockage could be a potential therapeutic target of AKI.
Disregulated Chromogranin A Expression in Acute Kidney Injury
Saiful A. Mir, Jacob Story, Anneke Arlene Stengel, Linda Awdishu, Prabheleen Singh, Ravindra L. Mehta, Sucheta M. Vaingankar. Medicine, Univ of California at San Diego, La Jolla, CA.

Background: Chromogranin A (CHGA) is a component of the adrenergic pathway and the index granin protein in dense core vesicles of the adrenal medulla and sympathetic axons. It is co-stored and co-released with catecholamine and is elevated in human hypertension and certain conditions of hypertension. CHGA expression in human sympathetic axons is a complication associated with AKI, therefore CHGA expression was investigated in AKI patients. Mouse model over-expressing CHGA was employed to understand the consequence of dysregulated CHGA expression.

Methods: Serum samples from AKI patients and healthy controls were tested for CHGA using in-house sandwich ELISA and kidney tissue by qPCR. CHGA overexpression was validated in AKI mice, a mouse model expressing excess CHGA, by immunohistochemistry and western blotting.

Results: AKI patients displayed higher BP and HR contrasting with mice expressing normal levels of CHGA. Mice mimicking this human phenotype of elevated CHGA also displayed higher BP and HR contrasting with mice expressing normal levels of CHGA. The adrenal medullary cells of mice expressing excess CHGA showed an increase in total number and size of vesicles and mitochondrial abundance. The physiological consequences of elevated CHGA is increased adrenergic tone in humans line, caused upregulation of UCP2.

Conclusions: Upregulation of CHGA in AKI patients may contribute to increased regulatory T cells, which can modulate immune responses in AKI. Mortality rate of AKI patients is high due to increased inflammation, fibrosis, and increased CHGA in AKI patients. However, the specific contribution of tubular JNK signalling in kidney disease remains to be determined.

Benefit of Mineralocorticoid Receptor Antagonism in Acute Kidney Injury (AKI): Role of Smooth Muscle Rac1

TH-PO115
JNK Signaling in the Proximal Tubule Is Crucial for Renal Ischaemia Reperfusion Injury
Keren Grinberg,1 Elsey Ozols,2 William R. Mulley,2 Frank Yuanfang Ma,3 David J. Nikolic-Paterson.1,2
1Nephrology, Monash Univ, Clayton, VIC, Australia; 2Dept of Medicine, Monash Univ, Clayton, VIC, Australia.

Background: Activation of the JNK signaling pathway in tubular epithelial cells is evident in most forms of acute and progressive renal injury, including renal IR injury. However, the specific contribution of tubular JNK signaling in kidney diseases remains to be established. Kidney cells express the two main JNK isoforms (Jnk1 and Jnk2), with considerable redundancy. We created mice lacking the Jnk1 gene in proximal tubules (via gamma-glutamyl transpeptidase Cre with global Jnk2 gene deletion (termned Jnk2Cre)). These mice are viable with normal kidney structure and function but lack Jnk expression in the S3 segment of the proximal tubule.

Methods: Bilateral warm I/R injury was induced in groups (n=8) of Jnk2Cre, Jnk2−/−, and wild-type (WT) mice. Mice were killed 24hr after IR surgery. Controls underwent sham surgery.

Results: Renal I/R injury caused acute renal failure in both WT and Jnk2−/− mice (178±6 vs 170±23 umol/L serum creatinine, respectively; both P<0.001 vs 12±4 umol/L in sham operated). In contrast, Jnk2Cre mice undergoing IR showed marked protection from renal failure (121±21 umol/L; P<0.01 vs other I/R groups). This protection was associated with reduced tubular damage [79±3% WT, 75±4% Jnk2−/−, 61±8% Jnk2Cre]; P<0.01 vs other I/R groups and a 35% reduction in Kim-1 mRNA levels in Jnk2Cre vs other I/R groups; p<0.05]. A 60% reduction in infiltrating neutrophils and a 40% reduction in macrophages was evident in Jnk2Cre vs other I/R groups (p<0.01). Up-regulation of mRNA levels for pro-inflammatory molecules (CCL2, NSO2, IL-6) was substantially reduced in Jnk2Cre vs other I/R groups (p<0.05).

Conclusions: This study establishes that JNK signaling in proximal tubular epithelial cells plays a critical role in cell damage and renal dysfunction in acute IR injury. Funding: Government Support - Non-U.S.

TH-PO116
P2X7 Receptor Activation Induces Renal Tubular PAD4 to Excacerbate Ischemic AKI
H. Singh, Ravindra Mir,2, Jacob Story,2 Anneke Arlene Stengel,2 Linda Awdishu,2 Prabheleen Singh,1 Saiful A. Mir,2
1Anesthesiology, Columbia Univ, New York, NY; 2Pathology, Columbia Univ, New York, NY.

Background: Acute kidney injury (AKI) due to ischemia and reperfusion (IR) is a major clinical problem without effective therapy. We recently demonstrated that peptidylarginine deiminase 5 (PAD5) is induced after renal IR to exacerbate ischemic AKI. Moreover, ATP is a recently recognized DAMP molecule and exacerbates ischemic AKI via P2X7 purine receptor activation. Therefore, we tested whether P2X7R activation directly exacerbates ischemic AKI by inducing PAD4, PAD4 WT or PAD4 KO mice were pretreated with 5mg/kg BaATP or with vehicle 24 hr prior to 20 min renal IR injury.

Results: ATP and ATP plus BaATP induced P2X7R expression and activity in mouse and human renal proximal tubule cells, implicating a critical role for P2X7R activation in AKI. P2X7R blocking and BaATP mimicked the ATP-mediated induction of renal tubular PAD4, respectively. Consistent in our in vitro findings, BaATP significantly increased mouse kidney PAD4 expression and activity in vivo. Supporting a critical role for PAD4 in ischemic AKI, mice overexpressing PAD4 were protected from ischemic AKI. AKI mice, treated with 10µM BaATP and 0.1N HCl or with vehicle 24 hr prior to 20 min renal IR injury.

Conclusions: Taken together, our studies show that ATP via P2X7R activation induces renal tubular PAD4 in vitro and in vivo. We also show here a critical role for P2X7R-mediated exacerbation of ischemic AKI via induction of PAD4.

Benefit of Mineralocorticoid Receptor Antagonism in Acute Kidney Injury

TH-PO118
Renal Afferent Neurons Are Altered by Lipopolysaccharides

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

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Conclusions: LPS significantly decreased the ease of AP production of renal neurons while the responsiveness to acidic milieu was increased. Neurogenic renal CRGP release was also increased by LPS. These findings may contribute to the complex sympatho-paracrine alterations seen in SIRS affecting kidney and the cardiovascular system. *Funding:* Other NIH Support - Deutsche Forschungsgemeinschaft

**TH-PO119**

Resolvin D1 Modulates Renal Cell Apoptosis in Lipopolysaccharide-Related Acute Kidney Injury

**Yu Li, Feng Fu, Yidong Zhou, Wanderley R. de Carvalho, Jianwu Zhang, Claude M. Shoelson, Yong Chen, Garcia, S. John, and Yang Min.**

**Background:** Resolvin D1 (RvD1) is a newly found anti-inflammatory bioactive compound derived from polyunsaturated fatty acids. Our previous research revealed a renal protective effect on Lipopolysaccharide (LPS)-related AKI of RvD1 by down-regulating NF-κB signaling pathway. The current study aims to observe the influence of RvD1 on renal cell apoptosis during LPS-related AKI in *in vivo* and *in vitro*.

**Methods:** Male BALB/c mice and human proximal tubule epithelial cells (HK-2) were randomly divided into control group (saline), LPS group (LPS) and RvD1 group (LPS+RvD1) and blockage group (LPS+RvD1+Boc-MLP). Boc-MLP is a RvD1 receptor blocker. The drugs were intraperitoneally injected or added into culture medium at targeted concentrations. The mice kidneys and HK-2 cells were harvested at different time points respectively.

**Results:** *In vivo* experiment, RvD1 inhibited the up-regulation of Bax/Bcl-2 mRNA ratio by LPS, which was mitigated in blockage group. LPS activated the expression of Caspase-3 mRNA in mice kidney, but RvD1 inhibited its activation. TUNEL staining indicated RvD1 suppressed cell apoptosis in mice kidney. *In vitro* study, RvD1 was effective in down-regulating Caspase-3 mRNA expression in renal tubular epithelial cells. Interestingly, RvD1 also increased Bax/Bcl-2 mRNA ratio. Flow cytometry recorded a higher proportion of apoptosis in RvD1 group than in LPS group (P=0.002) and control group (P=0.002) and control group (P=0.002) and control group (P=0.002). (figure 1)

**Conclusions:** In LPS-related AKI, the effect of RvD1 on renal cell apoptosis is complex. RvD1 imposed a pro-apoptotic influence directly on tubular epithelial in *in vivo*, while showing a general anti-apoptotic effect *in vitro*. The underlying mechanism needs further research.

**Figure 1. flow cytometry of HK-2 cell apoptosis (A: control group; B: LPS group; C: RvD1+LPS group)**

**TH-PO120**

Shikonin Elicits a Nephroprotective Effect in a Murine Model of LPS-Induced Septic AKI by Triggering Nrfl2 Activation with Anti-Oxidative Responses

**Qiu Yu, Sheng Qian, Bo Yin, Di Wang, Min Xu, Qian Wang, and Tao Wang.**

**Background:** Sepsis-induced AKI is developed frequently in the patients with decreased immunocompetence, resulting in severe renal failure. For the effective treatment of septic AKI, infusion therapy and/or anti-inflammatory treatments are provided, however, the efficacy is insufficient to reach recovery of survival rates, requiring development of therapeutics. Shikonin is a naturally occurring herbal medicine extracted from the red root wormwood, possessing proteasome inhibition and antioxidant effects. The present study explored a preventive effect of shikonin against LPS-induced septic AKI and its molecular events.

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

**Underline represents presenting author.**

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**TH-PO123**

**Urine Exosome Excretion Varies Diurnally in Rats**  
Erik H. Koritzinsky, Jonathan Street, Robert A. Star, Peter S.T. Yuen.  
NIDDK, Bethesda, MD.

**Background:** Urine exosomes are a promising source of non-invasive biomarkers for kidney health. Kidney transport and function have circadian patterns. Normalization by urine creatinine is thought to account for most physiologic diurnal variation in kidney function, allowing for diagnosis using a spot urine collection rather than a timed 24 hr collection. It is unknown if urine exosome excretion similarly varies throughout the day in normal animals.

**Methods:** Timed 4-hour urine collections were obtained from healthy, untreated male SD rats over a 24 hour period with free access to food and water and housed in a facility with a 24 hr light/dark cycle [Light: 6AM – 6PM; Dark: 6PM – 6AM]. Urines were centrifuged for 4 hr urine fractions by ultracentrifugation. Quantification of exosome concentration (number/mL) was assessed by Nanosight analysis. Because of variability in total 24 hr urine exosome excretion rate between animals, hourly exosome excretion rates for each 4-hour fraction were normalized to peak exosome excretion in each animal.

**Results:** The normalized urine exosome excretion rate increased during the light period, peaking at the start of the dark period, then subsequently fell during the dark period. The observed circadian pattern of exosome excretion did not temporally correspond to that of urine flow rate. The relative amplitude of the variation (peak to trough ratio) was 5.4-fold for exosome excretion and 3.85-fold for urine flow.

**Conclusions:** Urine exosome excretion in rats displayed a circadian pattern that was not directly linked to that of urine flow. Because of a large daily variation in normal urine exosome excretion rates, the time urine of collection must be considered. Prospective urine exosomal biomarkers should be evaluated for circadian rhythms. As exosomes serve as a form of cell-cell communication in other contexts, the functional significance of this circadian pattern in urine exosome excretion is unknown.

**Funding:** NIDDK Support

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**TH-PO124**

**Enrichment of miR192 in Urinary Exosomes following Ischemia-Reperfusion Injury in Rats**  
Erik H. Koritzinsky, Jonathan Street, Tiffany R. Bellomo, Hua Zhou, Robert A. Star, Peter S.T. Yuen.  
NIDDK, Bethesda, MD.

**Background:** We previously identified urine exosomal miR192 as a candidate biomarker for renal ischemia-reperfusion injury in rats (Zhou et al, ASN 2008). Two hypotheses arose from these observations: a) the number of exosomes were increasing with a constant abundance of miR192 or b) the number of exosomes was relatively unchanged with an increased abundance of miR192 per exosome. We used Nanosight analysis to determine exosome number, and then measured the temporal excretion of exosomes by collecting timed urine fractions.

**Methods:** Male Sprague-Dawley rats (250-290 g) underwent bilateral ischemia-reperfusion injury in rats. Acute kidney injury was confirmed by a rise in BUN 24 hours after surgery. Urine was collected in metabolic cages for 24 hours. Exosomes were isolated from 4 hr urine fractions by ultracentrifugation. Quantification of exosome concentration (number/mL) was assessed by Nanosight analysis. Because of variability in total 24 hr urine exosome excretion rate between animals, hourly exosome excretion rates for each 4-hour fraction were normalized to peak exosome excretion in each animal.

**Results:** The normalized urine exosome excretion rate increased during the light period, peaking at the start of the dark period, then subsequently fell during the dark period. The observed circadian pattern of exosome excretion did not temporally correspond to that of urine flow rate. The relative amplitude of the variation (peak to trough ratio) was 5.4-fold for exosome excretion and 3.85-fold for urine flow.

**Conclusions:** Urine exosome excretion in rats displayed a circadian pattern that was not directly linked to that of urine flow. Because of a large daily variation in normal urine exosome excretion rates, the time urine of collection must be considered. Prospective urine exosomal biomarkers should be evaluated for circadian rhythms. As exosomes serve as a form of cell-cell communication in other contexts, the functional significance of this circadian pattern in urine exosome excretion is unknown.

**Funding:** NIDDK Support

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**TH-PO125**

**Stoichiometry of the Protein TSG101 in Urine Exosomes**  
Erik H. Koritzinsky, Jonathan Street, Tiffany R. Bellomo, Angel M. Aponte, Robert A. Star, Peter S.T. Yuen.  
NIDDK, Bethesda, MD; NHBLI, Bethesda, MD.

**Background:** Novel biomarkers for kidney health, including miRNAs, have been identified in urine exosomes. Surprisingly, miRNAs are stoichiometrically present in a small fraction of biofluid-derived exosomes (~1%), making miRNA unsuitable to normalize exosomal biomarkers. As TSG101 is a protein in the ESCRT complex involved in exosome biogenesis, it is assumed to be present in exosomes in high copy number, and thus is commonly used as a surrogate marker for exosome number. However, the number of molecules of TSG101 per exosome is not known, nor is it known to be constant.

**Methods:** Spot urine samples were obtained from 7 healthy volunteers (3 M, 4 F; Age 21-55) then treated with protease inhibitors. Urine exosomes were isolated by ultracentrifugation. Absence of quantification of molecules of exosomal TSG101/mL was assessed by Western blot using a 4 point dilution series (standard and samples) with a TSG101 standard of known concentration. Quantification of exosome concentration (number/mL) was assessed by Nanosight Nanoparticle Tracking Analysis.

**Results:** In 7 healthy adults, samples ranged from 4.39x10^10 to 7.87x10^10/umL/mL urine and 3.37x10^9 to 1.08x10^10/umL/mL urine. The stoichiometry of molecules of TSG101 per exosome in urine averaged 10.2 ± 4.0 (SD) copies per urine exosome (range of 5.2 to 15.8).

**Conclusions:** Exosome concentration and TSG101 concentration varied 18-fold and 32-fold from person to person, but the stoichiometry of TSG101 per exosome was relatively stable across healthy human subjects. There were ~10 TSG101 molecules/urine exosome. TSG101 may be a valid surrogate for exosome number to normalize urine exosomal biomarkers. Normalization using TSG101 is easier and less costly than Nanosight analysis, and easier to interpret than normalization using miRNA.

**Funding:** NIDDK Support

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**TH-PO126**

**Urinary Activin A: A Novel Urinary Biomarker for Acute Kidney Injury**  
Dept of Medicine and Clinical Science, Gunma Univ Graduate School of Medicine, Maebashi, Gunma, Japan.

**Background:** Activin A, a member of the TGF-β superfamily, is known to regulate cell growth and differentiation in various tissues. We previously reported that activin A, which was absent in normal kidney, was increased in the post-ischemic rat kidney and negatively regulates the repair process of renal tubules after injury (Maeshima et al. JASN 2001). This study was conducted to examine whether activin A can be detected in the urine from mice with renal ischemia-reperfusion injury and patients with acute kidney injury (AKI).

**Methods:** Ischemia-reperfusion injury was induced in C57BL/6 mice. Mice were sacrificed at 6, 24, 48, 72, 120 hours after operation, and the kidneys and urine were collected for analysis. Urine samples were collected from patients with AKI as well as from eight healthy volunteers. Urinary activin A was measured by ELISA. Correlation of urinary activin A with urinary N-gal, urinary KIM-1, and clinical parameters were analyzed.

**Results:** The expression of activin A was markedly up-regulated in the post-ischemic mouse kidney. Immunoreactive activin A was detected in KIM-1-positive proximal tubular cells of the outer medulla in ischemic kidneys, but not in normal kidneys. Activin A was absent in the urine of normal mice. In contrast, activin A was detectable in the urine of ischemic mice. Urinary activin A was almost undetectable in healthy volunteers, but was significantly increased in patients with AKI (19.6 ± 2.3 vs. 257.9 ± 174.6 ng/gCr, p<0.001). There was a significant correlation of urinary activin A level with urinary N-gal and follistatin (activin antagonist), but not with urinary KIM-1 or eGFR.

**Conclusions:** Activin A can be detected in the urine of patients with ATN and may serve as a useful biomarker for renal proximal tubule injury.

**Funding:** Pharmaceutical Company Support - Astellas Pharma Inc.
TH-PO127
Profile of Urinary Microparticles in Cisplatin Nephrotoxicity in Mice
Gabor Bodonyi-Kovacs, Christine Rudy, Thu H. Le, Uta Erdbraugger. Renal Div, Univ of Virginia, Charlottesville, VA.

Background: Acute kidney injury (AKI) is associated with increased mortality and risk of progression to chronic kidney disease. Its diagnosis is based on rising levels of serum creatinine - a late and nonspecific marker of reduced kidney function. Urinary microparticles (uMP) are candidate biomarkers for earlier and minimally invasive diagnosis and prognosis of AKI. We hypothesized that a distinct uMP profile characterizes cisplatin-induced AKI.

Methods: 11-19 week old 129S6 male mice received either ip. injection of 25 mg/kg cisplatin or equal volume of saline. Serum and urine were collected 72 hours later. Serum creatinine was measured using an enzymatic, colorimetric kit (Crystal Chem). Urine was frozen and stored in -80 C. A uMP pellet was generated from thawed urine with differential centrifugation. Enumeration and phenotyping of uMPs was performed with imaging flow cytometry using the following markers: podocalyxin (podocyte derived), Insulin-like growth factor-binding protein 7 (IGFBP7, inducer of G1 cell cycle arrest, implicated in AKI), collectrin (tubular cell marker) and Annexin V. Results were analyzed by a two sided t-test.

Results: The cisplatin treated mice had significantly elevated serum creatinine (n=4, 2.35 ± 0.54 mg/dl) compared to saline treated controls (n=4, 0.1 ± 0.07 mg/dl), p=0.003. Animals with AKI had lower level of IGFBP7 positive microparticles compared to controls, 1.8 x 10^5 and 7 x 10^6 particles per ml respectively, (p=0.044), Figure 1.

Conclusions: Severe cisplatin induced AKI is associated with significantly lower IGFBP7 positive uMP levels. Future studies are needed to examine the diagnostic role of these vesicles in earlier stages of AKI and assess their potential mechanistic and prognostic roles.

Funding: NIDDK Support

TH-PO128
Differentiation of Human Kidney Organoids in High Throughput-Compatible Formats Modeling Nephrotic Injury
Stefan Czernecki, Ramila E. Gulieva, Laura V. Islas, Yong Kyun Kim, Neal A. Paragas, Benjamin S. Freedman. Div of Nephrology, Kidney Research Inst, and Inst for Stem Cell and Regenerative Medicine, Dept of Medicine, Univ of Washington, Seattle, WA.

Background: Kidney organoids derived from human pluripotent stem cells (hPSCs) are a potentially powerful tool for high throughput discovery, but their complexity poses a challenge for miniaturization and automation. We tested whether kidney organoids could be generated in high throughput formats for modeling nephrotoxicity.

Methods: hPSCs were seeded and differentiated in 96-well and 384-well plates both 1) manually, using multi-channel pipettors, and 2) automatically, using liquid handling robots to perform all steps. Kidney markers were characterized by high content imaging analysis, compared to kidney tissue sections. Injury biomarker induction was monitored by flow cytometric analysis, compared to kidney tissue sections. Injury biomarker induction was monitored by a two sided t-test.

Results: Differentiation was robustly achieved in 96-well and 384-well formats with several hPSC lines using both manual and fully-automated protocols. Each 384-well contained ~30 miniature kidney organoids (~300 organoids/cm^2). Analysis of >20 tubular and podocyte markers revealed transporters and nephron sublineages similar to developing kidney. Kidney treatment induced 4-fold upregulation of kidney injury molecule 1 (KIM-1) in proximal tubules, using a high throughput-compatible assay.

Conclusions: hPSC-derived kidney organoids can be generated and analyzed in fully-automated, high throughput-compatible formats. Miniaturized cultures retain sufficient complexity to model nephrotoxicity in proximal tubules. High throughput compatibility, coupled with human specificity, makes this platform an attractive starting point for screening approaches, focusing on therapeutic discovery, toxicity, and regenerative medicine. (Supported by Northwest Kidney Centers)

Funding: NIDDK Support, Pharmaceutical Company Support - Northwest Kidney Centers (Unrestricted Gift), Private Foundation Support

TH-PO129
Probiotics Attenuate Progression of CKD via Expanding Tregs in Mesenteric Lymph Node
Sang-Kyung Jo, Jihyun Yang, Sung Yoon Lim, Young Ju Na, Myung-Gyu Kim, Won-Yong Cho. Dept of Internal Medicine, Div of Nephrology, Korea Univ Medical College, Seoul, Republic of Korea.

Background: Emerging evidence showed the presence of kidney-gut crosstalk and alterations in intestinal barrier or dysbiotic gut microbiota have been demonstrated in diverse pathological processes including chronic kidney disease (CKD). Regulatory T cells (Tregs) exert anti-inflammatory effect and the decrease of Tregs has been shown to be associated with inflammatory phenotype and disease severity. The purpose of this study was to investigate the effect of probiotics on the progressive CKD and also the mechanisms. TLR2, 4 and 9 compared to controls (all, P<0.05). TLR2 and 4 co-localized with endothelial CD68, CD15, nephrin, and TLR ligands fibrinogen and high mobility group box 1 (HMGB1).

Methods: Kidney biopsies from patients with a first presentation of AA V (38), Lupus (8), and controls (minimal change and thin membrane disease, 10) were examined by confocal microscopy for the distribution of TLR2, 4 and 9 and evaluates altered TLR expression in relation to the severity of renal injury.

Results: Kidney biopsies from patients with a first presentation of AAV (38), Lupus (8), and controls (minimal change and thin membrane disease, 10) were examined by confocal microscopy for the distribution of TLR2, 4 and 9 and evaluates altered TLR expression in relation to the severity of renal injury.

Conclusions: This study first demonstrated that alteration of normal intestinal immune homeostasis (decreased Tregs in colon, mesenteric LN) and barrier disruption (colon epithelial cell apoptosis) was associated with inflammation, progression of CKD. Probiotics seem to be promising as one therapeutic strategy in progressive CKD as their immune modulatory mechanisms.

Funding: Private Foundation Support

TH-PO130
Toll-Like Receptor 4 Is Dominantly Expressed Compared to Toll-Like Receptor 2 and 9 in Kidneys of Patients with Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis
Kim M. O’Sullivan,1,2 Sharon Lee Ford,1,2 A. Richard Kitching,1,2 Stephen R. Holdsworth,1,2 Centre for Inflammatory Diseases, Dept of Medicine, Monash Univ; Clayton, Australia; 1Dept of Nephrology; Monash Health, Clayton, Australia.

Background: Infections can initiate and exacerbate disease in patients with anti-neutrophil cytoplasmic antibody associated vasculitis (AAV). Toll-like Receptors (TLRs) may be the link between infection and autoimmunity. This study investigates the distribution of kidney TLR2, 4 and 9 and evaluates altered TLR expression in relation to the severity of renal injury.

Methods: Kidney biopsies from patients with a first presentation of AAV (38), Lupus (8), and controls (minimal change and thin membrane disease, 10) were examined by confocal microscopy for the distribution of TLR2, 4 and 9 and evaluates altered TLR expression in relation to the severity of renal injury.

Results: Kidney biopsies from patients with a first presentation of AAV (38), Lupus (8), and controls (minimal change and thin membrane disease, 10) were examined by confocal microscopy for the distribution of TLR2, 4 and 9 and evaluates altered TLR expression in relation to the severity of renal injury.

Conclusions: This study first demonstrated that alteration of normal intestinal immune homeostasis (decreased Tregs in colon, mesenteric LN) and barrier disruption (colon epithelial cell apoptosis) was associated with inflammation, progression of CKD. Probiotics seem to be promising as one therapeutic strategy in progressive CKD as their immune modulatory mechanisms.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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Elevated Microparticle Tissue Factor Activity Predicts Venous Thromboembolism in ANCA Vasculitis

Elizabeth J. Brant, 1,3 Carmen E. Mendoza, 1 Matthew L. Medemott, 1 Yuchun Hu, 1 Susan L. Hogan, 1 J. Charles Jennette, 1 Ronald J. Falk, 2 Patrick H. Nachman, 2 Vimal K. Deregail, 1 Donna O. Bunch, 1 (UNC Kidney Center; Dartmouth-Hitchcock Medical Center)

Background: Venous thromboembolism (VTE) is a complication of ANCA vasculitis (AAV). While AAV patients and the cells involved have not been elucidated, but tissue factor (TF)-bearing microparticles (MP) may play a role. We hypothesized that elevated microparticle tissue factor activity (MPTFa) is associated with VTE in AAV and analyzed the cellular source.

Methods: Patients with VTE (VTE++, n=21) were enrolled during active disease. Patients with VTE (VTE++, n=11) were included whether active or in remission at the time of VTE. Longitudinal platelet-free plasma samples were assayed for MPTFa and compared to 15 healthy controls (HC). Isolated MP were incubated with Factor Xa and Factor X. Absorbance was measured after adding Factor Xa chromogenic substrate. Recombinant, relipidated human TF was the standard used to determine TF concentration. Values were expressed as percent relative to positive controls. Surface expression of TF was measured by flow cytometry. A Mann-Whitney test was used to compare continuous variables.

Results: Demographics were similar among patients and HC. VTE++ and VTE++ patients did not differ in ANCA serotype or titer, BVAS, D-dimer or other laboratory data, or organ involvement. VTE++ patients had significantly higher peak MPTFa than VTE++ patients (median 16.1 vs 3.4; p<0.0001). MPTFa of VTE++ patients was similar to HC (2.4 ± 0.3). Four of six VTE++ patients with available stored samples had elevated MPTFa within 6 months prior to VTE++. VTE++ patients had higher %TF-C14 monocytes than HC (median 19.9 vs 1.8; p=0.009), and CD14+CD16- inflammatory monocytes than HC (23.8 vs 9.5; p<0.03) and VTE++ patients (4.1, p=0.04). Our other preliminary in vitro data show that ANCA IgG triggers release of MP with TFa in HC blood.

Conclusions: Patients with AAV who develop VTE have increased MPTFa, whereas those without VTE rarely exhibit MPTFa higher than HC. Our data suggest that elevated TFa may be a potential target for therapeutics.
Conclusions: We conclude that ABIN1 dysfunction mediates a novel intrinsic podocyte-neutrophil interaction that determines the severity of podocyte injury in GN. Our data suggest that genetic regulation of podocyte NF-κB activity controls injury through release of cytokines that recruit neutrophils. Inhibition of neutrophil granule release is a novel therapeutic intervention for preventing podocyte injury in GN.

Funding: NIDDK Support, Other NIH Support - NIAIM AR063124, NIADDK AI0800, NIDDK DK102542, VA Support, Clinical Revenue Support

TH-PO136
Function of the Atypical Chemokine Receptor 2 in Murine Immune Complex Glomerulonephritis - Andrea Bidak, Volker Vielhauer. Nephrologisches Zentrum, Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-Universität, Munich, Germany.

Background: The atypical chemokine receptor 2 (ACKR2), also named D6, is unable to induce cell signaling but can regulate local chemokine levels by internalization and degradation. Here we characterize the role of ACKR2 in murine autologous nephrotic nephritis (NTN).

Methods: NTN was induced in C57/B6 wild-type and Ackr2-deficient mice by injection of sheep antibodies against mouse glomerular basement membrane.

Results: At 2 weeks Ackr2+/- mice showed increased albuminuria, serum creatinine and urea levels than wild-type controls. Histological analysis revealed increased structural damage in the glomerular and tubulointerstitial compartment of Ackr2+/- kidneys. By flow cytometry these findings correlated with a higher renal leukocyte infiltration of CD4+ T cells and mononuclear phagocytes in Ackr2+/- mice. As a possible cause, Ackr2+/- mice demonstrated higher levels of inflammatory chemokines CCL2 and CCL5 in nephritic kidneys. Further histological analysis revealed that increased leukocyte infiltration resulted from higher numbers of T cells and macrophages in the tubulointerstitial compartment of Ackr2+/- mice, whereas leukocyte numbers in glomeruli were comparable. Accordingly, in vitro experiments with TNF-stimulated renal cells showed that increased chemokine levels in Ackr2+/- mice resulted from a reduced ACKR2-mediated chemokine degradation in the tubulointerstitial compartment. Furthermore, Ackr2-/- mice showed decreased T-cell activation resulting in a reduced adaptive cellular immune response.

Conclusions: These results are consistent with the known expression of Ackr2 in interstitial lymphatic endothelial cells, assuring efflux of activated leukocytes into locoregional lymph nodes. However, the decreased adaptive immune response shown in Ackr2-/- mice did not result in decreased renal inflammation during NTN because of simultaneously increased tubulointerstitial chemokine levels and a higher renal leukocyte infiltration in Ackr2-/- mice. Our data indicate that ACKR2 plays an important role in limiting renal inflammation in NTN and therefore identifies ACKR2 as a potential target molecule for therapeutic approaches in immune complex-mediated glomerulonephritis.

Funding: Government Support - Non-U.S.

TH-PO137
A Novel Targeting Strategy to Inhibit Deleterious TNF Signaling in Nephrotic Nephritis - Rudolf Lucas, Maggie McMenamin, Nino Kvikvelia, Supriya Sridhar, Maritza J. Romero, Istdvan Czikora, Michael P. Madaio. Vascular Biology Center and Dept of Medicine, Medical College of Georgia, Augusta Univ, Augusta, GA.

Background: Activation of the p38 MAPK pathway by TNF in glomerular endothelial cells (GEC) represents a central mechanism of renal inflammation in nephrotic serum (NTS)-induced nephritis (NTN). Strategies to inhibit TNF receptor signaling, using neutralizing antibodies or soluble TNF receptors, can impair host defense to infection. In this study, we evaluated the therapeutic potential of the TNF-derived TIP peptide in NTN. This peptide mimics the lectin-like domain of TNF, blunts acute lung injury in several species and does not affect TNF receptor-mediated anti-bacterial activities.

Methods: TIP peptide or inactive mutant peptide were evaluated when applied systemically in murine NTN (13.5 μg/g NTS). To determine whether the effects were local or systemic, glomerular targeting was evaluated after linking the peptide to the human F1,1 mAb directed against α2(HIV) collagen, in more severe NTN (14.5 μg/g NTS). All agents were given i.p. after induction of nephritis every second day from day 2 on (n=10 per group). To further evaluate the glomerular specific effects of TIP peptide its actions on TNF-induced p38 MAPK activation in GEC were assessed using Western blotting analysis of the phosphorylated p38 ratio.

Results: Systemic delivery of active, but not mutant TIP peptide significantly reversed nephritis (histology, proteinuria, BUN, macrophage infiltration) on day 7, and this was associated with reduced plasma levels of TNF, IL-6, IL-1β and MCP-1. Renal delivery of TIP peptide-F1 complex reduced mortality from 100% to 20% on day 6 and improved histology in more severe NTN. In culture, TIP peptide abrogated TNF-induced activation of p38 MAP kinase in GEC.

Conclusions: Local actions of TNF-derived TIP peptide ameliorate ongoing nephritis, at least in part, due to direct effects on glomerular cells. Therefore, application of strategies that specifically target deleterious effects of TNF in acute glomerulonephritis (GN) locally, without either interfering with beneficial anti-bacterial activities of the cytokine or inciting inflammation, has therapeutic potential.

Funding: NIDDK Support

TH-PO138
APOL1 mRNA Is Partially Retained in the Nucleus and Is Associated with Increased Levels of Phosphorylated Protein Kinase R Koji Okomato,1 Maarten Hoek,2 Myung Shin,2 Jeffrey B. Kopp,1 NIDDK, NIH, Bethesda, MD; 2Merk Research Laboratories, Kenilworth, NJ.

Background: APOL1 coding variants G1 and G2, compared to ancestral G0, are strongly associated with glomerular diseases. We have previously found that APOL1 renal risk variants contribute to podocyte injury by activating interferon-inducible, double-stranded RNA-activated protein kinase (PKR). Cytoplasmic PKR is central to the cell stress pathway, activating the metabolic inflammasome and suppressing protein synthesis. PKR also resides in the nucleus where its function is unclear, although nuclear PKR levels are increased in leukemia and neurodegenerative disease (e.g. Huntington disease, in which PKR preferentially binds mutant huntingtin transcripts).

Methods: BAC/APOL1 transgenic mice bear the APOL1 gene locus. We conducted knock-down experiments using conditionally immortalized human podocyte cell lines established from human urine and we generated stable HEK293 cell lines over-expressing APOL1 variants.

Results: In BAC/APOL1 transgenic mice, the amount of nuclear phosphorylated PKR was increased, G1=G2>G0. By confocal microscopy, phosphorylated PKR formed nuclear speckles. APOL1 G1/G2 heterozygous podocytes manifested strong signals for nuclear phosphorylated PKR (intensity: 759±169), which was lacking in G0/G0 podocytes (intensity: 328±119). In APOL1 G1/G2 dual heterozygous podocytes but not in G0/G0 podocytes, knock-down of APOL1 RNA reduced nuclear phosphorylated PKR by 28.7%. In APOL1 over-expressing HEK293 cells, APOL1 nuclear mRNA was increased with the G1 (152±9%) and G2 variants (176±8%) compared to cells that were transfected with the G0 variant (106±13%) (100% set as nuclear ratio in housekeeping genes). Nuclear mRNA retention was 70-fold higher than housekeeping genes (β-actin, GAPDH), and APOL1 nuclear RNA levels were 12-fold higher following transfection of the coding sequence and 3’ UTR, compared with transfection of coding sequence alone.

Conclusions: APOL1 mRNA and phosphorylated PKR were present in the nucleus, at higher levels with the risk variants. The APOL1 3’UTR contributes to nuclear localization of mRNA. Nuclear PKR may serve as a reservoir for delivery to the cytoplasm, contributing to the stress response.

Funding: NIDDK Support

TH-PO139
APOL1 Renal Risk Variant Alleles Reduce Cholesterol Efflux in Murine Bone Marrow-Derived Macrophages June-Hwa Ryu,1 Hidefumi Wakashiu,1 Alex Dinh,1 Alan Remaley,1 Maarten Hoek,2 Myung Shin,2 Alessia Fornoni,3 Jeffrey B. Kopp,1 NIDDK, National Insts of Health, Bethesda, MD; 2Merk, Kenilworth, NJ; 3Univ of Miami School of Medicine, Miami, FL.

Background: Apolipoprotein L1 (APOL1) genetic variants G1 and G2, compared to the common allele G0, are major risk factors for non-diabetic kidney disease in African descent populations. APOL1 is a protein component of HDL. Reverse cholesterol transport(RCT) involves the transport of cholesterol to HDL by cellular ABCA1, with subsequent delivery from peripheral tissues to the liver. With impaired RCT, macrophages become foam cells, releasing inflammatory factors. We asked whether the APOL1 risk variants alter macrophage cholesterol efflux.

Methods: Bone marrow monocytes were isolated from wild-type mice(WT) and from BAC/APOL1 transgenic(G0, G1, and G2) mice, which carry a bacterial artificial chromosome with the human APOL1 genomic region. Monocytes were differentiated into macrophages using M-CSF(50 ng/mL) for 7d. Macrophages were stimulated for 24h with IFN-γ(20 ng/mL) to induce the M1 phenotype or with IL-4(20 ng/mL) to induce the M2 phenotype. For cholesterol efflux assays, cells were incubated with [3H]-cholesterol for 24h. After incubation with efflux ligands for 4h, [3H]-cholesterol in the supernatant and cell lysates were quantified.

Results: M1 and M2 macrophages showed the expected polarization according to cytokine stimulation. M1 and M2 macrophages derived from APOL1 G1 and G2 mice showed significantly decreased cholesterol efflux compared to WT or G0 macrophages.

Conclusions: We found that APOL1 G1 and G2 variants decrease cholesterol efflux in macrophages. These results have potential therapeutic implications for treatment of diabetic kidney disease.

Funding: NIDDK Support

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

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TH-PO140

Spleen Tyrosine Kinase Inhibitor Ameliorates Tubular Inflammation in IgA Nephropathy

Wai Han Yu, Dickson W.L. Wong, Haojia Wu, Kam Wa Chan, Yang Liu, Loretta Y.Y. Chan, Joseph C.K. Leung, Kar Neng Lai, Sydney C.W. Tang. *Dept of Medicine, The Univ of Hong Kong, Queen Mary Hospital, Hong Kong.

Background: Spleen tyrosine kinase (Syk) is a non-receptor tyrosine kinase involved in signal transduction in a variety of immune responses. It has been demonstrated that inhibition of Syk has therapeutic effects in antibody-mediated glomerulonephritis and this protein tyrosine kinase plays a pathogenic role in orchestrating inflammatory responses and cell proliferation in human mesangial cells in IgA nephropathy (IgAN). However, the therapeutic potential of Syk inhibition in tubulointerstitial damage in IgAN remains unknown.

Methods: Human proximal tubular epithelial cells (PTECs) were stimulated with conditioned medium prepared from human mesangial cells incubated with polymeric IgA (IgA-HMC) from patients with IgAN or healthy control subjects. The effect of Syk inhibitor R406 on the expression of inflammatory cytokines was detected by real-time qPCR and ELISA, and NFκB signal transduction in activated PTECs was determined by Western blotting. Furthermore, expression of phosphorylated Syk protein was examined on renal biopsies from patients with IgAN and normal control by immunohistochemistry.

Results: The synthesis of IL-6, IL-8 and ICAM-1 in PTECs were upregulated at both mRNA and protein levels after incubation with IgA-HMC conditioned medium from IgAN patients when compared to that from healthy control subjects. Pretreatment with R406 significantly suppressed IgA-HMC conditioned medium-induced pro-inflammatory cytokine production and also attenuated the phosphorylation of NFκB p65 subunit in the activated PTECs. Finally, the phosphorylated level of Syk was increased in renal tubules of patients with IgAN compared to that of the healthy controls.

Conclusions: Syk mediates inflammatory responses in tubular cells, suggesting a role for this kinase in tubulointerstitial damage of IgAN. These data also supported a therapeutic potential of Syk inhibitor in IgAN. Fund support: Hong Kong Society of Nephrology and Hong Kong Kidney Foundation Research Grant (2015).

TH-PO141

TLR9 Activation Induced Overproduction of Aberrantly Glycosylated IgA Via Activation of BAFF in Patients with IgA Nephropathy

Yuko Makita, Hitoshi Suzuki, Toshihiko Kano, Atsiko Takahata, Bruce A. Julian, Jan Novak, Yusuke Suzuki. 1*Nephrology, Juntendo Univ Faculty of Medicine, 2Univ of Alabama at Birmingham.

Background: Involvement of Toll-like receptor (TLR)9 has been discussed in the pathogenesis of IgA nephropathy (IgAN). There is increasing evidences that galactose-deficient IgA1 (Gd-IgA1) and immune complexes (ICs) consisting of Gd-IgA1 are important players in the pathogenesis of IgAN. We recently demonstrated that IL-6 can enhance the production of Gd-IgA1 and IgA1 transformed T cells in IgAN patients, but not in healthy controls. Moreover, B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL) may be involved in the overproduction of nephritogenic IgA1. However, the mechanisms leading to overproduction of nephritogenic IgA and progression of IgAN are still unclear. In present study, we examine the mechanisms of TLR9-mediated activation of IgA-producing cells.

Methods: Commercially available quiescent ddY mice were divided into two groups with (n=8) or without (n=8) stimulation by TLR9 agonist (Cpg-ODN) for 12 weeks. Renal histological lesions and serum levels of IgA, IgG, IgA-IgG ICs and aberrantly glycosylated IgA were measured. Results: Cpg-ODN administration caused increase of monocyte chemoattractant protein-1 (MCP-1) mRNA in cultured MCs, but not in cultured PTECs. Fund support: Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 24390291 and 16H06558.

Results: Mice treated with Cpg-ODN showed overexpression of TLR9, MyD88, BAFF, APRIL, and B cell maturation antigen (BCMA). These mice had elevated serum levels of aberrantly glycosylated IgA and IgA-IgG ICs. Serum levels of aberrantly glycosylated IgA and IgA-IgG IC correlated with BAFF expression. In vitro, Cpg-ODN stimulation induced secretion of soluble BAFF via elevation of IL-6, resulted in production of aberrantly glycosylated IgA. The production of aberrantly glycosylated IgA correlated with increased soluble BAFF. In human IgA1-secreting cell lines, TLR9 activation enhanced production of Gd-IgA1 through the same pathways, i.e., IL-6-mediated BAFF production.

Conclusions: TLR9 activation exacerbated murine IgAN by enhancing production of aberrantly glycosylated IgA and nephritogenic ICs. This TLR9-mediated activation involved IL-6 and BAFF overproduction in murine as well as human IgA-secreting cells.

TH-PO142

(Pro)relin Receptor-Mediated ERK1/2 and Wnt Signaling Pathway in Crescent Glomerulonephritis

Maki Urushihara, Takashi Nagai, Shuji Kondo, Yasumasa Ikeda, Toshihiko Tamaki, Shoji Kagami. 1Dept of Pediatrics, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan; 2Dept of Pharmacology, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan.

Background: (Pro)relin receptor (P(R)R)-bound renin and (pro)relin not only become enzymatically active but also cause intracellular signaling pathway activation. We recently showed that direct renin inhibition ameliorated the magnitude of crescent glomerulonephritis (GN) using rat experimental model and suggested that inflammation and cell proliferation via (P(R)R) involved in the pathophysiology of glomerular crescent formation.

Methods: To clarify the mechanism of (P RR)-mediated intracellular signaling in glomerular crescent formation, we induced crescentic GN model by anti-glomerular basement membrane antibodies in WKY rats and treated with direct renin inhibitor (DRR).

Furthermore, we examined the signal transduction in cultured mesangial cell (MCs) and proximal tubal epithelial cell (PTECs) transfected with (P RR) specific small interference RNA (siRNA).

Results: Anti-GMN nephritis model developed severe glomerular crescent, accompanied by increased CD68 positive macrophage infiltration and glomerular expression of MCP-1. Administration of phospho-ERK1/2 and phospho-phospho-histone H3 were present in crescent GN model and not in isolated glomeruli. Treatment with DRR markedly suppressed those augmentations. Recombinant renin (rRenin) stimulation induced cell proliferation in cultured PTECs and increase of monocyte chemoattractant protein-1 (MCP-1) mRNA in cultured MCs, but not in cultured PTECs. siRNA transfection of PTECs suppressed signal transduction in activated PTECs by Western blotting. Furthermore, expression of phosphorylated Syk protein was examined on renal biopsies from patients with IgAN and normal control by immunohistochemistry.

Conclusions: These data suggest that ERK1/2 and Wnt4 signaling pathways via (P RR) are involved in cell proliferation and macrophage infiltration in crescentic GN.

TH-PO143

Autotaxin Inhibition Decreases Inflammation and Fibrosis in Experimental Model of Crescentic Glomerulonephritis

Makoto Makita, Takeshi Murata, Hideaki Shimada, Akira Maeda, Naoshi Fukushima, Christos Chatziantoniou, Masahiro Tani, Laura Badi, Christoph Ullmer, Roche Basel Innovation Center, Hoffmann- La Roche, Basel, BS, Switzerland; 1Clinical Pathology Dept, Univ of Hospital of Geneva, Geneva, Ge, Switzerland; 2INSERM UMR S 1155, Hopital Tenon, Paris, France.

Background: Autotaxin (ATX) is a secreted enzyme catalyzing the conversion of lysophosphatidylcholine to choline in the majority of extracellular lipids. ATX produced from activated G-protein coupled receptors (LPRs). In a number of organs, elevated plasma levels of LPA have been associated to fibrosis. Specifically in kidney, preclinical evidence in ATX knockout model showed LPA deficiency ameliorated ATX activity demonstrated in the same model where fibrosis was significantly attenuated in LPA-RKO mice compared with wild type mice. In addition to that specific role in fibrosis, LPA is associated to a vast number of tissues to inflammation. All findings let us investigate the mechanism of ATX inhibition in preserving renal function and its specific mode of action (MoA) in that model.

Methods: Sv129 mice were injected with nephrotoxic serum (NTS) and a selective ATX inhibitor was administered 1 day prior lesion induction. Functional assessment was carried out at 4, 7 and 14 days post NTS injection with evaluation of blood urea nitrogen, proteinuria or urine cystatin C. Mice were euthanized 14 days post NTS injection and kidney collected for histology, immunohistochemical and morphometric analysis. Gene expression profile was performed for all mice.

Results: ATX inhibition significantly improved renal function measured by proteinuria or urine cystatin C. These functional results were paralleled by a correspondent effect on tubule-interstitial fibrosis, tubular injury or total number of infiltrating inflammatory cells. Gene expression profile of all treated animals pointed out to a key role of ATX inhibition on T-cell recruitment.

Conclusions: Our findings support a key role of LPA axis in renal function preservation in NTS model of crescentic glomerulonephritis and possibly in other renal diseases.

TH-PO144

DDRI Inhibition Decreases Experimental Induced Glomerulosclerosis

Marco Prunotto, Takeshi Murata, Hideaki Shimada, Akira Maeda, Naoshi Fukushima, Christos Chatziantoniou,1 Marcus J. Moeller,2 Diana Rubei,1 Oliver Gross,3 Yukari Yasui,4 Fujio-Gotemba Research Labs, Chugai Pharmaceutical Co., Ltd., Gotemba, Japan; 1INSERM UMR S 1155, Hopital Tenon, Paris, France; 2Clinic of Nephrology and Rheumatology, Univ Medicine Goettingen, Goettingen, Germany; 3Dept of Nephrology and Clinical Immunology, RWTH Univ, Aachen, Germany; 42O, Clinical Development, Roche Product Ltd., Basel, Switzerland.

Background: Discoidin Domain receptor 1 (Ddrr1) is tyrosine kinase collagen receptor that has been shown to be involved in progression of cancer and fibrosis. Specifically in kidney, an impressive series of papers highlighted a major role for this receptor in the pathogenesis of renal fibrosis, crescentic glomerulonephritis and in Alport syndrome. The pathomechanisms underlying its expression in the kidney have been elucidated. Ddrr1 selective pharmacological inhibition in experimental-induced glomerulosclerosis models.

Methods: Selective DDR1 pharmacological inhibition on progression of experimental-induced glomerulosclerosis by injection of alloimmune sheep nephrotic serum (NTS) in Sv129 mice and in a model of acquired progressive glomerular sclerosis (NEP25) was tested. Functional parameters were collected during the study and tissues submitted to histology, immunohistochemistry and gene expression profile.

Results: DDR1 selective inhibition, assessed by reduction of DDR1 phosphorylation in renal parenchyma, showed a dose-dependent decrease in disease severity assessed by blood urea nitrogen and albuminuria in both models. This functional improvement was paralleled by a marked reduction of expression levels of the principal fibrotic markers. Network analysis on gene expression profile from all treated mice showed a preserved gene expression of all treated animals pointed to a key role of ATX inhibition on T-cell recruitment.

Conclusions: Our preclinical data suggest DDR1 inhibition as a possible therapeutic intervention strategy in treating glomerulosclerosis and in advanced stages of chronic kidney disease.
Intraglomerular Crosstalk between Mesangial Cells and Macrophages in Glomerular Injury
Shuyo Umemoto, Takashige Kuwabara, Manabu Hayata, Daiisuke Fujiimoto, Tomoko Kanki, Yuichiro Izumi, Yukata Kakizoe, Masashi Mukoyama. Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto City; Kumamoto, Japan.

Background: We previously reported that myeloid-related protein 8 (MRP8: S100A8) - toll-like receptor 4 (TLR4) signaling activated by ER-stressed macrophages (MΦ) could be involved in the progression of diabetic nephropathy. Besides, ER stress associated with glucolipotoxicity might contribute to diabetic complications along with the MRP8/TLR4 upregulation in the kidney. Since glomerular infiltrated MΦ showed obviously high MRP8 positivity compared to tubulointerstitial MΦ, we speculated the intraglomerular crosstalk between infiltrated MΦ and resident cells in glomeruli. However, detailed mechanisms remain to be elucidated.

Methods: Macrophages (mouse RAW264.7 cells) were co-cultured or stimulated with rat mesangial cells (Mes) or Mes-conditioned media (Mes-sup), respectively. Expression of MΦ marker, pro-inflammatory genes and ER stress-associated genes were determined using TaqMan real-time PCR. Furthermore, experiments using the dual reporter assay revealed that Mes-sup stimulation induced TLR4 signaling, which could cause ER stress, as well as NFκB pathway in a concentration-dependent manner. Such induction was partially (by ~50%) abrogated by the TLR4 antagonist.

Results: These results indicate that humoral factors secreted from Mes would contribute to the intraglomerular crosstalk between Mes and MΦ during the course of MRP8 activation, which might play an important role in the inflammation and ER stress partly through TLR4 signaling.

TH-PO146
CXCL10-Deficient Mice Reveal a Pro-Proliferative Role for IP-10 in Mesangial Proliferative Glomerulonephritis
Xiang-Mei Chen, Lingling Wu, Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing.

Background: IFN-γ-inducible protein 10 (IP-10, CXCL10), a small chemokine belonging to the CXC chemokine family, has been widely documented to be involved in activating the PI3K-AKT signaling pathway. These results provide a novel insight into the mechanisms of the deleterious action of MT remain unclear. We hypothesized that at least part of these effects may be mediated by inducing inflammation (Inflamm) and proliferation (Prol) as part of a nonspecific cellular response to aggression.

Methods: We analyzed retrospectively, by IHC, renal tissue from 15 sham-operated (S) and 30 adult male Munich-Wistar rats subjected to 5/6 renal ablation (Nx). For each experiment, glomerular transcapillary hydraulic pressure difference (ΔP), glomerular volume (Vg), and glomerulosclerosis index (GSI) had been obtained 30 (Nx30) or 60 (Nx60) days after Nx. The (ΔP - Vg) and glomerulosclerosis index (GSI) had both strong correlations with % area for Caspase-1.

Results: Western blotting showed that the expression levels of cell cycle-related proteins, extracellular matrix and proliferation of mesangial cells. The PCNA-positive cells in the mesangial cells were also examined.

Results: MRP8 and pro-inflammatory genes in MΦ were dramatically induced by co-culture with Mes (by 25-fold and 12-fold, respectively). These results were mostly reproduced by stimulation with Mes-sup, rather than with protein tubular cell-conditioned media. Furthermore, experiments using the dual reporter assay revealed that Mes-sup stimulation induced IFN-γ signaling, which could cause ER stress, as well as NFκB pathway in a concentration-dependent manner. Such induction was partially (by ~50%) abrogated by the TLR4 antagonist.

Conclusions: These results indicate that humoral factors secreted from Mes would contribute to the intraglomerular crosstalk between Mes and MΦ during the course of MRP8 activation, which might play an important role in the inflammation and ER stress partly through TLR4 signaling.

TH-PO147
Transcriptome Analysis Suggests That Vorinostat Is Antiapoptotic and Anti-Inflammatory in Experimental Aplastic syndrome
Vanessa R. Williams,1 Eun Hui Bae,2 Ana Konvalinka,3 York P. Pei,4 James W. Scholey.5 1Medical Science, Univ of Toronto, Canada; 2Internal Medicine, Chonnam National Univ, Korea; 3Nephrology, Univ Health Network, Canada; 4Genomic Medicine, Univ Health Network, Canada.

Background: Alport syndrome (AS) is a hereditary disorder characterized by early proteinuria and progressive chronic kidney disease (CKD). Currently few effective treatments are available. We previously identified vorinostat, a lysine deacetylase (KDAC) inhibitor, as a novel therapeutic approach to AS. Here, we tested our hypothesis that CD11b-activation mediated suppression of leukocyte kidney infiltration reduces tissue infiltration of leukocytes by reducing transmigration. Here, we tested our hypothesis that CD11b-activation mediated suppression of leukocyte kidney infiltration reduces tissue infiltration of leukocytes by reducing transmigration.

Methods: CD44a+ (KO) and wild-type (WT) mice on a congenic 129 background were treated with vorinostat (50 mg/kg/day) or vehicle from 4 to 7 weeks of age (n = 5 per group). Plasma and urine samples were collected, and kidney histological analyses were performed. Global RNA expression profiling of renal cortical samples was performed with Affymetrix Mouse Gene 2.0 ST arrays at 7 weeks, followed by differential expression, gene ontology (GO), and pathway analyses.

Results: KO mice developed proteinuria, elevated plasma creatinine and blood urea nitrogen, glomerulosclerosis, and tubulointerstitial fibrosis, however vorinostat treatment tended to attenuate these changes. Transcriptional profiles of untreated KO mice compared to WT mice showed enrichment of genes involved in activation of NF-κB, toll-like receptor, and TNF inflammatory signaling pathways. Genes involved in apoptosis, and lipid and carbohydrate metabolism were also enriched. Interestingly, vorinostat-treated KO mice showed downregulation of pathways involved in apoptosis, particularly p53 signaling, compared to untreated KO mice. GO analysis of vorinostat-treated KO mice revealed enrichment of biological processes involved in negative regulation of inflammation and necrosis.

Conclusions: Unbiased transcriptome analysis suggested that vorinostat exerts therapeutic effects by reversing changes in gene expression and biological processes contributing to progression of CKD in AS, particularly apoptosis, inflammation, and necrosis.

Future studies will thoroughly investigate specific mechanisms of KDAC inhibition in AS.

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

TH-PO148
Capillary Mechanical Tension Cause Glomerular Injury through Activation of Innate Immunity in the Renal Kidney
Simone C. A. Arias, Victor F. Avila, Camilla Fanelli, Denise M. Malheiro, Niels O.S. Camara, Roberto Zatt, Clarice K. Fujihara. Univ of Sao Paulo.

Background: Mechanical tension (MT) is thought to initiate and perpetuate glomerular injury, a notion supported by in vitro studies. The mechanisms of the deleterious action of MT remain unclear. We hypothesized that at least part of these effects may be mediated by inducing inflammation (Inflamm) and proliferation (Prol) as part of a nonspecific cellular response to aggression.

Methods: We analyzed retrospectively, by IHC, renal tissue from 15 sham-operated (S) and 30 adult male Munich-Wistar rats subjected to 5/6 renal ablation (Nx). For each experiment, glomerular transcapillary hydraulic pressure difference (ΔP), glomerular volume (Vg) and glomerulosclerosis index (GSI) had been obtained 30 (Nx30) or 60 (Nx60) days after Nx. The (ΔP - Vg) and glomerulosclerosis index (GSI) had both strong correlations with % area for Caspase-1.

Results: Western blotting showed that the expression levels of cell cycle-related proteins, extracellular matrix and proliferation of mesangial cells. The PCNA-positive cells in the mesangial cells were also examined.

Results: MRP8 and pro-inflammatory genes in MΦ were dramatically induced by co-culture with Mes (by 25-fold and 12-fold, respectively). These results were mostly reproduced by stimulation with Mes-sup, rather than with protein tubular cell-conditioned media. Furthermore, experiments using the dual reporter assay revealed that Mes-sup stimulation induced IFN-γ signaling, which could cause ER stress, as well as NFκB pathway in a concentration-dependent manner. Such induction was partially (by ~50%) abrogated by the TLR4 antagonist.

Conclusions: These results indicate that humoral factors secreted from Mes would contribute to the intraglomerular crosstalk between Mes and MΦ during the course of MRP8 activation, which might play an important role in the inflammation and ER stress partly through TLR4 signaling.

TH-PO149
Suppression of Inflammation by Leukadherins Ameliorates Diabetic Kidney Disease
Mehdi Hafezi Faridi,1 Samia Khan,1 Shereyar J. Khaliqdeni,1 Alessia Fornoni,1 Vineet Gupta.2 1Internal Medicine, Rush Univ Medical Center, Chicago, IL; 2Div of Nephrology and Hypertension, Miller School of Medicine, Univ of Miami, Miami, FL.

Background: Systemic Inflammation governs the pathology of several diabetic complications including diabetic nephropathy (DN). Increased infiltration of inflammatory leukocytes in the glomerular milieu has been reported in DN in recent studies. We recently described that CD11b activation using a novel compound, Leukadherin-1 (LA1), suppresses tissue infiltration of leukocytes by reducing transmigration. Here, we tested our hypothesis that CD11b-activation mediated suppression of leukocyte kidney infiltration reduces diabetic kidney injury.

Methods: BTBR ob/ob mice were treated with LA1 at 2mg/kg/day for 8 weeks. Blood glucose level, body weight, and urine albumin-creatinine ratio were measured weekly. Histochemical and immunofluorescence analyses were used to quantify LA1 treatment mediated tissue protection.

Results: Blood glucose level, body weight, and urine albumin-creatinine ratio were measured weekly. Histochemical and immunofluorescence analyses were used to quantify LA1 treatment mediated tissue protection.

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

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Results: KO mice developed proteinuria, elevated plasma creatinine and blood urea nitrogen, glomerulosclerosis, and tubulointerstitial fibrosis, however vorinostat treatment tended to attenuate these changes. Transcriptional profiles of untreated KO mice compared to WT mice showed enrichment of genes involved in activation of NF-κB, toll-like receptor, and TNF inflammatory signaling pathways. Genes involved in apoptosis, and lipid and carbohydrate metabolism were also enriched. Interestingly, vorinostat-treated KO mice showed downregulation of pathways involved in apoptosis, particularly p53 signaling, compared to untreated KO mice. GO analysis of vorinostat-treated KO mice revealed enrichment of biological processes involved in negative regulation of inflammation and necrosis.

Conclusions: Unbiased transcriptome analysis suggested that vorinostat exerts therapeutic effects by reversing changes in gene expression and biological processes contributing to progression of CKD in AS, particularly apoptosis, inflammation, and necrosis. Future studies will thoroughly investigate specific mechanisms of KDAC inhibition in AS.

Funding: Private Foundation Support, Government Support - Non-U.S.
significantly reduced albuminuria and improved renal function. Histochimical analyses showed that LAI significantly reduced leukocyte infiltration and glomerular injury, including mesangial sclerosis, as compared to the untreated animals.

**Conclusions:** Pharmacologic activation of CD11b with alloretic agonists can be a therapeutically relevant strategy to reduce leukocyte kidney infiltration and inflammatory injury in the setting of diabetes.

**Funding:** NIDDK Support

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**TH-PO150**

**Integrative Analysis of Transcriptome Alterations in Kidney Tissues of Diabetic Nephropathy Revealed Significant Enrichment of M1 Macrophages, Mature Dendritic Cells and Activated Helper T Cells**

**Tao Wei, John N. Calpey, Philip Ebert, Suntara Cahya, Zhonghua Qiu, Bhaskarjyoti Sarmah, Matthew D. Breyer, Kevin L. Duffin. Eli Lilly and Company, Indianapolis, IN.**

**Background:** Recent studies suggested tissue inflammation may play a significant pathogenic role in diabetes kidney disease (DKD). We carried out an integrative analysis with objectives to identify major cellular players associated with diseased kidney tissues.

**Methods:** Multiple independently generated DKD transcriptome datasets involving different cohorts of human subjects were analyzed to identify a consensus set of differentially expressed genes (DEGs) in kidney tissues (glomeruli and tubuli) associated with DKD. Pathway analysis and leukocytes specific gene signatures were employed to identify major pro-inflammatory leukocytes.

**Results:** 2,000 genes were identified as DEGs by at least two different studies. Pathway enrichment and coherence analysis revealed significant up-regulation of inflammatory pathways and down-regulation of metabolism and mitochondrial activities. Leukocyte specific gene signatures for macrophages, dendritic cells (DCs), neutrophils, natural killer cells (NKs), T cells and B cells were developed from a published human immune cell transcriptome profile. Enrichment analysis, together with pathway analysis, revealed significant enrichment of macrophages, DCs and helper T cells in diseased kidney tissues. Further analysis revealed significant enrichment of pro-inflammatory M1 macrophages when compared to M2 macrophages, and mature or activated DCs when compared to immature or tolerogenic DCs. Metabolic and mitochondrial activity profiles of M1 and mature dendritic cells are similar to what was observed in DKD kidney tissue, further confirming the involvement of M1 macrophages and mature dendritic cells in DKD development.

**Conclusions:** Integrative analysis confirmed the significant association of inflammation with DKD. We discovered the dis-regulated enrichment in kidney tissues of M1 macrophages, mature DCs and activated helper T cells that is the main cellular basis that underlies the chronic tissue inflammation observed in DKD kidney.

**Funding:** Pharmaceutical Company Support - Eli Lilly and Company

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**TH-PO151**

**A Macrophage COX-2/PGE2/EP4 Axis Protects against Development of Diabetic Nephropathy**

**Xin Wang, Yingju Wang, Suwan Wang, Xiaofeng Fan, Haichun Yang, Agnes B. Fogo, Ming-Zhi Zhang, Raymond C. Harris. Medicine, Vanderbilt Univ School of Medicine, Nashville, TN; Pathology and Microbiology and Immunology, Vanderbilt Univ School of Medicine, Nashville, TN.**

**Background:** Alterations of intrinsic kidney cyclooxygenase-2 (COX-2) expression are observed in development of diabetic nephropathy (DN), and increased COX-2 expression in macula densa contributes to hyperfiltration in the early stage of diabetes. More advanced DN is characterized by increased infiltration of macrophages. COX-2-derived PGE2 plays an important role in macrophage polarization. In the present studies, we investigated the potential roles of macrophage COX-2 in development of DN.

**Methods:** Mice with hematopoietic cell COX-2 knockout (129/Sv) and mice with deletion of macrophage COX-2 (CD11b-Cre; COX-2^flox/flox) or EP4 receptors (CD11b-Cre; EP4^flox/flox) on an FVB background were used. Type 1 diabetes was induced by streptozotocin.

**Results:** At 20 weeks of diabetes, hematopoietic cell COX-2 deletion increased albuminuria, in association with increased renal profibrotic and fibrotic markers (CTGF, fibronectin) and macrophage infiltration. Similarly, macrophage COX-2 deletion also significantly increased albuminuria (ACR: 314 ± 43 vs. 137 ± 32 µg/mg of WT, P < 0.01, n = 5-9) with increased renal fibrotic markers (α-SMA, collagen I) and macrophage infiltration. Macrophage COX-2 deletion also led to greater glomerulosclerosis index (0.48 ± 0.09 vs. 0.24 ± 0.04 P < 0.05, n = 5) and podocyte loss (podocytes/glomeruli: 13.65 ± 0.54 vs. 21.34 ± 0.95, P < 0.001, n = 5). Macrophage COX-2 depletion resulted in decreases in mRNA levels of M2 markers (mannose receptor and YM-1) as well as the number of M2 macrophages (mannose receptor positive macrophages). Finally, macrophage COX-2 depletion caused reduction in autophagy (lower LC3A expression) and increases in endoplasmic reticulum (ER) stress (higher CHOP expression). Similar results were also observed in mice with macrophage EP4 deletion.

**Conclusions:** Our studies indicate that macrophage COX-2 protects against development of DN through multiple mechanisms, including modulation of macrophage polarization and induction of autophagy and increases in ER stress.

**Funding:** NIDDK Support, VA Support

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**TH-PO152**

**High Glucose Induces Dedifferentiation in Podocytes but Prevents Parietal Epithelial Cells Transition through Up Regulation of Micro-RNA193a**

**Manoj K. Tembhe,1 Waqar Khawar,1 Seyedeh Shafadarin Marashi Shohistani,1 Judith Eng,2 Catherine Meyer-Schwesinger,3 Ashwani Malhotra.1 Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; 2Medicine, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.**

**Background:** In recent studies, MicroRNA (miR) 193a has been implicated for the development of glomerulosclerosis in several models of chronic kidney diseases, mir193a is a regulator of Wilms tumor (WT1) suppressor gene. Enhanced expression of WT1 in glomerular epithelial cells is associated with the expression of podocalyxin and nephrin, markers of podocytes. On the other hand, down regulation of WT1 enhances the expression of the epithelial marker of parietal epithelial cells (PEC). A better understanding of PECs as a source of cellular products to replenish injured podocytes. We hypothesize that high glucose milieu up regulates miR193a contributing to dedifferentiation of podocytes and preventing the transition of PECs to podocytes.

**Methods:** Renal tissues of 8 week wild type and BTBR^+/+ mice were evaluated for the expression of WT1, nephrin, and PAX2. In situ hybridization studies, renal cortical sections of control and diabetic mice were labeled for miR193a. In vitro studies, human podocytes and human parietal epithelial cells were incubated in media containing either normal glucose (5mM) or high glucose (30 mM) for 48 hours and probed for miR193a. In other sets of experiments, control and high glucose treated (48 hours) podocytes were evaluated for the expression of podocalxin, PAX2, and nephrin.

**Results:** In situ hybridization studies revealed podocyte expression of miR193a in diabetic mice. In vitro studies showed enhanced miR193a expression in high glucose treated podocytes and PECs. Renal tissues of diabetic mice displayed attenuated expression of WT1 and nephrin. High glucose treated podocytes also displayed attenuated expression of podocalyxin and nephrin. High glucose did not alter PAX2 expression in PECs.

**Conclusions:** High glucose down regulates podocytes's but preserves PEC's molecular phenotype through modulation of miR193a. The present study provides mechanistical insight into the development of glomerulosclerosis in majority of diabetic patients.

**Funding:** NIDDK Support

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**TH-PO153**

**IL17A Blockade Improves Renal Damage en BTBR ob/ob Animal Model**

**Carolina Lavoz,1 Yennifer Sanchez,1 Maria Alejandra Drogueut,1 Paola Krall,1 Daniel Carpio,2 Marta Ruiz-Ortega,2 Sergio A. Mezzano.1 Div of Nephrology, School of Medicine, Univ Austral, Valdivia, Chile; 2Renal Diseases Laboratory, Univ Autonoma Madrid, Madrid, Spain.**

**Background:** Chronic inflammation is a main feature of the progressive renal disease, including diabetic nephropathy (DN), the most prevalent chronic kidney disease. Among potential therapeutic targets of diabetic renal damage the Interleukin 17A might be a promising one. IL17A is the hallmark cytokine of the T helper 17 cell. The mouse model strain BTBR ob/ob (leptin deficiency mutation) has been widely used for the study of DN, develops histological features that resembles human DN, and offer an opportunity to study the mechanisms that may lead to more specific therapies aimed at regression of DN. Our aim was to investigate the involvement of the Th17 effector cytokine IL17A in the pathogenesis of DN.

**Methods:** To evaluate the direct effects of IL17A on DN progression, a neutralizing antibody against IL17A (osimotocipimus, 5 mg/kg of b.w) was administered to mice between 15 and 20 weeks (sacrifice). The results were analyzed by Western blot, ELISA, and RTPCR.

**Results:** In the obob animal model, IL17A renal production was observed at 16 weeks, sustained up to 20 weeks as well as activated BORyT. Moreover, positive IL17A expressing CD4 lymphocytes, mastocytes and tubular epithelial cells were found. IL17A neutralization diminished blood glucose and body weight compared to IgG control-treated mice, whereas renal weight and serum creatinine levels were not affected. Importantly, IL17A blockade improved Albumin/Creatinine Ratio during all period of study. Moreover, downregulation of the kidney damage markers (KIM1 and Ngal) and the proinflammatory factors (MCP1 and Rantes) were found in response to IL17A neutralization. Podocytes markers like WT1 and Fden tend to recover after treatment. Histologically was observed a decrease in the inflammatory infiltrating cells in anti-IL17A-treated mice. In biopsies of DN patients we have detected IL17A expression in tubular epithelial cells.

**Conclusions:** These data demonstrate that IL17A participates in diabetic-mediated renal damage and could be a novel therapeutic target for ND. PAI 8240017.

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

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**TH-PO154**

**Tissue Plasminogen Activator Modulates Macrophage Polarity Shift**

**Ling Lin, Kebin Hu. Medicine, Penn State Univ College of Medicine, Hershey, PA.**

**Background:** Macrophage polarization plays an important role in tissue inflammation and fibrogenesis. Generally, M1 macrophages promote inflammation, whereas, M2 macrophages activate anti-inflammatory mechanisms. Recent studies have shown that macrophages, in response to kidney injury, can shift their polarity. However, the underlying mechanisms remain largely unknown.

**Methods:** We investigated the role of tissue plasminogen activator (tPA) in macrophage polarity shift using integral in vivo and in vitro approaches.

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129A
**Results:** We found that there were more CD11b+TNFα+ or CD11b+F4/80+ M1 macrophages in the obstruction-induced fibrotic kidneys from wildtype mice than than from iP Außen knock mice. iP Außen also induced chemokine expression, including IFN-γ, IL-1β, and TNF-α, both in vivo and in vitro, suggesting that iP Außen may be an endogenous factor that modulates M2 macrophage shifts towards M1 phenotype. 3774 macrophages were treated with JQ1 and were found to be downregulated as indicated by decreased expression of angiogenin 1, SOCS3, and Ym1. Intriguingly, it’s found that IL-4-mediated M2 macrophages, after iP Außen treatment, lost their M2 markers such as arginase 1 and SOCS3, indicating that iP Außen promotes a polarity shift from macrophages to M2 skewed towards M1. Possible contamination of endotoxin was ruled out as iP Außen failed to induce IL-1β expression. Additionally, knockdown of LRP-1, a by siRNA, one of the known iP Außen receptor, had little effect on iP Außen-induced macrophage polarity shift. Instead, it’s found that annexin A2 mediated iP Außen-induced macrophage polarity shift, because annexin A2 siRNA abolished iP Außen effects.

**Conclusions:** We speculate that iP Außen promoted macrophage polarity shift from M2 to M1 through annexin A2-mediated pathway.

**Funding:** NIDDK Support, Private Foundation Support

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**TH-PO155**

Cell Specific Targeted PCR and RNA Sequencing of Renal Collecting Duct Epithelial Cells Reveals Novel Innate Immune Signature in Murine Intercalated Cells  Andrew L. Schwaderer, Vijay Saxena, Raoul D. Nelson, George J. Schwartz, David S. Hains. 1CCTR, Nationwide Children’s Hospital, Columbus, OH; 2Pediatrics, Le Bonheur Children’s Hospital, Memphis, TN; 3Pediatrics, Univ of Utah, Salt Lake City, UT; 4Pediatrics, Univ of Rochester Medical Center, Rochester, NY.

**Background:** The urinary tract is usually culture negative despite its close proximity to microbial flora. The precise mechanisms by which the kidneys and urinary tract defends against uropathogenic flora is not well understood. The initial kidney cells to encounter ascending pathogens are the collecting tubule cells which consist of principal cells (PC) that express the aquaporin 2 (AQP2) and intercalated cells (IC) which express vacuolar H⁺-ATPase (V-ATPase). We have previously shown that intercalated cells are involved in the innate immune defense of the kidney in humans.

**Methods:** In this study we generated two reporter mice, V-ATPase-cre+Tdt+ mice to fluorescently tag IC and AQP2-cre-PC mice and enriched them by fluorescence-activated cell sorting (FACS).

**Results:** We found that there were more CD11b + macrophages in the obstruction-induced fibrotic kidneys from wildtype mice than in the iP Außen knock mice. iP Außen also induced chemokine expression, including IFN-γ, IL-1β, and TNF-α, both in vivo and in vitro, suggesting that iP Außen may be an endogenous factor that modulates M2 macrophage shifts towards M1 phenotype. 3774 macrophages were treated with JQ1 and were found to be downregulated as indicated by decreased expression of angiogenin 1, SOCS3, and Ym1. Intriguingly, it’s found that IL-4-mediated M2 macrophages, after iP Außen treatment, lost their M2 markers such as arginase 1 and SOCS3, indicating that iP Außen promotes a polarity shift from macrophages to M2 skewed towards M1. Possible contamination of endotoxin was ruled out as iP Außen failed to induce IL-1β expression. Additionally, knockdown of LRP-1, a by siRNA, one of the known iP Außen receptor, had little effect on iP Außen-induced macrophage polarity shift. Instead, it’s found that annexin A2 mediated iP Außen-induced macrophage polarity shift, because annexin A2 siRNA abolished iP Außen effects.

**Conclusions:** We speculate that iP Außen promoted macrophage polarity shift from M2 to M1 through annexin A2-mediated pathway.

**Funding:** NIDDK Support, Private Foundation Support

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**TH-PO156**

**BET Bromodomain Inhibition Ameliorates Experimental Renal Damage**


**Background:** The urinary tract is usually culture negative despite its close proximity to microbial flora. The precise mechanisms by which the kidneys and urinary tract defends against uropathogenic flora is not well understood. The initial kidney cells to encounter ascending pathogens are the collecting tubule cells which consist of principal cells (PC) that express the aquaporin 2 (AQP2) and intercalated cells (IC) which express vacuolar H⁺-ATPase (V-ATPase). We have previously shown that intercalated cells are involved in the innate immune defense of the kidney in humans. We have previously shown that intercalated cells are involved in the innate immune defense of the kidney in humans.

**Methods:** In this study we generated two reporter mice, V-ATPase-cre+Tdt+ mice to fluorescently tag IC and AQP2-cre-PC mice and enriched them by fluorescence-activated cell sorting (FACS).

**Results:** We found that there were more CD11b + macrophages in the obstruction-induced fibrotic kidneys from wildtype mice than in the iP Außen knock mice. iP Außen also induced chemokine expression, including IFN-γ, IL-1β, and TNF-α, both in vivo and in vitro, suggesting that iP Außen may be an endogenous factor that modulates M2 macrophage shifts towards M1 phenotype. 3774 macrophages were treated with JQ1 and were found to be downregulated as indicated by decreased expression of angiogenin 1, SOCS3, and Ym1. Intriguingly, it’s found that IL-4-mediated M2 macrophages, after iP Außen treatment, lost their M2 markers such as arginase 1 and SOCS3, indicating that iP Außen promotes a polarity shift from macrophages to M2 skewed towards M1. Possible contamination of endotoxin was ruled out as iP Außen failed to induce IL-1β expression. Additionally, knockdown of LRP-1, a by siRNA, one of the known iP Außen receptor, had little effect on iP Außen-induced macrophage polarity shift. Instead, it’s found that annexin A2 mediated iP Außen-induced macrophage polarity shift, because annexin A2 siRNA abolished iP Außen effects.

**Conclusions:** We speculate that iP Außen promoted macrophage polarity shift from M2 to M1 through annexin A2-mediated pathway. 

**Funding:** NIDDK Support, VA Support

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**TH-PO158**

**Role of Claudins in Tumor Necrosis Factor-Induced Permeability and Migration Changes in Tubular Cells**

Katalin Szasz,1-2 Shaista Anwer,1 Yasaman Amoozadeh,1 Emily Branchard,1 Qinghong Dan,1 1Keenan Research Center St. Michael’s Hospital, Toronto, ON, Canada; 2Surgery, Univ of Toronto, Toronto, ON, Canada.

**Background:** Tumor Necrosis Factor (TNF) is a key pathogenic cytokine in kidney disease. We showed that TNF causes a biphasic transcellular resistance (TER) change in immune system-derived cells that consists of an early drop followed by recovery (1-3h), and a late increase (>8h). TNF also enhances tubular cell migration. However, the underlying mechanisms are not fully known. TER is determined by the claudin (Cldn) family of tight junction proteins. The combination of claudin isoforms expresses paracellular permeability of a cell. Claudins are also shown to affect migration. The aim of this work was to assess how claudins contribute to TNF-induced changes in permeability and motility of tubular cells.

**Methods:** We used LLC-PK1 tubular cells. TER and cell migration was quantified by Electric Cell-substrate Impedance Sensing (ECIS). Claudin expression was followed using non-targeting siRNA. Claudin knockdown was confirmed by western blotting. Claudin knockdown was confirmed by immunohistochemistry (IHC).

**Results:** TNF alters expression of several claudins. It causes a biphasic change in Cldn-2 and 3 expression. Specifically, an initial transient increase due to reduced degradation (1-3h) is followed by a drop in mRNA and protein levels (>8h). Prolonged TNF treatment also increases cldn-1, 4 and 7 protein and mRNA. The ERK and JNK pathways are required for the expression changes of Cldn-1, 4 and 7, and have a key role in the late TER increase. To correlate TNF-induced claudin expression and TER changes, we silenced each claudin and monitored TER using ECIS. Cldn-1 is necessary for the early TNF-induced TER change. In contrast, Cldn-2 decrease is the main contributor to the late TER increase, with only minor roles for Cldn-1, 4 and 7. Finally, we assessed the role of the various claudins in migration. Silencing Cldn-1, 2 or 3 significantly slowed wound healing in LLC-PK1 cells. Our ongoing studies explore the role of these claudins in migration-associated cytoskeleton remodeling.

**Conclusions:** Altered Claudin expression may have consequences beyond permeability changes. By affecting epithelial regeneration following injury claudins may contribute to the pathogenesis of kidney disease.

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

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**TH-PO159**

**Fibroblast CD37 Controls the Intestinal Adenosine Microenvironment, Inflammation and Fibrosis after Kidney Ischemia-Reperfusion Injury (IRI)**

Nicole Groll,1 Sun-Sang J. Sung,1 LiPing Huang,1 Jessica R. Lawler,1 Hong Ye,1 Ann L. Arndt,2 Diane M. Crichlow,1 Pierluigi E. Mattia,3,1 Mark D. Okusa.1 1Div of Nephrology and Center for Immunology, Inflammation and Regenerative Medicine, Univ of VA; 2Dept of Pharmacology, Univ of Virginia, Charlottesville, VA; 3Inst of Molecular Cardiology, Heinrich-Heine-Univ, Duesseldorf, Germany.

**Background:** Molecular mechanisms after IRI are poorly understood. ATP, released by apoptotic/necrotic cells, promotes pro-inflammatory responses but is rapidly metabolized by CD39 to AMP and then by CD73 to adenosine, which activates its specific receptors to regulate immune response and healing processes. Loss of CD39 increases inflammation

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

Underlines represent presenting author.
after IRI, but its contribution to late kidney fibrosis has not been examined. We hypothesize that CD73 mediates fibrosis after AKI by blocking inflammation-induced fibroblast-myofibroblast transformation.

**Methods:** Fossli[+][CD73][3] (fibroblast CD73KO) and Fossli[−] (C) mice were subjected to 20 unilateral IRI, and kidney function, immune cell infiltration and histology were assessed at 14d. In a subset of mice simultaneous unilateral IRI and contralateral nephrectomy were performed to compare initial effects of IRI after 24h.

**Results:** 24h after IRI, fibroblast CD73KO and C mice had similar initial injury as assessed by plasma creatinine (PCr), KIM-1 and NGAL mRNA, but 14 d after IRI, PCr was higher in fibroblast CD73KO. Collagen formation, myofibroblast marker expression and the area occupied by PDGFR-β² cells were higher in fibroblast CD73KO 14d after IRI, suggesting a role of CD73 in regulating fibroblast-myofibroblast transformation. Furthermore inflammation was higher in fibroblast CD73KO 14d after IRI resulting in impaired resolution of immune cell infiltration. Fibroblasts from CD73− mice cultured in vitro showed a hyperproliferative phenotype.

**Conclusions:** These results demonstrate that mice with fibroblasts deficient in CD73 have increased fibrosis after injury and enhanced fibroblast-myofibroblast transformation, and their fibroblasts have a hyperproliferative phenotype. Understanding the molecular mechanism of regulation by fibroblast CD73 on phenotype transformation could provide an important therapeutic approach to blocking progressive kidney fibrosis.

**Funding:** NIDDK Support

**TH-PO160**

**AIF-1 Expression in Macrophages Promotes Fibroblasts to a Pro-Fibrotic Phenotype and Renal Interstitial Fibrosis**

**Yushu Li, Lirong Hao, Xingzhi Wang. Nephrology, The 1st Hospital Affiliated of Harbin Medical Univ, Harbin, Heilongjiang, China.**

**Background:** Macrophages have been identified as key cells in the pathogenesis of renal interstitial fibrosis, but the mechanism is still unclear. This research focuses on effects and possible mechanism of Allograft Inflammatory Factor-1 (AIF-1) in promoting renal interstitial fibrosis.

**Methods:** Mice were subjected to Unilateral Ureteric Obstruction (UUO), and sacrificed after 14d. Kidney sections were analyzed by Masson stain. Presence of AIF-1, CD68 and α-smooth muscle actin (α-SMA) were analyzed by immunohistochemistry. Double immunofluorescence stain of AIF-1 and CD68 was also used. AIF-1 expression in RAW264.7 stimulated by aldosterone was detected in vitro. To identify the role of AIF-1 in promoting fibrosis, AIF-1 expression was reduced by transfection of AIF-1 small interfering RNA (siRNA) in RAW264.7. Expressions of α-SMA, Phosphorylation P38 kinase (P-P38) and fibronectin (FN) in BHK-21 (fibroblasts cell line) were examined after co-culture with normal or AIF-1/siRNA RAW264.7.

**Results:**

- **Masson staining:** Normal kidney showed less staining compared to UUO.
- **CD68:** CD68 expression was higher in UUO compared to normal.
- **α-SMA:** α-SMA expression was increased in UUO compared to normal.

**Expressions of AIF-1, CD68 and α-SMA were up-regulated in UUO model. AIF-1 expression colocalized with CD68-positive macrophages in kidneys. The increase of AIF-1 expression (above basal levels) was confirmed in RAW264.7 responded to aldosterone. After 24 hours of co-culture between fibroblasts and macrophages, the α-SMA expression was induced in BHK-21 with increasing expressions of FN and P-P38. Expressions of α-SMA, P-P38 and FN were reduced in BHK-21 co-cultured with RAW264.7 with AIF-1/siRNA.

**Conclusions:** The expression of AIF-1 in macrophages is critical for the activation of renal fibroblasts to a pro-fibrotic phenotype. AIF-1 expression could be up-regulated in macrophages, and it is a novel mechanism linking macrophages to the promotion of renal interstitial fibrosis, which should be via P38 pathway.
Methods: The expression of TLR4, MyD88, NF-κB signaling pathway and TGF-β/Smad signaling pathway and fibrosis proteins in renal fibrosis. To test the contribution of the Th1 response to kidney fibrosis, we hypothesized that AT1R activation would modulate the progression of CKD.

Results: FXII KO animals exhibited markedly prolonged activated partial thromboplastin time (aPTT) and lower basal and stimulated bradykinin levels than WT animals, as expected. WT 5/6 NX animals developed hypertension, kidney hypertrophy, proteinuria, GFR reduction, kidney fibrosis and tubular injury, consistent with our understanding on the model. FXII KO 5/6NX group displayed significantly lower blood pressure, renal injury, and increased expression of TGF-β/Smad pathway, renal inflammation and fibrosis factors in both human renal proximal tubular cell line, and rat fibroblasts than the WT 5/6NX group.

Conclusions: Our data suggest that FXII deficiency confers a modest renal beneficial effect in 5/6 NX rat model. Future studies will be necessary in further determining the role of FXII-mediated activation of plasma Kallikrein-kinin system (PKKS) in CKD development in the 5/6 NX rat model.

Funding: Pharmaceutical Company Support - Merck & Co.

TH-PO165

Renal Pharmacology and Preclinical Attributes of Sparsentan, a Dually Active Endothelin A and Angiotensin I Receptor Antagonist

Kevin Leach, Xin-Ru Pan-Zhou, Wayne Deats, Ma Becon, Retrophin, Inc., Cambridge, MA.

Background: Sparsentan (RE-021) is a first-in-class, potent, dual endothelin A (ETₐ) and angiotensin 1 (AT1) receptor antagonist currently in clinical development to treat focal segmental glomerular sclerosis (FSGS). Here we report the results of in vitro potency studies and in vivo pharmacology studies and the effects of sparsentan in 2 different renal pharmacological models.

Methods: In vitro potency was assessed by competition with the appropriate ligand. Pharmacological activity was measured in either the 5/6 nephrectomy or Passive Heymann Nephritis models in rats. Long-term toxicity studies were performed in the Sprague Dawley rat and the Cynomolgus monkey.

Results: In vitro, sparsentan is a potent agonist of the AT1 receptor (Ki=0.9 nM) and the ETₐ receptor subtype (Ki=13 nM), with selectivity over the endothelin B subtype (Ki=652 nM). In the 5/6 nephrectomy rat model of glomerular sclerosis, where animals carried the homozygous deletion at exon 6, 2 patients, a 18-mg/kg/day dose of sparsentan reduced systolic blood pressure compared with the 5/6 nephrectomized control rats at the 18- and 60-mg/kg/day does. At 60 mg/kg/day, sparsentan significantly reduced proteinuria compared with the control group after 4 (-65%, P<0.05) and 8 weeks (-84%, P<0.05) of treatment. The 18-mg/kg/day dose showed a positive trend toward reduction in proteinuria at 8 weeks. In the anti-FXIIA-induced passive Heymann Nephritis model, 60 mg/kg/day oral sparsentan led to a 59% (P<0.009) decrease in proteinuria, significant preservation of podocytes in the glomerulus (P=0.02) and significant reduction in fibrosis (H&E score 0.03 vs 0.08). In a non-diabetic diabetic nephropathy mouse model of FSGS, the 18-mg/kg/day dose of sparsentan showed a significant reduction in albuminuria (-53%) and a significant reduction in renal fibrosis (Collagen I/IV stain). In vivo, sparsentan significantly reduced hypertension in the Cynomolgus monkey and 80 mg/kg/day in Sprague-Dawley rats; the corresponding AUC-0-24 were 14 and 209 µg×hr/mL, respectively.

Conclusions: The combined preclinical characteristics of sparsentan—potency, selectivity, pharmacology, and toxicology—are consistent with a molecule that may be safe and effective to treat FSGS.

Funding: Pharmaceutical Company Support - Pharmacoepia, Inc. funded the long-term toxicity studies. Retrophin, Inc. acquired sparsentan from Ligand Pharmaceuticals (formerly Pharmacoepia) and funded the other preclinical studies. Retrophin, Inc. participated in the writing, reviewing, and approving this abstract for presentation.
TH-PO168
HDAC1 Inhibition Ameliorates Renal Inflammation in Unilateral Ureteral Obstruction Induced Renal Fibrosis Jin Han Lim,1 Kyung Pyo Kang,1 Tung Nguyen-Thanh,1 Won Kim,1 Sik Lee,1 Sung Kwang Park.1 1Dept of Internal Medicine, Chonbuk Natl Univ Medical School, Jeonju, Korea; 2Dept of Internal Medicine, Research Inst of Clinical Medicine, Chonbuk Natl Univ Hospital.

Background: Renal fibrosis begins from localized activation of inflammatory processes, which include infiltration of inflammatory cells and production of proinflammatory cytokines and chemokines. Histone deacetylases can remove acetyl-residue from histones and result transcriptional regulation of DNA. Inhibition of these histone deacetylase (HDAC) might have potential protective effect against fibrosis of the liver, heart, and kidney. However, modulation of renal inflammation by HDAC inhibition was still elusive in renal fibrosis processes. Therefore, we evaluate whether class I HDAC inhibitor have anti-inflammatory effect on unilateral ureteral obstruction (UOU)-induced renal fibrosis.

Methods: Renal fibrosis was induced by UOU in the six-week-old C57BL/6 mice for 14 days. Treatment with 5-15 ppm of valproic acid (VPA, 300 mg/kg), was administrated by intraperitoneal injection for 5 days before induction of renal fibrosis and continued for 14 days. Tubular injury, fibrosis and macrophage infiltration were evaluated by histologic examination. Expression of inflammatory cytokines and chemokines were evaluated by Western blot analysis and ELISA.

Results: After 14 days of ureteral obstruction, renal tubular injury and fibrosis were significantly increased compared to sham operation group. VPA treatment group has significantly attenuated the UOU-induced renal tubular injury and fibrosis. The number of F4/80 (+) macrophage infiltration after UOU surgery was significantly decreased after VPA treatment. In immunohistochemistry study, VPA treatment significantly decreased UOU-induced increase of ICAM-1 and MCP-1 expression in the tubulo-interstitial area. We also found that total kidney ICAM-1 and MCP-1 expression were decreased after VPA treatment in UOU model by Western blot analysis and ELISA.

Conclusions: In conclusion, VPA have anti-inflammatory effect on UOU-induced renal inflammation through regulation of ICAM-1 and MCP-1 expression and decreases renal fibrosis.

Funding: Government Support - Non-U.S.

TH-PO169
D-Pinitol Alleviates Cyclosporine-Induced Renal Fibrosis via the Activation of Sirt1 and Nrf2 Antioxidant Pathways Minyoung Kim,1 Soojong Kim,2 Eun Sil Koh,1 Hyung Wook Kim,1 Sungsin Chung,2 Seok Joon Shin.1 1Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Korea; 2Dept of Biochemistry, College of Medicine, The Catholic Univ of Korea, Seoul, Korea.

Background: D-pinitol, 3-methoxy analogue of D-chiroinositol, is one of the most abundant cyclitol present in soybean seeds, legumes and soy food. According to previous studies, d-pinitol has been suggested to possess multifunctional properties including anti-inflammatory, anti-hipidemic and anti-diabetic effects. The aim of this study was to evaluate of the effect of D-pinitol on renal fibrosis through the antioxidant signaling pathway in an experimental model of cyclosporine A (CsA)-induced nephropathy.

Methods: Renal effect of oral treatment of D-pinitol at 50 mg/kg body weight for 28 days was evaluated against CsA-induced renal injury in male ICR mice. Results: Treatment with D-pinitol significantly prevented the rise in albuminuria, urine volume and urea osmolality and the decrease in renal function as compared to CsA control group. Additionally, D-pinitol attenuated CsA-induced tubulointerstitial fibrosis and inflammation as assessed by Masson’s trichrome and α-SMA staining. Administration of D-pinitol increased the expression of heme oxygenase-1, NADPH quinone oxidoreductase 1 and Nrf2 in the kidneys. These renoprotective effects of D-pinitol were attributed to the increase in level of sirtuin 1 (Sirt1) and total and nuclear expressions of nuclear erythroid factor 2-related factor 2 (Nrf2), as well as an elevated level of Kelch-like ECH-associated protein 1, indicating that Sirt1 increased by D-pinitol regulates Nrf2 and in turn the activated Nrf2 affects the cellular antioxidant system.

Conclusions: These findings show that the renoprotective effect of D-pinitol against renal fibrosis in CsA-induced nephrotoxicity may result from the inhibition of oxidative stress through Sirt1 and Nrf2 activation and subsequent enhancement of antioxidant enzymes.

Funding: Government Support - Non-U.S.

TH-PO170
Ligand-Bound Thyroid Hormone Receptor on Macrophages Ameliorate Kidney Injury via Inhibition of Nuclear Factor-κB Activities Yoshiaji Ito, Fumihiko Furuya, Kenichiro Kitanura. 3rd Dept of Internal Medicine, Univ of Yamashina, Chuo, Yamashina, Japan.

Background: In chronic kidney disease (CKD) patients, inflammation plays a pivotal role in the tubulointerstitial injury and the progression of renal fibrosis, however it remains unclear how its processes are initiated and regulated. Hypothyroidism is associated with an increased occurrence of atherosclerosis and inflammation, suggesting the protective roles of thyroid hormones and its receptors against inflammatory processes. However, the contribution of thyroid hormone receptors to the macrophage differentiation has not been well documented.

Methods: We focused on the endogenous thyroid hormone receptor α (TRα) in macrophages and examined the role of ligand-bound TRα in the macrophage polarization-mediated anti-inflammatory effects.

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

Results: TRα-deficient irradiated chimeric mice exacerbated tubulointerstitial injury in the UUO model when compared with wild type mice. Macrophages isolated from obstructed kidneys of mice lacking TRα were mainly derived from bone marrow and displayed increased expression of proinflammatory cytokines such as IL-1β. In bone marrow-derived macrophages from wild type mice, T3-depleted culture medium augmented the production of proinflammatory cytokines (IL-1β, TNF-α) and enhanced the translocation of NF-κB to the nucleus via IKK-β, MAPK phosphae pathway. TRα-deficient macrophages also increased the release of proinflammatory cytokines accompanied with the increased nuclear translocation of p65. Evaluation of TRα-deficient bone marrow-derived macrophages confirmed the propensity of these cells to produce exaggerated levels of IL-1β, and co-culture of TRα-deficient bone marrow-derived macrophages with renal epithelial cells induced more severe damages to the epithelial cells via IL-1 receptor (IIIR) activation compared with wild type bone marrow-derived macrophages.

Conclusions: Our study indicates that ligand-bound TRα on macrophages plays protective role in the kidney inflammation through the inhibition of NF-κB pathway, possibly by affecting the pro- and anti-inflammatory balance that controls the development of CKD.

TH-PO171
Canonical Wnt Signaling Promotes Macrophage Proliferation and Migration and Potentiates Kidney Fibrosis in Mice with Obstructive Nephropathy Ye Feng, Jiaying Liu, Chunsun Dai. Nanjing Medical Univ.

Background: Macrophage accumulation plays a critical role for kidney fibrosis in chronic kidney diseases. However, the underlying mechanisms regulating macrophage accumulation during kidney fibrosis remain to be investigated.

Results: In this study, we found that canonicwnt/β-catenin signaling was robustly activated in macrophages from the fibrotic kidneys after UUO or IRI. A mouse model with specific deletion of β-catenin in macrophages was generated by using the Cre-LoxP system. Compared to control littermates, the knockout developed less kidney injury, interstitial inflammatory matrix deposits formation, macrophage accumulation or macrophage proliferation in kidney tissue at 2 weeks after UUO. In the primary cultured bone marrow-derived macrophages (BMMs), compared with wild type macrophages, cell proliferation and cytokin D1 expression stimulated by M-CSF were markedly decreased in β-catenin-deficient macrophages. Additionally, cell motility for β-catenin-deficient macrophages was also largely inhibited compared to the wild type macrophages.

Conclusions: Taken together, this study suggests that Wnt/β-catenin signaling may regulate macrophage proliferation and migration, which may potentiate kidney fibrosis in mice with UUO nephropathy.

Funding: Government Support - Non-U.S.

TH-PO172
Inhibition of Inflammation Attenuates Hypertensive Renal Injury Satoko Oka, Yoko Obata, Kentarou Torii, Miki Sawa, Takehiko Kojii, Tomoyo Nishino.1 1Dept of Nephrology, Nagasaki Univ Hospital, Nagasaki, Japan; 2Dept of Histology and Cell Biology, Nagasaki Univ Graduate School of Biomedical Sciences, Nagasaki, Japan.

Background: Chronic inflammation is closely linked to the development of organ damage by hypertension. Inflammammasomes are involved in the production of IL-1β and play an important role in the progression of inflammation. Thus, inflammammasomes may be involved in the development of hypertensive renal injury.

Methods: Using the Dahl salt-sensitive (DS) rats as a model of hypertensive renal injury, we examined the involvement of inflammasomes in the development of hypertensive renal injury and investigated whether colchicine (Col), an inhibitor of tubulin polymerization which is essential for activation of inflammasomes, attenuated hypertensive renal injury. Ninety rats were divided into seven groups: (1) DS rats fed a normal salt diet, defined as DS + NS group; (2) DS rats fed a high-salt diet, defined as DS + HS group; (3) DS rats fed a high-salt diet with oral Col administration, defined as DS + HS + Col group. After 6 weeks salt loading, we collected renal tissue, blood and urine sample. We examined the morphological changes, expression of inflammasomes associated protein (NLRP3 and caspase-1) by immunohistochemistry, and measured the urinary IL-1β by ELISA.

Results: Systolic blood pressure significantly elevated from 2 weeks after salt loading, but Col administration did not affect blood pressure. Serum creatinine, interstitial fibrosis and glomerulosclerosis significantly increased in the DS + HS group compared to the DS + NS group. These changes were significantly suppressed by Col administration. NLRP3 and caspase-1 expressions were limited to renal tubules and these expressions in the DS + HS group were significantly enhanced than those in the DS + NS group. Col administration significantly suppressed these expression. Moreover, urinary IL-1β was significantly increased in the DS + HS group than that in the DS + NS group, but Col tend to decrease urinary IL-1β levels.

Conclusions: Our results suggest that the inhibition of inflammasomes activation may be a therapeutic target in the hypertensive renal injury.

TH-PO173
shRNA Mediated Knockdown of DPP4 in the Kidney Ameliorates Kidney Inflammation and Proteinuria Ravi Nistala, Jianzhong An. Medicine, Univ of Missouri-Columbia, Columbia, MO.

Background: Dipeptidyl peptidase 4 (DPP4) inhibition is widely used for type 2 diabetes mellitus (T2DM) management. The Sxaglaptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction 53
TH-PO175
Role of Innate Immunity in the Progressive Nephropathy That Ensues after Brief NO Inhibition and Salt Overload

Background: NO inhibition by L-NNAME plus salt overload (HS+) leads to marked hypertention (HT) and renal injury. With cessation of treatment, most of these changes subside, but progressive renal injury/inflammation develops. Here we investigated whether activation of innate immunity (InIm) is involved in this process.

Methods: Male Munich-Wistar rats received HS and L-NAME, 32 mg/Kg/d. Control rats received HS only. Treatments ceased at 4 wk (18 rats studied). Additional rats (N=36) were studied at 8 wk and 28 wk. Assessed at each time point: tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/d), glomerulosclerosis (GS, %), ischemic glomeruli (IG, %), interstitial collagen 1 (COLL1, %), AngII, and macrophages (Mo, cells/mm²), and the renal protein content of IL1β (pg/mg), Casp1, TLR4, and NFκB (x HS).

Results:

<table>
<thead>
<tr>
<th></th>
<th>4wk</th>
<th>8wka</th>
<th>28wka</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS</td>
<td>HS+N</td>
<td>HS</td>
<td>HS+N</td>
</tr>
<tr>
<td>TCP</td>
<td>146±3</td>
<td>213±3*</td>
<td>146±3</td>
</tr>
<tr>
<td>ALB</td>
<td>9±2</td>
<td>160±27*</td>
<td>5±1</td>
</tr>
<tr>
<td>GS%</td>
<td>0±0</td>
<td>2±1*</td>
<td>0±0</td>
</tr>
<tr>
<td>COL1%</td>
<td>1±0</td>
<td>4±1*</td>
<td>2±0</td>
</tr>
<tr>
<td>MΦ</td>
<td>26±4</td>
<td>225±19*</td>
<td>34±5</td>
</tr>
<tr>
<td>AngII</td>
<td>3±0</td>
<td>10±1*</td>
<td>3±0</td>
</tr>
<tr>
<td>Casp1</td>
<td>1±1</td>
<td>4±1*</td>
<td>1±1</td>
</tr>
<tr>
<td>IL1β</td>
<td>2±0</td>
<td>4±1*</td>
<td>2±1</td>
</tr>
<tr>
<td>NFκB</td>
<td>1±1</td>
<td>2±1</td>
<td>1±1</td>
</tr>
<tr>
<td>TLR4</td>
<td>1±1</td>
<td>2±1</td>
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</tbody>
</table>

*p<0.05 vs HS; #p<0.05 vs 4 wk; *p<0.05 vs 8 wk

Expectedly, 4 wk HS+N caused severe HT, ALB and renal injury and increased Casp1, IL1β and TLR4. At 8 wk, renal injury/inflammation regressed partially, but InIm remained activated. At 28 wk, GS worsened, while inflammation and InIm activation persisted.

Conclusions: InIm activation may contribute to the initiation of renal injury in the HS+-L-NNAME model, and for autonomous progression of the nephropathy even after cessation of the original insult. FAPES/P CNpq.

Funding: Government Support - Non-U.S.

TH-PO176
Useful of Presepsin and Procalcitonin in Cardiorenal Syndrome Type 5 Diagnosis
Alessandra Brocca, Grazia Maria Virzi, Anna Clementi, Massimo di Cal, Claudia Ronco. IRRIV.

Background: Procalcitonin (PCT) has been shown to predict bacteremia and bacterial DNAemia. Presepsin is the soluble N-terminal fragment of CD14, which is the receptor for LPS and LPS-binding protein complexes; its level increases in response to bacterial infections, and it is considered a new, emerging, early marker for sepsis. The aim of this study was to investigate the role of Presepsin and PCT in the diagnosis of patients with Cardiorenal Syndrome Type 5 (CRS5).

Methods: We enrolled 8 ICU patients with trauma (4 male; age 61±22.9), 36 CRS5 patients (30 male; age 64±15.7) and 19 healthy controls (CTR) (10 male; age 42.3±11.4). Plasma levels of Presepsin and PCT, IL6, IL18, TNFα, NGAL and endotxin level were detected at diagnosis. Serum endotoxin activity was measured by the EAAtm.

Results: Presepsin levels were divided into two groups: 25% of patients had low endotoxin activity level (negative EAA), while 75% of patients showed high endotoxin activity level (positive EAA). Plasma PCT in CRS5 patients were significantly higher than those in ICU patients with trauma and CTR (both p<0.000). PCT levels was higher in pts with positive EAA results compared to negative EAA pts (p<0.000). Presepsin was significantly higher in trauma and in CRS5 patients than in CTR (both p<0.000). There were a positive correlations between Presepsin and IL6 (r=0.583), TNFα (r=0.411), IL18 (r=0.636) and NGAL (r=0.646)(all p<0.001).

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: Our results suggest that the levels of PCT are increased in CRS5 patients compared to trauma patients and CTR and PCT discriminate patients with positive EAA from the others. Presepsin correlates with pro-inflammatory cytokines and NGAL level, but it cannot discriminate between CRS5 and trauma pts in our ICU population. In conclusion, presepsin may underlie an inflammatory process and PCT may be useful as a biomarker of systemic process and in particular of septic condition.

TH-PO177
Identification of Myeloid-Derived Fibrosis-Inducing Cells Presumably Accounting for Cardiorenal Connection in Chronic Kidney Disease
Akihiro Sagara,1 Norihiro Sakai,1 Yasunori Iwata,2 Kengo Furuichi,3 Yasuhiko Yamamoto,1 Takashi Wada,1
1Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan; 2Dept of Biochemistry and Molecular Vascular Biology, Kanazawa Univ Graduate School of Medical Sciences, Kanazawa, Japan.

Background: Chronic kidney disease (CKD) is a serious risk factor for cardiovascular diseases, which is known as cardio-renal syndrome (CRS). Dysregulation of tissue repair such as fibrosis is a pathological process leading to the end stage of organ failure. However, fibrosis mediators in CRS under CKD are not fully defined.

Methods: To seek the functional cell mediator, unilateral ureteral obstruction (UUO) plus angiotensin II (AII) infusion (AII-UUO) CRS model was established and used with employing CAG-GFP mice and Col1a2 (Col)-GFP mice along with procedures of parabiosis and bone-marrow transplantation (BMT). We performed flow cytometry to identify newly recruited cells into hearts or kidneys and gene expression analyses followed by cell sorting. We also used immunohistochemistry and co-culture system of sorted cells with mouse embryonic fibroblasts (MEFs) from Col-Luciferase mice.

Results: We newly identified a cluster of myeloid cells, which was tracked by GFP using mouse parabiosis or BMT and thereby found to be double-positive for CD45 and Sca1 in hearts as well as kidneys of the CRS model. The cells of the cluster were oval-shaped and mononuclear and significantly increased in number in proportion to heart fibrosis. Gene chip analyses further led to subdividing the population and then identifying fibrosis-triggering cells using Col-reporter MEF co-culture system. The number of the fibrosis-inducing cells in peripheral blood was also significantly increased in the CRS model.

Conclusions: We identified a new population of myeloid-derived fibrosis-inducing cells which were associated with cardiac and kidney fibrosis using our CRS mouse model. Novel strategies targeting the cell population would be therapeutic means against CRS in CKD.
Selective Tubular Activation of Hypoxia-Inducible Factor-2α Has Dual Effects on Renal Fibrosis

TH-PO182

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

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Methods: To address these questions and identify key regions responsible for nuclear translocation of TAZ, we generated a “molecular-mass ruler” toolkit fusing wild type or mutant TAZ to fragments of a large tag (56Citrine) that cannot passively diffuse through the nuclear pore. We expressed these in LLC-PK1 proximal tubular cells and tested their distribution under various conditions.

Results: We show that TAZ transport is active.

Conclusions: We identify a conserved and unique (non-canonical), negatively charged NLS in the C-terminal tail. The NLS is both necessary and sufficient for nuclear TAZ entry; its uptake is mediated in an unsual, Ran-GTPase activity-independent manner; and is mitigated by charge neutralization. Importantly, cyclic stretch or phosphorylation of Rho promote the nuclear entry of the 56Citrine-NLS, which binds neither 14-3-3 nor TAZ. Using mutagenesis and rapamycin-sensitive TAZ constructs, we also identify an N-terminal NES, which is masked by TEAD binding, but exposed through 14-3-3 mediated displacement of TEAD.

Funding: Government Support - Non-U.S.

TH-PO187

Gremlin Signaling in Kidney Development and Disease

Derek P. Brazil,1 Rachel H. Church,1 Imam H.A. Ali,1 Mitchel Tate,1 Deborah P. Lavín,1 Ellen Kok,1 Roel Goldschmeding,1 1Centre for Experimental Medicine, Queen’s Univ, Belfast, Northern Ireland, United Kingdom; 2Dept of Pathology, Univ Medical Centre Utrecht, Utrecht, Netherlands; 1UCD Conway Inst, Univ College Dublin, Dublin, Ireland.

Background: Gremlin is a secreted glycoprotein antagonist of bone morphogenetic proteins (BMPs) that is found in the extracellular matrix. Gremlin homodimers bind to and antagonise BMP homodimers, regulating normal limb, kidney and lung formation.

Grem1−/− mice on a C57Bl/6 background die at birth due to renal agenesis, and display lower limb abnormalities. Gremlin is implicated in fibrotic diseases of kidney, lung and other tissues. Our study has demonstrated increased levels of Gremlin in a range of cancers of the colon, brain and pancreas. Levels of Gremlin are elevated in rheumatoid arthritis in both synovial fluid and chondrocytes. Gremlin has also been suggested to drive angiogenesis via activation of VEGFR2 signalling.

Results: We generated grem1−/− mice on a mixed C57Bl/6/FVB background, and showed that levels of Grem1 were highest in colon, brain and spleen. In contrast, levels of Grem2 were highest in kidney, followed by colon, brain and liver. Only 8% of grem1−/− offspring were viable, and these surviving grem1−/− mice were, on average, 33% smaller in size and weight compared to wild-type. Grem1 staining was evident in the muscularis layer of the colon, and increased pSmad1/5/9 levels were detected in grem1−/− colon. The right kidney was absent in the majority of grem1−/− mice of both genders, with an enlarged left kidney evident, likely explaining the survival of these animals. Mice lacking Greml1 specifically in the kidney tubule epithelial cells (Grem1-TEC−/−) developed normal kidneys, and were partially protected from acute kidney injury induced by folic acid. Compensatory increases in Gremi2 expression were seen in Grem1-TEC−/− kidneys. Grem1 and Grem2 displayed differing affinities for BMP-2, 4 and 7 using C2C12 BRE-luciferase readouts, with Grem2, but not Grem1, inhibiting BMP-2.

Conclusions: We also show that Grem1 but not Grem2 are weak activators of VEGFR2 activation, suggesting that the current model of Grem1-mediated angiogenesis needs to be reconsidered.

Funding: Government Support - Non-U.S.

TH-PO188

Extracellular Matrix Alterations Induced by Renal Fibrosis Perturb Epithelial Tubulogenesis in a Decellularized Whole-Kidney Model

Joseph S. Uzarski,1 Ryan C. Hill,2 Kirk Hansen,2 William M. Miller,3 Jason Wertheim,1,4 1Comprehensive Transplant Center, Northwestern Univ Feinberg School of Medicine, Chicago, IL; 2Dept of Biochemistry and Molecular Genetics, Univ of Colorado Denver, Denver, CO; 3Dept of Chemical and Biological Engineering, Northwestern Univ, Evanston, IL; 4Dept of Surgery, Jesse Brown VA Medical Center, Chicago, IL.

Background: The growing number of patients suffering from renal failure has led to a severe shortage of donor kidneys for transplantation. Development of functional renal tissue by combining recipient cells with a scaffold derived from an unsuitable kidney would alleviate this shortage and create new platforms for modeling diseases or drug-induced nephrotoxicity.

Methods: Rat kidneys with or without 7 days of ureteral obstruction to induce extracellular matrix (ECM) accumulation were decellularized to produce normal or fibrotic ECM scaffolds. Proteomic analysis was performed for quantitative comparison of various protein fractions comprising normal, fibrotic, and decellularized kidney matrices. Scaffolds were repopulated with human distal tubule-derived renal cortical tubular epithelial cells (RCTECs) and cultured in a perfusion bioreactor for 7 days.

Results: Decellularization reduced the cellular fraction of kidneys by >90%, yet scaffolds retained fibrillar collagen (types I, III) basement membrane proteins (collagen IV, laminin), and proteoglycans (perlecan) organized in a 3D framework. Fibrotic ECM scaffolds were characterized by excessive interstitial collagen deposition. RCTECs cultured within normal ECM scaffolds formed tubules displaying proper basolateral (Na+/K+-ATPase, E-cadherin) and apical (α-tubulin + cilia) protein expression. In contrast, RCTECs injected into fibrotic ECM scaffolds formed non-polarized, multi-layered interstitial aggregates.

Conclusions: ECM scaffolds derived from healthy or diseased kidneys are useful to investigate cell–cell matrix interactions that mediate renal tubule development or degeneration. These studies will also inform on the use of healthy or abnormal kidney scaffolds as 3D biological templates for generating patient–customized renal tissue for transplantation.

Funding: NIDDK Support, VA Support, Private Foundation Support

TH-PO189

Deletion of AMPK Regulatory Sites in ACC 1 and 2 Increases Epithelial Mesenchymal Transformation following Renal Injury

Mardiana Lee,1,2 Peter F. Mount,1,2 Marina Katerelos,1 Kurt Gleich,1 David A. Power,1,2 1Nephrology, Austin Health, Melbourne, Victoria, Australia; 2Medicine, The Univ of Melbourne, Heidelberg, Victoria, Australia.

Background: AMP-activated protein kinase (AMPK) is a major regulator of fatty acid oxidation in tissues, mainly through phosphorylation of acetyl CoA carboxylase 1 and 2 (ACC1 and ACC2), which increase fatty acid (FA) oxidation and reduce FA synthesis. Previous studies have shown that activation of AMPK reduces renal fibrosis following injury, and also has an effect on epithelial-mesenchymal transformation (EMT). It is not known, however, whether these effects are mediated through regulation of fatty acid metabolism by AMPK.

The aim of this study is to determine the effect of phosphorylation of ACC by AMPK on renal interstitial fibrosis and EMT in a model of renal tubular injury.

Methods: Male C57BL/6 mice with a combined knock-in mutation of the regulatory S79 and S212 phosphorylation sites in ACC1 and 2, respectively (ACC1/2 KI mice), were given an intraperitoneal injection of folic acid to induce renal injury. Kidneys were removed for analysis after 2 weeks.

Results: There was increased expression of α-smooth muscle actin (α-SMA) by Western blot analysis in the ACC1/2 KI mice when compared to the WT folate group (P<0.01).

Funding: University of Melbourne, Heidelberg, Victoria, Australia.

TH-PO190

Loss of β-1 Integrin in Collecting Duct Principal Cells Downregulates AQP2 Expression and Induces Severe Renal Fibrosis and Kidney Failure

Fahmy Mamuya,1,2 Lei Lei,1 Dongping Xie,1 Kenji Tsuji,2 Diane E. Capen,2 Teodor G. Paunescu,1 Hua Ann Jenny Lu,1 1Program in Membrane Biology and Div of Nephrology, Massachusetts General Hospital; 2Harvard Medical School, Boston, MA.

Background: Renal collecting duct principal cells are highly regulated epithelial cells and play a major role in salt and water transport via ENaC sodium channels and aquaporin-2 (AQP2) water channels, respectively. Understanding their signaling mechanisms is crucial for developing therapeutic approaches to enhance and support the role of the kidney in homeostasis. A major cause of kidney failure is renal fibrosis, and β-1 integrin has been shown to play a role in fibrosis in the kidney and other organs. Recent studies are now showing interaction between AQP2 and β-1 integrin in principal cells, suggesting that β-1 integrin is involved in AQP2 trafficking.

Methods: To investigate the role of β-1 integrin in principal cells we conditionally deleted β-1 integrin in mouse medullary principal cells under a specific AQP2 Cre promoter. We investigated water homeostasis in these mutant mice by urine osmolality measurements, and assessed fibrosis by histopathological analyses and transmission electron microscopy. We also characterized AQP2 expression by immunohistochemistry, immunoblotting, and RT-PCR.

Results: There was no difference in expression of α-cadherin by Western blot. Interstitial fibrosis was not increased in the ACC1/2 KI mice, as determined by Sirius Red staining measured by image analysis. Measurement of the expression of key regulatory enzymes by PCR suggested that FA oxidation (ACox1, CPT1) and glycolysis (PK) were reduced in the mice receiving folate compared to untreated controls, but there was no difference between WT and ACC1/2 KI mice.

Conclusions: The data suggests that control of energy metabolism by AMPK following tubular injury is of particular importance in preventing EMT, and that EMT and fibrosis are controlled separately in these mice.

Funding: University of Melbourne, Heidelberg, Victoria, Australia.

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

Underline represents presenting author.

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Results: Although the mutant mice appeared normal at birth and successfully grew into adulthood, they died around half of their wild-type littermates’ weight. Remarkably, the mutant mice exhibited very low urine osmolality (404 ± 52 mOsm/kg, compared to 2403 ± 203 mOsm/kg in wild types). Starting around 5 weeks of age, we observed a steep time-dependent decrease in AQP2 protein levels in the mutant mouse collecting ducts along with increased evidence of fibrosis and cell death. Towards the end of their lives, AQP2 expression was barely detectable in mutant mice. This phenotype progressed to renal medullary fibrosis, which ultimately caused kidney failure and premature death.

Conclusions: Our data strongly suggest that β-1 integrin is required for maintaining AQP2 expression in medullary collecting duct principal cells, and that its loss induces renal medullary fibrosis and kidney failure.

Funding: NIDDK Support

TH-PO191
Muscle-Kidney Crosstalk via A Myokine, Irisin, Suppresses Renal Metabolic Reprogramming and Fibrosis in Mice
Hui Peng,1,2 Gianqian Wang,1,2 Yanlin Wang,3 William E. Mitchell,2 Zhaoanging Hu.1
1Div of Nephrology, Dept of Medicine, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; 2Div of Nephrology, Dept of Medicine, Baylor College of Medicine, Houston, TX.

Background: Beneficial effects of exercise on muscle metabolism are associated with improved survival of patients with ESRD but the mechanisms underlying this observation are unknown. Potential mediators are myokines which are released from muscle by exercise. We hypothesized that myokines could mediate muscle-kidney crosstalk to limit the development of renal fibrosis and chronic kidney disease (CKD).

Methods: Since skeletal muscle-specific PGC-1α overexpression (mPGC-1α) stimulates myokines expression, we created several CKD models in the transgenic mice and evaluated the kidney function and the degree of fibrosis. Using a metabolomics approach, we accessed energy metabolic reprogramming in kidneys of wild-type and mPGC-1α with or without CKD. We also performed a PCR-based myokines array on muscle of PGC-1α mice and serum fraction assay to identify renal protective myokines.

Results: In mPGC-1α mice with CKD, we found that serum creatinine was lower than it in wild-type mice with CKD, this response was associated with less degree of interstitial fibrosis and glomerulosclerosis. Using a metabolomics approach, we found that CKD-induced energy metabolic reprogramming in kidney cells was blocked in kidney of mPGC-1α mice. To identify renal protective myokines present in serum of mPGC-1α mice, we divided serum from mPGC-1α mice into 4 fractions and found that only the fraction 3 (10KD–30KD) significantly increased mitochondrial respiration capacity in kidney cells. We knockdown the the myokines array in muscle of PGC-1α mice and identified that irisin was the most likely candidate to protect kidney. The underneath mechanism is that irisin counteracts TGF-β1 signaling by competitive inhibiting TGF-β1 type 1 receptor.

Conclusions: Based on previous identification that metabolic reprogramming in kidney cells contribute to the development of fibrosis and CKD, we conclude that myokine irisin can block metabolic reprogramming in kidney cells and limit the development of renal fibrosis and CKD.

Funding: Other NIH Support - NIAAMS, Government Support - Non-U.S.

TH-PO192
Oral Treatment with PBI-4050 Reduces Kidney Fibrosis
Lyne Gagnon, Brigitte Groux,1 Meng-Zhi Zhang,2 Martin Leduc,1 Mikael Tremblay,1 François Sarra-Bourret,1 Léiliane Geerts,1 Kathy Hince,1 Léa Gervais,2 Mathias Trouvé2, Jean-Simon Duquette,1 Boulous Zarabiea,1 Raymond C. Harris,1 Pierre Launir,1 ProMetic BioSciences Inc., Laval, QC, Canada; 2Vanderbilt Univ School of Medicine, Nashville, TN.

Background: PBI-4050 is a first-in-class novel orally active compound which displays anti-inflammatory/antifibrotic activities via a novel mechanism of action. PBI-4050 also displays metabolic properties by reducing blood glucose levels. In a double-blind single ascending dose (400 to 2400 mg) in healthy volunteers, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant adverse effects (SAEs). Similarly, PBI-4050 was well tolerated in chronic kidney disease (CKD) patients with no SAEs observed at 800 mg. PBI-4050 is presently in Clinical Phase II in diabetes (T2D) associated with metabolic syndrome and in idiopathic pulmonary fibrosis (IPF). Preliminary data from the open labelled T2D associated with metabolic syndrome clinical phase shows that PBI-4050 significantly reduced glycated hemoglobin (HbA1c, -0.77%, p<0.001), and biomarkers (IL-18, resistin, and pentraxin-3) from the first 12 enrolled patients.

Results: PBI-4050 has demonstrated strong anti-fibrotic activities in different kidney models: 5/6-nephrectomized rats (end-stage renal failure, early and late treatment), doxorubicin-induced nephrotoxicity (acute kidney injury), renal ischaemia, db/db and db/db eNOS−/− mice (diabetic kidney disease), DTR (a spontaneous tubulointerstitial fibrosis in homozgyous HB-EGF mice), and unilateral ureteral obstruction (UUO). PBI-4050 plays a key in inflammation/fibrosis regulation by reducing pro-fibrotic cytokines and growth factors (MCP-1, CTGF, TGFβ1, IL-5, endothelin 1 (EDN1), EGF, PDGFα, VEGFα, Inhibin βE, TGF-β2), myofibroblast activation and epithelial-to-mesenchymal transition markers (α-SMA, collagen III, ILK, MMP2, MMP9, and TGFβ-1, 2 and 3), remodeling enzymes (LOX, MMP1, MMP2, MMP9, MMP13, uPA, PAI-1, TIMP3 and ILK) and fibrootic markers, resulting in significant improvement of organ function.

Conclusions: Taken together, these pre-clinical results suggest that PBI-4050 offers the potential as a novel therapy for the treatment of kidney fibrosis.

TH-PO193
Imaging Renal Fibrosis with Two Photon Excitation (TPE), Second Harmonic Generation (SHG), and Fluorescence Lifetime Imaging Microscopy (FLIM)
Evgenia Dobrinskikh,1 Xiaoxin Wang,1 Yuhuan Luo,1 Suman Ranjit,2 Avi Rosenberg,3 M. Scott Lucia,1 Vivette D. D’Agati,2 Moshe Levi.1 1Univ of Colorado; 2Columbia Univ; 3NIH; UC Irvine.

Background: Glomerulosclerosis and tubulointerstitial fibrosis occurs in many diseases and signals poor renal functional outcomes. In view of recent therapies aimed at the pathogenesis of fibrosis, sensitive and quantitative techniques for documenting fibrosis have become highly desirable. Current stains have limited use for 3D imaging and they do not allow for determination of the metabolic state of the kidney.

Methods: We have applied TPE, SHG, and FLIM for label-free imaging of kidney sections. We have then applied the phasor approach for FLIM analysis, which allows for the determination of collagens and other extracellular matrix components, and metabolic state of the kidney (free to bound NADH ratio) taking advantage of the specific autofluorescence characteristics of these molecules. These techniques can be used in fresh or frozen or FFPE tissues. We have furthermore applied the novel multiphoton imaging microscope known as the DIVER which enables for imaging of thick tissues.

Results: In kidney biopsies obtained from diabetic humans, compared to biopsies obtained from nondiabetic subjects, we have determined that there is a strong SHG signal around the glomerulus and tubulointerstitial areas, which indicates presence of fibrosis. FLIM shows shift to the shorter lifetime in diabetic kidneys that corresponds to different metabolic state of the tissue and different matrix composition. FLIM also may determine relative degree of the disease progression based on differential lifetimes in diabetic compared to nondiabetic control kidneys. Application of the DIVER allows for 3D imaging of thick sections made from biopsies, which should give a better vision of the kidney ultrastructure and disease progression.

Conclusions: TPE, SHG and FLIM imaging allows for label-free and 3D imaging of the extracellular matrix and metabolic state of the kidney based on the autofluorescence of the corresponding molecules. In addition to the quantitative advantage it also allows for further processing of the same kidney biopsy slides for additional histochemical stains or biochemical studies.

Funding: NIDDK Support

TH-PO194
PHF14 as an Innate Brake to the Progression of Renal Fibrosis following Acute Kidney Injury
Bo Yang, Zhanguo Mao. Div of Nephrology, Changzheng Hospital, Shanghai, China.

Background: PHF14 is a newly identified regulator of mesenchyme growth in embryonic tissues. Studies showed that PHF14-null mutants were neonatally lethal due to interstitial tissue hyperplasia in major organs including kidney. We hypothesize that PHF14 may plays a protective role in renal fibrosis progression after the pro-fibrotic insults. It will help to elucidate the interactions of mediators in the process of renal fibrogenesis by illuminating the function of PHF14.

Methods: We determined the expression profile of PHF14 in fibrotic kidneys after folic acid (FA) injection in mice. Then, we generated PHF14 inducible knockout mice to explore the biological role of PHF14 in the progression of renal fibrosis following FA administration. Relationship of PHF14 expression with TGF-β signaling pathway was also examined in rat renal fibroblast cells. We also validated whether PHF14 performed as negative regulator of platelet-derived growth factor receptor-α (PDGFR-α) and eventually suppressed the expression of fibrosis related biomarkers.

Results: PHF14 was upregulated in fibrotic kidneys after FA insults in mice. Compared with sham control, induced PHF14 deletion in adult mice exacerbated renal fibrosis following FA associated renal injury. TGF-β stimulation induced the upregulation of PHF14 in vitro, and p-smad3 acts as transcription factor to enhance the PHF14 expression, which was proved by immunoprecipitation assay. Lack of PHF14 expression enhances collagen I and α-SMA synthesis induced by TGF-β in vitro.
PHF14 was involved in the inhibition of the PDGF signaling overactivation by selectively repressing PDGF receptor transcript.

Conclusions: PHF14 expression was upregulated in fibrotic models in vivo and in vitro with anti-fibrotic functions. The TGF-β/smad3/PHF14 pathway acted as a self-limiting mechanism in TGF-β dominated renal pro-fibrotic signaling by suppressing PDGF-receptor expression.

Funding: Government Support - Non-U.S.

TH-PO195
A Step Towards Clinical Application of Acellular Matrix: A Clue from Macrophage Polarization
Astgik Petrosyan,1,2 Stefano Da Sacco,1 Nikita Tripuraneni,1 Ursula Kreuser,1 Maria J. Lavareda-Pearce,1 Riccardo Tamburini,1 Roger E. De Filippo,1,2 Giuseppe Orlando,1 Paolo Cravedi,4 Laura Perin,1,2 1Univ. of Southern California; 2GOFARR Laboratory, Children’s Hospital Los Angeles; 3Wake Forest School of Medicine; 4Icahn School of Medicine at Mount Sinai.

Background: The outcome of tissue engineered organ transplants depends on the capacity of the biomaterial to promote a pro-healing response once implanted in vivo. Multiple studies, including ours, have highlighted the necessity of using the extracellular matrix (ECM) of animal organs as a platform for tissue engineering and more recently, discarded human organs have also been proposed as a scaffold source. It is known that natural matrices present diverse immune properties when compared to artificial biomaterials. However, how these properties compare between diseased and healthy ECM and artificial scaffolds has not yet been defined.

Methods: We used decellularized renal ECM derived from WT mice and from mice affected by Alport Syndrome as a model of renal failure with extensive fibrosis, at different time-points of disease progression. We characterized the morphology and composition of these ECMs and compared their in vitro effects on macrophage activation with that of synthetic scaffolds commonly used in the clinic (collagen type I and poly-L-(lactic) acid, PLLA).

Results: We showed that ECM derived from Alport kidneys differed in fibroin protein deposition (coll I, coll IV, and fibronectin) and cytokine content (Resistin, TIM-1, KIM-1, DPPIV/CD26 and Reg3g) when compared to ECM derived from WT kidneys. Yet, both WT and Alport renal ECM induced macrophage differentiation mainly towards a reparative (M2) phenotype (reduced CD86), while artificial biomaterials towards an inflammatory (M1) phenotype. Anti-inflammatory properties of natural ECMs were lost when homogenized, hence three-dimensional structure of ECM seems crucial for generating inflammatory (M1) phenotype. Anti-inflammatory properties of natural ECMs were lost when homogenized, hence three-dimensional structure of ECM seems crucial for generating inflammatory (M1) phenotype. Anti-inflammatory properties of natural ECMs were lost when homogenized, hence three-dimensional structure of ECM seems crucial for generating inflammatory (M1) phenotype. Anti-inflammatory properties of natural ECMs were lost when homogenized, hence three-dimensional structure of ECM seems crucial for generating inflammatory (M1) phenotype. Anti-inflammatory properties of natural ECMs were lost when homogenized, hence three-dimensional structure of ECM seems crucial for generating inflammatory (M1) phenotype.

Conclusions: Together, these data support the notion that natural ECM, even if derived from diseased kidneys promote a M2 protolerogenic macrophage polarization, thus providing novel insights on the applicability of ECM obtained from discarded organs as ideal scaffold for tissue engineering.

TH-PO196
Human Discarded Kidneys as a Source of Protolerogenic Extracellular Matrix Scaffolds for Bioengineering
Astgik Petrosyan,1 Stefano Da Sacco,1 Chiara Donadelli,1 Giuseppe Orlando,1 Laura Perin,1 Paolo Cravedi,1 Children’s Hospital Los Angeles; 2Icahn School of Medicine at Mount Sinai; 3Wake Forest School of Medicine.

Background: Human extracellular matrix (ECM) scaffolds produced through the decellularization of discarded kidneys represents a potential platform for kidney bioengineering. Studying their immune properties is crucial for their future implementation in the clinic.

Methods: We decellularized adult human kidneys not suitable for transplantation, dissected medulla from cortex and evaluated their relative immune effects on human naïve T cell proliferation (CFSE dilution in response to αCD3/αCD28 mAb) and conversion into functional regulatory T cells (cells were cultured with αCD3/αCD28 mAb, IL2 and no TGF-β), since we previously showed the TGF-β is present in ECM). We also seeded human macrophages on ECM and evaluated their cytokine expression.

Results: ECMs obtained from the cortex of discarded human kidneys inhibited expansion of activated human naïve CD4+ T cells and promoted their conversion into FoxP3+ regulatory T cells (Treg) (% Figure). Macrophages adhered onto human ECM and showed cellular activity including survival and proliferation. In addition after 5 days they secreted significant amounts of anti-inflammatory cytokines such as IL10, but no pro-inflammatory cytokines like INFγ and TNFα.

Conclusions: Our data demonstrate that hrECMs inhibit effector T cell expansion and promote naïve CD4 T cell conversion into FoxP3+ Treg, possibly through a TGF-β mechanism. They stimulate macrophages to secrete anti-inflammatory cytokines, supporting further studies for their clinical use.

Funding: Private Foundation Support
TH-PO198
Core Fucosylation Regulates the Transition of Pericytes to Myofibroblasts in Renal Interstitial Fibrosis
Nan Wang, Nephrology Dept, The First Affiliated Hospital of Dalian Medical Univ, Dalian, Liaoning Province, China.

Background: Chronic kidney diseases are irreversible diseases with high mortality. Renal interstitial fibrosis is the final common outcome of CKD. While myofibroblasts are the main contributors to the progression of RIF. Recently, pericytes have been confirmed as the main source of myofibroblasts in RIF. Cross-talks of multiple signaling pathways, such as TGF-β, PDGF pathways, are known to activate pericytes in the process of RIF. Researchers have found that single receptor blockage of these pathways can alleviate RIF. Our previous researches have found that some key receptors of these pathways are modified by fucosyltransferase 8-regulated core fucosylation.

Methods: Pericyte-myofibroblast transition and the expressions of core fucosylation were observed in renal biopsies of IgAN patients, UUO mice model and primary pericytes cultivation in vitro. FUT8shRNA-Adenovirus and FUT8siRNA were used for the knockdown of FUT8 in vivo and in vitro, Pericyte-myofibroblast transition and the expressions of core fucosylation were then observed.

Results: We found that core fucosylation of pericytes was increased with the severities of renal interstitial injuries in IgAN patients. Similar elevations of core fucosylation were found in UUO mice model and pericytes-myofibroblasts transition model in vitro. Adenoviral-mediated FUT8shRNA in vivo and FUT8siRNA in vitro were then used to inhibit the expressions of FUT8. Interestingly, we found that the inhibitions of core fucosylation could alleviate RIF dramatically and prevent pericytes transition both in vivo and in vitro.

Conclusions: Our findings suggested that core fucosylation could regulate the transition of pericytes to myofibroblasts in the progress of RIF. We believed that glycosylation may provide a novel hub target to prevent RIF and CKD.

Funding: Government Support - Non-U.S.

TH-PO199
The BET Bromodomain Inhibitor JQ1 Diminished Renal Fibrosis
Sandra Ravego-Mateus,1 Jose Morgado-Pascual,2 Beatriz Suarez-Alvarez,3 Pierre-Louis Tharaux,3 Alberto Ortiz,2 Carlos Lopez-Larrea,3 Marta Ruiz-Ortega,2

1Univ Autonoma Madrid; 2Paris Cardiovascular Centre, France; 3IJS-Fundacion Jimenez Diaz; 4Hospital Unv Central de Asturias, Spain.

Background: Bromodomain and extraterminal domain (BET) proteins participates in tumor development, autoimmunity, inflammation, and fibrosis. BET proteins bind to acetylated lysine residues on proteins to regulate the transcriptional program. Sex determining region Y-box 9 (SOX9) is a transcription factor involved in kidney regeneration, proliferation and migration. JQ1, a selective BET inhibitor, has demonstrated beneficial effects on murine pulmonary and liver fibrosis, but there is no data in renal fibrosis.

Methods: Experimental models of anti-glomerular basement membrane nephritis, induced by nephritic serum (NTS) administration and unilateral ureteral obstruction (UUO) were used. Mice were treated with JQ1 (100 mg/mouse/day). In vitro studies were done in TGF-β-treated mesangial cells and renal fibroblasts.

Results: JQ1-blocked Sox9 nuclear localization in injured kidneys and in TGF-β-treated cells.

Conclusions: Our results demonstrate that JQ1 regulates profibrotic and matrix-related components and reduces experimental renal fibrosis. These results suggest that BET inhibitors could have important therapeutic applications in chronic kidney diseases.

Funding: Government Support - Non-U.S.

TH-PO200
Niclosamide Ameliorates Fatty Acid Metabolism Disturbance of Tubular Epithelial Cells in Renal Fibrosis
Qi Yuan, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Renal fibrosis is the common pathological and histological pathway of chronic kidney disease. Mitochondrial dysfunction promotes tubular epithelial cells injury, playing a vital role in the progression of renal fibrosis. As the mitochondria rich cells, tubular epithelial cells are mainly used by fatty acid oxidation (FAO). Recent studies confirmed that proteins function as mitochondrial fatty acid anion exporters, modulating cellular fatty acid homeostasis. Niclosamide is a teniocide mediating the uncoupling of mitochondria. In this study, we investigate the role of niclosamide in the fatty acid metabolism of tubular epithelial cells in renal fibrosis.

Methods: C57BL/6J mice were randomly assigned into control group and three folic acid groups, mice in the folic acid groups sacrificed in the day 1, day 7 and day 30. The bilateral kidneys were used for morphology, western blot and RT-PCR analysis. C57BL/6J mice after injecting folic acid were treated with niclosamide, while the morphology of renal sections and the function of fatty acid oxidation were observed.

Results: 1. Folic acid induced the mitochondrial injury and fatty acid oxidation defect of the tubular epithelial cells. 2. The fibrotic matrix was expanded and the markers of collagen fibrils such as α-SMA, fibronectin (FN), Collagen I were increased in the kidneys after folic acid injecting in a time depended manner. 3. Niclosamide restored the structure and function of the tubular epithelial cells’ mitochondria after folic acid injecting. The fatty acid oxidation of the tubular epithelial cells was resumed by niclosamide treatment.

Conclusions: These results demonstrate that mitochondrial dysfunction leading to fatty acid metabolism disturbance in the tubular epithelial cells contribute to renal fibrosis. Niclosamide-induced mitochondrial uncoupling improves the mitochondrial structure and the fatty acid oxidation in the progress of renal fibrosis, finally resisting the lesion of renal fibrosis. Targeting mitochondrial uncoupling may be a potential treatment for renal fibrosis.

Funding: Government Support - Non-U.S.

TH-PO201
Proteomic Analysis of Glomerular Extracellular Matrix Demonstrates Differences between FSGS NOS and CFSGS
Beatriz Pascual,1 Laura Belez,1 Beatriz Martinez,2 Kenneth R. McLeish,2; 1Medicina, Univ of Louisville; 2Robley Rex VAMC, Louisville, KY.

Background: Histologic evidence for abnormal remodeling of the glomerular extracellular matrix (ECM) is a prominent feature of FSGS, however, the differences in glomerular ECM composition are unknown. The current study used label capture microdissection (LCMD) of glomeruli from human biopsy specimens and mass spectrometry (MS) to compare glomerular ECM composition among patients with FSGS NOS, collapsing FSGS (CFSGS), and normal subjects.

Methods: Glomerular sections were obtained by LCMD from de-identified formalin-fixed paraffin embedded renal biopsy tissue from 6 patients with FSGS NOS, 7 patients with CFSGS, and from 2 kidneys retrieved, but not used, for transplantation. Proteins were extracted by sequential decellularization with NTA40/HTrion X-100 and extraction of proteins with matrix with protease MAX surfactant. Peptides obtained by proteolysis with trypsin were identified by MS. Peptide data was analyzed by Mascot/Sequest, and label-free quantification compared among groups.

Results: Of the 1271 unique proteins identified, 161 were determined to be ECM proteins, by comparison to the matrixome database and previously published glomerular ECM identification. 110 ECM proteins were identified from normal glomeruli, 136 from FSGS NOS, and 155 from CFSGS. 106 ECM proteins were common between normal and FSGS NOS, while 30 proteins were unique to FSGS NOS. 109 ECM proteins were common between normal and CFSGS, while 46 were unique to CFSGS. 130 ECM proteins were common between FSGS NOS and CFSGS, 6 unique to FSGS NOS, and 25 unique to CFSGS. Protein quantification identified 8 proteins differentially expressed in CFSGS and 10 proteins differentially expressed in FSGS NOS, compared to the other two groups.

Conclusions: Proteomic analysis of glomeruli isolated by LCMD from renal biopsy tissue successfully identified differences in ECM protein expression in FSGS NOS and CFSGS. Differential ECM protein expression provides targets for biomarker identification for specific FSGS variants and suggests unique differences in ECM remodeling between FSGS NOS and CFSGS.

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

140A
FH-PO202
Fibroblast Growth Factor 23 Exacerbates Kidney Fibrosis Involving β-Catenin Signaling Activation and Extracellular Matrix Production in Tubular Cells Xin Liu, Chunsun Dai. Nanjing Medical Univ.

Background: The concentration of fibroblast growth factor 23 (FGF23) in the circulation is closely correlated with the decline of renal function in patients with chronic kidney diseases. However, whether FGF23 can directly promote kidney fibrosis and its underlying mechanisms are not clear.

Methods: In this study, we generated a mouse model with ectopic expression of exogenous FGF23 in CD-1 mice through tail vein hydraulic injection of FGF23 expression plasmid once a week.

Results: FGF23 was significantly increased at as early as one day and maintained at high level in the circulation during the observation period. The mice developed hypertension, anemia and hyokalemia but little kidney morphological damage after four times of pFGF23 injection. We then generated mouse models with kidney fibrosis including UUO nephropathy and ischemia/reperfusion injury. The mice with ectopic FGF23 expression developed more severe kidney fibrosis and inflammatory cell accumulation in kidney tissue after UUO, adriamycin injection or ischemia/reperfusion compared to those injected with control plasmid. In cultured NRK-52E cells, FGF23 treatment could exacerbate TGF-β-induced extracellular matrix production with a time and dose dependent manner. Additionally, in both FGF23 treated NRK-52E cells and UUO kidneys from mice with ectopic FGF23 expression, p-β-catenin (Ser675), an active form of b-catenin, was robustly elevated.

Conclusions: Thus, these results suggest that FGF23 exacerbates UUO nephropathy in mice, which may be associated with b-catenin signaling activation and extracellular matrix production in tubular cells.

Funding: Government Support - Non-U.S.

TH-PO203
Proximal Tubule Specific COMP-Angiopoietin-1 Overexpression Decreases Renal Injury in a Mouse Unilateral Ureteral Obstruction Model Woong Park, Yujin Jung, Tung Nguyen-Thanh, Kyung Pyo Kang, Won Kim. Dept of Internal Medicine, Chonbuk National Univ Medical School, Jeonju, Korea.

Background: Preservation of renal endothelial cells is one of promising strategies for renal fibrotic process. Angiopoietin-1 (Ang1) is an angiogenic factor through its endothelial receptor tyrosine kinase, Tie2. We have reported that adenoviral transfer of cartilage oligomeric matrix protein (COMP)-Ang1 overexpression plasmid from renal proximal tubular epithelial cell (Gr-1) was performed.

Results: COMP-Ang1 overexpression from renal proximal tubular epithelial cell ameliorated the UUO-induced decrease of PECAM-1-positive endothelial cells. After ureteral obstruction, tubular dilatation, desquamation and mononuclear cell infiltrations were increased in the WT mice. However, UUO induced tubular injury and fibrosis were significantly decreased in proximal tubular COMP-Ang1 overexpression mice. Immunofluorescence data for neutrophils (Gr-1-positive cells) and macrophages (F4/80 positive cells) showed that proximal tubular COMP-Ang1 overexpression mice suppressed UUO-induced increase of Gr-1 and F4/80 positive cells infiltration. In Western blot analyses, α-SMA and ICAM-1 expression were significantly decreased in proximal tubular COMP-Ang1 overexpression mice compared to WT mice.

Conclusions: Proximal tubular COMP-Ang1 overexpression might have a protective role in UUO-induced renal injury and fibrosis.

Funding: Government Support - Non-U.S.

TH-PO204
ErbB4 Deletion Accelerates Renal Fibrosis and Inflammation after Unilateral Ureteral Obstruction Toshiki Minazawa, 1Hiroaki Hisa, 1Yasuyuki Ohizumi, 1Yuko Fujisawa, 1Hiroshi Hasegawa, 1Masaaki Kimura, 1Hironori Hori, 1Takakazu Yoda, 1Masaharu Imamura, 1Masahiro Matsumoto, 1Yasuhiro Kato, 1Hitoshi Takahashi, 1Shintaro Inada, 1Makoto Kato, 1Kiyoshi Fujita, 1Shunji Sato, 1Shigeru Kojima, 1Yasuyuki Fujii, 1Shinya Furuhashi, 1Kazuo Akiyama, 1Takaya Kondoh, 1Makoto Hishikawa, 1Yuki Kojima, 1Fedde L. Jorgensen, 1Bjarne S. Pedersen, 2Nobuyuki Fujimoto, 12Masato Goto, 1Takashi Hara, 1Takashi Kanda, 1Hidenori Ishii, 1Kensuke Kudo, 1Eiji Arai, 1Yoshio Akamatsu, 1Tetsuji Ushijima, 1Shinya Matsumoto, 1Yoshinori Hashimoto, 1Tomohiro Ebina, 1Koiku Sato.

Background: Tubulointerstitial injury/fibrosis is a histological feature involved in the progression of chronic kidney disease (CKD) regardless of etiology. Our preliminary studies showed increased ErbB4 expression in the glomeruli and tubular epithelium of CKD kidneys. However, its role in the tubulointerstitial injuries remains to be determined.

Methods: Heart rescued ErbB4 deletion (ErbB4+/-) and wild-type (WT) mice were subjected to unilateral ureteral obstruction (UUO) or sham operation. Renal function and pathological changes were examined.

Results: ErbB4+/- mice tended to have higher BUN levels compared to WT mice after UUO, but the levels were not significantly different. However, in UUO kidneys, ErbB4+/- mice displayed accelerated interstitial fibrosis as early as 3 days after UUO, whereas similar levels of fibrosis shown by trichrome staining were only evident after 6 days in WT mice. ErbB4+/- kidneys had increased collagen I, SMA, and FSP-1 immunoreactivity. Macrophage infiltration as shown by F4/80 immunostaining and renal cell apoptosis by cleaved caspase 3 levels were also increased in ErbB4+/- kidneys.

Conclusions: ErbB4 deletion accelerates the development and progression of renal fibrosis in obstructive nephropathy. Increased expression of ErbB4 seen in the kidneys of CKD may reflect a compensatory effect to counteract the tubulointerstitial injury.

Funding: NIDDK Support, VA Support

TH-PO205
Serum Levels of a Type VI Collagen Fragment Predict Progression of Chronic Kidney Disease Signe Holm Nielsen, 1Anthony Fenton, 2Mark David Jesky, 3Charles Ferro, 4Morton Asser Karsdal, 1Paul Cockwell, 2Federica Genovese, 11Fibrosis Biology and Biomarkers, Nordic Bioscience, Herlev, Denmark; 2Dept of Nephrology, Univ Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom.

Background: Progressive renal fibrosis is the dominant process that leads to end stage renal disease (ESRD) in patients with chronic kidney disease (CKD). Collagen type VI (COL6) is over-expressed in progressive fibrosis, with prominent expression in renal disease. Pro-C6 is a COL6 fragment which reflects COL6 expression. We hypothesized that Pro-C6 levels were associated with CKD progression.

Methods: We measured Pro-C6 levels in the serum of 500 patients from the Renal Impairment in Secondary Care (RIBSC) study. This is a prospective cohort study of patients with high risk CKD, as defined by the UK NICE criteria (2008). Participants were followed up and data collected at 12 months for progression of CKD, defined as either commencement of RRT or decline in eGFR of >30%.

Results: The cohort was 61.6% male, with a median age of 64 years (IQR 50-76), and 72.2% caucasian. Median eGFR was 26.5 mL/min/1.73m² (19.5-53.6), and median ACR was 32.4 mg/mmol (6.2-128). 417 patients had 12-month follow-up, and of these 46 (11.0%) had experienced progression of CKD at 12 months. Median Pro-C6 level was 23.1 ng/mL (IQR 16.8-30.0), and on log transformation had a linear association with CKD-EPI eGFR (r=−0.74, p<0.001). An increase in Pro-C6 of 10 ng/mL was associated with a hazard ratio of 1.96 (95% CI 1.50-2.55, p=0.0001) for CKD progression, and participants in the highest quartile had a 9-fold higher risk than those in the lowest quartile. After adjusting for eGFR and ACR, a significant association between Pro-C6 and CKD progression at 12 months remains (HR 1.44 [01.02-2.04], p=0.039).

Conclusions: Serum Pro-C6 is an independent marker for CKD progression at 12 months. This indicates a potential pathological role for collagen type VI in progressive CKD.

TH-PO206
Inhibition of K-Ras in the Peri-AKI Period in a Murine Model of Aristolochic Acid Nephropathy Reduces Long-Term Progression to CKD in a Murine Model of Aristolochic Acid Nephropathy Suji K Kumar Sahni, Bruce M. Hendry, Claire C. Sharpe. Dept of Renal Sciences, King’s College London, London, United Kingdom.

Background: Acute Kidney Injury (AKI) is a recognised early forerunner of Chronic Kidney Disease (CKD). K-Ras expression is up-regulated in renal fibrosis and chronic K-Ras inhibition post-injury prevents scarring. Our aim was to investigate whether transiently reducing K-Ras expression prior to an AKI reduces progression to CKD.

Methods: CD1 mice received intra-peritoneal injections of 3.5mg/kg Aristolochic Acid (AA) or saline (NS) on Day 1 & on Day 5. A treatment group also received a single subcutaneous dose of 100mg/kg K-Ras murine Antisense Oligonucleotide (ASO) 2 days prior to the 1st AA dose. A vehicle group received NS 2 days prior instead. Blood urea nitrogen (BUN), Creatinine (Cr), Haemoglobin A1c (HbA1c) and urinary NGAL were measured at multiple time points. The degree of fibrosis was ascertained through a Hydroxyproline assay, Western blot (WB) for alpha SMA and Picrosirius Red (PSR) & Masson Trichrome (MT) staining. The effect on K-Ras was determined by QPCR and WB.

Results: Mice given AA transiently developed an AKI at day 5-20 before then recovering. There was a further rise in both BUN & Cr at day 80 indicating CKD. Administration of Murine K-Ras ASO reduced both the BUN & Cr at day 80 compared to vehicle by 37%. Fibrosis quantification through PSR & MT staining showed AA caused a 5 fold increase in collagen deposition by day 80. ASO treatment halved this amount of fibrosis at day 80 and reduced both hydroxyproline & αSMA. AA reduced in raised K-Ras expression throughout the model. ASO only transiently reduced K-Ras at day 0 as it was raised again by day 12 and remained elevated throughout the model before falling again at day 80. This is the initial fall in K-Ras with ASO that has resulted in the reduction in the CKD demonstrated at day 80.

Conclusions: Transiently reducing K-Ras expression in the peri-AKI period in a murine model of AA nephropathy reduces downstream fibrosis and prevents the decline in renal function. Targeting K-Ras may provide a future therapeutic option for preventing renal fibrosis and CKD following AKI.
Lipoxins Attenuate Kidney Disease Progression in Diabetic ApoE-/- Mice
Phillip Kanantharid,1 Mark E. Cooper,1 Muthukham Mohan,1 Aaron D. McClelland,1 Karin Jandeit-Dahm,1 Catherine Godson,2 Eoin P. Brennan,3 Stephen P. Gray,1 Raelene J. Pickering,1 Chris Tikellis.1
1JDRF Danielle Alberiti Memorial Centre for Diabetes Complications, Baker IDI Harrow Research Institute, Melbourne, Victoria, Australia; 2UCD School of Medicine and Medical Sciences, UCD Conway Inst of Biomolecular & Biomedical Research, Dublin, Ireland.

Background: Strategies based on the resolution of inflammation are an attractive approach for the treatment of diabetic kidney disease (DKD). Endogenous lipid mediators including Lipoxins (LXs) actively promote the resolution of inflammatory responses. Here we investigated the potency of endogenous (LXA4) and stable LX analogues (Benzo-LX) in ameliorating kidney disease in diabetic ApoE-/- mice.

Methods: 6-week-old apolipoprotein E (ApoE-) mice were randomly divided into control and diabetes groups. Diabetes was induced with low-dose streptozotocin. Mice in both groups were randomly divided into vehicle, LXA4 and Benzo-LX analogue groups, and followed for 10-20 weeks.

Results: Diabetic ApoE-/- mice presented with DKD, as evidenced by albuminuria and renal injury. Diabetes-induced glomerular expansion and mesangial matrix expansion were significantly attenuated by LXA4, and Benzo-LX (Glomerulosclerotic index: control 1.0±0.1, diabetic+vehicle 2.3±0.2, diabetic+LXA4 1.8±0.1, diabetic+Benzo-LX 1.5±0.1 arbitrary units, p<0.01 Benzo-LX vs vehicle; n=9). The increase in renal cortical collagen (COL1, COL3, COL4), alpha-smooth muscle actin (α-SMA), transforming growth factor beta 1 (TGF-β1), ICAM-1, VCAM-1, MCP-1, IL-6 and TNFα seen in diabetic apoe-/- mice was attenuated by both LXA4 and Benzo-LX. The Lipoxins had no significant effect on albuminuria.

Conclusions: Taken together, our data demonstrate that LXs may be used as novel anti-fibrotic and anti-inflammatory therapeutics in DKD.

Funding: Government Support - Non-U.S.

TH-PO208
Smad Anchor for Receptor Activation, which Regulates Wnt/β-Catenin Signaling, Is Transcriptionally Suppressed by Decl

Background: We previously reported that cultured renal epithelial cells (HKC) lacking Smad anchor for receptor activation (SARA) spontaneously undergo mesenchymal transition and become more fibrogenic, expressing higher TGF-β-stimulated COL1A2 mRNA content. In unilateral ureteral obstruction-mediated renal fibrosis, SARA is significantly downregulated, suggesting that SARA loss is a key event for progression. At least four mRNA species for human SARA exist and one major form, Z2.1 lacks the FYVE domain, thought to be required for SARA membrane localization. The Smad-binding domain was cloned into pGL2-basic vector. Expression vectors carrying the full-length or Z2.1 domain, thought to be required for SARA membrane localization. The Smad-binding domain were transfected into HKC. β-catenin or Smad2/3 dependent transcriptional activity was evaluated using TOPflash/FOPflash or ARE/BSE-luciferase reporter systems.

Results: Consistent with our previous finding that TGF-β decreases SARA mRNA expression, SARA-1036 promoter activity was reduced by TGF-β by 50% A-814 promoter construct demonstrated 3-fold higher basal transcriptional activity compared to the -1036 promoter. Analysis identified an binding site between -814 and -1036 for Dec1, and Dec1 knockdown yielded higher levels of SARA protein and resistance to TGF-β-mediated SARA downregulation. Cells expressing either Z2.1 or full-length SARA suppressed Wnt3a-induced β-catenin activity to a similar degree, while neither Smad2/3-dependent ARE nor Smad1-dependent SBE reporter was affected by Z2.1 or full-length SARA overexpression. Both SARA isoforms interacted with β-catenin and rendered β-catenin for degradation.

Conclusions: Dec1 ablation inhibits TGF-β-stimulated SARA downregulation. Despite lacking the membrane localization sequence, Z2.1 suppresses Wnt3a/β-catenin signal transduction. These findings suggest possible novel approaches to suppressing progression of renal fibrosis.

Funding: NIDDK Support

Renoprotective Effects of Angiotensin III: Role of Oxidative Stress and Extracellular Matrix Expansion
Rita de Cassia Cavagliere, Doug Yoon Lee, Robert T. Day, Yves C. Gorin, Denis Feliers. Dept of Medicine/Nephrology, Univ of Texas Health Science Center at San Antonio, San Antonio, TX.

Background: Glomerular injury is a prominent pathological feature of diabetic nephropathy (DN). Hypertension promotes extracellular matrix protein accumulation by glomerular mesangial cells (MCs) and oxidative stress plays an important role in the pathogenesis of these glomerular lesions in DN.

Methods: Type 1 diabetic mice displayed higher renal angiotensin (Ang) II and lower renal levels of Ang III, which correlated with a downregulation of aminopeptidase-A, which generates Ang III from Ang II. Both control and type 1 diabetic mice lacked the angiotensin converting enzyme (ACE) responsible for converting Ang II to Ang III. We provide the first evidence that Ang III, acting through the AT2R, protects MC from HG-induced oxidative stress and fibrotic injury via inhibition of NADPH oxidase activity, reactive oxygen species (ROS) generation induced by HG in the cells and the mitochondrial fraction. Ang III negatively regulated HG-mediated Nox4 expression via inhibition of Nox4 mRNA translation, and significantly attenuated upregulation of fibroactin induced by HG at 24 h. All these effects of Ang III were reversed by pharmacologic or genetic inhibition of the AT2R. The relevance of this pathway was confirmed by the finding that Nox4 expression, ROS production and fibrotic markers were attenuated in both control and type 1 diabetic mice lacking AT2R. The findings of renal disease in these mice are linked to a reduction in Ang III generation in the kidney.

Conclusions: We provide the first evidence that Ang III, acting through the AT2R, protects MC from HG-induced oxidative stress and fibrotic injury via inhibition of Nox4 expression. Our data unveil the anti-oxidant and anti-fibrotic effects of Ang III and demonstrate that a functional interplay between AT2R and Ang III accounts for these renoprotective action in the diabetic environment. Targeting of Ang III/AT2R axis may represent a promising therapeutic approach for the treatment of DN.

Funding: NIDDK Support, Private Foundation Support

The Cys-Knot C-Terminal Motif of CTGF Modulates Fibrotic Effects in Proximal Tubule Cells Alone and in Concert with TGFβ1
Matthew Potthie, Mysore Keshavarmy Phannish, Mark E. Dockrell. Renal, SW Thames Inst for Renal Research, Carshalton, Surrey, United Kingdom.

Background: Connective tissue growth factor (CTGF, CCN2) and Nors(CCN3) are both members of the CCN family of matricellular proteins; they are structurally similar, both consist of an IgGF motif and a von Willebrand factor type C motif linked by a hinge region to the thrombospondin and CYS knot motifs. CTGF in particular has been shown to play an important role in cell proliferation and extracellular matrix remodeling regulated by different motifs and is widely recognised as a key mediator in cardiac and tubulointerstitial fibrosis in the context of renal disease. Work by ourselves and others supports the hypothesis that CCN3 acts in opposition to CTGF with regard to the regulation of fibrosis.

Methods: Primary human PTEC were cultured on collagen IV in supplemented medium. At 75-80% confluence cells were treated with: the 11 kDa C-terminus term of CTGF (Peprotech, 0.5-50 nMol) for 24hr and 48 hr; or both TGFβ1 (30 pMol) and -C-terminus CTGF (0.5-30 nMol) for 60min and 24hr. The medium was collected and cells lysed. Western Blotting was used to detect protein expression and qPCR for mRNA expression. Antibodies (Ab) to the hinge regions of CCN3 and CTGF were used for protein detection.

Results: Exogenous Cys Knot C-terminus CTGF treatment at 24hr resulted in a dose dependent increase in CCN3 expression (p<0.05) in contrast to U – shaped response by CTGF with a trough at 5nMol. Cys Knot CTGF also caused a dose dependent inhibition of cell proliferation as determined by expression of proliferating cell nuclear antigen (PCNA) No intracellular signalling by Cys Knot CTGF was detected but a selective increase in phospho-Smad3 induction by threshold concentrations of TGFβ1 was observed.

Conclusions: Primary human PTEC in culture are sensitive to the effect Cys Knot CTGF protein. The effects observed were distinctly different from those reported for the c-terminus CTGF including the thrombospondin but possibly consistent with the binding of the 11 kDa Cys Knot protein.

Mechano Growth Factor Stimulated Collagen IV Expression Is Dependent on Connective Tissue Growth Factor
Yongxin Gao,1 Raafat Farag Makary,1 Lisa H. Long,1 James,1 Chang,1 Celia Whitlow,1 Dept of Laboratory Medicine and Hypertension, Univ of Florida, Jacksonville, FL; Dept of Pathology and Laboratory Medicine, Univ of Florida - Jacksonville, Jacksonville, FL.

Background: Increased extracellular matrix production is a hallmark of diabetic and hypertensive nephropathy, yet the pathogenesis of nephrosclerosis is incompletely understood. Amongst various signaling pathways associated with sclerosis, connective tissue growth factor (CTGF) has been implicated in mediating extracellular matrix production in diabetic and hypertensive kidney disease. Mechanosensitive growth factor (MFG) is implicated in several diseases such as cardiac muscle growth and survival, MFG has proliferative and anti-fibrotic properties. We have shown that MFG is glucose-responsive in that its expression is increased by high glucose in culture and in kidney of diabetic mice models.

Methods: To ascertain the interaction between CTGF and MFG in expression of matrix protein, we examined collagen IV and fibronectin levels in mesangial cells expressing MFG sense (MFG-S) and anti-sense (MFG-AS) transcripts. Immunohistochemistry (IHC) was performed for MGF, GLUT1, Type IV Collagen (Col-Iv), Fibronectin, CNTF, NFkB p50 and NFkB p65 in cultured mouse MC's, +/- MGF-overexpression or MGF-suppression.

Results: Both CTGF and collagen IV protein levels were increased in MGF-S cells (1.5 and 2-fold respectively, P<0.001) and significantly reduced in MGF-AS cells. NF-kB (p50 and p65) was translocated to the nucleus (activated) in MGF-S MC's. Activated NFkB p50 was increased 2.4-fold in MGF-S MC's, while activated NFkB p65 was increased 2.1- fold in MGF-S MC's compared to MGF-S MC's without MGF expression. In MGF-S cells with anti-CTGF antibody attenuated expression of collagen and fibronectin in MGF-S cells.

Conclusions: Thus, both CTGF and MFG expression associate with increased matrix properties. MFG-stimulated fibroblast and NF-kB signaling. Activation of ECM protein by CTGF antibody, suggest that CTGF may mediate part of the increased collagen production seen in MGF-S cells.
TH-PO212

Rac1 Is a Novel Fibrotic Transducer of TGF-β Pathway in Chronic Kidney Disease


1 Department of Nephrology and Hypertension, Vanderbilt University School of Medicine, Nashville, TN.

Background: Rac-GTPase, a major regulator of cytoskeletal remodeling, is a subset of the Rho GTPase family which generate reactive oxygen species. While the causative role of Rac in cancer progression and skin fibrosis is documented, whether Rac relays pathological TGF-β1 signals and contributes to CKD progression is not known.

Methods: We used both genetic and pharmacological approaches in vitro and in vivo to elucidate the role of Rac in renal fibrosis. We generated Rac1-deficient mice and crossed them with TGFβR1+/- mice to obtain a Rac1 deficient/ TGFβR1-/- double knockout (DKO) strain.

Results: TGFβ1 promotes rapid Rac-GTP loading in HK-2 human renal epithelial cells. Pharmacological blockade of Rac activation with a selective inhibitor, EHT1648 abrogated TGFβ1-induced gene expression. In vivo, mice with Rac1 deletion were protected from UUO-induced fibrosis, suggesting a role of Rac1 in fibrosis.

Conclusions: These findings suggest that Rac1 plays a critical role in TGFβ1-mediated fibrogenesis in the kidney.

TH-PO213

Autotaxin Promotes Renal Interstitial Fibrosis by Inducing Vascular Leak and Fibroblast Accumulation


1 Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan; 2 Department of Nephrology, Kanazawa University Hospital, Kanazawa, Japan; 3 Pulmonary and Critical Care Unit, Massachusetts General Hospital, Boston, MA.

Background: The expansion of fibroblasts is an important step in the development of organ fibrosis, but the mechanisms driving this in renal fibrosis remain to be fully clarified. Autotaxin (ATX), a secreted lysophospholipase, is upregulated in fibrotic tissues associated with fibrosis.

Methods: Renal fibrosis was induced by unilateral ureteral obstruction (UUO) in type 1 pro-collagen promoter-driven green fluorescent protein (GFP) mice to identify fibroblasts. The selective ATX inhibitor was used to inhibit ATX activity.

Results: ATX activity in renal fibrosis increases with ureteral ligation. ATX accumulates in the renal interstitium, and ATX produces LPA that drives fibroblast accumulation. Pharmacological inhibition of ATX activity protected mice from UUO-induced fibrosis, suggesting that ATX enters the renal interstitium from the circulation in this model.

Conclusions: These results suggest that during the development of renal fibrosis, ATX accumulation and further exacerbates renal interstitial vascular leak, thereby creating a vicious circle that amplifies fibrosis. Taken together, ATX inhibition may be a novel therapeutic strategy to combat renal fibrosis.

TH-PO214

Rac1 Is a Novel Fibrotic Transducer of TGF-β Pathway in Chronic Kidney Disease

Miho Shinji, Kanji Kitajima, Tadashi Toyama, Akinori Haru, Yasunori Iwata, Mito Shimizu, Kengo Furuchi, Andrew M. Tager, Takashi Wada.

1 Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan; 2 Department of Nephrology, Kanazawa University Hospital, Kanazawa, Japan; 3 Pulmonary and Critical Care Unit, Massachusetts General Hospital, Boston, MA.

Background: Rac-GTPase, a major regulator of cytoskeletal remodeling, is a subset of the Rho GTPase family which generate reactive oxygen species. While the causative role of Rac in cancer progression and skin fibrosis is documented, whether Rac relays pathological TGF-β1 signals and contributes to CKD progression is not known.

Methods: We used both genetic and pharmacological approaches in vitro and in vivo to elucidate the role of Rac in renal fibrosis. We generated Rac1-deficient mice and crossed them with TGFβR1+/- mice to obtain a Rac1 deficient/ TGFβR1-/- double knockout (DKO) strain.

Results: TGFβ1 promotes rapid Rac-GTP loading in HK-2 human renal epithelial cells. Pharmacological blockade of Rac activation with a selective inhibitor, EHT1648 abrogated TGFβ1-induced gene expression. In vivo, mice with Rac1 deletion were protected from UUO-induced fibrosis, suggesting a role of Rac1 in fibrosis.

Conclusions: These findings suggest that Rac1 plays a critical role in TGFβ1-mediated fibrogenesis in the kidney.

TH-PO215

Pro-Inflammatory Mediator Exocytosis from Murine Primary Macrophages Is Dependent on Protein Kinase C-θ

Nathalie Ronkind, Yulia Kiyan, Hermann G. Haller, Nelli Shushakova.

1 Nephrology and Hypertension, Hannover Medical School, Hannover, Germany; 2 Physiological Chemistry, Hannover Medical School, Hannover, Germany.

Background: The cooperation of several cell types is critical for a functioning inflammatory response to different kinds of injury. Protein kinase C-θ (PKC-θ) is well-known for its role in T-Cells. Recently we could demonstrate a function for PKC-θ in nephroprotection and recovery from renal ischemia as well as cytokine release in chronic hypertension in mice. Since the release of pro-inflammatory mediators from resident macrophages is a critical initial step in inflammation, we investigated the role of PKC-θ in this process.

Methods: Resident peritoneal macrophages isolated from healthy wild type (WT) or PKC-θ knockout (KO) mice were stimulated with LPS or vehicle with or without brefeldin A. Levels of the pro-inflammatory mediators TNF-a, CXCL1 and CXCL2 were measured by ELISA in conditioned cell culture medium and by Western Blots in cell lysates. Immunofluorescence microscopy in adherent stimulated macrophages and Western Blots were performed for evaluation of p38 MAPK activation and NFkB nuclear translocation. mRNA analysis was performed by RT-PCR.

Results: The release of pro-inflammatory mediators from LPS-stimulated KO macrophages was strongly impaired compared to WT, but no clear difference could be observed in mRNA levels. In line with the latter finding, neither activation of p38 MAPK nor nuclear translocation of NFkB was impaired in KO macrophages, suggesting a downstream target of PKC-θ. The analysis of exocytosis of WT and KO macrophages was further performed for TNF-a. LPS stimulation of WT macrophages resulted in transient intracellular accumulation of TNF-a, as well as cytokine release in chronic hypertension in mice. In line with these results, TNF-a levels in conditioned medium from WT and KO macrophages, intracellular TNF-a accumulation was significantly increased compared to WT starting 1h after stimulation. This difference was abrogated by co-incubation with brefeldin A, suggesting a defect in cytokine transport and exocytosis.

Conclusions: Our data demonstrates a role for PKC-θ in exocytosis of pro-inflammatory mediators from LPS-stimulated resident peritoneal macrophages.

TH-PO216

Suppressed microRNA-214 (miR-214) Dictates IGF-1 Receptor (IGF-1R) Expression to Stimulate mTORC1 Signaling for Proliferation of Renal Cancer Cells


1 Medicine,UTHSCSA, San Antonio, TX; 2 Pathology, UTHSCSA, San Antonio, TX.

Background: Elevated expression of IGF-1R in renal cell carcinoma correlates with tumor development and progression. The mechanism of hyper-expression of IGF-1R is not known.

Methods: VHL positive and negative renal cancer cells, immunoblotting, real-time qRT-PCR, site-directed mutagenesis, reporter transfection assays, DNA synthesis and proliferation assays were used.

Results: VHL positive and deficient renal cancer cells (ACHN, 786-O, RCC4 and A498) showed significantly reduced expression of mature, pre- and pro-miR-214 as compared to normal proximal tubular epithelial cells (HK2 and HRPTEC). Interestingly, in the 3’UTR of IGF-1R we identified a miR-214 recognition element (MRE) that responded to miR-214. When the MRE was mutated, the miR-214 responsiveness was abolished confirming its specificity. Overexpression of miR-214 inhibited IGF-1R mRNA and protein expression. IGF-1R increased phosphorylation of PRAS40 by Akt, leading to the activation of mTORC1

Conclusions: This novel approach for the first time provides boron-containing phospholipid derivatives as potential HGF mimetics.

TH-PO217

Suppressed microRNA-214 (miR-214) Dictates IGF-1 Receptor (IGF-1R) Expression to Stimulate mTORC1 Signaling for Proliferation of Renal Cancer Cells


1 Medicine, UTHSCSA, San Antonio, TX; 2 Pathology, UTHSCSA, San Antonio, TX.

Background: Elevated expression of IGF-1R in renal cell carcinoma correlates with tumor development and progression. The mechanism of hyper-expression of IGF-1R is not known.

Methods: VHL positive and negative renal cancer cells, immunoblotting, real-time qRT-PCR, site-directed mutagenesis, reporter transfection assays, DNA synthesis and proliferation assays were used.

Results: VHL positive and deficient renal cancer cells (ACHN, 786-O, RCC4 and A498) showed significantly reduced expression of mature, pre- and pro-miR-214 as compared to normal proximal tubular epithelial cells (HK2 and HRPTEC). Interestingly, in the 3’UTR of IGF-1R we identified a miR-214 recognition element (MRE) that responded to miR-214. When the MRE was mutated, the miR-214 responsiveness was abolished confirming its specificity. Overexpression of miR-214 inhibited IGF-1R mRNA and protein expression. IGF-1R increased phosphorylation of PRAS40 by Akt, leading to the activation of mTORC1

Conclusions: This novel approach for the first time provides boron-containing phospholipid derivatives as potential HGF mimetics.

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

Underline represents presenting author.
The Contribution of Transient Receptor Potential Channel 6 to Motility and Adhesion in the Podocyte Proteome of Novel Binding Partners

Louise K. Farmer,1 Moin Saleem,2,1 Gavin Iain Welsh,1 1 Bristol Renal. Univ of Bristol, Bristol, United Kingdom; 2Children’s Renal Unit, Bristol Childrens Hospital, Bristol, United Kingdom.

Background: Several genetic mutations in TRPC6 have been linked to familial forms of FSGS, identifying it as a treatment target for nephrotic syndrome. TRPC6 is a membrane expressed calcium channel and it has previously been suggested that several of these mutations cause a gain of function and subsequent increase in calcium influx. However the role of TRPC6 in disease progression is still unclear.

Methods: Conditionally immortalised podocyte cell lines have been generated from TRPC3 KO, TRPC6 KO and TRPC3/TRPC6 double KO C57Bl/6 mice. GFP tagged TRPC6 was stably reintroduced into the KO cell line through generation of a lentiviral construct. These were characterised to determine cell motility and adhesion using scratch and adhesion assays. GFP TRAP beads were used to pull down TRPC6 and proteomics was performed to identify novel binding partners. These interactions were confirmed through immunoprecipitation.

Results: Glomeruli from TRPC6, TRPC3 and TRPC6/3 KO mice were isolated and used to generate conditionally immortalised podocyte cell lines. All three cell lines appeared morphologically normal and expressed podocyte markers. Adhesion assays showed a significant increase in the adhesiveness of TRPC6 KO cells, whilst the TRPC3 KO and double KO cells were unaltered. The TRPC6 KO cells were also significantly less motile in a scratch assay. Reintroduction of GFP-TRPC6 to the TRPC6 KO cells returned the adhesive and motility phenotype towards that of the WT cell line. Immunoprecipitation with GFP TRAP beads identified interactions between TRPC6 and a number of calcium regulated protein tyrosine kinases and proteins involved in regulation of calcium dynamics.

Conclusions: These results suggest that TRPC6 plays a considerable role in the adhesion and motility of the podocyte. This contribution could be occurring through the novel protein interactions that have been identified in this study, giving new insight into the role of TRPC6 in glomerular injury.

The N-Recognin Ubr4 Controls Posttranslational Stability of Podocin/MEC-2 Supercomplexes

Markus M. Rinschen, Thomas Benzinger. Internal Medicine, Univ Hospital Cologne.

Background: The PHB-domain protein podocin maintains the renal filtration barrier. Podocin mutation causes hereditary nephrotic syndrome. Podocin and its Caenorhabditis elegans orthologue MEC-2 are components of mechosensitive membrane protein signalling complexes. Whereas podocin resides at a specialized cell junction at the podocyte slit diaphragm, MEC-2 is found in neurons required for touch sensitivity.

Methods: We performed mass-spectrometry based interactome analysis of podocin in vivo and in vitro to determine its interaction partners. We performed knockdown and knockout studies of Ubr4 in cell culture and C. elegans to determine its effect on podocin/MEC-2. We performed mass-spectrometry based ubiquitylomic analysis (using a Di-glycine antibody) to determine native podocin ubiquitylation sites in vivo. We modeled the biophysical effect of podocin ubiquitylation on the podocin structure using molecular dynamics simulations.

Results: Ubr4 was a key component of the podocin interactome purified both from cultured podocytes and native glomeruli. It localizes at the slit diaphragm and to the leading edge of podocytes in cell culture. Ubr4 regulates podocin stability in cell culture. In C. elegans, this process is conserved. Ubr4 knockdown or knockout increased the expression of Mec-2, the podocin orthologue. Ubr4 is also responsible for the degradation of mislocalized MEC-2 multisomers. Ubiquitylomic analysis of mouse glomeruli revealed that podocin is ubiquitylated at two sites in vivo. These ubiquitylation sites are essentially the same. The presence of Ubr4 and were conserved across species, also based on mass-spectrometry dependent evidence. Molecular dynamics simulations revealed that ubiquitylation of one site, K301, does not only target podocin/MEC-2 for proteasomal degradation, but may also affect stability and disassembly of the multimeric complex. Mutation of K301 and K370 shifted podocin to the lysosomal compartment, indicating that K301 and K370 are essential for degrading podocin.

Conclusions: We suggest that podocin degradation is tightly controlled and that Ubr4 is key regulator of podocin post process proteolysis. Funding: Government Support - Non-U.S.

Nephro: Tyrosine Phosphorylation Regulates Its Endocytosis through the Nck Adaptor Proteins

Claire E. Martin, Laura A. New, Nina Jones. Molecular and Cellular Biology, Univ of Guelph, Guelph, ON, Canada.

Background: Neph2 is a key structural component of the podocyte slit diaphragm, and proper expression of neph2 on the cell surface is critical to ensure integrity of the blood filtration barrier. Maintenance of neph2 within the slit diaphragm is proposed to require endocytosis, although, the molecular mechanisms that control neph2 recycling are poorly understood. We have recently demonstrated that tyrosine phosphorylation of neph2 is central to its function, via recruitment of intracellular signaling proteins including the Nck family of SH2/SH3 domain-containing cytoskeletal adaptors. We now reveal that Nck provides a connection between phosphorylated neph2 and the endocytic machinery, and that changes in neph2 tyrosine phosphorylation dynamically alter its expression on the cell surface.

Methods: Mice expressing a neph2 variant that cannot undergo tyrosine phosphorylation (neph2-Y3F) were used to characterize trafficking dynamics in healthy and injured podocytes. Complementary cell-based approaches were employed to assess molecular interactions that regulate neph2 endocytosis.

Results: We demonstrate that the neph2-Y3F protein is overexpressed on the cell surface in both in vitro and in vivo. Remarkably, mutations in the SH3 domain of Nck2 induce a similar pattern of neph2 localization, and fusion of the intact Nck2 SH3 domains to the neph2-Y3F protein can rescue this phenotype. We confirm that Nck2 preferentially associates with the endocytic regulator dynamin, and that disruption of dynamin GTPase activity promotes accumulation of neph2 on the cell surface. Lastly, we show that neph2 is transiently hyperphosphorylated and removed from the cell surface in a reversible model of proteinuric kidney injury, and that neph2-Y3F mice are protected from this injury.

Conclusions: Together these findings underscore the link between actin signaling and endocytosis in podocytes, and they suggest that precise regulation of neph2 tyrosine phosphorylation is required to maintain barrier homeostasis.

Ephrin-B1 Interacts with the Basal Site of the Extracellular Domain of Nephrin in Cis and Regulates the Barrier Function and the Signal Transduction Pathway of the Slit Diaphragm

Yoshiyasu Fukusumi, Ying Zhang, Hiroshi Kawachi. Dept of Cell Biology, Kidney Research Center, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background: We have previously reported that Ephrin-B1 is the component of the slit diaphragm (SD) (KL, 2008) and plays a role in the arrangement of the SD molecules (ASN, 2015). However, the role of Ephrin-B1 in regulating the SD function is not well understood.

Methods: (i) The molecular association between Ephrin-B1 and nephrin was analyzed with HEK cells. (ii) The phenotype of the podocyte-specific Ephrin-B1 knockout (KO) mice was analyzed by the RNA-seq with next-generation sequencer. (iii)To explore novel molecules associated with Ephrin-B1, gene expression profile of glomeruli from wild type and KO mice was analyzed by the RNA-seq with next-generation sequencer.

Results: We have previously reported that Ephrin-B1 is the component of the slit diaphragm (SD) (KL, 2008) and plays a role in the arrangement of the SD molecules (ASN, 2015). However, the role of Ephrin-B1 in regulating the SD function is not well understood. Therefore, in our preliminary results demonstrate that SHP2 may directly regulate Nephrin and Ephrin B1 activation. Using omics-wide scale mass spectrometric-based screen, we found that SHP2 interacts with Neph1 and Neph B1 in a phosphorylation dependent manner. Using a substrate trapping mutant we demonstrate that SHP2 preferentially associates with Neph B1, whereas Neph1 was a substrate for SHP2. Additionally, Neph B1 phosphorylation in cell culture, podocytes, suggesting that Neph B1 participate in HGF induced signaling in podocytes. Since injury to podocytes has been shown to induce Neph1 phosphorylation we hypothesized that such induction may affect SHP2 expression. Indeed, mRNA profiling of cultured podocytes treated with purumycin amicinolide showed fivefold reduction in SHP2 expression. These results are consistent with a role for SHP2 in regulating Neph1 phosphorylation and activation. We further hypothesized that SHP2 directly affects Neph1 endocytosis and to test this we created a chimeric Neph1 where Flag tag was introduced in the N-terminus of Neph1 that allows Neph1 to be extracellularly labeled with Flag antibody. Indeed, treatment of podocytes with HGF but not with other growth factors induced Neph1 endocytosis.

Conclusions: Collectively, these results provide compelling evidence that HGF can stimulate the signaling of slit diaphragm protein Neph1 in podocytes. Funding: National Institute of Diabetes and Digestive and Kidney Diseases.
Background: KIBRA, an upstream regulator of the Hippo signaling pathway encoded by the Wwc1 gene, shares the pro-survival properties of its putative binding partner dendrin and antagonizes the pro-survival signaling of downstream Hippo pathway effector YAP (Yes-associated protein) in Drosophila and MCF10A cells. Our group recently identified YAP as an essential component of the glomerular filtration barrier that promotes podocyte survival and injury in vivo mouse genetic interaction studies, and deoxycorticosterone (DOCA)/salt-induced glomerulosclerosis. However, the signaling pathways that mediate podocyte survival and injury in renal disease are not well understood. We test the hypothesis that similar to its role in other model systems, KIBRA promotes podocyte injury and death.

Methods: KIBRA/Wwc1 was overexpressed in marine podocytes using retrovirus and high content image analysis characterized YAP localization, focal adhesion metrics, and actin dynamics. KIBRA/Wwc1 was silenced in human podocytes using lentivirus. Apoptosis was assessed via caspase 3/7 activity assay. Quantitative PCR determined expression levels of YAP-associated genes. Albuminuria was qualitatively assessed via Coomassie staining. Mouse kidneys were harvested following pericardial perfusion with HBSS or protamine sulfate and/or 4% PFA. Foot processes were quantified using transmission EM images.

Results: We found increased KIBRA/Wwc1 gene expression in patient cohorts with biopsy-proven FSGS and CKD. Constitutive KIBRA/Wwc1 knockout mice were protected from TBx-induced podocyte injury. KIBRA/Wwc1 silencing in podocytes protected against adriamycin-induced apoptosis. Conversely, KIBRA/Wwc1 overexpression enhanced podocyte susceptibility to staurosporine-induced apoptosis, disrupted actin cytoskeleton architecture, and reduced focal adhesion size and number. KIBRA promoted LATS phosphorylation leading to subsequent YAP S127 phosphorylation, YAP cytoplasmic sequestration, and reduction in target gene expression.

Conclusions: These findings suggest an important role for KIBRA in the pathogenesis of podocyte injury and the progression of proteinuric kidney disease.

Funding: NIDDK Support, Private Foundation Support

TH-PO223

SLT2-Robo2 Signaling Pathway Inhibits Non-Muscle Myosin IIA Activity and Destabilizes Kidney Podocyte Apoptosis

Xueping Wang,1 Hongying Yang,1 Sudhir Kumar,1 Kathleen Tumelty,1 Anna Pisarek-Horowitz,2 Hila Milo Rasouly,3 Richa Sharma,1 Stefanie Chan,1 Edward Tyminskas,1 Michael Shamasheh,1 Mostafa Belghesem,1 Joel M. Henderson,1 Anthony J. Coyle,2 David J. Salant,1 Stephen Beras,1 Weining Lu1

Nephrology/Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: The repulsive guidance cue SLIT2 and its receptor ROBO2 are required for kidney development and podocyte foot process structure, but the SLIT2-ROBO2 signaling mechanism regulating podocyte cellular function is not well known. Here we report that a novel signaling pathway of SLIT2-ROBO2 Rho GTPase activating protein 1 (SRGAP1) and non-muscle myosin IIA (NM-IIA) regulates podocyte adhesion downstream of ROBO2.

Methods: We performed two-hybrid assay, co-precipitation and western blot analyses, immunofluorescent staining, podocyte cell culture and adhesion assays, MLR phosphorylation assay, in vivo mouse genetic interaction studies, and deoxyco nicotinate (DOCA)/salt-unknown proteinuria model study.

Results: We found that the myosin II regulatory light chain (MLCII), a subunit of NM-IIA, interacts directly with SRGAP1 and forms a complex with ROBO2-SRGAP1-NM-IIA in the presence of SLIT2. Immuno staining demonstrated that SRGAP1 is a podocyte protein and is co-localized with ROBO2 on the basal surface of podocytes. In addition, SLIT2 stimulation inhibits NM-IIA activity, decreases focal adhesion formation, and reduces podocyte cell attachment to collagen. In vivo studies further showed that podocyte-specific knockout of Robo2 protects mice from hypertension-induced podocyte detachment and albuminuria and also partially rescues the podocyte loss phenotype in Mymi/h knockout mice.

Conclusions: We report a novel SLIT2-ROBO2-SRGAP1-NM-IIA as a novel signaling pathway in kidney podocytes, which may play a role in regulating podocyte adhesion and foot process structure.

Funding: NIDDK Support, Private Foundation Support

TH-PO224


Dept of Medicine, Rush Univ Medical Center, Chicago, IL.

Background: Transient receptor potential channel (TRPC) family is a nonselective calcium-permeable cation channels that is widely expressed in cells and critical to cell behavior, physiology and pathology. The subfamily 5 of TRPC (TRPC5) is highly expressed in the kidney and is required for normal glomerular structure and function. While TRPC5 is known to be upregulated in kidney disease, the role of TRPC5 in causing proteinuria is not clear.

Methods: Two novel transgenic mouse models (C57BL/6 background) were developed by overexpressing either wild-type TRPC5 (TG) or the dominant negative TRPC5 (DN, pore mutant) respectively. Overexpressed animals were validated by genotyping. TRPC5 level in the kidney was measured by Western blot. TRPC5 overexpression in mice has never been studied before.

Results: In our transgenic mice, TRPC5 mRNA was significantly higher than control. Western blot showed abundant TRPC5 protein throughout various tissues. If demonstrated stronger staining of TRPC5 in glomeruli of TG and DN compared with BL/6. Histology analysis of TG and DN appeared to have no abnormalities at birth and after month 6. Neither TRPC5 mouse line did develop proteinuria. Kidney injury after LPS injection was similar among TG, DN and BL/6 at 0, 24 and 48 hour with no significant differences in albumin/creatinine ratio (ACR).

Conclusions: TRPC5 was overexpressed in our novel transgenic mice. However, overexpression of TRPC5 does not cause kidney damage per se. LPS treatment resulted in similar levels of proteinuric injury among TG, DN and BL/6.

Funding: NIDDK Support

TH-PO225

The Mechanisms of Dendrin Nuclear Translocation in Kidney Podocytes

Naritoshi Shirata,1,2 Kan-ichihiro Iharra,2,3 Motoko Yanagita,1,3 Katsuhiko Ishimori,1,3 Katsuhiko Asanuma,1,3 1Medical Innovation Center, TMK Project, Graduate School of Medicine, Kyoto Univ, Kyoto, Japan; 2Research Unit/Nephrological & Endocrinological Science, Sohaku, Innovative Research Div, Mitsubishi Tanabe Pharmaceutical Corporation, Toda, Saitama, Japan; 3Dept of Molecular Genetics, Inst of Biomedical Sciences, Fukushima Medical Univ, Fukushima, Japan; 1Dept of Molecular and Cell Biology, The Laboratory of Animal Breeding and Genetics, Graduate School of Agricultural Science, Tohoku Univ, Sendai, Miyagi, Japan; 2Dept of Nephrology, Graduate School of Medicine, Kyoto Univ, Kyoto, Japan.

Background: Previously we reported that dendrin, which is a component of the slit diaphragm, translocates to the injured podocyte and that nuclear translocated dendrin promotes podocyte apoptosis. We also demonstrated that dendrin nuclear translocation was increased in human renal biopsies with glomerulosclerosis. However, the regulatory mechanisms of dendrin localization have been still unknown.

Methods: In this study, we investigated the regulatory mechanisms of dendrin nuclear translocation using yeast two hybrid screening, Co-IP and newly generated the podocyte model of MAGI-2 KO mice.

Results: We identified Fyn (tyrosine kinase) and Nedd4-2 (ubiquitin ligase) as putative interacting proteins with dendrin. Proteolysis of dendrin was regulated by Fyn-mediated phosphorylation and Nedd4-2-mediated ubiquitination. Dendrin was downregulated and accumulated in the nuclei in podocytes of MAGI-2 KO mice. Western blot and glomerular immunofluorescence (IF). Urinary albumin levels were measured and histology analysis was performed up to 6 months. LPS-induced albuminuria was quantified and compared among TG, DN and BL/6 at baseline (0 hour), and at 24 hours and 48 hours after injection.

Conclusions: In our transgenic mice, TRPC5 mRNA was significantly higher than control. Western blot showed abundant TRPC5 protein throughout various tissues. If demonstrated stronger staining of TRPC5 in glomeruli of TG and DN compared with BL/6. Histology analysis of TG and DN appeared to have no abnormalities at birth and after month 6. Neither TRPC5 mouse line did develop proteinuria. Kidney injury after LPS injection was similar among TG, DN and BL/6 at 0, 24 and 48 hour with no significant differences in albumin/creatinine ratio (ACR).

Conclusions: TRPC5 was overexpressed in our novel transgenic mice. However, overexpression of TRPC5 does not cause kidney damage per se. LPS treatment resulted in similar levels of proteinuric injury among TG, DN and BL/6.

Funding: NIDDK Support

TH-PO226

New Structural and Biomechanical Insights Reveal the Importance of TRPC5 Phosphorylation in Modulating Cytoskeletal Network and Glomerular Podocyte Function

Dongcheng Liu,1,2 R. Ramaswamy Krishnan,1,3 Gabriel Birrane,1,3 Johannes S. Schlondorff,1,3 Martin R. Pollak,1,3 1Nephrology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA; 2Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA; 3Experimental Medicine, Beth Israel Deaconess Medical Center, Boston, MA.

Background: Mutations in the alpha-actinin-4 gene (ACTN4) cause podocyte injury and familial focal segmental glomerulosclerosis (FSGS) in humans. We recently found that in cultured human podocytes, ACTN4 can be phosphorylated at the serine 159 site (S159D) which is within all of the known disease-causing ACTN4 mutations. Phosphomimetic S159D ACTN4 protein (which mimics the effect of phosphorylation at S159), recapitulates the altered actin bundling activity of FSGS-associated mutant ACTN4. This study seeks to further investigate the mechanism by which phosphorylation of ACTN4 affects podocyte function.

Funding: Pharmaceutical Company Support - Mitsubishi Tanabe Pharma
Methods: We used x-ray crystallography to solve the structure of the ACTN4 BBD protein in complex with nephrin to quantify contractile forces exerted by podocyte foot processes and to determine membrane deformation compared to WT ACTN4. Across tissue, contractile force was consistently higher in WT ACTN4 podocytes (mean±SEM) than in non-phosphorylatable S159A ACTN4 podocytes. However, WT ACTN4 podocytes initially exerted similar contractile forces as S159D and K255E podocytes, but later decreased to lower levels compared with S159A podocytes. This decrease in force could be in part due to decreased phosphorylation of WT ACTN4.

Conclusions: Our results suggest that phosphorylation of ACTN4 at S159 alters ACTN4 protein characteristics and podocyte biomechanical force. These observations support our hypothesis that an intracellular signal “switch” can convert normal ACTN4 to a form similar to the human mutation associated forms, therefore mediating podocyte injury in non-genetic forms of FSGS. 

Funding: NIDDK Support

TH-PO227
Physiological Roles of Ezrin in the Regulation of Podocyte Foot Process Formation
Yuto Hatano, Kotoko Kagawauchi, Shijii Asano. Dept of Molecular Physiology, Ritsumeikan Univ, Kusatsu, Shiga, Japan.

Background: Ezrin is highly expressed in the glomerular podocytes, and is reported to form multi-protein complex with a scaffold protein Na+/H+ exchanger regulatory factor 2 (NHERF2) and podocalyxin, a major sialoprotein. Podocalyxin deficient mice died within 24 hrs after birth with anuric renal failure, whereas NHERF2 knockout mice did not show apparent renal phenotype. On the other hand, physiological roles of ezrin in glomerular podocytes still remain unclear.

Methods: To investigate the physiological roles of ezrin in the regulation of glomerular podocyte function, ezrin knockdown mice (Vil2kd/kd) were used in this study. Histological analysis of glomerulus was performed by H&E staining and electron microscopy. Western blotting and immunofluorescence analysis were performed to investigate the expression and localization of related proteins in the podocytes. Rho activities were investigated by ELISA-based pull down assay using isolated mouse glomeruli from WT and Vil2kd/kd mice before and 7 days after adriamycin treatment.

Results: Vil2kd/kd mice did not exhibit apparent glomerular dysfunction, morphological defects, and disturbance in the localizations of podocalyxin and NHERF2 in podocytes. In Vil2kd/kd glomeruli, RhoA activity was increased 1.3-fold compared to WT glomeruli, while Rac1 and Cdc42 activities in Vil2kd/kd glomeruli were comparable with those in WT glomeruli at baseline. Interestingly, in adriamycin-induced nephrotic condition, Vil2kd/kd mice showed reduced susceptibility to the drug-induced glomerular injury. In Vil2kd/kd glomeruli after adriamycin treatment, RhoA activity was increased 1.5-fold, but Rac1 activity showed 2-fold decrease compared to adriamycin-treated WT mice. Furthermore, interaction of ezrin with Rho GTP dissociation inhibitor (RhoGDI), a key regulator of Rho activities, was confirmed by coimmunoprecipitation in WT glomeruli.

Conclusions: Our results suggest that loss of ezrin protect the podocytes from injury-induced morphological change, and ezrin plays important roles in the regulation of podocyte motility by regulating Rho activities via the interaction with RhoGDI in glomerular podocytes.

TH-PO228
ARF6 Activation Is Necessary for Nephrin-Dependent Changes in Podocyte Cytoskeletal Dynamics
Jin Liu,1 Qinfei Fan,1 Hetty N. Wong,1 Jinsook Jeon,1 Lawrence B. Holzman.1 1Renal-Electrolyte and Hypertension Division, 2Pediatrics, Philadelphia, PA; 1Dept of Nephrology, Soon Chun Hyang Univ Hospital, Seoul, Korea.

Background: Nephrin is a slit diaphragm protein that regulates podocyte actin dynamics and cell signaling. Nephrin tyrosine-phosphorylated and underglycosylated is essential for cell adhesion and cytoskeletal dynamics subsequent to podocyte injury. This triggers cellular remodeling necessary for podocyte effacement. The functional significance of nephrin endocytosis remains uncertain. We hypothesized that ARF6, a small GTPase necessary for endocytic trafficking and cell motility, is necessary for nephrin activation-induced podocyte cytoskeletal dynamics that results in injury-induced effacement.

Methods: These experiments were performed in an inducible nephrin-expressing podocyte cell culture model or in a newly engineered podocyte-specific ARF6 null mouse model.

Results: ARF6 is enriched in podocytes in vitro and in vivo. In culture, nephrin activation resulted in increased ARF6 activity. Following nephrin activation, ARF6 was necessary for nephrin endocytosis, but not early nephrin trafficking, and was necessary for focal adhesion turnover and cellular ruffling. Mice deleted of ARF6 in podocytes had normal glomerular development and developed no evidence of proteinuria even when aged to eight months. When challenged with pro tease, podocyte-specific ARF6 null mice exhibited protection from injury. These results suggest that nephrin tyrosine phosphorylation dependent focal adhesion turnover and cellular ruffling in cell culture are ARF6 dependent. In vivo, ARF6 appears to be dispensable for normal podocyte development and maintenance, yet is necessary for changes in podocyte morphology following injury with protease. Further studies are necessary to clarify the specific role and mechanism of ARF6 involvement in podocyte pathophysiology.

Funding: NIDDK Support

TH-PO229
Von Willebrand Factor Release and Weibel-Palade Body Fusion Maintain Endothelial Cell Homeostasis after Complement Activation
Magdalena Riedl,1 Daniel Schlamp,1 Damien Gerard Noone,2 Christoph Licht.1,2 1Cell Biology, The Hospital for Sick Children, Toronto, Canada; 2Nephrology, The Hospital for Sick Children, Toronto, Canada.

Background: Complement dysfunction on endothelial cells causes EC activation and injury and leads to thrombotic microangiopathy. Different from previous concepts, our data demonstrate that complement activation does not result in EC death. The current study focuses on EC complement evasion strategies, especially plasma membrane (PM) repair.

We particularly focused on Von Willebrand Factor (VWF), which we recently identified as a new complement regulator on ECs. VWF is stored in EC Weibel-Palade bodies (WPBs) and can be released by ECs to inhibit plasma membrane (PM) integrity.

Methods: Complement activation was achieved by a previously established protocol on blood outgrowth endothelial cells (BOECs) from healthy controls and patients with two types of von Willebrand disease (VWD): VWD type 2a with dysfunctional VWF, and VWD type 3 with neither VWF nor WPBs. Calcein release was used to determine plasma membrane (PM) integrity.

Results: Complement activation resulted in PM insertion of Csb-9 pores in control followed by rapid intracellular Ca2+ elevation. In response, VWF was recruited to the EC surface via WPBs merging with the PM and releasing VWF multimers. Importantly, only BOECs with WPBs (control and VWD type 2a BOECs) were able to reseal the PM within 30 min. VWD type 3 BOECs - lacking WPBs - were not able to reseal. In control BOECs known cellular mechanisms for PM repair (endocytosis of Csb-9, lysosomal recruitment) were not involved in this complement inhibition. Defective or missing VWF also resulted in increased Csb deposition on the EC surface.

Conclusions: ECs have evasion strategies allowing for survival of complement attack. We have identified a new mechanism of complement evasion via VWF release of VWF from complement activation on ECs, and PM fusion of WPBs repairs complement induced PM injury. This repair mechanism may contribute to EC homeostasis beyond complement-mediated injury.

TH-PO230
Activated Neutrophil-3 Receptor TrkC Transmits Signals to the Podocyte Actin Cytoskeleton
Sascha Grommertz, Hermann Pavcnstajcdt, Britta George. Molecular Nephrology, Inst of Internal Medicine D, Univ Hospital Münster, Münster, Germany.

Background: Podocyte malfunction is central to glomerular disease and is characterized by defective podocyte intercellular junctions and actin cytoskeletal dynamics. Recently, TrkC was shown to be located at the podocyte slit diaphragm. TrkC knockout mice developed proteinuria shortly after birth (Lefèvre et al., PLoS Genet. 2010). The aim of this study is to further investigate the role of TrkC in podocytes and its relevance in glomerular disease.

Methods: Mouse podocyte lines were generated that inducibly express wild-type TrkC or TrkC with mutations of specific tyrosine-residues known to mediate TrkC signaling. Wound healing assays following live cell imaging were performed. Glomeruli were isolated from murine kidneys and treated with Lipopolysaccharide (LPS) or Adriamycin (ADR) to induce podocyte injury.

Results: We confirmed that TrkC was expressed in mouse glomerular podocytes and co-localized with the slit diaphragm marker Nephrin. Activation of endogenous TrkC by adding the ligand Neurotrophin-3 (NT-3) to cultured mouse podocytes resulted in tyrosine-phosphorylation of TrkC as well as activation of the downstream target proteins Erk and Akt. Activation of overexpressed or endogenous TrkC by NT-3 lead to increased formation of filopodia in cultured mouse podocytes. Increased filopodia formation could not be observed in podocytes expressing kinase dead TrkC. Consistently an increased migration of podocytes in vitro was observed upon TrkC activation. Injury induced by treatment isolated murine glomeruli with ADR or LPS resulted in a significant increase in tyrosine-phosphorylation of endogenous TrkC.

Conclusions: Currently, genetic mouse models with the potential to conditionally express or knock out TrkC in podocytes or nephrons are generated to test whether TrkC is essential for the podocyte and to dissect TrkC signaling in vivo. These models will be employed to test whether TrkC can be therapeutically-targeted to treat glomerular disease. Our results imply that TrkC is activated during glomerular injury, signals to the podocyte actin cytoskeleton and regulates cell migration.

Funding: Government Support - Non-U.S.

TH-PO231
Dasatinib Induces Nephrotoxicity through Selective Disruption of Podocyte Biomechanics
Rhodora C. Calizo,1 Johah G.C. Van Hasselt,1 Gomathi Jayaraman,1 Jenny Wong,2 Kirk N. Campbell,2 Evren U. Azeloglu,1 Phillip L. Van Nostrand,1 Istvan School of Medicine at Mount Sinai, New York, NY; 1Nephrology (Medicine), Icahn School of Medicine at Mount Sinai, New York, NY.

Background: The toxicity induced by kinase inhibitors (Kis) is a bottleneck in targeted oncological therapies, where it may limit the efficacy of treatment or lead to the failure of a trial. It is thought that KIs lead to nephrotoxicity through nonspecific inhibition of VEGF; however the exact mechanisms are poorly understood.

Materials and Methods: We used retrospective analysis of FDA Adverse Event Reporting System (FAERS) to rank clinical nephrotoxicity of all FDA-approved KIs. We then used atomic
force microscopy (AFM), high-content imaging, and differential phospho-proteomics to assess the cellular biomechanics of cultured podocytes under different KI treatments and to identify the mechanisms through which dasatinib induced podocyte cytoskeletal remodeling. 

Results: Dasatinib had the highest odds ratio for glomerulonephritis within FAERS compared to other KIs. Interestingly, VEGF inhibitor vandetanib was ranked very low as well as other Bcr-Abl inhibitors such as imatinib. High-content imaging of cultured podocytes showed significant and specific alterations to the actin cytoskeleton, number and size of focal adhesions, and cell morphology under dasatinib but not with other VEGF or Bcr-Abl inhibitors. AFM elastography also revealed that elastic modulus of podocytes was significantly reduced under dasatinib treatment alone. Network analysis of differential phospho-proteomics of dasatinib treated podocytes showed “protein-protein interaction in the podocyte” and “regulation of actin cytoskeleton” as the highest enriched terms, and highlighted a number of upstream kinases that may be responsible for dasatinib’s effects.

Conclusions: We conclude that dasatinib induces nephrotoxicity independent of VEGF inhibition. Its unique mechanism of action is specific to podocytes, and it acts through altered cellular cytoskeleton and biomechanics. Our results suggest that leukemia patients that are receiving targeted therapy with dasatinib should be monitored closely for nephrotoxicity.

Funding: Private Foundation Support

TH-PO232
Mediation Complex Protein 22 Is Essential for the Maintenance of the Glomerular Filtration Barrier
Patricia Rodriguez, Ping Guo, Lwaki Ebara, Jaakko Patrakka, KL/Integrated CardioMetabolic Center, Dept of Medicine, Karolinska Inst, Huddinge, Stockholm, Sweden; 1Clinical Research Center, Dept of Laboratory Medicine, Karolinska Inst, Huddinge, Stockholm, Sweden; 2Div of Matrix Biology, Dept of Medical Biochemistry and Biophysics, Karolinska Inst, Stockholm, Sweden.

Background: Mediator complex protein 22 (Med22) is a component of the mediator complex, a multisubunit assembly that mediates signals from DNA binding transcription factors to RNA polymerase II. The role of Med2 in the biology of cells and organs is not entirely known. In this study, we identified Med22 as a highly podocyte-enriched transcript.

Methods: To establish its biological role in podocytes, we inactivated Med22 in zebrafish and mouse.

Results: In zebrafish larvae, Med22 knockdown prevents the formation of pronephros capillary loops and proper kidney filtration at 4dpf. Dye filtration assay shows that Med22 knockdown results in proteinuria in zebrafish larvae. Mice lacking Med22 specifically in podocytes develop normal kidneys and appear healthy until 8 weeks of age. After this the mice develop progressive albuminuria and renal insufficiency resulting in death by 16 weeks of age. Histologically, Med22-deficient mice exhibit large cytoplasmic vacuoles in podocytes that are positive for endosomal marker caveolin and lysosomal marker Lamp2.

Conclusions: Thus, Med22 is critical for the maintenance of podocyte homeostasis probably by regulating endosomal trafficking. This is the first time that a component of the mediator complex is shown to have a critical role in the kidney.

Funding: Government Support - Non-U.S.

TH-PO233
Nanoscopy of Slit Diaphragm Proteins in Optically Cleared Kidney Tissue
David Von Malarski, Lena Scott, Hans Blom, Hjalmar Brismar, 1Applied Physics, Royal Inst of Technology, Solna, Sweden; 2Women’s and Children’s Health, Karolinska Inst, Solna, Sweden.

Background: Previously, the finest elements of the filtration barrier have only been possible to visualize using electron microscopy. However, electron microscopy is mostly restricted to ultrathin two-dimensional samples, and the possibility to simultaneously visualize different proteins is limited. With the advent of super-resolution light microscopy new possibilities are available. We have developed a fluorescence-based protocol for studying the filtration barrier in human and rat kidneys. The strict requirements of staining conditions, making our protocol a possible tool for diagnosis.

Funding: Government Support - Non-U.S.

TH-PO234
Angiomitin Mutation in Rats Causes Proteinuria and Podocyte Foot Process Effacement
Yaochen Zhang, Isaac Liu, Chang-Yien Chan, Hui Kim Yap, Kar Hui Ng. Paediatrics, National Univ of Singapore, Singapore.

Background: Using next generation sequencing, we identified in a Singapore Chinese family with X-linked recessive nephropathy a putative missense mutation in the AMOT gene which codes for angiomitin. The mutation segregates with renal disease, is not present in the exomes of healthy population and public databases. It changes a hydrophobic to hydrophobic amino acid. Although the amino acid is not conserved across different species, all species carry hydrophilic amino acids. AMOT occurs in the X chromosome in humans and rats and is known to affect tight junctions and actin cytoskeleton in epithelial cells. This study aimed to elucidate the function of AMOT in rat kidneys.

Methods: Using CRISPR/Cas9 system, we created a founder rat with a missense mutation corresponding to the human mutation. The phenotypes of the mutant F2 generation rats were compared with control rats. Total RNA were extracted from peripheral blood mononuclear cells and sent for RNA-Seq.

Results: All male mutant rats developed significant proteinuria by 6 months old and had significantly higher body weight than controls at 10 months old. Light microscopy showed minor glomerular changes but electron microscopy confirmed podocyte foot process effacement at 8 months old. There appeared to be no involvement in other organ systems. The renal tubular function was normal in mutant rats as shown by similar serum electrolytes and acid-base based to controls. In contrast, both heterozygous and homozygous mutant females had no or very mild proteinuria, affirming the X-linked recessive inheritance. RNA-Seq results showed more than 300 differentially expressed genes including Smad7, Rac1 and pldm1. Analysis using IPA revealed altered effector pathways in glomerular injury, renal necrosis, and nephritis.

Conclusions: To our knowledge, this is the first study that suggests that AMOT play important roles in podocytes. AMOT may exert its function in podocytes through Rho/GAP complex affecting activation status of Rho GTPases or via interactions with slit diaphragm and actin cytoskeleton proteins. More studies are needed to further elucidate the mechanism.

Funding: Government Support - Non-U.S.

TH-PO235
Podocyte-Based HCS Assays Identify Paulolone Derivatives as Novel Reno-Protective Agents
Ha Won Lee, Ehtesham Arif, Deepak Nihalani, Vineet Gupta. 1Dept of Internal Medicine, Rush Univ Medical Center, Chicago, IL; 2Dept of Medicine, Nephrology Div, Medical Univ of South Carolina, Charleston, SC.

Background: Injury and loss of podocytes are early hallmarks of a variety of glomerular diseases. Targeting podocytes is an approach for the kidney-directed therapies. Damaged podocytes change their morphology and skeleton structure. To identify small molecules that protect podocytes from injury, we performed cell-based high content screening (HCS) using a phenotypic assay. The HCS assay revealed a family of small molecules, paullolines, which are GSK3β inhibitors as potent podocyte-protective agents.

Methods: Phenotypic changes of podocytes were analyzed using automated methods. For in vitro podocyte damage, murine podocytes were treated with puromycin aminomycinoglycose (PAN). qPCR was used for the quantification of mRNA expression. Caspase 3/7 activities were measured using luciferase substrate-based system. Annexin V-positive cell population was quantified using flow cytometry. For glomerular injury in zebrafish, Adriamycin was added in growth medium. Percardial edema was calculated by dividing cardiac area by whole body area.

Results: 3 paulolone derivatives showed dose-dependent protection of podocytes from PAN-induced injury. Alsterpaullone, which showed most protective effects reduced the expression of a podocyte damage marker, Desmin, and inhibited PAN-induced increase in podocyte migration. Furthermore, alsterpaullone reduced PAN-induced apoptosis of podocytes. As a control, GSK3β inhibitor, SB216763, also protected podocytes from PAN-mediated injury apoptosis. Both alsterpaullone and SB216763 protected zebrital from Adriamycin-induced glomerular damage.

Conclusions: Screening of a chemical library using our newly developed podocyte-based HCS assay resulted in identification of paulolone family of compounds as novel podocyte-protective compounds. Paulolines mediate their protective effects by targeting GSK3β, a well-known protein target in podocytes and showed protection of podocytes from injury in both in vitro and in vivo assays.

Funding: NIDDK Support
A T2A-Peptide Based Knock-In Mouse Model for Enhanced Cre Recombinase Activity and Fluorescent Labeling of Podocytes

Sybille Köhler, Sebastian Braehler, Fabian Braun, Markus M. Rinschen, Bernhard Schermer, Thomas Benzing, Paul T. Brinkkötter.

Dept of Internal Medicine and Center for Molecular Medicine, Univ of Cologne, Cologne, Germany; Cologne Excellence Cluster on Cellular Stress Response in Ageing-Associated Diseases (CECAD), Univ of Cologne, Cologne, Germany; Systems Biology of Ageing Cologne (Sybacol), Univ of Cologne, Cologne, Germany; Dept of Pathology & Immunology, Div of Immunobiology, Washington Univ School of Medicine, St. Louis.

Background: Podocyte injury is a key event in glomerular disease leading to proteinuria and opening the path towards glomerular scarring. As a consequence glomerulonephritis research strives to discover molecular mechanisms and signaling pathways affecting podocyte health.

Objectives: Here, we generated a novel podocyte-specific Cre reporter mouse combining enhanced Cre efficiency and fluorescent cell labeling. To this end, we targeted the Nphs2 locus to generate a tricistronic mRNA linking Nphs2 to a codon improved Cre recombinase (iCre) via a viral 2A sequence followed by a second 2A sequence and mTomato allowing direct podocyte labeling. Podocin, iCre, T2A and mTomato are expressed in equimolar amounts under the control of the endogenous Nphs2 promoter. Immunofluorescence and FACS-analysis revealed exclusive mTomato expression in podocytes. Nphs2.T2A.iCre. T2A.mTomato mice did not develop glomerular disease confirming that the knock-in procedure was not harmful.

Methods: We assessed Cre recombinase efficiency by mating the mice to Pibh2+;Pod2ACre mice with aggravated glomerular injury already evident after 2-3 weeks of age and premature lethality after 4 weeks while the onset of disease in conventional Pibh2+;Pod.cre+ mice was delayed by approximately 7 days.

Results: Taken together, we generated a tricistronic podocyte reporter mouse that combines improved Cre recombinase activity and expression of a membrane-tagged tomato for easy visualisation and identification of podocytes.

VEGFA Expression by the Stromal Lineage Is Critical for Glomerular and Peritubular Capillaries in Kidney

Hendrik Dinke, Rizaldy P. Scott, Yoshio Mazzawa, Vera Eremia, Paul S. Thörner, Yashpal S. Kanwar, Susan E. Quaggin.

Dept of Cardiovascular and Renal Research, Univ of Southern Denmark, Odense, Denmark; Lunenfeld-Tanenbaum Research Inst, Toronto, ON, Canada; Feinberg Cardiovascular Research Inst and Div of Nephrology, Northwestern University, Chicago, IL; Dept of Pediatric Laboratory Medicine, Hospital for Sick Children, Toronto, ON, Canada; Deps of Pathology and Medicine, Northwestern Univ, Chicago, IL.

Background: VEGFA is essential for the glomerular endothelium and peritubular capillaries, respectively. Given the importance of VEGFA in maintaining select microvascular beds, we aimed to determine whether the stromal compartment in kidney could be important for renal microvasculature.

Methods: To further understand the effector pathways downstream of the MC1R in podocytes, a phosphoproteomic approach was used. The study was conducted on wt-MC1R treated with the MC1R agonist, BMS. Stress fiber rearrangement was studied in real-time using LifeAct on podocytes treated with proline sulfamate, either overlapping a constitutively active MC1R or a wt-MC1R treated with BMS. Assignment of significant MC1R regulated phosphoproteins were identified, with the top ranked regulated pathways at the early timepoint (15 min of BMS exposure) being actin cytoskeleton signaling following integrin, paxillin, FAK and RhodGTPase signaling. At a later stage (60 min of BMS) the activated pathways were shifted to tight junction followed by mTOR, the cytoskeleton and adherent junction signaling. The regulation of the actin cytoskeleton signaling by MC1R was further supported by LifeAct experiments where both BMS activation of wt-MC1R overexpressing cells and overexpression of the constitutively active MC1R showed a protective effect against PS induced stress fiber rearrangement.

Results: This study demonstrates the mechanisms behind the beneficial effects of MC1R-activation, with the top ranked function being actin cytoskeleton stabilization in podocytes, which is known to be crucial for the maintenance of kidney filtration barrier function. It also demonstrates how an unbiased phosphoproteomic approach can be used to identify regulated signaling pathways important in podocyte function.

Funding: Government Support - Non-U.S.

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Funding: Government Support - Non-U.S.
The TGFB-1-induced changes of DNA methylation levels in promoter and Enhancer Regions of WT1 Gene in Human Podocytes. Based on the hypothesis that epigenetic modification plays a role in this process, we examined if TGFB-1 changes WT1 methylation levels in its promoter and three enhancer regions. Conditional immortalized human podocytes were treated with 3 ng/ml of TGFB-1 for 10 days. A human renal tubular epithelial cell line (HK2) was used as the control cells, which do not express WT1. The degree of DNA methylation was determined by quantitative methylation-specific PCR (Q-MSP), bisulfite sequencing, and pyrosequencing. Results: Both WT1 mRNA and protein expression were reduced by the treatment of TGFB-1, as previously reported. Interestingly, TGFB-1 reduced mRNA expression of WT1 by 45% (P<0.05), while cell size, proliferation rate, and F-actin pattern were comparable to control HP. The active form of Trio (GEF-D1 domain) was activated in control HP, but not in TGFB-1-treated podocytes. In contrast, examination of WT1 5 enhancer and intron 3 enhancer showed lower levels of methylation in HK2 (99±1±0% P<0.01) compared to untreated podocytes (2.9±4.5%). And that TGF-β1-treated podocytes tended to increase DNA methylation (14±3±0.5%, P=0.16, vs untreated podocytes). In conclusion, methylation levels at 3' enhancer did not differ among HK2, untreated podocytes and TGF-β1-treated podocytes.

Conclusions: Our data suggest that TGFB-1 changes the methylation levels of WT1 promoter and enhancers of podocytes. The reduction of WT1 expression by TGFB-1 may be partly due to the DNA methylation changes.

Funding: Government Support - Non-U.S.

TH-PO231

Hannover Medical School, Germany.

Background: Wilms' Tumor Suppressor (WT1) is essential for normal podocyte function. Previous reports have shown that WT1 downregulation is correlated with transcriptional silencing. We have reported that TGFB-1 downregulates WT1 expression in podocytes. Based on the hypothesis that epigenetic modification plays a role in this process, we examined if TGFB-1 changes WT1 methylation levels in its promoter and three enhancer regions. Conditional immortalized human podocytes were treated with 3 ng/ml of TGFB-1 for 10 days. A human renal tubular epithelial cell line (HK-2) was used as the control cells, which do not express WT1. The degree of DNA methylation was determined by quantitative methylation-specific PCR (Q-MSP), bisulfite sequencing, and pyrosequencing. Results: Both WT1 mRNA and protein expression were reduced by the treatment of TGFB-1, as previously reported. Interestingly, TGFB-1 reduced mRNA expression of WT1 by 45% (P<0.05), while cell size, proliferation rate, and F-actin pattern were comparable to control HP. The active form of Trio (GEF-D1 domain) was activated in control HP, but not in TGFB-1-treated podocytes. In contrast, examination of WT1 5 enhancer and intron 3 enhancer showed lower levels of methylation in HK2 (99±1±0% P<0.01) compared to untreated podocytes (2.9±4.5%). And that TGF-β1-treated podocytes tended to increase DNA methylation (14±3±0.5%, P=0.16, vs untreated podocytes). In conclusion, methylation levels at 3' enhancer did not differ among HK2, untreated podocytes and TGF-β1-treated podocytes.

Conclusions: Our data suggest that TGFB-1 changes the methylation levels of WT1 promoter and enhancers of podocytes. The reduction of WT1 expression by TGFB-1 may be partly due to the DNA methylation changes.

Funding: Government Support - Non-U.S.

TH-PO241

Protein 4.1O is a novel linker of nephrin to the Actin Cytoskeleton

FRMD3 has been proposed as a candidate gene for susceptibility of diabetes mellitus and its complications. Protein 4.1O is expressed in human podocytes and interacts with nephrin. Protein 4.1O directly interacts with actin. Injection of FRMD3 in zebrafish. Injection of fluorescently labeled FITC-dextran was monitored via eye lens. There was marked reduction in H2O2 translocation of NF-κB and activation of IL-6 with no further upregulation of CYP2B6. This study suggests that phosphorylated nephrin is able to recruit c-Abl to the actin cytoskeleton.
Results: mTORC1 target genes were significantly induced in both human FSGS cohorts and murine FSGS models. Mouse models with constitutive mTORC1 activation closely recapitulated human FSGS. Unexpectedly, the complete knockout of mTORC1 by induced deletion of both Raptor alleles accelerated the progression of murine FSGS models. However, curtailed mTORC1 signaling by genetically deleting just one Raptor allele ameliorated progression of glomerulosclerosis in murine FSGS model. This non-linear mTORC1 gene dosage effect was further substantiated by low dose Rapamycin treatment of murine FSGS models ameliorating disease progression. Mechanically, complete mTOR inhibition shifted the cellular energy metabolism towards reduced rates of oxidative phosphorylation and anaerobic glycolysis, which was linked to an increased reactive oxygen species production. Moderate mTOR inhibition however preserved mitochondrial function in the presence of FSGS.

Conclusions: Together these data suggest that podocyte injury and loss is initially followed by an adaptive mTOR activation precluding the use of long-term and high dose mTOR inhibition. However as prolonged mTOR activation results in podocyte differentiation and cellular stress with our models we propose incomplete mTOR inhibition as a novel and individualized treatment rationale.

Funding: Government Support - Non-U.S.

TH-PO246
An In Vitro Model of the Glomerulus
Jack P. Tuffin,1 Gavin Iain Welsh,1 Moin Saleem,2 Simon C. Satchell.1
1 Bristol Renal, Uniy of Bristol, Bristol, United Kingdom; 2UCB Pharma Ltd, Slough, United Kingdom.

Background: Our lab has previously developed conditionally immortalised human podocytes and glomerular endothelial cell (GenCs) lines. The purpose of this project has been to develop a 3D in vitro model of the glomerulus for the purpose of developmental research as well as pharmaceutical-compound screening.

Methods: Cells were cultured using a variety of scaffold culture techniques including a novel gel/scaffold hybrid platform utilizing cocultured, growth factor-treated cells. Magnetic levitation as well as magnetic bioprinting techniques were also used. Cell types were identified using stable GFP/RFP labelling. Cultured tissues were paraffin embedded, sectioned and stained for confocal immunofluorescence microscopy.

Results: Experiments show that 3D cocultured podocytes and GenCs reorganise in a similar, glomerular-like manner regardless of the culture platform used. Podocytes were seen to wrap around GenCs, with tube formation identified. Magnetic spheroids were used to manually and readily organise cells in this way to form glomerulus sized tissues that express the glomerular basement membrane protein collagen IV in a location concurrent with its in-vitro deposition.

Conclusions: We have developed an in-vitro 3D coculture model of human podocyte and GenC glomerular cell lines, with self organizing properties, that show early hallmarks of GBM formation.

Funding: Pharmaceutical Company Support - UCB pharma, Government Support - Non-U.S.

TH-PO247
Akt Pathway Plays a Critical Role in Podocyte Injury and Recovery in Glomerular Disease
Tetsuya Kikao,1 Melinda A. Chanley,1 Kazunari Kaneko,2 William E. Smoyer,1 Shripa Agrawal,1 CCTR, The Research Inst at Nationwide Children’s Hospital, Columbus, OH; 2Pediatrics, Kansui Medical Univ, Osaka, Japan; 1Pediatrics, The Ohio State Univ, Columbus, OH.

Background: Tight regulation of mTOR and Akt pathways has recently been reported in the context of chronic kidney disease and in apoptosis control of podocytes. Furthermore, we have previously reported the beneficial roles of glucocorticoids (GCs) and pioglitazone (Pio) in nephrotic syndrome (NS). We hypothesized that Akt pathway downstream of PI3K and mTOR plays a critical role in podocyte injury and recovery in NS.

Methods: Phosphorylated and total forms of Akt and Mdm2 were analyzed in the glomeruli or kidney sections of rats and mice with single or multiple proteinuria (Pio) in nephrotic syndrome (NS). We hypothesized that Akt pathway downstream of PI3K and mTOR plays a critical role in podocyte injury and recovery in NS.

Results: Akt phosphorylation at earlier time point while it was activated in the Adr- treated mice only. This was however attributed to proximal tubule cells and not podocytes as assayed by immuno-fluorescence microscopy. Moreover, while PAN induced apoptosis in cultured differentiated human podocytes and treatment with GCs inhibited apoptosis, activator of Akt at Ser473 Thr408 enhanced the anti-apoptotic effects while the inhibitor at Ser473 Thr408 enhanced apoptosis and reduced the anti-apoptotic effects of GCs.

Conclusions: Akt regulation by both mTORC2 and PI3K pathways is associated with podocyte injury and recovery in glomerular disease and its activation provides beneficial protective effects.

Funding: NIDDK Support

TH-PO248
Glomerular Podocyte to Endothelial Cell Cross-Talk in Kidney Disease
Jia E. Kyung (Kim) Lee,1 Stuart Shankland,2 John C. He.1 Icahn School of Medicine at Mount Sinai, New York; 2Univ of Washington School of Medicine, Seattle.

Background: Podocytes and glomerular endothelial cells (GECs) are major components of the glomerular filtration barrier, and cross-talk between these two cell types is critical for maintaining this barrier. Recent studies suggest that podocyte injury leads to the progression of glomerular disease. It is hypothesized that podocyte injury could cause GEC injury through a cross-talk mechanism. Here, we sought to test this hypothesis in vivo using RNA sequencing of GECs in an animal model of podocyte injury.

Methods: We used a transgenic mouse model in which GECs are labeled with yellow-fluorescent protein (YFP) in the nuclei which allowed us to effectively sort GECs by flow cytometry. Podocyte injury was induced by injection of mice with a specific anti-podocyte antibody generated in Dr. Stuart Shankland’s laboratory. Mice were sacrificed at day 14 after antibody injection, glomeruli were isolated and YFP-positive GECs were sorted for RNA sequencing. The key pathways were validated by real-time PCR, western blot analysis, and functional assays for apoptosis and ROS production.

Results: Antibody-injected mice developed significant proteinuria, focal glomerulosclerosis, and podocyte depletion. Interestingly, number of GECs was also reduced and appeared detached from glomerular basement membrane. GECs were sorted from these mice and expression of endothelial cell-specific markers was confirmed in the sorted cells. Analysis of the differentially expressed genes (DEGs) in GECs between the diseased and control mice revealed significant alteration of the pathways related to apoptosis, tight-junction, and oxidative stress. Expression of key DEGs was confirmed by real-time PCR and western blot analysis. We validated that apoptosis and production of ROS increased in the GECs of the diseased mice.

Conclusions: Podocyte injury can propagate to GEC injury through a crosstalk mechanism that mediates the progression of glomerular disease.

Funding: Other NIH Support - NIH R01DK078897; NIH R01DK088541; NIH P01-DK-56492, VA Support

TH-PO249
Mutant Actinin-4 in the Pathogenesis of Focal Segmental Glomerulosclerosis
Albert Yee,1 Joan Papillon, Julie Guillermite, Daniel Robert Kaufman, Andrey V. Cybulsky, Medicine, McGill Univ, Montreal, Canada.

Background: Mutations in actinin-4 are associated with heritable focal segmental glomerulosclerosis (FSGS) in humans. Previously, we showed that actinin-4 K256E is a misfolded protein that undergoes aggregation and degradation in cultured glomerular epithelial cells (GECs). There is associated proteotoxicity, i.e. induction of endoplasmic reticulum (ER) stress and “chocking” of the proteasome. The present study examined whether small molecules could improve the folding and function of mutant actinin-4, and if autophagy is upregulated by actinin-4 K256E and is responsible for its degradation.

Methods: GFP-tagged actinin-4 wild type (WT) or K256E were expressed in GECs or COS-1 cells by transfection. Interaction of actinin-4 with the cytoskeleton was assessed by detergent-extraction of cells and monitoring actinin-4 by immunoblotting. Autophagy was monitored by immunoblotting of endogenous LC3II or by expression of RFP-LC3 and quantifying formation of LC3II puncta.

Results: After extraction of cells with Triton X-100, actinin-4 WT was found mainly in the Triton-soluble fraction (69.8%), however, K256E was predominantly Triton-insoluble (78%). Incubation with ammonia caused actinin-4 F-actin (81.6%) to dissolve. Incubation of cells with the chemical chaperone, 4-phenylbutyrate, decreased the proportion of Triton-insoluble actinin-4 K256E (from 81.6% to 68.6%), but celastrol, a drug that enhances expression of cytosolic and ER chaperone, 4-phenylbutyrate, decreased the proportion of Triton-insoluble actinin-4 K256E (from 81.6% to 68.6%), but celastrol, a drug that enhances expression of cytosolic and ER chaperones, had no effect. After treatment of cells with chloroquine (to block fusion of autophagosomes with lysosomes), actinin-4 K256E stimulated autophagy, as reflected by a 1.5-fold greater accumulation of endogenous LC3II, compared to WT. Moreover, RFP-LC3II puncta occupied a 45% greater area in cells expressing actinin-4 K256E, reflecting abnormally tight binding to F-actin. In conclusion, actinin-4 K256E causes increased autophagy, which is critical for maintaining this barrier. Recent studies suggest that podocyte injury leads to the progression of glomerular disease. It is hypothesized that podocyte injury could cause GEC injury through a cross-talk mechanism. Here, we sought to test this hypothesis in vivo using RNA sequencing of GECs in an animal model of podocyte injury.

Conclusions: Actinin-4 K256E in the Pathogenesis of Focal Segmental Glomerulosclerosis

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
CD147/Basigin Deficiency Prevents the Development of Podocyte Injury through the Integrin/FAK Signaling Pathway
Tomoki Yoshika, Tomoki Kosugi, Kayahou Maeda, Tomohiro Masuda, Yuika Sato, Hiroshi Kojima, Noritoshi Kato, Takujii Ishimoto, Shouchi Maruyama. Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya-shi, Aichi-ken, Japan.

Background: CD147/Basigin (Bsg) is a glycosylated transmembrane protein belonging to the immunoglobulin superfamily. Basg contributes to cell survival, migration, cancer invasion and inflammation. We have so far demonstrated its pathophysiological roles in the kidney diseases, ranging from the occurrence of acute kidney injury accompanied by ischemia and inflammation to progression of renal fibrosis and lupus nephritis. However, little is known in the development of proteinuria. We therefore investigated the role of Bsg in the development of podocyte injury leading to the augmentation of proteinuria, using adriamycin nephropathy mouse model.

Methods: Wild-type (Bsg+) for Bsg-deficient (Bsg−) mice were injected with adriamycin (16mg/kg BW), and were then sacrificed at 2 weeks later for histological and biochemical analyses. [151A] Podocytes rarely expressed Bsg, but began to exhibit Bsg induction upon adriamycin exposure, using in situ hybridization and immunohistochemistry. Furthermore, Bsg expression was observed in immortalized human podocyte cells, and Bsg silencing with siRNA in podocyte cells suppressed the phosphorylation of focal adhesion kinase (FAK) under TGF-β stimulation. Interestingly, Bsg expression in podocyte has the association of integrin. Additionally, Bsg silencing on podocytes after TGF-β stimulation caused the decreases of endothelin-1 and MMP 2 levels.

Conclusions: Basg plays an indispensable role in the development of podocyte injury leading to the augmentation of proteinuria through the activation of FAK signaling pathway.

Podocyte Effacement Precedes Albuminuria and Glomerular Hypertrophy in CD2 Associated Protein Deficient Mice
Michael M. Basgen, Susanne H. Kosugi, Pravin Chandel, Nirupama Mehta, Kayaho Kato, Takuji Yoshioka, Kirk N. Campbell, James Kirk, Nils Michael Kronenberg, David James Harrison, Malte C. Gather, Paul Reynolds. School of Medicine, Univ of St. Andrews, United Kingdom; SUPA, School of Physics and Astronomy, Univ of St. Andrews, United Kingdom.

Background: Podocyte damage is a pivotal event underlying the pathogenesis of multiple glomerular diseases. When damaged podocytes lose the ability to adhere to the glomerular basement membrane, they detach, resulting in impaired glomerular filtration. However, the mechanism underlying podocyte detachment remains poorly understood. In this study we sought to characterize the mechanical forces exerted by differentiated podocytes by using a novel force detection assay.

Methods: A hamster podocyte cell line containing a stably integrated sensor was differentiated over the course of 12 days at the non-permissive temperature of 37°C. Differentiated podocytes were treated with 25μg/mL Puromycin Aminonucleoside (PAN) for 24 hours, followed by washout with fresh RPMI for 5 days. Podocyte mechanical forces were assessed with a novel continuous force detection assay, Elastic Resonator Interference Stress Microscopy (ERISM).

Results: Podocytes demonstrated a pulling force at focal points along the cell periphery that co-localized with foot processes. A pushing force was observed under the cell body that was 3 times greater than the force exerted by T3T fibroblasts (n=18). PAN treatment resulted in foot process effacement and membrane blebbing as evidenced by scanning electron microscopy, F-actin rearrangement, and a reduction in expression of NP-HS1, NPHS2, CD2AP, and SYNO. PAN treatment resulted in a significant increase in podocyte force transmission by a factor of 1.4, followed by a complete loss of either pushing or pulling force (n=4), despite continued cell attachment. Following PAN washout, partial recovery of force transmission of up to 60% of the initial value was observed.

Conclusions: Herein we present a novel biological application of the ERISM force detection assay. Our results indicate that, in a PAN model of glomerular injury, loss of podocyte mechanical force transmission is partially reversible. These results highlight podocyte mechanical force transmission as an integral feature of healthy podocytes, and suggest that changes in mechanical force play a pivotal role in the development of podocyte injury.

Podocyte Vitamin D Receptor Deficit Induces Activation of Renin Angiotensin System via SIRT1 Modulation
Kosugi, Kayaho, Kato, Takuji, Basgen, Pravin C. Singhal. Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.

Background: Vitamin D receptor (VDR) deficient status has been shown to be associated with the activation of renin angiotensin system (RAS). However, the involved mechanism is not clear. We hypothesized that lack of VDR would enhance p53 expression associated with the activation of renin angiotensin system (Angiotensin) (Ang) and angiotsigenin type 1 receptor (ATIR) leading to the activation of RAS.

Methods: Renal tissues of 4 week old control and VDR mutant (M, n=4) were analyzed for expression of SIRT1, p53, angiotsigenin, and ATIR (n=4). Human podocytes (HPs) were transfected with either scrambled or VDR siRNAs and evaluated for expression of above mentioned molecules. Renal tissues from VDR(M) and HPs lacking SIRT1 were evaluated for acetylation of p53 and lysine (K) 382 residues.

Results: Renal tissues of VDR mutant (M) mice displayed increased expression of p53, Ang, renin, PPAR-y, and ATIR. In vitro studies, VDR knockout podocytes not only displayed up regulation p53 but also displayed enhanced expression of Ang, renin and ATIR. VDR deficient podocytes also displayed an increased in mRNA expression for p53, Ang, renin, PPAR-y and ATIR. Interestingly, loss of VDR-M lacking (PAN) mice displayed alternated expression of denectylyase SIRT1. Renal tissues of VDR-M mice showed acetylation of p53 at lysine (K) 382 residues inferring that enhanced p53 expression in renal tissues could be the result of ongoing acetylation, a consequence of SIRT1 deficiency in VDR-M mice. VDR-deficient podocytes lacking SIRTI not only showed acetylation of p53 at lysine (K) 382 residues but also displayed enhanced p53 expression. Since renal tissues of VDR-M mice also showed enhanced expression of PPAR-y, it is plausible that the deficient of SIRT1 has de-repressed expression of PPAR-y or enhanced podocyte expression of PPAR-y (in the absence of VDR) has contributed to the down regulation of SIRT1.

Conclusions: VDR deficiency activates the RAS via SIRT1 modulation.

Mapping Podocyte Mechanical Force In Vitro
Kathryn E. Halej, Nils Michael Kronenberg, David James Harrison, Malte C. Gather, Paul Reynolds. School of Medicine, Univ of St. Andrews, United Kingdom; SUPA, School of Physics and Astronomy, Univ of St. Andrews, United Kingdom.

Background: Podocyte damage is a pivotal event underlying the pathogenesis of multiple glomerular diseases. When damaged podocytes lose the ability to adhere to the glomerular basement membrane, they detach, resulting in impaired glomerular filtration. However, the mechanism underlying podocyte detachment remains poorly understood. In this study, we sought to characterize the mechanical forces exerted by differentiated podocytes by using a novel force detection assay.

Methods: A hamster podocyte cell line containing a stably integrated sensor was differentiated over the course of 12 days at the non-permissive temperature of 37°C. Differentiated podocytes were treated with 25μg/mL Puromycin Aminonucleoside (PAN) for 24 hours, followed by washout with fresh RPMI for 5 days. Podocyte mechanical forces were assessed with a novel continuous force detection assay, Elastic Resonator Interference Stress Microscopy (ERISM).

Results: Podocytes demonstrate a pulling force at focal points along the cell periphery that co-localized with foot processes. A pushing force was observed under the cell body that was 3 times greater than the force exerted by T3T fibroblasts (n=18). PAN treatment resulted in foot process effacement and membrane blebbing as evidenced by scanning electron microscopy, F-actin rearrangement, and a reduction in expression of NP-HS1, NPHS2, CD2AP, and SYNO. PAN treatment resulted in a significant increase in podocyte force transmission by a factor of 1.4, followed by a complete loss of either pushing or pulling force (n=4), despite continued cell attachment. Following PAN washout, partial recovery of force transmission of up to 60% of the initial value was observed.

Conclusions: Herein we present a novel biological application of the ERISM force detection assay. Our results indicate that, in a PAN model of glomerular injury, loss of podocyte mechanical force transmission is partially reversible. These results highlight podocyte mechanical force transmission as an integral feature of healthy podocytes, and suggest that changes in mechanical force play a pivotal role in the development of podocyte injury.

Functional Interaction of USP40 with Nestin in Podocyte
Shohei Takashaki, Yukino Nishibori, Kunimasa Yan. Pediatrics, Kyorin Univ School of Medicine, MKtaka, Tokyo, Japan.

Background: We previously showed that gene knockdown of ubiquitin specific protease-40 (USP40) leads to disorganized glomerulus in zebrafish morphants. Nestin is currently speculated to be a protective molecule against podocyte injury. The aim of the present study was to explore a functional role of USP40 in the acquired podocyte disease.

Methods: USP40 KO mice and wild type mice were analyzed as an integral feature of healthy podocytes, and suggest that changes in mechanical force play a pivotal role in the development of podocyte injury.

Results: KO mice did not reveal pathological proteinuria and apparent alterations in kidney morphology and urinary abnormality. The isolated glomeruli from 3 KO mice and 3 wild type mice were analyzed to determine the data of proteomic analysis. Cultured mouse podocytes were stained with cell line-labeling immunofluorescence, and disagreement in the genowhom experiments to determine a functional relationship between USP40 and nestin. Glomeruli and kidney sections from adriamycin nephropathy and control mice were analyzed to compare protein expression of USP40 and nestin in podocytes.

Conclusions: Our findings collectively show that USP40 is a novel ligand protein for nestin and that their interaction may be involved in the pathophysiology of the acquired podocyte disease. Absence of phenotypic change of USP40 KO mice suggests the possible presence of the compensatory mechanism for nestin protein turnover in podocytes.
Mechanism of TIMAP Action: Competition with MYPT1 for the PP1c

**TH-PO255**

Mechanism of TIMAP Action: Competition with MYPT1 for the PP1c

Catalytic Subunit Xin Wang,1 Laiji Li,1 Barbara J. Ballermann,1 Medicine, Univ of Alberta, Edmonton, AB, Canada; 1Nephrology, The First Affiliated Hospital of Sun Yat-Sen Univ, Guangzhou, China.

**Background:** Actomyosin activation by phosphorylated myosin-light chain 2 (MLC2) increases endothelial permeability in glomeruli and other capillaries, and myosin phosphatase inhibition maintains MLC2 phosphorylation (pMLC2). Myosin phosphatase consists of regulatory (MYPT1) and catalytic protein phosphatase 1 (PP1c) subunits, and is inhibited by Rho-kinase-dependent phosphorylation of MYPT1. TIMAP is an endothelial cell (EC)-predominant member of the MYPT family. Surprisingly, overexpression of TIMAP increases pMLC2 in glomerular EC by inhibiting myosin phosphatase activity without activating RhoA and TIMAP phosphorylation. We investigated how TIMAP inhibits MYPT1/PP1c action in EC.

**Methods:** Western blots (WB) with densitometric quantification were performed on lung (rich in EC) lysates from wild-type and TIMAP deficient mice, and cultured human glomerular EC lysates. Glomerular EC were transduced with Adenoviruses (Ad) expressing GFP (Ad-GFP), GFP-TIMAP (Ad-GFP-TIMAP) or the PP1c binding mutant Ad-GFP-PP1MP-1 (Ad-GFP-PP1MP-1). PP1c was specifically precipitated with microcinin sepharose.

**Results:** Similar to our findings of increased pMLC2 in glomerular EC overexpressing TIMAP, the pMLC2/Actin ratio was higher in lung lysates of WT than TIMAP deficient mice (0.56 ± 0.19 vs. 0.32 ± 0.07, mean ± SD, n=4, P=0.019). The MYPT1-Actin ratio was 57 ± 23% (mean ± SD, n=3, P=0.026) lower in glomerular EC expressing GFP-TIMAP vs. GFP. GFP-TIMAP-, which cannot bind PP1c, had no discernable effect on pMLC2 or MYPT1 abundance. Microcinin co-precipitated PP1c and MYPT1, but not TIMAP, from EC expressing GFP or GFP-TIMAP-, but co-precipitated only PP1c and TIMAP, and not MYPT1 from EC expressing GFP-TIMAP-, even when equivalent MYPT1 was loaded.

**Conclusions:** The data indicate that TIMAP competes for PP1c with MYPT1, implying that PP1c regulatory subunits like MYPT1 and TIMAP exist in excess over their catalytic subunits in EC, and that TIMAP inhibits, while MYPT1 potentiates PP1c activity towards pMLC2. Also, expression of TIMAP reduces the MYPT1 abundance in EC. Hence, pMLC2-dependent endothelial permeability may be controlled in a Ying-Yang fashion by TIMAP and MYPT1.

**Funding:** Clinical Revenue Support

**TH-PO256**

Loss of Nonmuscle Myosin II in Postnatal Mouse Renal Tubules Results in Chronic Kidney Disease

Indra Chandrasekara,1 Karla L. Otterpohl,1 Ryan G. Hart,1 Kameswaran Surendran,1 Bruce A. Molitoris,1 2Sanford Children’s Health Research Center, Sanford Research, Sioux Falls, SD; 1Dept of Medicine, Univ of Indiana, Indianapolis, IN.

**Background:** Nonmuscle myosin II (MII) is an actin associated motor protein that contributes to the cellular processes of migration, adhesion, and division and is essential for brain and heart development. Our recent work demonstrated that MII function (isoforms MIIA and MIIB) is critical for both compensatory and constitutive receptor mediated proliferation of single endothelial precursor cells within glomeruli.

**Methods:** We hypothesized that the underlying mechanism in MII related kidney disorders is compromised renal tubular endothelial function resulting in decreased protein reabsorption. We inactivated one or both MII genes, Myh9 and Myh10, within the postnatal renal tubules using the doxycycline inducible Pax-6;rtTA, Tet-O-Cre system. Doxycycline was administered in the drinking water to mice at 1 month of age to inactivate the Myh9 and Myh10 genes.

**Results:** Urine analysis revealed proteinuria as early as two months after doxycycline. Histological evaluation of kidneys from single MIIA knock-out males revealed mild tubular dilation and inflammation younger mice, that progressed to glomerular sclerosis, loss of cytosolic staining in the proximal tubules and the presence of polymorphonuclear leukocytes and macrophages. Interestingly, knockout of both Myh9 and Myh10 in the postnatal tubules results in dysplastic kidney disease within two months of initiating doxycycline treatment.

**Conclusions:** Our data support the hypothesis that postnatal loss of MII in renal tubules results in tubular dysfunction and progression to chronic kidney disease.

**Funding:** Other NIH Support - P20GM103620

**TH-PO257**

mPGES-1-Derived PGE2 Stimulates Stat3 to Promote Podocyte Injury

Jing Yu,1 Zhanjun Jia,1 Wei Gong,1 Shuzhen Li,1 Yue Zhang,1 Guixia Ding,1 Alfiau Zhang,1 Songming Huang.1 1Dept of Nephrology, Nanjing Children’s Hospital affiliated to Nanjing Medical Univ, Nanjing, China; 1Nanjing Key Lab of Pediatrics, Nanjing, China.

**Background:** We previously reported that microsomal prostaglandin E synthase-1 (mPGES-1) contributed to nephrotoxic enalapril injury (Yu et al., J Am Soc Nephrol, 2015). However, the molecular mechanisms mediating mPGES-1 effect on inducing podocyte damage is still unknown. Here to performed experiments to test the role of mPGES-1-PGE2 cascade in activating Stat3 and its contribution in PGE2- and Adr-induced podocyte injury.

**Methods:** PGE2 and Adr were administered to the podocytes to induce podocyte injury. Specific Stat3 inhibitor, JAKSTATS, and mPGES-1 siRNA were investigated to determine the roles of Stat3 and mPGES-1-derived PGE2 in this pathological process.

**Results:** By administration of PGE2 to podocytes, we observed a dose- and time-dependent upregulation of p Stat3 (>3folds), indicating an activation of Stat3, in line with the significant podocyte injury as evidenced by the remarkable cell apoptosis and the reduction of nephrin expression. Consistently, Stat3-driven cytolysis like IL-6, IL-17, and MCP-1 were enhanced by 2-4 folds (p<0.05) by PGE2 treatment. By inhibiting Stat3 with a specific Stat3 inhibitor S3I-201, PGE2-induced podocyte apoptosis was blocked by 71% (~3folds, p<0.05). Then the podocytes were further subjected to the Adr treatment. As expected, Adr remarkably elevated pStat3 levels by more than 3 folds after 6 h treatment in line with the stimulation of mPGES-1/PGE2 cascade. Blockade of Stat3 by S3I-201 significantly ameliorated Adr-induced cell apoptosis by 60% and nephrin reduction by 45%. More interestingly, silencing mPGES-1 in podocytes by mPGES-1 siRNA almost abolished Adr-induced increments of Stat3 phosphorylation, PGE2 production, and Stat3-driven inflammatory cytokines.

**Conclusions:** The current study highly suggested that mPGES-1-derived PGE2 could activate Stat3 signaling to promote podocyte injury. Targeting mPGES-1/PGE2/Stat3 signaling might be a potential strategy for the treatment and prevention of podocytopathy.
Conclusions: These findings suggest that FcRn is needed to optimize the expression of MHC II as well as facilitate trafficking of antigen-antibodies to lysosomes.

**Funding:** NIDDK Support, Private Foundation Support

**TH-PO260**

**C14orf142 Is the 5th Member of the Highly Conserved KEOPS Complex and Is Mutated in Galloway-Mowat Syndrome (GMS)**

Gerardine Mollet, Bruno Collinet, Christelle Arrondel, Olivier Gibrail, Patrick Revy, Daniella Magen, Daniela A. Braun, Friedhelm Hildebrandt, Herman Van Tilburgh, Corinne Antignac, Inserm U1163, Paris Descartes Univ, Paris, France; 1Dept of Biologie Integrative de la Cellule, CNRS, Univ Paris Sud, Orsay, France; 2Pediatric Nephrology Inst, Ramhan Health Care Campus, Technion Faculty of Medicine, Haifa, Israel; 3Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston.

**Background:** The evolutionarily conserved KEOPS complex is composed of at least 4 subunits (LAGE3, C14orf142, TPRK, and TPRKB), and is the genome-wide mapped gene in 5 families with GMS and showed that the C14 protein, which is predicted to be a nuclear protein, plays a role in transcription and telomere maintenance. However, KEOPS function in humans is unknown. We have recently identified mutations in all four members of KEOPS in patients with GMS associating nephrotic syndrome with microcephaly and neurological impairment.

**Methods:** To identify new genes involved in GMS and characterize new potential partners of the KEOPS complex, we performed exome sequencing, proteomic and co-purification experiments. To assess one of the known functions of KEOPS, we performed Telomere Restriction Fragment analysis and Telomere dysfunction-Induced Foci assays.

**Results:** We identified 2 homozygous truncating mutations in the C14orf142 (C14) gene in 5 families with GMS and showed that the C14 protein, which is predicted to be largely unstructured and of similar size as G07, strongly interacts with LAGE3. We further demonstrated that h-tagged C14 co-purified with all KEOPS members when over-expressed in bacteria and that this complex is stable during gel filtration purification. We did not find any telomere length modifications or telomere dysfunction suggesting that telomere maintenance is not the primary function of KEOPS in humans.

**Conclusions:** The human KEOPS complex binding to the LAGE3 subunit, in a similar way as does G07 in yeast. The role of C14 within the KEOPS complex and the role of this complex in the pathogenesis of GMS remain unclear.

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

**TH-PO261**

**Induction of Interdigitating Cell Processes in Cultured Podocytes**

Eishin Yodaota, Yutaka Yoshida, Hiroki Takimoto. Dept of Structural Pathology, Kidney Research Center, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.

**Background:** Interdigitating cell processes characterize glomerular podocytes in vivo. However, podocytes in primary culture and in cell lines have a simple morphology lacking cell processes, especially upon reaching confluence. Some culture conditions have been reported to induce podocyte-specific gene expressions, but no reports have succeeded in inducing morphology close to that of in vivo conditions. In this study, we tried to establish culture conditions under which cultured cells spread cell processes at confluence.

**Methods:** Rat primary cultured podocytes were used to investigate the effects of cell density, low concentrations of fetal bovine serum (FBS), heparin, retinoic acid (RA), and extracellular matrices (collagen type I, fibronectin and laminin) on their morphology.

**Results:** Cell processes were extensively induced when cells were seeded at a cell density equivalent to in vivo and cultured in the presence of heparin and RA on laminin-coated dishes, and in decreasing concentration of FBS as shown in the phase-contrast micrograph figure. Cell seeding density and decreasing FBS concentrations were critical to inducing interdigitating cell process formation. Without laminin coating, heparin or RA, cell processes were formed, although limited to a small area. Like primary processes in vivo, the processes contained vimentin filaments, occasionally overlapping each other, and stretched under adjacent cell bodies. Intercellular junctions as shown by staining for podocin, heparin or ZO-1 were located between the cell processes and under cell bodies as elaborate squiggles, where actin filaments accumulated, suggesting primitive foot processes. Local formation of slit diaphragm was demonstrated by electron microscopy.

**Conclusions:** We have succeeded in establishing culture conditions in which cultured cell phenotypes are closer to those in vivo.

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

**Underline represents presenting author.

153A
TH-PO264

High Throughput In Vitro Drug Screening Assay for Proximal Tubule Cell Function in Cystinosis

Manoe J. Jansen,1 Nienke Van Andel,1 Martijn J. Wilmer,2 Elena N. Levchenko,1 Rosalinde Masereeuw,1 1Pharmacology, UIPS, Netherlands; 2Pediatric Nephrology, Radboudumc, Netherlands; 3Pediatric Nephrology & Growth and Regeneration, KU Leuven, Belgium.

Background: Cystinosis is a lysosomal storage disorder caused by mutations in cystinosin (CTNS). Patients develop renal Fanconi syndrome at 6 months and kidney failure before the age of ten. Here we developed a high-throughput in vitro assay to evaluate proximal tubular cell function for identification of potential drugs.

Methods: Receptor-mediated endocytosis was determined in conditionally immortalised proximal tubular cells (ciPTEC) from cystinotic patients and healthy controls by uptake of receptor associated protein (RAP-GST). RAP-GST uptake and transport to early endosomes (EEA1 staining) and late endosomes/lysosomes (LAMP1 staining) was quantified using a CV7000 high-content confocal imager. Cell viability was determined by PrestoBlue conversion.

Results: RAP-GST was efficiently taken up by ciPTEC in a vesicular pattern co-localizing with endosomes and lysosomes. After 1 hr incubation RAP-GST staining was significantly increased in cystinotic cells (28% ± 10%, p<0.03) and vesicles were prone to forming larger clusters (Figure 1, p<0.02) with higher intensity (Figure 2, p<0.003). This suggest a delay in protein degradation rather than protein uptake in cystinotic cells. Next, we determined the toxicity of two potential drug candidates selected after Prestwick library screening and found that the EC50 values after 7 days exposure were 49±2 and 54±3 µM (R2=0.99). Pathological cystine accumulation is reduced at 10 µM, suggesting that the compounds will be non-toxic in the pharmacological range in cystinotic patients.

Figure 1

Figure 2

Conclusions: Our assay provides insight into lysosomal patterning and protein degradation in proximal tubule cells and can be used as a functional readout to identify drug compounds that may improve kidney function in cystinosis.

Funding: Government Support - Non-U.S.

TH-PO265

Determination of Plasma 2,8-Dihydroxyadenine with Ultra-Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS/MS)

Vidar O. Edvardsson,1,2,3 Unnur A. Thorsteinsdottir,4,5 Hrafnhildur L. Runolfsdottir,4,5 Inger M. Agustsdottir,4,5 Finnur Freyr Eiriksson,4,5 Margret Thorsteinsdottir,4,5 Runolfur Palsson,4,5 Landspitali - The National Univ Hospital of Iceland, Reykjavik, Iceland; 2Univ of Iceland, Reykjavik, Iceland; 3ArcticMass, Reykjavik, Iceland.

Background: Adenine phosphoribosyltransferase deficiency (APRTd) is a hereditary disorder caused by a deficiency of the enzyme adenine phosphoribosyltransferase (DHA) excretion, causing nephrolithiasis and crystal nephropathy. Allopurinol treatment is inefficient. Recently, the pathogenic role of DHA was recognized by detecting high levels of DHA in plasma patients with APRTd.

Methods: We developed a novel method for determination of DHA in plasma of APRTd patients. This method was validated by using plasma samples from known APRTd patients in concentrations of 786 and 371 ng/mL, respectively.

Results: DHA was detected in plasma samples from the 2 APRTd patients and in the spiked control sample but not in a plasma sample from the healthy control. The DHA signal intensity observed in the 2 patient samples indicated a concentration of 786 and 371 ng/mL, respectively.

Conclusions: For the first time, DHA was detected in plasma samples from patients with APRTd. This new assay may enhance the diagnosis and monitoring of pharmacotherapy in APRTd, particularly in patients with kidney failure.

Funding: NIDDK Support, Other NIH Support - Rare Kidney Stone Consortium (U54DK085908), Rare Diseases Clinical Research Network, Government Support - Non-U.S.

TH-PO266

2,4-Dihydroxybenzoic Acid Improves Survival and Demonstrates Renoprotective Effect in a Podocyte-Specific Coq6-Knockout Mouse Model of Nephrotic Syndrome

Eugen Widmer,1,2 Merlin Airik,1 David Schapira,1 Hadas Iyel,1 Rannar Airik,1 Friedhelm Hildebrandt,1,3 1Div of Nephrology, Boston Children’s Hospital, Harvard Medical School, Boston, MA; 2Dept of Medicine, Univ of Freiburg Medical Center, Freiburg, Germany; 3Div of Nephrology, Children’s Hospital of Pittsburgh, Pittsburgh, PA.

Background: Steroid resistant nephrotic syndrome (SRNS) inevitably progresses to end-stage renal disease. Human mutations in the CoQ6 gene cause SRNS (Heeringa JCI 121:2013, 2011). To study the function of COQ6 in podocytes we generated a podocyte-specific Coq6-knockout mouse model.

Methods: Nphp2Cre mice were crossed with Coq6lox/lox mice, to generate podocyte specific Coq6-knockout mice (Coq6lox/lox on a C57BL/6 background. Treatment with 2,4-dihydroxybenzoic acid (2,4-DHB) at a 25 mM concentration in the drinking water was started at 5 months. Kidneys were harvested for histological and ultrastructural analysis at 10 months, and urine was collected monthly for metabolic studies.

Results: Coq6lox/lox mice displayed an onset of proteinuria in 4 months. Non-treated Coq6lox/lox mice displayed a significant reduction in survival, with all mice being moribund at 10 months of age (p<5). In contrast, Coq6lox/lox mice treated with 2,4-DHB (n=5) showed significantly improved survival, comparable to their untreated Coq6lox/lox and wild type littermates. Histological analysis of Coq6lox/lox kidneys at 10 months demonstrated severe glomerular and tubulointerstitial fibrosis.

Conclusions: Our data demonstrate that 2,4-DHB, an intermediary metabolite of the CoQ10 biosynthesis pathway efficiently ameliorates proteinuria and prevents the development of FSGS as well as foot process effacement in all treated mice (n=5).

Funding: Other NIH Support - DK076683, Government Support - Non-U.S.

TH-PO267

A Genetically Defined RhoA-Regulating Protein Module Elucidates Effects of Steroid Treatment in Steroid-Dependent Nephrotic Syndrome

Friedhelm Hildebrandt, Jia Rao, Jennifer A. Lawton, Weizhen Tan, Eugen Widmer, Svjetlana Lovric, Jillian Kateri Warejko, Daniela A. Braun, Shazia Ashraf, Div of Nephrology, Boston Children’s Hospital, Harvard Medical School, Boston, MA.

Background: Nephrotic syndrome (NS) is categorized into steroid sensitive (SSNS) and steroid resistant forms (SRNS). For SSNS no efficient treatment exists. And mechanisms of steroid action in SSNS are still unknown. We recently identified multiple novel recessive genes as causing NS if mutated: MAGI2, TENC1, DLC1, CDK20, and ITSN1. We showed that DCL1 molecularly interacts with TENC1 and CDK20. Interestingly, the affected individuals had steroid-dependent nephrotic syndrome (SDNS).

Methods: Because the individuals with mutations in these genes shared the clinical phenotype of SDNS, and because DCL1 is a known GTPase activating protein of RhoA/Rac1/Cdc42, and ITSN1 is a known GTPase exchange factor of the same, we hypothesized that the pathogenesis of mutations in these genes involves steroid-dependent dysregulation of RhoA/Rac1/Cdc42 activation. We performed a G-LISA assay to quantitate the active components of RhoA/Rac1/Cdc42 in a HEK293T cells, following knockdown (kd) versus overexpression (oe) of MAGI2, TENC1, DLC1, or CDK20.

Results: No effects were observed for the active Rac1 and Cdc42. However, we found that kd of DCL1 increased active RhoA, while oe of DCL1 decreased active RhoA. Kd and oe of the DCL1 interaction partners MAGI2, TENC1 and CDK20 behaved opposite to the effects of DCL1, revealing a RhoA regulatory cluster of interacting proteins in HEK293T cells.

Conclusions: Our findings for the first time may elucidate cell autonomous podocyte mechanisms of treatment response in SDNS, and may make specific genetic variants of NS amenable to treatment.

Funding: Other NIH Support - DK076683
TH-PO268

Mutation in Human Class II α-Isomerase of Phosphatidylinositol 3-Kinase Cause a Syndrome with Kidney, Bone and Retinal Involvement
Markus Schueler,1 Karl Knap,1 Parisa Westergerling,1 David R. Powell,2 Johanna Stocek,1 Kai-Uwe Eckardt,1 Michael Sean Wiesner,1
1Dept of Nephrology and Hypertension, Friedrich-Alexander Univ of Erlangen-Nuernberg, Erlangen, Germany; 2Lexicon Pharmaceuticals, Inc, TX.

Background: Phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases involved in a large set of biological processes, including membrane receptor signaling, cytoskeletal organization, and endocytic trafficking. PI3KCA2 has been proposed to play an important role in endothelial cells, where it promotes endosomal trafficking and regulation of PtdIns3P levels. Whole exome sequencing (WES) provides a novel means of establishing an etiologic diagnosis. By revealing the causative monogenic mutation, it thereby contributes to our knowledge of the gene function, biological mechanisms and pathways, and will provide important knowledge about disease mechanisms under the pathophysiology.

Methods: In one affected child of consanguineous parents we performed WES to identify the underlying single-gene disease-causing mutation. We then harvested fibroblasts from skin biopsies of the affected individual and healthy control for performing diagnosis. By revealing the causative monogenic mutation, it thereby contributes to our knowledge of the gene function, biological mechanisms and pathways, and will provide important knowledge about disease mechanisms under the pathophysiology.

Results: Through WES we detected a homozygous obligatory splice site mutation (c.1640+1T>G) in the gene PIK3C2J (phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha) in the affected individual. The mutation segregated with the affected status in this family and was absent from healthy controls. The affected individual showed right kidney agenesis and a complex tubulopathy, retinal degeneration with severe and progressive visual impairment, skeletal dysplasia, dental anomalies, brachydactyly and disproportionate short stature. By immunofluorescence studies we demonstrate that PIK3C2J localizes in endosomes, the trans-Golgi network and clathrin-coated vesicles, whereas the mutation of PIK3C2J lacks this. By immunoblotting we show that the mutation alters the phosphorylation status of GSK3beta, a major player of Wnt signaling.

Conclusions: PIK3C2J is critically involved in development and function of the kidney, bone and retina.

TH-PO269

Variant-Prioritization Coupled with Ontology-Based Algorithm Identified Disease-Causing Mutation in a Family with Atypical Hemolytic Uremic Syndrome
Masafumi Goto, Hirofumi Kaneko, Ichiei Narita.

Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare form of thrombotic microangiopathy. Recently, personal genome sequence analysis identified numerous disease-causing variants in aHUS, mainly in complement-related genes. However, variant prioritization tools are needed to effectively discriminate true causative variants from a number of non-related variants, especially in a small family. To dissect causative genes in a family with aHUS, we applied prioritization strategies (pedigree V AAST) coupled with an ontology-based algorithm (Phevor) to whole exome sequencing analysis.

Methods: We carried out an exome sequence analysis of a Japanese multiplex family composed of three patients diagnosed with aHUS in infancy, clustered in a dominant transmission mode. Variants identified by exome sequencing were prioritized by pVAAST, which combines variant frequency data, mutation severity, and conservation into a single score. Then, the prioritized gene list was analyzed in the genome of the affected individual.

Results: Exome sequencing in this family detected a total of 83 heterozygous and 21 homozygous variants. The most severe mutations were identified in the genes PIK3C2J, C3, FHL1, F5, and TFPI. By functional studies we reveal that the NRIP1 altered protein does not translocate to the nucleus, does not interact with the retinoic acid receptor alpha (RARα) and fails to inhibit retinoic acid dependent transcriptional activity. In addition, we show that both NRIP1 expression and its binding to RARα are enhanced in the presence of retinoic acid. By expression and knockdown experiments in Xenopus laevis we confirm an evolutionary conserved role for NRIP1 in retinoic acid signaling.

Conclusions: These data indicate that dominant NRIP1 mutations cause C4AUS by interfering with retinoic acid transcriptional signaling, thus shedding light on the well documented association between abnormal vitamin A levels and renal malformations in humans, and suggest a possible gene environment pathomechanism.

TH-PO271

A Dominant Mutation in NRIP1 Causes Urinary Tract Malformations
Masafumi Goto, Hirofumi Kaneko, Ichiei Narita.

Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease in the first three decades of life. Identification of monogenic mutations that cause CAKUT permits insights into related disease mechanisms.

Methods: We performed whole exome sequencing, transcriptional reporter assay, protein-protein interaction studies, as well as in vivo studies in Xenopus laevis.

Results: We investigated a three-generation Yemenite Jewish family with an autosomal dominant form of CAKUT. By whole exome sequencing, we identified a heterozygous truncating mutation (c.2796delG, p.Trp936*) of the NRIP1 gene in all seven affected members. NRIP1 encodes a nuclear receptor transcriptional co-factor, which directly interacts with the retinoic acid receptors to modulate retinoic acid transcriptional activity. By functional studies we reveal that the NRIP1 altered protein does not translocate to the nucleus, does not interact with retinoic acid receptor alpha (RARα) and fails to inhibit retinoic acid dependent transcriptional activity. In addition, we show that both NRIP1 expression and its binding to RARα, are enhanced in the presence of retinoic acid. By expression and knockdown experiments in Xenopus laevis we confirm an evolutionary conserved role for NRIP1 in retinoic acid signaling.

Conclusions: These data indicate that dominant NRIP1 mutations cause CAKUT by interfering with retinoic acid transcriptional signaling, thus shedding light on the well documented association between abnormal vitamin A levels and renal malformations in humans, and suggest a possible gene environment pathomechanism.

TH-PO272

Misidentification of Dihydroxyadenine Kidney Stones by Conventional Stone Analysis Techniques
Hashifuddin L. Runofsiddoti,1 David S. Goldfarb,2 John Andrew Sayer,1 Mini Michael,1 Runolfrur Palsson,1 Vidur O. Edvardsson,1,2
1Univ of Iceland, Iceland; 2NYU Langone Medical Center; 3Newcastle Univ, United Kingdom; 4Texas Children’s Hospital; 5Landspitali – The National Univ Hospital of Iceland, Iceland.

Background: Adenine phosphoribosyltransferase deficiency (APRTd) is an inherited disorder of purine metabolism that leads to excessive renal excretion of 2,8-dihydroxyadenine (DHA), resulting in kidney stones and crystal nephropathy. Analysis of crystal or kidney stone material using infrared (IR) spectroscopy has been considered diagnostic for APRTd. Recently, we have encountered cases misidentified as DHA stone formers by IR spectroscopy. The objective of this study was to examine the accuracy of stone analysis for identification of DHA kidney stones.

Methods: Records of all 40 patients referred to the APRT Research Group of the Rare Kidney Stone Consortium from 2010 to 2016 were reviewed.

Results: Fifteen patients were referred to our program with the diagnostic program of APRTd based on stone analysis. Seven of these 15 patients did not have APRTd as DHA had been misidentified as a stone component in 2 cases in the US, 2 from the UK, 2 from South Africa, and 1 from Austria. Median age at the time of identification was 50 years old (50-74 years old). IR spectroscopy was the stone analysis technique used in 6 cases, yielding 12-100% (median of 60%) DHA in stone samples from 5 patients, while only trace amounts were found in a stone from 1 individual. X-ray diffraction was applied in one case suggesting 90% DHA.

Conclusions: Our experience demonstrated that the diagnostic program of APRTd based on stone analysis is not reliable. APRTd should be considered a possible gene environment pathomechanism.
None of the 7 patients had APRTd, demonstrated by undetectable DHA in spot urine samples using a novel mass spectrometry assay. The absence of APRTd was further confirmed by APRT enzyme activity measurements in 4 cases and genetic testing in 1 case.

Conclusions: Misidentification of kidney stones as DHA stones using gold standard stone analysis techniques appears to be more common than previously thought. The results of kidney stone analysis are based on human interpretation of different spectra and thus subject to error. The diagnosis of the APRTd should be confirmed by more reliable diagnostic methods, such as enzyme activity measurements or genetic testing.

Funding: NIDDK Support

TH-PO273
Podocyte Hypertrophy and Globotriaosylceramide (GL-3) Accumulation Are Strong Predictors of Podocyte Loss in Enzyme Replacement Therapy Naïve Male Patients with Fabry Disease Behzad Najafian,1 Camilla Tondel,2 Einar Svarstad,3 Michael Maurer.4 1Univ of Washington; 2Haukland Univ; 3Univ of Minnesota.

Background: Podocyte (PC) injury and loss play crucial roles in progressive chronic kidney disease (CKD) in Fabry disease. While PCs accumulate more GL-3 than other renal cells, they are far more resistant to GL-3 clearance following enzyme replacement therapy (ERT). Identifying parameters associated with PC loss may be crucial to halt CKD in Fabry disease. We assessed the relationship between PC GL-3 accumulation and PC number density per glomerulus [Nv(PC/glm)].

Methods: Biopsies from 38 male ERT-naïve Fabry patients aged 33[13-60], median [range], years with GFR 114±45 ml/min/1.73 m² were studied using electron microscopy unbiased stereology, including modified point-sampled intercept method.

Results: By linear regression, age correlated directly with protein creatinine ratio (PCR) (r=0.55, p=0.0001) and inversely with GFR (r=-0.47, p=0.0006). Nv(PC/glm) correlated inversely with mean PC volume (VPC) (r=-0.77, p=0.0001) and total GL-3 inclusion volume/PC [V(Inc/PC)] (r=-0.69, p=0.0001), but not with GL-3 volume fraction [Vv(Inc/PC)] or foot process width (FPW). Using piecewise linear regression analysis, 88% of Nv(PC/glom) was directly correlated with VPC (r=0.91, p<0.0001), with the V(Inc/PC) breakpoint at 1965 um³ and the FPW breakpoint at 5201 um², beyond which the slope of decline in Nv(PC/glom) was markedly increased.

PCR correlated with VPC (r=0.44, p=0.01) and V(Inc/PC) (r=0.40, p=0.02), but not with Vv(Inc/PC) or FPW.

Conclusions: PC enlargement and total GL-3 accumulation are important determinants of PC loss in Fabry disease. The observed V(Inc/PC) and VPC breakpoints suggest thresholds beyond which PC hypertrophy and GL-3 content are associated with marked acceleration of PC loss. Such thresholds may suggest new treatment targets for Fabry nephropathy.

Funding: Other NIH Support - NCATS

TH-PO274
Aging Is Associated with Reduced %Podocytes (Podo), but Not %Parietal Epithelial Cells (PECs) with Fabry Phenotype in Females with Fabry Disease Fu-Pang Chang.1 Michael Maurer.2 Luiz A. Moura,1 Behzad Najafian.3 1Univ of Washington; 2Haukland Univ; 3Univ Federal de São Paulo, Brazil.

Background: In Fabry nephropathy (FN), globotriaosylceramide (GL-3) accumulation in Podo leads to disease progression. In females with FN, due to X-inactivation, the distribution of GL-3 inclusions in Podo is heterogeneous, and related to Podo injury. Recent studies suggest PECs may replace lost Podo. Thus, PECs may be important in pathophysiology of FN. We studied the distribution of Podo and PEC involvement in female Fabry patients, and their relationships to clinical parameters.

Methods: Kidney biopsies from 20 treatment-naïve female Fabry patients (age 20.5 [8-49], median [range]) were studied by electron microscopy. Urine protein excretion (UPE) was estimated by urine protein creatinine ratio (UPCR) (r=12) or total urine protein/day (r=8).

Results: GFR was 96.64±21.01 ml/min/1.73 m². UPE was 61 (0-1150) mg/day. In all 20 biopsies, 51±30% (mean ± SD) of Podo per glomerulus contained no GL-3 inclusions, classified as non-Fabry Podo (NFPO). In 14 biopsies which allowed reliable evaluation, of PECs, 47±31% of PECs per glomerulus had no GL-3 inclusions, classified as non-Fabry PECs (NFPEC). %NFPO per glomerulus (%NFPO/glom) was directly correlated with age (r=0.64, p=0.003), but %NFPEC per glomerulus (%NFPEC/glom) was not. %NFPO/glom and %NFPEC/glom were not correlated. Neither %NFPO/glom nor %NFPEC/glom showed relationships with GFR or UPE. The inter-glomerular variation in %NFPO/glom in a given patient’s biopsy was smaller than %NFPEC/glom.

Conclusions: Direct relationship between age and %NFPEC/glom is suggestive of a survival disadvantage for Podo with Fabry phenotype. The differential relationships of %NFPO/glom and %NFPEC/glom to patients’ age may reflect different regeneration capacity or injury response to GL-3 inclusions in Podo and PECs.

TH-PO275
High Prevalence of Proteinuria and Reduced Renal Function in 14 Adolescents and Young Adults with Antenatal and Classic Bartter Syndrome Martin Könhoff,1 Stefanie Weber,2 Günter Klaus.3 1Univ Children’s Hospital, Dept of Pediatric Nephrology, Philippus-Univ, Marburg, Germany; 2Kuratorium für Heimodialyse, Marburg, Germany.

Background: Antenatal Bartter syndrome (aBS) and classic BS (cBS) are characterized by renal salt wasting resulting in hypokalemia, enhanced production of prostaglandin F2α, renin and aldosterone as well as hypercalciuria in aBS. The long-term outcome of glomerular and tubular function in adolescents and young adults is largely unknown. We here describe extensive follow-up data based on our single center experience with aBS and cBS.

Methods: 14 adolescents and young adults (seven females and males; aBS type I: n=7; aBS type II: n=3; and cBS: n=4), with a mean age of 21.2 years. All subjects were continuously treated with prostaglandin synthesis inhibitors and supplement electrolytes. We analyzed retrospectively endogenous creatinine clearance (CCR), the urinary excretion of electrolytes and protein and 24 h-ABDM.

Results: The average renal excretion of sodium and chloride were 153±75.1 and 185.5± 90.6 mmol/d, respectively. FE Na correlated with systolic day blood pressure SDS (r=0.46, p=0.015). CCR was 81.5 ± 29.9 ml/min/1,73m², ten patients had a CCR<90, three patients (CCR: 26 ± 17, Alb/Crea 130± 120 mg/g), of these, five patients had tubular proteinuria. CCR correlated negatively with proteinuria (r=-0.4, p=0.01). Patients with aBS type I showed the most pronounced renal impairment (CCR: 68± 15, Alb/Crea 290 ± 379 mg/g), followed by patients with aBS type II (CCR: 77± 15, Alb/Crea 171 ± 261 mg/g) and patients with cBS (CCR: 107 ± 44, Alb/Crea 50 ± 40 mg/g). Two patients had increased blood pressure on 24 h-ABDM.

Conclusions: Reduced CCR and proteinuria were present in the majority of patients and clearly exceeded values from two previously published case series describing younger patients (Reinalter et al., 2001; Puricelli et al, 2010). Genotype, chronic renal salt wasting with continuous activation of renin and aldosterone synthesis and the cumulative exposure to prostaglandin synthesis inhibitors may all contribute to this so far unanticipated impairment in renal function.

TH-PO276
Defects in N-Glycosylation of Cubilin Result in Tubular Proteinuria Tomohiro Fujita,1 Ken-Ichiro Miura,2 Akihiko Saito,2 Yutaka Harita.3 1Pediatrics, Graduate School of Medicine, The Univ of Tokyo, Tokyo, Japan; 2Applied Molecular Medicine, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan; 3Pediatric Nephrology, Tokyo Women’ s Medical Univ, Tokyo, Japan.

Background: Mutations of either cubilin (CUBN) or amnionless (AMN) cause low-molecular weight proteinuria and megaloblastic anemia, due to defects in endocytosis through cubilin-amnionless receptor complex (IGS: Imerslund-Gräbeck Syndrome). The pathogenic mechanism of IGS is largely unknown. We found a novel missense G653R mutation of CUBN in a boy with IGS. Renal histology demonstrated that cubilin and amnionless were not targeted to brush border of proximal tubular cells in the patient.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: To analyze the pathogenic mechanism of the mutations found in IGS, we quantitatively determined the membrane targeting of cubilin and amnionless in cultured cell by flow cytometry. We analyzed the effect of mutations causing IGS on glycosylation and membrane targeting of cubilin and amnionless.

Results: While wild-type cubilin and amnionless were interdependently targeted to the cell membrane, G653R and previously reported missense mutations of CUBN inhibited amnionless-dependent glycosylation, membrane expression of cubilin, and amnionless, and endocytosis. Notably, all the previously reported missense mutations of AMN also inhibited cubilin glycosylation, and causes ER retention of amnionless and cubilin. N-linked glycosylation of cubilin did not affect cubilin-amnionless interaction, but was required for transport from ER to Golgi. Mass spectrometric and mutagenesis analysis identified the combination of glycosylations in CUB domain of cubilin which are crucial for surface expression of cubilin and amnionless.

Conclusions: N-glycosylation of cubilin is essential for endocytosis in renal and intestinal epithelial cells, and its defects result in tubular proteinuria.

TH-PO277

Morphological and Immunohistochemical Presentation of Complement Disorders in Native and Transplant Renal Biopsies

Christof Assfanger,1 Martina M. Gegg,1 Zoltan Prohaska,2 Ahmad Altale,3 Gere Sunder-Plasmon,4 Alice Schmidt,1 Renate Kain.1
1Dept of Medicine III, Div of Nephrology and Dialysis, Medical Univ of Vienna, Vienna, Austria; 2IIIrd Dept of Internal Medicine, Research Laboratory, Semmelweis Univ, Budapest, Hungary; 3Clinical Dept of Pathology, Medical Univ of Vienna, Vienna, Austria.

Background: Complement-mediated Thrombotic Microangiopathy (TMA), C3-glomerulonephritis (C3GN) and Dense Deposit Disease (DDD) are diseases of the alternative complement pathway and associated with the same genotypic background. However, the reasons for the different phenotypes remain unexplained.

Methods: We analysed 35 biopsies of 5 patients followed for an average of 14 years. All underwent renal transplantation (KTX) and analysis of morphologic and glomerulonephritis (C3GN) and Dense Deposit Disease (DDD) are diseases of the

Results: We identified 5 patients with complement associated disorders, all of which developed C3GN in the transplants. Treatment followed standard regimens in patients with biopsy proven rejection and 3 patients with persistent TMA received Eculizumab. All patients developed GN with a range of morphological presentation and variable C3d/C4d, no C5b-9, but prominent C3c deposits.

Conclusions: We present 5 patients, all of which developed C3GN after KTX, which indicates a phenotype-switch between complement associated disorders. Neither mutations nor deposition of complement products in renal biopsies allowed to predict presentation or indicate a phenotype-switch, but may be rare as reported however morphological presentation may be influenced by therapies or immunological events in graft rejection.

TH-PO278

Focal Global Glomerulosclerosis Is Common in Dent Disease and Associates with Kidney Function

Xiaoling Wang,1 Franca Anglani,2 Lada Beara Lasic,3 Anila Mehta,1 Lisa E. Vaughan,1 Loren Paola Herrera Hernandez,2 Andrea G. Cogal,3 Steven J. Scheinman,4 Gema Ariceta,2 Lawrence A. Copelovitch,6 Felicity T. Enders,7 Peter C. Harris,2 John C. Lieske.2 Mayo Clinic; 2UCLA; 3TMC; 4U Hospital Vall d’Hebron; 5U Penn.

Background: Dent disease (DD) is a rare X-linked disorder characterized by low molecular weight proteinuria and chronic kidney disease. However, focal global glomerulosclerosis (FSGS) was recently reported in several patients.

Methods: To characterize pathological findings in a cross section of DD patients, renal pathology reports and slides (where available) were obtained from 30 male patients in eight countries who had undergone clinically indicated renal biopsy.

Results: Median (25th, 75th) age at biopsy was 75 (51, 19) years with an estimated glomerular filtration rate (eGFR) of 69 (44, 94) ml/min/1.73m2 and a 24hr protein excretion of 2000 (1325, 2936) mg. A repeat biopsy for steroid-resistant proteinuria was performed in 13% (4/30) of the patients. Prominent histological findings included FSGS in 83% of patients (25/30) affecting 16% ± 19% glomeruli, mild segmental foot process effacement in 57% (13/23), focal interstitial fibrosis in 60% (18/30), interstitial lymphocytic infiltration in 53% (16/30) and tubular damage in 70% (21/30).

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

Thrombotic Microangiopathy: A Novel Presentation for TREX1 Mutation

Ashima Gulati,1 Gabriel M. Danovich,2 Margaret J. Bia,1 Allen E. Bale,3 Gilbert W. Moeckel,1 Stefan Somlo,1 Nerea K. Dahl.1 Yale Univ School of Medicine, CT. 2David Geffen School of Medicine at UCLA, CA.

Background: Thrombotic microangiopathy (TMA) is a systemic condition with prediction for the kidney. Genetic determinants have been identified mainly related to complement dysregulation. Since a significant proportion of TMA remains etiologically undefined, exome sequencing may uncover novel genotype correlations.

Methods: Genomic DNA from proband with familial TMA was subjected to exome sequencing and variant filtering using bioinformatics pipeline and data analyzed on a priori suggestion for autosomal dominant TMA.

Results: Proband is a Caucasian male (5th decade) with persistent proteinuria (1g/d) and gradual serum creatinine elevation during 3-yr follow up (eGFR 48 ml/min/1.73m2) with controlled hypertension. He had no neurologic or visual symptoms and unremarkable physical examination. Kidney biopsy (fig.A) showed TMA with duplication of glomerular basement membrane. Family history is significant for kidney transplant in deceased father; retinal hemorrhage and chronic kidney disease with TMA in his brother (fig.B). CBC, CFI, C3, C4, antiphospholipid panel were unremarkable. Proband exome sequencing revealed a heterozygous 4 bp duplication in carboxyl terminus of TREX1 (Three Prime Repair Exonuclease) resulting in a non-truncating frame shift (NM_033629:exon1: c.828_831dupGAAG:p.D278Efs*48).

Conclusions: C-terminal mutations in TREX1 known to alter its subcellular localization while preserving exonuclease activity cause microangiopathy predominantly of retina and brain. We report an exclusive renal phenotype of TMA and chronic kidney disease with mutation in TREX1 in absence of symptomatic multisystem microangiopathy. While awaiting familial genetic testing, we emphasize the clinical importance of recognizing TREX1 mutation as a cause of non complement mediated TMA and an opportunity for delineating novel TMA pathophysiology.
Clinical Follow-Up of Female Fabry Disease Patients Receiving Enzyme Replacement Therapy for up to 2 Years

Evelyne C. Barreto,1,2 Tanmy Verralhna Rocha Almeida,1 Bruna Fernanda de Castro,1 Felipe T.M. Novak,1 Lidio Derossi,1 Caroline de Paula Cassanego,1 Mariza G. Rosa,1 Gilson Biajini,1 Pontificia Univ Católica do Paraná; 2Univ Federal do Paraná; 3Human Genetics, Univ Hospital Cologne, Cologne, Germany.

Proteogenomic Analysis of a Disease-Causing Actinin-4 Mutation

(2500mg/24h) at baseline. Kidney biopsy performed before ERT in a patient without overt Renal function remained stable for most patients at the two different time points of follow after 5 yrs (median) of the diagnosis. All patients received antiproteinuric medication.

Results: Seventeen female patients (age: 29.1 ± 16.2 years) were included. The median age at diagnosis was 21 (13-65) years. The most frequent clinical manifestations were as follows: left ventricular hypertrophy (59%), septal hypertrophy (29%), cardiac fibrosis (35%), white matter lesion (43%), acroparesthesia (59%) and nephropathy (59%). 6/17 follows: left ventricular hypertrophy (59%), septal hypertrophy (29%), cardiac fibrosis (35%), white matter lesion (43%), acroparesthesia (59%) and nephropathy (59%). 6/17

Methods: Proteogenomic analysis was performed homogenously. We performed whole exome sequencing (WES) to identify novel disease-causing genes in a worldwide cohort of ~2,000 individuals with severe disease.

Results: Twenty-six women (median age: 29.1 ± 16.2 years) were included. The median age at diagnosis was 21 (13-65) years. The most frequent clinical manifestations were as follows: left ventricular hypertrophy (59%), septal hypertrophy (29%), cardiac fibrosis (35%), white matter lesion (43%), acroparesthesia (59%) and nephropathy (59%). 6/17

Conclusions: Proteogenomic analysis is an efficient method to identify novel disease-causing genes and mechanisms of treatment response in NS and will make specific genetic variants of NS amenable to treatment.

Funding: Other NIH Support - DK076683

Proteogenomic Analysis of a Disease-Causing Actinin-4 Mutation

Markus M. Rinscheg,1 Malte P. Bartram,1 Caroline Pahnemeyer,1 Thomas Benzing,1 Bodo B. Beck,2 Internal Medicine, Univ Hospital Cologne, Cologne, Germany; 2Human Genetics, Univ Hospital Cologne, Cologne, Germany.

Background: In children, genetic diseases are the most important cause for end-stage renal disease. Mutations in the ACTN4 gene are a rare cause of autosomal dominant familial focal segmental glomerulosclerosis (FSGS). We here identified a novel, disease-causing ACTN4 mutation (p.G195D, de novo) in a sporadic case of childhood FSGS.

Methods: We utilized next generation sequencing to identify a novel ACTN4 mutation in a sporadic case of childhood FSGS. In vitro studies (actin sedimentation assay, immunofluorescence analyses and migration assays) were used to judge actin cytoskeleton function. Primary renal epithelial cells of the patient were subjected to proteomic analysis. Results were complemented with interactomic and ubiquitomic analyses of ACTN4 G195D in vitro.

Results: In vitro studies demonstrated that ACTN4 G195D had a detrimental effect on actin cytoskeleton function. Proteome analysis by quantitative mass spectrometry of patient-derived urinary epithelial cells indicated that ACTN4 levels were significantly decreased when compared with healthy controls. By resolving the allele bearing the mutated residue on a protein level, we demonstrated that the mutant protein is less abundant when compared with the wild-type protein. Molecular dynamics simulations revealed a decrease in ACTN4 CH-domain stability upon mutation. Further analyses revealed that the decreased stability of p.G195D is associated with increased ubiquitination in the vicinity of the mutation site. We next defined the ACTN4 interactome, which was predominantly composed of LIM domain proteins. Interestingly, this entire group of proteins, including several ACTN4 interactors, was globally decreased in the patient-derived cells. Further ACTN4 mutations may demonstrate a similar phenotype.

Conclusions: Our findings advance the understanding of dominant effects exerted by ACTN4 mutations in FSGS. This study illustrates the potential of genomics and complementary, high-resolution proteomics analyses to study the pathogenicity of rare gene variants ("proteomendeliomics").

Funding: Government Support - Non-U.S.

Recessive Mutations in 5 Novel Genes of Interaction Partners Elucidate Steroid Sensitivity in Nephrotic Syndrome

Shazia Ashraf,1,2 Jia Riao,1 Jennifer A. Lawson,1 Weizhen Tan,1 Eugen Widmeier,1 Svjetlana Lovric,1 Jillian Kateri Warejko,1 Daniella A. Braun,1 Hoon Yung Gee,3 Mohamad Aman Jairajpuri,1 Martin Zenker,1 Friedhelm Hildebrandt,1 and with

Conclusions: Idiopathic nephrotic syndrome is a common pediatric kidney disease. 80% of all cases are steroid sensitive (SSNS). First insights into the pathogenesis of steroid-resistant nephrotic syndrome (SRNS) came from identification of ~30 single-gene causes. However, mechanisms of treatment sensitivity vs. resistance remain unknown.

Funding: DK076683

Steroid Sensitivity in Nephrotic Syndrome

Deborah P. M. van den Berg,1,2 Kristina Kim,3 C. K. Ishola,4 Amber J. McGowan,5 Bonnie M. Horn,6,7 Paul A. Clendenon,8,9 Tomasz F. Kloczewiak,10,11 Ashraf,1,2 Jia Riao,1 Jennifer A. Lawson,1 Weizhen Tan,1 Eugen Widmeier,1 Svjetlana Lovric,1 Jillian Kateri Warejko,1 Daniella A. Braun,1 Hoon Yung Gee,3 Mohamad Aman Jairajpuri,1 Martin Zenker,1 Friedhelm Hildebrandt,1

Background: Idiopathic nephrotic syndrome is a common pediatric kidney disease. 80% of all cases are steroid sensitive (SSNS). First insights into the pathogenesis of steroid-resistant nephrotic syndrome (SRNS) came from identification of ~30 single-gene causes. However, mechanisms of treatment sensitivity vs. resistance remain unknown.

Funding: DK076683

IgA Glomerulonephritis Caused by ENTPD3 Mutations and with Drusen Suggesting Low Grade Complement Activation

Judith A. Savige,1 Terence L. Kirley,2 Deb J. Colville,1 1Medicine and Nephrology, The Univ Dept of Medicine, Melbourne, VIC, Australia; 2Dept of Pharmacology and Cell Biophysics, Univ of Cincinnati College of Medicine, Cincinnati, OH; 3The Univ of Queensland, QLD, Australia.

Background: IgA disease is the commonest glomerulonephritis worldwide affecting 1% of the population, one third of whom go on to develop end-stage renal failure. The aim of this study was to use whole exome sequencing and bioinformatics analysis in a family with biopsy-proven IgA glomerulonephritis to identify the mutant gene.

Methods: Nine members of the family provided DNA that underwent whole exome sequencing (Ogenetics, Atlanta). The results were analysed for variants that segregated with affected status in an in-house bioinformatics pipeline. Pathogenicity was then confirmed with protein modelling experiments and functional assays using cells from family members.

Results: The whole exome sequencing demonstrated a missense mutation (R143C, rs360719510) in the ectonucleoside triphosphate diphosphohydrolase 3 (ENTPD3) gene that segregated with disease in this family. ENTP3 is important in purinergic signalling, with roles in phagocytosis, inflammation and apoptosis. The R143C variant is very rare (0.0001%, www.exac.broadinstitute.org). It affected enzyme function in modelling experiments, and in an in vitro transfection system. Affected peripheral blood monocytes from family members with the R143C mutation also demonstrated reduced enzyme activity and abnormal phagocytosis. We identified a further pathogenic variant (rs34268068, R264Q) that resulted in the same phagocytic defects in an unrelated individual with apparently sporadic IgA disease.

Conclusions: These results indicate a novel gene locus for IgA glomerulonephritis, and that some apparently sporadic cases also have a genetic basis. ENTP3 mutations impair phagocytosis which potentially contributes to the development of mesangial deposits. This represents the second gene identified in IgA glomerulonephritis, and the corresponding proteins belong to interacting pathways.

Funding: Other NIH Support - DK076683

Retinal Temporal Thinning Is More Pronounced in Males with X-linked Alport Syndrome and Early Onset Renal Failure

Judith A. Savige,1 Hong Chen,1 Andrew S. Talbot, Deb J. Colville, Medicine and Nephrology, The Univ of Melbourne (NH and NH), Melbourne, VIC, Australia.

Background: Alport syndrome is an inherited disease characterised by renal failure, hearing loss, and ocular abnormalities, including retinal temporal thinning. This study examined retinal thinning in Alport syndrome.

Methods: Alport syndrome was diagnosed on renal biopsy or genetic testing, and the mode of inheritance was determined by genetic testing. Age at end-stage renal failure and current eGFR were recorded. Retinal thinning was determined from optical coherence tomography (OCT), using the formula of temporal thickness index (TTI) = (nasal – temporal thickness) ÷ nasal thickness x 100% compared with the normal range for age group (Ahmed, 2013). Statistical analysis was performed using Stata (StataCorp).

Results: By WES and high-throughput sequence analysis, in families who mostly had steroid-dependent NS (SDNS), we identified multiple recessive mutations in the following genes: MAG2, TENC1, DCL1, CDK20, and ITSN1 in 2, 5, 4, 1, and 3 unrelated families, respectively. Knockout mice of Mag2 or Tenc1 have been previously shown to develop NS. By Co-IP, we now show that MAG2 interacts with TENC1 and DCL1 and these interactions are abrogated by the two MAG2 mutants. Knockdown of MAG2, DCL1 or ITSN1 in cultured podocytes exhibited a decreased podocyte migration rate. Immunofluorescence studies showed that TENC1 and DCL1 colocalize with phosphotyrosine at focal adhesions in human podocytes. We discover CDK20 as a novel renal regulator of DCL1. In addition, we discover ITSN1 as a novel GEF for Cdc42, relevant for podocyte function.

Conclusions: Thus, by identification of 5 novel monogenic causes of NS we define a functional network of proteins at the intersection between steroid sensitivity vs. steroid resistance of NS. These findings for the first time may elucidate cell autonomous podocytic mechanisms of treatment response in NS and will make specific genetic variants of NS amenable to treatment.

Funding: Other NIH Support - DK076683

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: Temporal thickness index was 11.47 ± 5.3% in males (n=20) and 7.51 ± 1.79% in females (n=28) with X-linked-nephropathy; 14.5 ± 1.36% (n=51) in recessive disease; 7.03 ± 2.12% (n=12) in Thin membrane nephropathy; and 6.34 ± 2.53% (n=12) in other causes of renal failure. In X-linked disease, 15 males (75%) and 19 females (68%) had retinal thinning, and thinning was more pronounced in males (p<0.01), and, in males, correlated with early onset renal failure (p<0.01). Thinning did not correlate with GFR in females. (R² = 0.016). The degree of thinning did not distinguish X-linked disease in women from Thin basement membrane nephropathy. Overall the sensitivity of retinal thinning for Alport syndrome was 72% and specificity was 58%.

Conclusions: The difference in retinal thinning in males and females with X-linked Alport syndrome and renal failure suggests that the loss of the collagen IV α5 chain from affected membranes contributes to renal failure in men, but that there is a further non-genetic contribution to renal deterioration in women such as hypertension.

Funding: Clinical Revenue Support

TH-PO285

Function of Focal Segmental Glomerulosclerosis Disease Protein Inverted Form 2 (INP2) in Podocytes — Baijali Karthick Subramanian,1,2 Paul Yan,1 Johannes S. Schlondorff,1,2 Martin R. Pollok,2 Div of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; Harvard Medical School, Boston, MA.

Background: Mutations in Inverted form 2 (INP2) gene cause an autosomal dominant human kidney disease characterized by focal segmental glomerulosclerosis (FSGS) with or without Charcot-Marie-Tooth disease. Aberration in actin dynamics are manifested due to pathogenic mutations in vitro and have been hypothesized to play a major role in INP2 mediated FSGS. In addition, recent studies with a human pathogenic R218Q knockin mutation in INP2 expressed in podocytes recapitulated FSGS found in human patients. These studies push forward our understanding of the role of actin cytoskeleton in podocytes. In this study, we aimed to elucidate the role of INP2 in podocytes in vitro and in vivo.

Methods: Human podocyte specific INP2 splice variant expressions were analyzed both by RT-PCR and Immunoblottting. CRISPR edited INP2 knockout cells were generated and evaluated for changes in cytoskeleton and lipid raft trafficking using migration assays.

Results: Splice variant analysis of INP2 in human podocytes showed the expression of INP2-CAAX isoform (NCBI ID: NM_022489.3) and a short splice isoform corresponding to a region from N-terminus exon 1 to exon 5 (NCBI ID: NM_023714.2). Unlike in normal cells, CRISPR edited INP2 knockout podocytes lacking these isoforms exhibited polypodium, polyglutamylated tubulin and cortactin structure defects in the lamellipodium region during migration. In addition, lipid raft trafficking, an actin and polyglutamylated tubulin structure dependent process, as measured through GM1 marker also exhibited defects in INP2 knockout podocytes.

Conclusions: INP2 functions in podocytes are associated with the regulation of podocyte cytoskeleton and lipid raft trafficking. Further understanding of INP2 function in these processes and their relation to slit diaphragm proteins would provide the critical mechanistic insights into INP2 associated FSGS.

Funding: NIDDK Support

TH-PO286

The Acadian Variant of Fanconi Syndrome Is Caused by Mitochondrial Respiratory Chain Complex 1 Deficiency due to a Non-Coding Mutation in NADH Dehydrogenase Complex 1 Assembly Factor 6 (NDUFAF6) — Anthony J. Bleyer,1 Yves Thibault,2 Philip D. Accott,3 Stanislav Kmoch.1

1Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC; 2Section on Nephrology, Dr. Georges L Dumont Univ Hospital Centre, Moncton, New Brunswick, Canada; 3Section of Pediatric Nephrology, Dalhousie Univ, Halifax, NS, Canada; 4Inst for Inherited Metabolic Disorders, First Faculty of Medicine, Charles Univ, Prague, Czech Republic.

Background: The Acadian Variant of Fanconi Syndrome (AVFS) occurs in the Acadian population of Canada and is characterized by autosomal recessive inheritance of Fanconi syndrome and progressive CKD with ESRD by age 21 and 41. 

Methods: 12 individuals with AVFS were identified and phenotyped. Fibroblasts were obtained from a skin biopsy of an affected patient. Whole exome sequencing, homozygosity mapping, whole genome sequencing (WGS), and Sanger sequencing were performed. Additional whole-exome sequencing identified a region on chromosome 8 (chr8:90958427-90960579) that was homozygous in 3 affected but not present in one unaffected family member. Using WGS, we identified one ultra-rare noncoding variant, chr8:9046914T>C in the gene NDUFAF6 that was homozygous in the 9 affected individuals, whereas 13 healthy siblings were either heterozygotes or lacked the mutant allele. NDUFAF6 encodes assembly factor 6 of the NADH dehydrogenase (ubiquinone) complex (1NDUFAF6). This variant is located in intron 2. Mutation interpretation software predicted that the c.298-768 T>C nucleotide change would create a novel splice acceptor site. Whole blot analysis of affected and control fibroblast skin fibroblasts revealed loss of the mitochondrial NDUFAF6 isoform V-1 in affected fibroblasts, while the NDUF AF6 isoform V-2 was reduced but present in the cytoplasmic fraction. Affected fibroblasts had defects in mitochondrial respiration and complex 1 biosynthesis that corrected with NDUFAF6 cDNA transfection. All affected individuals have a homozygous mutation.

Conclusions: AVFS is caused by a mutation in NDUFAF6 that results in mitochondrial respiratory chain complex 1 deficiency. Progressive pulmonary fibrosis occurs in all affected individuals.

Funding: Clinical Revenue Support

TH-PO287

Prevalence of UMOD and MUC1 Mutations in Families with Autosomal Dominant Tubulo-Interstitial Kidney Disease — Anthony J. Bleyer,1 Kendrah O. Kidd,1 Anna Greka,2 Stanislav Kmoch.1

1Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC; 2Broad Inst of Harvard-MIT, Harvard Medical School, Boston, MA; 3First Faculty of Medicine, Charles Univ, Prague, Czech Republic.

Background: Mutations in UMOD, MUC1, REN, and HNF1beta genes are known causes of autosomal dominant tubulo-interstitial kidney disease (ADTKD). We analyzed the relative prevalence of these conditions in ADTKD.

Methods: Since 1996 we have been referred 698 families. We suspected ADTKD in 446 of these families and were able to obtain 2076 DNA samples on 1702 individuals from 308 families. These families underwent analysis for UMOD, MUC1, REN, and HNF1beta mutations. We also obtained information regarding a family history of gout. UMOD mutation analysis was performed at Athena Diagnostics, Worcester, MA, or the First Faculty of Medicine, Charles University, Prague, Czech Republic. Genetic analysis for a cytosine duplication in the variable number of tandem repeat region of the MUC1 gene was performed at the Broad Institute, Cambridge, MA. Other mutational analyses were performed at Charles University.

Results: Of the 308 families, 140 (45.5%) had UMOD mutations, 59 (19.2%) MUC1 mutations, 113 (3.7%) REN mutations, one family (0.3%) had an SEC64L1 mutation and one (0.3%) a hepatocyte nuclear factor one beta mutation. 86 of 140 families with UMOD mutations (62%) had a strong family history of gout, and 21 of 59 (36%) families with MUC1 mutations had a strong history of gout. All 11 REN families had a history of gout. We also performed mutational analysis in 23 individuals with tubulo-interstitial kidney disease that was discordant for a family history of gout and no family history of kidney disease; one individual (4.3%) was found to have a MUC1 mutation, while no mutations were found in the other individuals.

Conclusions: UMOD and MUC1 mutations make up the majority of mutations causing autosomal dominant tubulo-interstitial kidney disease, though the cause of inherited kidney disease remains unclear in a number of families. Gout is more prevalent in UMOD families, but can be seen in both disorders. Patients with tubulo-interstitial kidney disease and no family history of ADTKD rarely are found to have a UMOD or MUC1 mutation.

Funding: NIDDK Support, Private Foundation Support

TH-PO288

The Genetic and Phenotypic Spectrum of DGKE Nephropathy — Mathieu Lemare,1 Karoliz Azukaitis,2 Eva Simkova,2 Baerbel Lange-Sperandio,2 Anuradha A. Gajjar,2 Haie Il Cheong,3 Zoltan Prohaszka,4 Veronique Fremeaux-Bacchi,2 Franz S. Schefer.1

1Nephrology Div & Cell Biology Program, Univ of Toronto, Toronto, ON, Canada; 2Dept of Paediatrics, Seoul National Univ, Seoul, Korea; 3Dept of Internal Medicine, Semmelweis Univ, Budapest, Hungary; 4Dept of Immunology, Hôpital Européen Georges-Pompidou, Paris, France; 5Div of Paediatric Nephrology, Heidelberg Univ Hospital, Heidelberg, Germany.

Background: Diacylglycerol kinase e (DGKE) is a recently discovered gene that causes a novel form of glomerulopathy. Our objective is to combine data from 9 new cases with previously published reports to gain insights into the phenotype and natural history of DGKE nephropathy.

Methods: Genetic testing was done in certfified laboratories. Previously reported cases were identified with PubMed search. Time to ESRD was assessed by Kaplan-Meier analysis.

Results: We present the clinical characteristics for 9 patients from 8 unrelated kindreds. Novel disease-causing mutations were found in 23 individuals with tubulo-interstitial kidney disease. DGKE mutations make up the majority of mutations causing autosomal dominant tubulo-interstitial kidney disease, though the cause of inherited kidney disease remains unclear in a number of families. Gout is more prevalent in UMOD families, but can be seen in both disorders. Patients with tubulo-interstitial kidney disease and no family history of ADTKD rarely are found to have a UMOD or MUC1 mutation.

Funding: NIDDK Support, Private Foundation Support

TH-PO289

Abstract Withdrawn
TH-PO290

Acute and Stable CRISPR/Cas9 Zebrafish Models of KEOPS Protein Defects Recapitulate Microcephaly of Galloway-Mowat Syndrome Tillman Jobst-Schwan, 1 Johanna Magdalena M. Schmidt, 2 David Schapiro, 1 Daniela A. Braun, 2 Corinne Antignac, 2 Friedhelm Hildebrandt. 1

1. Div of Nephrology, Boston Children’s Hospital, Boston, MA; 2Imagine Inst, Univ Paris Descartes, Sorbonne Paris Cité, Paris, France.

Background: Galloway-Mowat syndrome (GMS) is a severe neurorenal disorder that combines nephrotic syndrome with microcephaly. We performed whole exome sequencing and homozygosity mapping on a cohort of GMS patients and identified in a total of 31 families recessive missense mutations in the 4 genes LAGE3, OSGEP, TP53RK and TPRKR which constitute the evolutionary conserved KEOPS complex. To study the pathogenesis of this newly defined disease entity, we generated zebrafish animal models.

Methods: We used CRISPR/Cas9 to develop an acute knockdown (KD) approach based on injections of multiple guide RNAs to study larval-onset developmental phenotypes for the zebrafish orthologues ogxeg, tp53rk and tpkrh. Also by CRISPR/Cas9, we generated stable knockout (KO) zebrafish lines for ogxeg and tpkrh. Survival curves were generated by monitoring larvae twice a day until reaching a steady state. The microcephaly phenotype was determined by measuring the head diameter to body length ratio (HD/BL-R).

Results: All gene specific groups in the acute KD show a significant reduction of HD/BL-R and long term survival compared to scrambled and uninjected controls for ogxeg, tp53rk and tpkrh. Immunoblotting shows efficient KD of all 3 proteins in protein extracts from pooled zebrafish larvae. DNA damage response (DDR) is induced in the ogxeg group compared to controls. Stable zebrafish KO lines reproduce the microcephaly phenotype for ogxeg and tpkrh. No larval homozygous for truncating mutations survived for more than 15 days.

Conclusions: CRISPR/Cas9 zebrafish models of KEOPS protein defects partially reflect the human disease phenotype in GMS patients, including microcephaly and early mortality. Early death in zebrafish may mask a nephrotic phenotype. Acute CRISPR/Cas9 KD reproduces the early phenotype in stable KO lines and provides a viable alternative to morpholino KO. Our zebrafish models implicate DDR in the pathogenesis of KEOPS related GMS.

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

TH-PO291

“Humanize” Zebrafish to Model Nephrotic Syndrome Weinib Zhou, Mi-Sun Lee, Sulochana Devi. Pediatrics and Communicable Diseases, Univ of Michigan, Ann Arbor, MI.

Background: Nephrotic syndrome (NS) is a disease characterized by proteinuria caused by disruption of the glomerular filtration barrier (GFB). The NPHS1 gene encodes NEPHRIN, a protein component of the interpodocyte-spanning slit diaphragm essential for the normal GFB. Our objective is to study the function of nephrin mutations in vivo and model NS in zebrafish.

Methods: Zebrafish nphs1 mutants were made using CRISPR targeted to exon 2 of nphs1. nphs1 heterozygotes were crossed to obtain nphs1 homozygotes for morphological and histological analyses. The pathogenic human NPHS1 mutations were introduced into zebrafish nphs1 and specifically expressed in the podocytes of zebrafish.

Results: We have established two zebrafish nphs1 mutant lines carrying 5 bp or 28 bp deletion that leads to ORF shifts and hence a premature stop-codon. Different from a previous report that morpholino-mediated knockdown of nphs1 in zebrafish resulted in pericardial edema at 4 days post fertilization (dpf), these mutants did not show any morphological abnormality until after 5 dpf, when periorbital edema (POE) (similar to the phenotype seen in children with NS) was observed. The edematous phenotype become progressively severe and led to whole-body edema and lethality within two weeks of age. We generated transgenic fish expressing wild-type zebrafish nphs1 in podocytes to rescue the edematous phenotype. We also generated transgenic fish to model two new NPHS1 mutations discovered in NS patients (p.Asp105Asn and p.Tyr398Cys) to demonstrate their functional consequences in vivo.

Conclusions: The zebrafish nphs1 mutants generated by CRISPR genome editing avoid the possible off-target effect by morpholino-mediated knockdown and thus demonstrate a more reliable and convincing nephrotic phenotype for zebrafish, which is consistent with that of the zebrafish model of inducible podocyte injury previously published by us. Given the efficiency of generating transgenic zebrafish, our new zebrafish model is potentially a useful platform to perform functional studies of pathogenic alleles for nphs1 and other genes related to podocyte diseases. The “humanized” zebrafish model of NS will be used to screen for therapeutic compounds for this disease.

Funding: NIDDK Support

TH-PO292

OSGEP and TP53RK, Two Novel Monogenic Causes of Steroid Resistant Nephrotic Syndrome, Interact with Components of the ARP2/3 Complex and Regulate Cell Migration David Schapiro, 1 Daniela A. Braun, 1 Jennifer A. Lawson, 1 Jia Rao, 1 Geraldine Moller, 2 Olivier Gibrilouvi, 2 Christelle Arrondel, 1,2 Weizhen Tan, 1 Tilman Jobst-Schwan, 1 Olivia Boyer, 1 Johanna Magdalena M. Schmidt, 1 Svjetlana Lovric, 3 Shazia Ashraf, 1 Shirley Shril, 1 Martin Zonker, 2 Corinne Antignac, 2 Friedhelm Hildebrandt. 1

1. Div of Nephrology, Boston Children’s Hospital, Boston, MA; 2INSERM, Laboratory of Hereditary Kidney Diseases, Paris, France; 3Univ Paris Descartes, Sorbonne Paris Cité, Imagine Inst, Paris, France; 4Inst of Human Genetics, Univ Hospital of Magdeburg, Magdeburg, Germany.

Background: Steroid resistant nephrotic syndrome (SRNS), an inherited disease of the renal glomerular filter, is one of the most frequent causes of end-stage renal disease in childhood. We have recently identified mutations of OSGEP and TP53RK, two components of the highly conserved KEOPS complex, as novel monogenic causes of SRNS and microcephaly in humans. The role of the KEOPS complex in higher organisms is not well understood.

Methods: We generated human podocyte cell lines with stable knockdown of OSGEP and TP53RK, and examined the effect of loss-of-function of these genes on cytoskeletal architecture and cell migration using videomicroscopy.

Results: We show that knockdown of OSGEP and TP53RK impairs cell migration as well as lamellipodia formation in immortalized human podocytes. Both proteins show distinct localization to lamellipodia and co-localize with components of ARP2/3 complex in this compartment. Upon overexpression, OSGEP and TP53RK interact with four proteins of the ARP2/3 complex, which was confirmed with half-endogenous CoIP.

Conclusions: We have recently identified mutations of OSGEP and TP53RK as novel monogenic causes of SRNS. Here, we show that OSGEP and TP53RK interact with components of the ARP2/3 complex and that knockdown of these genes impairs cell migration, a well-established surrogate phenotype of SRNS. We thus show for the first time that the KEOPS complex may regulate cytoskeletal architecture and cell migration via ARP2/3 in human podocytes and that this might represent the pathogenic link between OSGEP and TP53RK mutations and SRNS in humans.

Funding: NIDDK Support

TH-PO293

AVIL Mutations Are a Novel Cause of Steroid-Resistant Nephrotic Syndrome Jin Rao, 1 Shazia Ashraf, 1 Weizhen Tan, 1 Amelie van der Ven, 1 Svjetlana Lovric, 1 Eugen Widmeier, 1 Tobias F. Hermle, 1 Daniela A. Braun, 1 Heon Yung Gee, 1 Kristzina Feher, 1 Mohan Shenoy, 1 Vincent Tse, 1 Martin Bald, 1 Jose C. Martins, 2 Friedhelm Hildebrandt. 1

1. Div of Nephrology, Boston Children’s Hospital, Harvard Medical School, Boston, MA; 2Dept of Pediatric Nephrology, NMR and Structural Analysis Group, Univ of Gent, Krijlsga, Belgium; 3Royal Manchester Children’s Hospital, Manchester, United Kingdom; 4Great North Children’s Hospital, Newcastle, United Kingdom; 5Inst of Pathology, Univ Hospital Hamburg-Eppendorf, Stuttgart, Germany.

Background: Steroid resistant nephrotic syndrome (SRNS) is the second most frequent cause of end-stage renal disease in the first 3 decades of life. Identification of single-gene causes of SRNS has furthered the understanding of its pathogenesis.

Methods: We combined homozygosity mapping with whole exome sequencing (WES) in 100 families with SRNS. To identify additional mutations, we screened a cohort of ~800 individuals with SRNS by microfluidic multiplex PCR and next generation sequencing.

Results: By WES and next generation sequencing, we identified 4 recessive mutations of the avil (AVIL) gene in three unrelated families with SRNS. A homozygous missense mutation in AVIL was found in an individual of consanguineous parents with SRNS, deafness, cataracts, microcephaly, mental retardation. The other two individuals had compound heterozygous mutations in AVIL. AVIL is a member of the gelsolin superfamily of actin binding proteins with 6 gelsolin domains. We show that AVIL localizes to WT1 positive podocytes in rat kidney. Molecular dynamics simulations with enhanced sampling for changes of AVIL indicate that the two missense mutant alleles potentially influence the structure and therefore the function of AVIL. In human podocytes the truncating mutant allele of AVIL caused mislocalization of F-actin. We identified PLCγ1 and ARP2/3 as new interaction partners of avil which regulate podocyte migration through the EGF-induced DAG signal pathway.

Conclusions: We identified recessive mutations of AVIL as a novel monogenic cause of SRNS. Further genetic and functional studies will shed light on the pathogenic pathway involved.
TH-PO294

Mutations in Genes Encoding Members of the KEOPS Complex Are a Novel Cause of Nephrotic Syndrome with Microcephaly
Daniela A. Braun,1 Jia Rao,1 Geraldine Mollet,2,3 Olivier Gribouval,2,3 David Schapiro,2 Christelle Arrondel,2,3 Weiwen Tan,4 Tilman Jost-Buchan,5 Olivia Boyer,5 Johanna Magdalena M. Schmidt,1 Jennifer A. Lawson,5 Svjetlana Lovric,1 Sharia Asfaha,1 Shirlee Shiril,1 Martin Zenker,1 Corinne Amigou,1 Friedrich Hildebrandt.1
1Nephrology, Boston Children’s Hospital, Boston, MA; 2Laboratory of Hereditary Kidney Diseases, INSERM, Paris, France; 3Imagine Inst, Univ Paris Descartes, Paris, France; 4Inst of Human Genetics, Univ Hospital of Magdeburg, Magdeburg, Germany.

Background: Galloway-Mowat syndrome (GMS) is an autosomal-recessive disorder that manifests with steroid-resistant nephrotic syndrome (SRNS) and severe developmental anomalies of the central nervous system. So far, mutations in the gene WDR73 are the only identified monogenic disease cause.

Methods: To identify novel monogenic causes of GMS, we performed whole exome sequencing, homoygosity mapping, and targeted exon sequencing. To investigate molecular mechanisms of 4 newly identified GMS genes in vitro, we generated immortalized human podocyte cell lines with stable knockdown of the genes of interest.

Results: By next-generation sequencing, we identified mutations of the genes LAGE3, OSGEP, TP53RK, and TPRKB that encode proteins of the evolutionary highly conserved KEOPS complex (Kinase, Endopeptidase and Other Proteins of Small size) in 31 families with microcephaly and childhood-onset nephrotic syndrome. We show that knockdown of OSGEP TP53RK, and TPRKB results in severe proliferation defects, and upregulation of the CDK inhibitor p21 in human podocytes. To confirm pathogenicity of the identified alleles, we show that wildtype but not mutant constructs rescue the proliferation deficiency. Furthermore, knockdown of OSGEP TP53RK, and TPRKB increased phosphorylation of hTAX as an indicator of activated DNA damage response signaling, and ultimately resulted in apoptotic cell death.

Conclusions: We here identified recessive mutations of all four members of the KEOPS complex (LAGE3, OSGEP, TP53RK, and TPRKB) in patients with severe developmental anomalies and SRNS. We provide evidence that the disease phenotype is caused by defects in cell proliferation, accumulation of DNA damage, and induction of apoptosis in human podocytes.

Funding: NIDDK Support

TH-PO295

Applying the Drosophila Garland Cell Nephrocyte to Model Mechanisms of Monogenic Forms of Human Nephrotic Syndrome
Tobias F. Hermlle, Daniela A. Braun, Friedhelm Hildebrandt. Nephrology, Boston Children’s Hospital/Harvard Medical School, Boston, MA.

Background: Steroid-resistant nephrotic syndrome (SRNS) is characterized by podocyte dysfunction. The Drosophila garland cell nephrocyte (GCN) is a podocyte-like cell that forms membrane invaginations bridged by autocellular slit diaphragms (SD). GCN represent a potential in vivo model to study the pathogenesis of SRNS. However, relevant pathomechanisms of SRNS such as interaction with the extracellular matrix (ECM) or CoQ deficiency have not been studied in GCN.

Methods: RNAi and CRISPR-Cas9 in larval GCN, transmission electron microscopy, confocal imaging of immunoabstains of SD-proteins and uptake of fluorescent tracers.

Results: Drosophila SD-proteins colocalize within a fingerprint-like staining pattern that correlates with ultrastructural morphology of SD. Using RNAi and conditional CRISPR-Cas9 in GCN we found this pattern to be mutually dependent on the orthologues of human NPHS1, NPHS2, CTNS, and WDR73. CRISPR-Cas9 knockdown of SD-proteins shows tubular dysfunction but lacking the early glomerular phenotype.

Conclusions: Taken together, Our GCN loss-of-function zebrafish mutant seems like a suitable animal model for studying the mechanisms involved in the pathogenesis of the disease and for the experimentation of potential new therapeutic agents.

Funding: Private Foundation Support

TH-PO296

Cms Loss-of-Function Zebrafish Mutant Shows Early Larval Glomerular and Tubular Dysfunction: A New Animal Model for Nephrotic Pathology
Mohamed A. Elmonem,1,2 Ramzi Khalil,1 Ladan Khodaparast,1 Lalch Khodaparast,4 Hans J. Baedle,3 Lambertus P.W. Van den Heuvel,1,5 Elena N. Levchenko.1
1Pediatric Nephrology & Growth and Regeneration, Univ Hospitals Leuven, KU Leuven, Leuven, Belgium; 2Clinical and Chemical Pathology, Faculty of Medicine, Cairo Univ, Cairo, Egypt; 3Pathology, Leiden Univ Medical Center, Leiden, Netherlands; 4Cellular and Molecular Medicine, Univ Hospitals Leuven, KU Leuven, Leuven, Belgium; 5Pediatric Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: The human ubiquitous protein cystosin is essential for transporting the amino acid cystine out of the lysosomal compartment into the cytosol. Pathogenic mutations of the coding gene CNTS lead to defective cystosin function and the intralysosomal accumulation of cystine. Kidneys are first affected with renal Fanconi syndrome; however, unless properly treated the diseases progresses rapidly towards end stage renal disease and multiple organ dysfunction. Animal models to study nephrotic cystinosis are limited, with only a Cms-knockout mouse reported, showing cystine accumulation and signs of tubular dysfunction but lacking the early glomerular phenotype.

Methods: In our study we used a morpholino injected knock-out model (MO) and established a stable model (cmt+) with a homoygous nonsense mutation in exon 8 of the zebrafish cns gene. We evaluated early development, morphophysics, motor activity and cystine levels in mutant larvae. We further investigated the glomerular and tubular renal functional involvement.

Results: cmt−/− mutant larvae showed cystine accumulation, delayed development, signs of glomerular and tubular proteinuria and significantly reduced glomerular filtration rate, which closely resemble the early phenotype observed in cystinotic patients. Furthermore, cns−/− larvae showed a gradual and significant decrease in cystine levels when treated with increasing concentrations of cysteamine, the only available cystine depleting therapy for human patients.

Conclusions: Taken together, Our Cms loss-of-function zebrafish mutant seems like a suitable animal model for studying the mechanisms involved in the pathogenesis of the disease and for the experimentation of potential new therapeutic agents.

Funding: Private Foundation Support

TH-PO297

Early Induction of MMCP-4 in Podocytes May Underlie Endothelin-1 Activation in Alport Glomeruli
Dominic E. Cosgrove, Daniel T. Meehan, Brianna M. Dufek, Duane C. Delimont. Genetics, Boys Town National Research Hospital, Omaha, NE.

Background: We recently showed that active endothelin-1 protein, but not mRNA, is elevated in glomeruli and urine of pre-proteinuric Alport mice. In this same study we showed that endothelin-1 activation in pre-proteinuric Alport mice mimics the phenotype observed in renal Fanconi syndrome. To understand the mechanism underlying elevated endothelin-1 we performed a transcriptional analysis of isolated glomeruli from pre-proteinuric Alport mice. The mMCP-4 protein localized to the podocyte foot processes and the GBM. Cultured podocytes and glomerular endothelial cells express mMCP-4 mRNA. Expression was not detected in mesangial cells.

Methods: By next-generation sequencing, we identified mutations of the genes LAGE3, OSGEP, TP53RK, and TPRKB that encode proteins of the evolutionary highly conserved KEOPS complex (Kinase, Endopeptidase and Other Proteins of Small size) in 31 families with microcephaly and childhood-onset nephrotic syndrome. We show that knockdown of OSGEP TP53RK, and TPRKB results in severe proliferation defects, and upregulation of the CDK inhibitor p21 in human podocytes. To confirm pathogenicity of the identified alleles, we show that wildtype but not mutant constructs rescue the proliferation deficiency. Furthermore, knockdown of OSGEP TP53RK, and TPRKB increased phosphorylation of hTAX as an indicator of activated DNA damage response signaling, and ultimately resulted in apoptotic cell death.

Results: We here identified recessive mutations of all four members of the KEOPS complex (LAGE3, OSGEP, TP53RK, and TPRKB) in patients with severe developmental anomalies and SRNS. We provide evidence that the disease phenotype is caused by defects in cell proliferation, accumulation of DNA damage, and induction of apoptosis in human podocytes.

Funding: NIDDK Support

TH-PO298

COL4A3/4/5-Sequencing by NGS in Chilean Alport Patients: Significant Applications in Diagnosis and Renal Transplant
Paola Krell,1 Bernardo Pavez Nuñalt,1 Daniel Carpo,2 Carolina Lavoz,2 Sergio A. Mezzano.1
1Unidad de Nefrologia, Univ Austral de Chile, Valdivia, Region de los Rios, Chile; 2Inst de Anatomia Patologica, Univ Austral de Chile, Valdavia, Region de los Rios, Chile.

Background: Alport syndrome (AS) is an inherited kidney disease associated with mutations in COL4A3/4/5 genes. Altogether the three genes contain 151 exons turning genetic analysis by Sanger sequencing (SS) a challenge. NGS emerges as a cost-time-labor effective protocol to identify mutations in benefit of AS patients and their families.

Methods: 7 Chilean males with AS clinical diagnosis were recruited; 6 of them were in dialysis and/or waiting for cadaveric donor transplantation. Genomic DNA was extracted...
from blood samples and analyzed with the ALPORT MASTR kit covering COLA3/4/5 in 140 amplicons combined with Illumina MID barcodes and sequenced with MiSeq Reagent Kit (600c).

Results: 100% of exonic and exon-intron regions in COLA3/4/5 were covered with more than 100x. Data analysis resulted in the identification of 345 SNV, which represent 86 different SNV. After filtering procedures, 6 different SNV were identified as “disease causing” (table 1) and confirmed by SS.

In silico tools predicted truncating, missense, in-frame deletion and synonymous mutations. In case #1, skipping of exon 36 was observed by cDNA/RNA sequencing in blood and hair root. Genetic analysis by SS of the mutated exon was offered to families.

Conclusions: NGS is being implemented worldwide as a very useful tool to identify mutations. To our knowledge, NGS has never been offered to AS patients in Chile. Our results allowed us to confirm diagnosis in 6 AS patients carrying different mutations. Additionally, we were able to identify three first-degree relatives as safe kidney donors, discard AS in one patient’s sister and provide early diagnosis in one patient’s son.

FONDECYT 11110422.

Funding: Government Support - Non-U.S.

TH-PO299
Pathogenicity of the Human LamininB2 S80R Mutation Revealed by Its Impact on Alport Syndrome

Stephen Daniel Funk, Jeffrey H. Miner. Internal Medicine, Renal Div, Washington Univ; St. Louis, MO.

Background: Mutations that affect the GBM component laminin (LAMB2) cause either Pierson syndrome or isolated congenital nephrotic syndrome, depending on the severity of the mutation. We investigated the pathogenicity of LAMB2-S80R, a mutation reported as homozygous in a child with nephrotic range proteinuria, ocular abnormalities, and mild diffuse mesangial sclerosis, which are all features consistent with Pierson syndrome. LAMB2-S80R is located in the laminin polymerization domain and is predicted to affect GBM integrity.

Methods: LAMB2-S80R mice were engineered to express a rat LAMB2-S80R transgene driven by the nephrin promoter (Neph-LAMB2-S80R) or mated to mice carrying the S80R point mutation that was knocked into LAMB2 with CRISPR technology (LAMB2-S80Rct).

To determine if the LAMB2-S80R mutation could exacerbate kidney disease in another GBM disease model, LAMB2-S80Rct mice were mated to Col4a3-/- Alport mice and analyzed for proteinuria and GBM defects.

Results: LAMB2-S80Rct mice with uniform Neph-LAMB2-S80R expression or exclusively LAMB2-S80Rct allele expression never showed signs of proteinuria up to ~1 year of age. Interestingly, the LAMB2-S80Rct allele exacerbated proteinuria in LAMB2-S80Rct/Ct; Col4a3-/- mice, and all LAMB2-S80Rct/Ct; Col4a3-/- mice reached ESRD at 36-63 days, earlier than LAMB2-S80Rct/Ct; Col4a3-/- littersmates and pure 129 Col4a3-/- mice (typically 75 to 90 days).

Conclusions: A lack of significant proteinuria in mice expressing only the LAMB2-S80R mutant protein was unexpected. This result could stem from an inherent difference between human and mouse laminin or GBM biology, a resistance to proteinuria in the mixed C57/6 and 129 strain background, or a lack of pathogenicity of the homozygous LAMB2-S80R point mutation despite the Pierson-like features of the patient. However, the enhanced proteinuria and reduced survival of Alport mice harboring just one LAMB2-S80Rct allele indicates that the LAMB2-S80Rct variant is pathogenic in the context of glomerular stress. Our results demonstrate the power of modelling specific human variants in mice and using genetic interactions to identify pathogenicity that would otherwise be missed.

Funding: NIDDK Support

TH-PO300
Functional Assessment of a Novel COLA4A5 Splice Region Mutation in an Alport Family

Andrew F. Malone, Steven Daniel Funk, Jeffrey H. Miner. Nephrology Dept, Washington Univ School of Medicine, St. Louis, MO.

Background: Alport syndrome is a hereditary disease caused by mutations in COLA4A5 in 85% of cases. Approximately 13% of variants described in Alport Syndrome patients are third of mutations are only probably pathogenic requiring further segregation/functional testing. The advent of next generation sequencing (NGS) has tremendously facilitated the genetic diagnosis in hereditary FSGS, and podocyte gene panels are increasingly used as the first step of genetic analyzes in familial cases.

Methods: We aimed to determine the causative gene mutations through Sanger sequencing and NGS in a large worldwide cohort of 140 families (253 patients) with FSGS starting during childhood or adulthood and an apparent autosomal dominant (AD) inheritance.

Results: Monogenic cause was identified in 67 families (48%). The mutation rate did not differ according to the size of pedigrees or the number of affected generations. The most prevalent gene mutations were the following: INF2 (20/67 families, 30%), COLA4A5 (17/67, 25%), and WT1 (10/67, 15%). ACTN4 and TRPC6 mutations were detected in only 1 and 5 families (1% and 7.5%) respectively. An X-linked transmission was also possible in the 8 families with COLA4A5 mutations and at least one affected relative had microscopic hematuria in 5/8, but no deafness was reported. Interestingly, we identified WT1 mutations in families with late-onset FSGS diagnosed at a median age of 19 years and no Wilms’ tumor, including 3 pedigrees with fertile males who transmitted the mutation. Among the 60 different mutations identified, 30 were published pathogenic mutations (50%), 6 were novel truncating mutations (10%), 12 were novel missense variants in functional domains of the protein (20%) and 12 were predicted damaging missense variants (20%).

Conclusions: We conclude that 1) a high mutation rate is observed in families with AD-FSGS 2) isolated FSGS could result from mutations in collagen and developmental genes (sensitivity ~70%) has enabled faster assessment of TMA cases.

Funding: Government Support - Non-U.S.

TH-PO301
Appropriate Use of a Rapid Genetic Assay to Confirm the Diagnosis of Complement-Mediated Thrombotic Microangiopathy

Jan C. Hofmann, Dept of Medicine, California Pacific Medical Center, San Francisco, CA.

Background: Improved diagnostic tests and greater understanding of thrombotic microangiopathy (TMA) have led to rapid differentiation of various types of TMAAs. Availability of “Next-Gen” aHUS genetic testing (GT) allowing rapid detection (2-5 days) of >230 known or suspected polymorphisms possibly associated with aHUS, including 12 common mutations, (sensitivity ~70%) has enabled faster assessment of TMA cases.

Methods: From 4/14-4/16, we evaluated 124 patients (pts) with TMA. 86/124 (69%) pts had TMA. 86/124 (69%) pts had TMA. 86/124 (69%) pts had TADMA (TMA) pts p/w mean plt ct 59 x 109/L (18-153 x 109/L), LDH 827 (457-1336), Cr 4.3 (2.0-7.1). STEC HUS pts p/w mean plt ct 59 x 109/L (18-153 x 109/L), LDH 827 (457-1336), Cr 4.3 (2.0-7.1), and AD-FSGS 2) isolated FSGS could result from mutations in collagen and developmental thrombomodulin, or plasminogen genetic abn) or equivocal; 29% were negative. 11/14 (79%) pts received eculizumab.

Conclusions: With development of improved genetic testing (ie, increased speed and sensitivity), aHUS genetic assays may represent a “real-time” diagnostic tool enabling more rapid assessment of complex TMA cases.

TH-PO302
A Monogenic Cause in Half of Cases of Autosomal Dominant FSGS


Background: The advent of next generation sequencing (NGS) has tremendously facilitated the genetic diagnosis in hereditary FSGS, and podocyte gene panels are increasingly used as the first step of genetic analyzes in familial cases.

Methods: With development of improved genetic testing (ie, increased speed and sensitivity), aHUS genetic assays may represent a “real-time” diagnostic tool enabling more rapid assessment of complex TMA cases.

Funding: NIDDK Support
Novel TRPC6 Loss-of-Function Mutations Associated with FSGS
Marios Kassamias, 1 Marc Richle, 2 Anja K. Böscher, 3 Björn-Oliver Gohike, 1 Jan H. Braesen, 4 Mato P. Nagel, 1 Jan U. Becker, 5 Peter F. Hoyer, 5 Robert Preisser, 5 Dietmar Krautwurst, 5 Maik Gollasch, 2 Christian Harteneck, 2 Stefanie Weber, 4 Experimental and Clinical Research Center (ECRC), Charité Univers Medizin Berlin, Berlin, Germany; 5 Eberhard Karls Univ Tübingen, Tübingen, Germany; 6 Univ of Duisburg-Essen, Essen, Germany; 7 Univ Hospital of Hannover, Hannover, Germany; 8 Center of Nephrology and Metabolism, Weisswasser, Germany; 9 Univ Hospital of Cologne, Cologne, Germany; 10 Deutsche Forschungsanstalt für Lebensmittelchemie, Molekulare Zellphysiologie und Chemorezeption, Freising, Germany; 11 Philips-Univers Marburg, Marburg, Germany.

Background: FSGS is a CKD with heavy proteinuria that eventually progresses to ESRD. Hereditary forms of FSGS have been linked to mutations in the transient receptor potential cation channel subfamily C, member 6 (TRPC6) gene encoding a nonselective cation channel. Most of these TRPC6 mutations cause a gain-of-function phenotype, leading to calcium-triggered podocyte cell death, but the underlying molecular mechanisms are unclear.

Methods: We studied the molecular effect of disease-related mutations using tridimensional in silico modeling of tetrameric TRPC6. Our results indicated that G757 is localized in a domain forming a TRPC6-TRPC6 interface and predicted that the amino acid exchange G757D, a mutation which was found in FSGS-affected patients earlier, causes local steric hindrance and disruption of the channel complex. Notably, functional characterization of model interface domain mutants suggested a loss-of-function phenotype.

Results: Characterizing 19 human FSGS-related TRPC6 mutations by Ca2+ fluorescence measurements, we found that the majority caused gain-of-function mutations. However, five mutations (N125S, L395A, G757D, L780P, and R895L) caused loss of TRPC6 function as an additional concept of hereditary FSGS and provides a new concept of FSGS.

Conclusions: Our comprehensive analysis of human disease-causing TRPC6 mutations reveals loss of TRPC6 function as an additional concept of hereditary FSGS and provides molecular insights into the mechanism responsible for the loss-of-function phenotypes of TRPC6 G757D and L780P in humans.

Funding: Government Support - Non-U.S.

Whole Exome Sequencing of 121 Unrelated CAKUT Patients Identifies Novel Pathogenic Variants in Kidney Development Genes and in Genes Previously Not Associated with CAKUT

Background: Steroid resistant nephrotic syndrome (SRNS) inevitably progresses to end-stage renal disease, requiring dialysis or transplantation for survival. To date, more than 40 monogenic causes of SRNS have been identified. The Australian SRNS Cohort (AS/TBMN) was performed at the Yale Center of Mendelian Genomics. By using a candidate gene approach, we examined the sequenced exome data for mutations in 40 genes known to underlie cause of NS in children. WES is a viable and now cost-effective way to diagnose the underlying cause of NS in children. With our candidate gene approach, our report is the largest and most in-depth study of monogenic causes of NS in children using WES to date. Variants of uncertain significance (VOUS) were identified in an additional 22/135 (16%) families. Median age and gender proportion were similar between adults and children.

Conclusions: The diagnostic rate difference between adults and children challenges dogma that such testing is limited by a high false positive rate and large numbers of Sanger sequencing required to confirm variants.

Methods: We therefore studied the underlying genetic cause of 382 patients from 295 families with nephrotic syndrome (NS) by employing whole exome sequencing (WES).

Results: Sampled for a total of 98,146, 17 years. WES sequencing (10 multilane panels; 137 genes). DNA was sequenced (Illumina TruSightOne, HiSeq2500) and variants assessed with bioinformatic filters and a multidisciplinary team (MDT). Pathogenic variants were confirmed (Sanger). MLPA/microarray were utilized to identify copy number variants.

Conclusions: The diagnostic rate of 79% solve in consanguineous individuals and 15.5% solve rate in non-consanguineous individuals (Sadowski 2015).

Funding: Other NIH Support - NIH R01-DK076883

Whole Exome Sequencing in a Large International Cohort of 430 Pediatric Patients with Nephrotic Syndrome

Background: Whole Exome Sequencing in a Large International Cohort of 430 Pediatric Patients with Nephrotic Syndrome

Jillian Kateri Warekoizil, Weizhen Tan, Svjetlana Lovric, Ankana Daga, Jia Rao, Shazia Ashrif, David Schapiro, Jennifer A. Lawson, Daniela A. Braun, Tobias F. Hennle, Tilman Jobst-Schwan, Benedikt Widmeier, Shirley Reilly, Friedrich Hildebrandt, Div of Nephrology, Children's Boston Hospital, Harvard Medical School, Boston, MA.

Background: SRNS is a monogenic disease of the kidney, and hence targeted genetic testing should be considered. We performed targeted Sanger sequencing in 58/135 families (43%). There was not a significant difference between paediatric and adult cohorts (31/68 vs 27/67, p=0.53). The subcohorts with the greatest diagnostic rate were paediatric AS/TBMN (7/8, 88%), tubulointerstitial (6/8, 75%) and adult AS/TBMN (15/19, 79%). Despite a high prevalence, a number of conditions remain undiagnosed. Variants of uncertain significance (VOUS) were identified in an additional 22/135 (16%) families. Median age and gender proportion were similar between adults and children.

Conclusions: The diagnostic rate of 79% solve rate in consanguineous individuals and 15.5% solve rate in non-consanguineous individuals (Sadowski 2015).

Methods: Whole Exome Sequencing of 121 Unrelated CAKUT Patients Identifies Novel Pathogenic Variants in Kidney Development Genes and in Genes Previously Not Associated with CAKUT

Amy B. Wilfert, Donald Conrad, Sanjay Jain.

Background: Congenital anomalies of the kidneys or lower urinary tract (CAKUT) encompasses a spectrum of more than 10 different kidney malformations and are collectively the biggest cause of renal failure in children. These are genetically heterogeneous disorders with high heritability. The prevailing view is that these are monogenic disorders, and hence targeted genetic testing should be considered.

Whole Exome Sequencing of 121 Unrelated CAKUT Patients Identifies Novel Pathogenic Variants in Kidney Development Genes and in Genes Previously Not Associated with CAKUT

Nephron, 267, Iss 1, pp 71-83.

Funding: Other NIH Support - NIH R01-DK076883

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

Underline represents presenting author.

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and discoveries in mechanisms of early kidney development and resulting defects, we focused on the role of CUBK pathways, since patients with CUBK mutations are more likely due to defects in UB induction, ureteral obstruction, or branching morphogenesis.

Methods: We performed Whole Exome Sequencing using Illumina platform and 50Mb Agilent clinical exome kit on 121 unrelated CAKUT cases with renal agenesis, hypoplasia, dysplasia or ureteric defects to identify pathogenic rare or novel variants.

Results: By first interrogating 81 genes implicated in kidney development or CUBK we found pathogenic variants identified by at least 3 different tools in 28 of these 81 genes in 48 cases. Many of these variations occurred in key functional domains that explain the known phenotypic defects. While the common polymorphism frequency in CAKUT cases and public datasets were similar, there was significant difference in rare variants in our cases compared to controls. We then used an unbiased approach that combined the prediction tools above, survey of large public datasets including 1000 genome, ESP6500, and Population Sampling Probabilities or PSAP tool that ranks pathogenicity from variant data of > 60000 exomes in ExAC and found pathogenic variants in 24 novel genes in additional 22 cases with a PSAP probability <1E-05. The novel ones includes genes important in histone and RNA modification and apoptotic signalling.

Conclusions: Our work provides one of the firsts of the exomie landscape of CAKUT cohort that informs on pathogenetic mechanisms and diagnosis of these disorders.

Funding: NIDDK Support, Private Foundation Support

TH-PO308
Exome Sequencing in Patients with Rhabdomyolysis Reveals Heterogeneous Single-Gene Etiology in 47% of Cases
Hadas Itziv,1 Asaf Vivante,2 Ben Podé Shakked,3,4 Jing Chen,1 Shirlee Shril,1 Amelie van der Ven,1 Nina Mann,1 Johanna Magdalena M. Schmidt,1 Yuval E. Landau,1 Yair Anikster,1,4 Friedhelm Hildebrandt,2 1Dept of Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA; 2The Dr. Pinchas Borenstein Talmi Pediatric Leadership Program, 3Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; 4Medical Disease Unit, Edmond and Lily Safra Children’s Hospital, Sheba Medical Center, Tel-HaShomer, Israel.

Background: Rhabdomyolysis is a clinical emergency accounting for around 10% of all cases of acute kidney injury (AKI) in the US. Rhabdomyolysis can be acquired or due to single-gene causes. In the clinical setting, identifying the underlying molecular diagnosis is challenging, due to nonspecific presentation, high number of causative genes and lack of clinical criteria for differential diagnosis of monogenic causes.

Methods: We employed whole exome sequencing (WES) to reveal the percentage of rhabdomyolysis cases that can be explained by single-gene mutations. We investigated a cohort of 19 unrelated families, in whom no underlying etiology was previously established.

Results: By using WES, we identified the causative mutation in nine of the 19 families (47%). We detected disease causing mutations in eight different known genes which can be grouped into the following categories: 1) disorders of glycolysis metabolism (PFK and PGM2), 2) disorders of fatty acid metabolism (CPT2), 3) disorders of abnormal skeletal muscle relaxation and contraction (RYR1, SCN4A, CACNA1S and MYH7), and 4) disorders of purine metabolism (ATIC).

Conclusions: Our findings suggest a high prevalence for monogenic etiologies as well as broad genetic heterogeneity for rhabdomyolysis. This highlights the importance of molecular genetic diagnostics by WES of rhabdomyolysis to allow for personalized therapy. In addition, it helps establishing an etiologic diagnosis for an important subgroup of recurrent acute kidney injury.

Funding: Other U.S. Government Support

TH-PO309 Exome Sequencing Discovers Syndromes in Patients with Consanguineous Families with Congenital Anomalies of the Kidneys and Urinary Tract Shirlee Shril,1 Asaf Vivante,1 Daw-Yang Hwang,2 Stefan Kohl,1 Jing Chen,1 Julian Jakob Schulz,1 Amelie van der Ven,1 Ghaleh H. Daouk,1 Nevene Solomon,2 Velibor Tasic,2 Friedhelm Hildebrandt,2 1Dept of Medicine, Boston Children’s Hospital, Boston, MA; 2Dept of Pediatrics, Kazar Al Shareef School of Medicine, Cairo, Egypt; 3Medical Faculty Skopje, Univ Children’s Hospital, Macedonia, The Former Yugoslav Republic of.

Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the leading cause of CKD in children, featuring a broad variety of malformations. A monogenic cause can be detected in around 12% of patients. Nevertheless, in clinical practice, the genetic basis of most patients with CAKUT is elusive because of a very weak genotype-phenotype correlation.

Methods: To determine the likelihood of detecting causative recessive mutations, we performed whole exome sequencing (WES) and homozygosity mapping to identify such mutations that might also cause CAKUT. We screened and analyzed individuals with CAKUT from 33 different consanguineous families.

Results: Using homozygosity mapping and WES, we identified the causative mutations in nine of the 33 families studied (27%). We detected recessive mutations in nine known disease–causing genes: ZBTB24, WFS1, HPSE2, ATRX, ASPH, AGXT, AQP2, CTNS, and PKHD1. Notably, when mutated, these genes cause multiorgan syndromes that may include CAKUT as a feature (spondylocardiomyopathy or CUBK) or cause renal diseases that may manifest as phenocopies of CAKUT. None of the above monogenic disease–causing genes were suspected on clinical grounds before this study. Follow-up clinical characterization of those patients allowed us to revise and detect relevant new clinical features in a more appropriate pathogenic context.

Conclusions: Applying WES to the diagnostic approach in consanguineous families with CAKUT provides opportunity for an accurate and early etiology–based diagnosis and improved clinical management.

Funding: Other NIH Support – R01

TH-PO310 The Circadian Clock Provides Beneficial Effects against the Endothelial Dysfunction to Promote Atherogenesis by Regulating PDGF and TGF-β Generation
Hideyuki Negoro, Medicine, Harvard Medical School, The Graduate School of Project Design, Tokyo, Japan.

Background: The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial structure and vascular stiffness. Chronic circadian clock disruptions are also associated with dysfunction in endothelial signaling and responses. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF-β) which play important part in the progression of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of PDGF and TGF-β in the knocked down cells.

Results: Endothelial function was decreased in aorta from Bmal1-KO mice. In aorta from Bmal1 KO mice, there was an increase in PDGF and TGF-β expression in mice with a dysfunctional circadian rhythm. Moreover, Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include PDGF and TGF-β which are significantly elevated in Bmal1 KO mice. We also confirmed that plasmogen activator inhibitor-1 and PDGF levels follow a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating PDGF and TGF-β generation. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Other U.S. Government Support

TH-PO311 Therapeutic Restoration of Endothelial Glyocalyx in Sepsis
Jong Wook Song,1 Joseph A. Zullo,1 Matthew A. Dragovich,2,3,4 Michael S. Goligorsky,1 1New York Medical College, Valhalla, NY; 2Lehigh Univ, Bethlehem, PA.

Background: Endothelial glyocalyx (EG) is disintegrated during sepsis. We (Zullo et al. Am J Pathol, 2016) showed that this occurs very early in the course of sepsis and its prevention improves survival of mice with sepsis. The goal of the present study was to investigate pharmacologic tools capable of accelerating the restoration of disintegrated EG in sepsis.

Methods: We used a soilage injection model to induce sepsis in C57/B6 mice. We measured total body EG by comparing the dilution curves of dextran-80 and dextran-500 and their subtraction approximated the volume of EG. En face aortic preparations were used for staining with antibodies against heparan sulfate (HS) and atomic force microscopy (AFM) was used in vitro to measure EG.

Results: In vitro studies showed that in cultured endothelial cells exposed to LPS showed a robust ability of HS, sulodexide [Alfa Wassermann S.p.A., Alanno (PE), Italy], or high-molecular weight hyaluronic acid (HA) to accelerate EG regeneration (immunofluorescence and AFM). In vitro studies revealed the potential for inhibitors of hyaluronidase (Hase) and heparanase (HEPase) to accelerate EG regeneration. We demonstrated through in vivo studies showed that total volume of EG in control mice averaged 57±24 µm, whereas in septic mice it was reduced to 1±30 µm within 24 hours of sepsis. Administration of components of the EG such as HA or HS did not produce dramatic acceleration of EG restoration. When HA or HS were administered in combination with inhibitors of Hase and HEPase, the restoration of EG was remarkably accelerated. Notably, a heparan-sulfate like compound resistant to HEPase degradation, sulodexide, demonstrated a remarkable capacity for regeneration in vitro and in vivo. This combined treatment instituted 24 hr after induction of severe sepsis was associated with the improved animal survival.

Conclusions: 1) EG is disintegrated in sepsis, the event which contributes to animal survival; 2) the process of endogenous restoration of EG is protracted; 3) pharmacologic acceleration of EG restoration can be achieved using the combination of hyaluronan and sulodexide with inhibitors of hyaluronidase and heparanase.

Funding: NIDDK Support

TH-PO312 Thrombospodin-1 and Its Glyocalyx Binding Partners Are Engaged in Endothelial Microparticles Formed under High Glucose Conditions
Madison Turner, Mercedes N. Munkonda, Shareef Akbari, Dylan Burger. Kidney Research Centre, Ottawa Hospital Research Inst, Ottawa, ON, Canada.

Background: Diabetes is typified by the development of endothelial dysfunction; an independent predictor of poor prognosis linked to renal and cardiovascular disease. Microparticles are small (0.1-1.0 µm) membrane vesicles secreted following cell stress/
Conclusions: In summary we show that high glucose increases the formation of eMPs and leads to alterations in their molecular composition including the enrichment in thrombospondin-1. Such alterations may contribute to the development of vascular and renal injury in diabetes.

TH-PO313
CD4+CD28- T-cells Are Cytomegalovirus Specific Cytotoxic Endothelial Takeda Cells at Independent Singulators. Arterial Stiffness in Renal Disease
Dirk Hugo Taki
H. Harper.
Sagmeister, Charles
Medicine, Vanderbilt Univ, Nashville, TN.

Background: CD4+CD28- T-cells are associated with cardiovascular disease (CVD) in inflammatory conditions. We previously showed that in ANCA associated vasculitis (AAV) they are associated with mortality and are specific to Cytomegalovirus (CMV) seropositivity. Using AAV as a model, we sought to characterize these cells further and determine their contribution to arterial stiffness, an independent predictor of CVD.

Methods: Peripheral blood mononuclear cells from 53 CMV seropositive AAV patients with renal involvement in remission and 30 age-matched healthy volunteers (HV) were cultured overnight with CMV lysate and stained for surface and intracellular markers by immunostaining. GEC growth factor signaling was assessed by Western or IP/Western activity was measured by IP/PTP assay and oligomerization status was assessed by nanoparticle tracking analysis. To assess the protein composition, 10 proteins most highly enriched in high glucose eMPs were the pro-coagulant protein Thrombin and its effects on GECs proliferation and tube formation were assessed. CD148 catalytic activity was measured by IP/PTP assay and its oligomerization status was assessed by nanoparticle tracking analysis.

Results: AA V patients had higher % of CD4+CD28- cells compared to HV (median 11.3%[IQR 3.4-19.8] vs 6.7%[2.3-9.8];p=0.02). In comparison to CD4+CD28+ cells, CD4+CD28- cells displayed a CXCR3+CCR6+ Th1 phenotype (80.5%[85.0-89.8] vs 31.0%[25.0-35.4];p=0.01) and expressed the Th1 transcription factor T-bet (83.5%[75.8-90.9] vs 12.94.7%[22.0];p=0.01). They expressed endothelial receptors (CXCR1+CD49d+CD11b+ 51.6%[42.7-64.4] vs 4.9%[1.7-6.3];p=0.01) and cytotrophic molecules (perforin+granymeB+ 74.5%[83.9-72] vs 2.9%[1.8-5.4];p=0.01) at high levels and produced IFN-γ (21.2%[8.2-37.6] vs 0.7%[0.3-1.4];p=0.01) following CMV lysate stimulation compared to CD4+CD28+ cells. The CD4+CD28- % was independently linked to increased PWV in AAV after controlling for age, mean arterial pressure, proteinuria, CD4 count and CD4+CD28- % (R=0.482, R=0.075[0.018-0.132];p=0.01).

Conclusions: CD4+CD28- cells are powerful cytotoxic, proinflammatory Th1 subset that possess endothelial targeting receptors and are independently associated with increased arterial stiffness in renal disease. In a linked clinical trial submitted for ASN 2016, we also show that blocking subclinical CMV reactivation in AAV led to a reduction in CD4+CD28- cells, implicating CMV as a driving force behind their expansion and offering novel therapeutic opportunities in inflammatory renal disease.

TH-PO314
Creation of the CD148-Specific TSP1 Fragment and Its Effects in Glomerular Endothelial Cells Keiko Takahashi.
Rachel H. Kim, Katherine Sumarriva, Ray Mernaugh, Takamura Takahashi.
Medicine, Vanderbilt Univ, Nashville, TN.

Background: CD148 is a transmembrane tyrosine phosphatase expressed in renal endothelial cells. Previous studies have shown that it plays a role in negatively regulating cell growth and growth factor signaling. Recently, we further found that thrombospondin-1 (TSP1) serves as a ligand for CD148 (PNAS 109:2012), then characterized its interaction and created the CD148-specific TSP1 fragment (148-TSP1) (PLoS One 11:e0154916). This study set out to determine the effects of 148-TSP1 in glomerular endothelial cells (GECs).

Methods: Human GECs were treated with monomeric or trimeric 148-TSP1 fragments and its effects on GECs proliferation and tube formation were assessed. CD148 catalytic activity was measured by IP/PTP assay and oligomerization status was assessed by immunoblotting. GEC growth factor signaling was assessed by Western or IP/Western using phospho-specific antibodies. The effect of angioinvasion was assessed by mouse sponge assay using VEGF as an inducer. Specificity of the effects was evaluated by CD148 knockdown and knockin mouse.

Results: Trimeric, but not monomeric, 148-TSP1 fragment; 1) increased CD148 catalytic activity with its accumulation on cell surface in GECs, although both forms bound to CD148 effectively, indicating CD148 oligomerization is required for this effect.; 2) dose-dependently inhibited GEC proliferation (~80%) and tube formation (~50%) in culture; 3) remarkably (~80%) suppressed VEGF angiogenesis in vivo. These effects were largely attenuated or abolished by CD148 knockdown or knockout (mice). Furthermore, the 148-TSP1 fragment reduced tyrosine phosphorylation of VEGFR2, HGF, Tie2, ERK1/2 and Src in GECs, while it showed no effects for EphA2, FGFR, Akt, and Src P416.

Conclusions: The trimeric 148-TSP1 fragment increases CD148 activity and inhibits GEC proliferation and tube formation in culture and angiogenesis in vivo. This fragment is a promising agent for targeting angiogenesis in vivo without altering Akt or Src activity. Given the fact that Akt cell survival signal is preserved, this agent and pathway may provide a new and safer strategy for inhibiting glomerular angiogenesis.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO315
Vascular Endothelial Growth Factor Augments Arginine Transport and Nitric Oxide Generation via a KDR Receptor Signaling Pathway Idir F. Schwartz, Moshe Shashar, Doron Schwartz.
Nephrology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

Background: Vascular endothelial growth factor (VEGF) is an endothelium-specific peptide that stimulates angiogenesis via two receptor tyrosine kinases, Flt-1 and KDR. Endothelial nitric oxide synthase (eNOS) plays a major role in VEGF signaling. Delivery of arginine to membrane bound eNOS by the cationic amino acid transporter-1 (CAT-1) has been shown to modulate eNOS activity. The current studies were designed to test the hypothesis that VEGF enhances eNOS activity via modulation of arginine transport by CAT-1.

Methods: Using radio-labeled arginine ([14]H-L-arginine) uptake was determined in HUVEC following incubation with VEGF with and without silencing the VEGFR receptors Flt-1 and KDR. Subsequently we tested the involvement of CAT-1 and its phosphorylated forms were performed. NO generation was measured by the Griess reaction.

Results: VEGF (50 and 100 ng/ml) significantly augmented endothelial arginine transport in a time dependent manner, an effect which was prevented by Sunlinitib (2 μM), a multi targeted receptor tyrosine kinase inhibitor.

The increase in arginine transport velocities by VEGF was not affected by silencing Flt-1 while silencing KDR abrogated VEGF effect. Furthermore, incubating cells with 50 and 100 ng of VEGF for 30 minutes significantly augmented CAT-1 abundance. The expression of PKC-α, JNK, and ERK2/1 and their phosphorylated forms were unchanged following incubation of HUVEC with VEGF. The concentration of NO2/NO3 following incubation with VEGF was significantly higher than from untreated cells.

Conclusions: VEGF increases arginine transport via modulation of CAT-1 in endothelial cells. This effect is exclusively dependent on KDR rather than Flt-1.

TH-PO316
Akt Signaling Modulates a Novel Transcription Factor to Promote the Re-Vascularization of Kidney Microvascular Endothelial Cells following Injury Lan Dang, Bryce Gordon Johnson, Graham Marsh, Ivan G. Gomez, Jeremy Stuart Duffield.
Cell Stress and Innate Immunity, Biogen, Cambridge, MA.

Background: Acute kidney injury and chronic kidney disease are characterized by the progressive loss of kidney peritubular capillaries, which leads to local areas of hypoxia, induction of profibrotic responses, and ultimately the deterioration of renal functions. While many vascular beds have significant regenerative potential following tissue injury, the renal microvasculature fails to adequately regenerate. The unique property of the kidney microvasculature has prompted the investigation of new tissue-specific regulatory mechanisms that can provide new therapies for promoting re-vascularization following injury and thereby minimize the progression to chronic kidney disease.

Methods: We have developed new methods to isolate and study mouse and human Kidney Microvascular Endothelial Cells (KMVECs) ex vivo. Using in vitro and ex vivo assays that recapitulate features of angiogenesis, we demonstrated that both mouse and human derived KMVECs fail to generate new vascular sprouts in response to VEGF stimulation, compared to endothelial cells isolated from large vessel beds, such as Human Umbilical Vascular Endothelial Cells (HUVECs).

Results: Western blotting analysis showed that the PI3K/Akt pathway in KMVECs was severely attenuated in response to VEGF. PI3K/Akt signaling plays a critical role during endothelial invasion and sprouting and its activation is inhibited by the phosphatase PTEN. To determine the possibility that PTEN mediates the effect of VEGF on cell invasion, we evaluated whether the inhibition of PTEN can ameliorate the re-vascularization capacity of KMVECs following ischemia re-perfusion injury in adult mice. Interestingly, PTEN inhibition dramatically enhanced the capacity of KMVECs to form new blood vessels in vivo, as shown by the increase in vessel density.

Conclusions: These results provide critical insight into the role of the PI3K/Akt signaling pathway in regulating functional re-vascularization of injured kidneys to prevent progressive capillary regression and chronic kidney disease.

Funding: Pharmaceutical Company Support - Biogen
Increased Angiogenic Potential of Endothelial Cells Isolated from Patients with End-Stage Kidney Disease Using Combined Cell Therapy

Brooke M. Huuskes,1 Peter G. Kerr,2 Christian S. Samuel,1 Sharon D. Ricardo.1
1Dept of Anatomy and Developmental Biology, Monash Univ, Clayton, Victoria, Australia; 2Dept of Medicine, Monash Medical Centre and Monash Univ, Clayton, Victoria, Australia; 2Dept of Pharmacology, Monash Univ, Clayton, Victoria, Australia.

Background: We have recently shown that the administration of the anti-fibroblast hormone, relaxin (Rln) in combination with mesenchymal stem cells (MSCs) abrogates fibrosis in a model of obstructive nephropathy, yet their effect on revascularization is still to be elucidated. Endothelial progenitor cells (EPCs) play a key role in this process and it is known that patients on dialysis have reduced circulating EPCs. Therefore, enhancing angiogenic potential in end-stage kidney disease (ESKD) patients warrants investigation.

Methods: Mononuclear cells were isolated from patients with ESKD and control binding confirmed endothelial cell function. Endothelial lineage was determined using immunocytochemistry and confirmed with flow cytometry. Tube formation in matrigel was assessed over 6 hours using live cell time-lapse microscopy in the presence of MSCs/Rln. Wound healing over 24 hours and proliferative capacity with/without MSC or Rln further quantified angiogenic potential. All assays were replicated and compared with primary human endothelial cells (HECs).

Results: Patient EPCs were positive for Dil-AC-LDL and had impaired CFU compared to controls. EPCs transitioned into mature endothelial cells as confirmed by morphology and positive immunostaining for vWF, CD31 and VEGR2. Flow cytometry identified CD34+/CD31-KDR+ CD345- cells confirming endothelial lineage. HECs cultured directly with MSCs and Rln had a significant increase in branch points and length in tube forming assays (p<0.05). Additionally, wound closure was accelerated (p<0.01) and proliferation capacity was increased (p<0.05) when combination therapy was used.

Conclusions: EPCs can be successfully isolated from patients with ESKD and matured into endothelial cells. Their angiogenic potential can be modulated and enhanced with MSCs and Rln, which may have implications in kidney revascularization after injury.

Funding: Government Support - Non-U.S.

Methods: Eight-week old male Sprague-Dawley rats were divided into three groups: nondiabetic (control), streptozotocin-diabetic rats (DM), and diabetic rats treated with Aspirin (DM+Aspirin). The determination of PMPs was used by flow cytometry and confocal microscopy. The inflammatory cytokines released from PMPs was checked by protein microarray, immunohistochemical staining, or Western blot. The aortic endothelial progenitor cells were evaluated through measurement of NO concentration, measuring the expression of endothelial nitric oxide synthase (eNOS), the change of glycoalkaly and aortic endothelial permeability by electron microscopy, immunofluorescent staining and Western blot.

Results: Compared to the control, the serum level of PMPs increased significantly in diabetic, which was inhibited by Aspirin. Aspirin treatment decreased the production of inflammatory cytokines from serum PMPs and aorta. Using confocal microscopy, the enhanced interaction between PMPs and aortic endothelium was observed in DM rats, which was inhibited by Aspirin. Interestingly, the elevated PMPs and production of inflammatory cytokines from PMPs were correlated with the aortic endothelial injury by decreasing the NO excretion, the expression of eNOS, glycoalkaly thickness and increasing endothelial permeability in DM rats. Decreased serum PMPs and production of inflammatory cytokines by Aspirin ameliorated the aortic endothelial injury compared to the DM group.

Conclusions: Elevated serum PMPs contribute to aorta endothelial injury through the release of inflammatory cytokines from PMPs, which accelerate the progression of atherosclerosis in diabetes.

TH-PO318

Direct Evidence of Vascular Oxidative Stress and Inflammation in Chronic Kidney Disease

Kristen L. Nowalk,1 Wei Wang,1 Laurel Thur,1 Heather Farmer-Bailey,2 Anna Jeanette Jovovich,3 Michel Chonchol,2 1Univ of Colorado Anschutz Medical Campus; 2Denver VA Medical Center.

Background: Chronic kidney disease (CKD) is associated with vascular dysfunction, as indicated by impaired vascular endothelial function and increased large-elastic artery stiffness. Vascular dysfunction in CKD is thought to be related to vascular oxidative stress and inflammation, but direct evidence is lacking.

Methods: We studied 21 patients (60±12 years) with stage 3-4 chronic kidney disease (CKD, mean estimate glomerular filtration rate (eGFR) 34±11 ml/min/1.73 m² and 15 healthy controls (42±8 years; eGFR 94±12 ml/min/1.73 m²) and assessed brachial arterial flow-mediated dilation (FMD), aortic pulse-wave velocity (aPWV), and the carotid artery β-stiffness index. Vascular endothelial cells were collected from a peripheral vein and were available for analysis in 18 CKD patients and 11 controls. Vascular endothelial cell protein expression of eNOS, glycocalyx thickness and increasing endothelial cell protein expression of β-stiffness index-6 (IL-6) were measured using quantitative immunofluorescence.

Results: Consistent with previous evidence, FMD was lower and aPWV and the β-stiffness index were higher in CKD patients (p<0.01) compared to healthy controls. Vascular oxidative stress was also higher in CKD patients, as indicated by greater endothelial cell protein expression of NADPH oxidase (p=0.04), eNOS (p=0.05) and pro-inflammatory cytokines interleukin-6 (IL-6) (p<0.05). These differences persisted after statistical correction for age (p<0.01). Participants with NADPH oxidase above the median had lower FMD and higher aPWV and β-stiffness index compared to those below the median.

Conclusions: These results provide direct support for the hypothesis that endothelial oxidative stress and inflammation develop with CKD and are related to vascular dysfunction. Therapies targeting a reduction in oxidative stress and/or inflammation may improve vascular dysfunction in CKD.

Funding: Private Foundation Support

TH-PO319

Sclavening of Lipid Aldehydes Lessens Kidney Injury-Driven Atherosclerosis

Yan Shen,1 Sean Stephen Davies,1 Macrè F. Linton,2 Valentina Kon,1 Tori Kaminski,2 Vanderbilt Univ Medical Center; Nashville, TN; 1 Medicine, Vanderbilt Univ Medical Center, Nashville, TN.

Background: Chronic kidney disease (CKD) accelerates atherosclerosis. Reactive aldehydes, including isoprostanes and isolevuglandins (IsoLG), are key pro-atherogenic factors carried by high density lipoprotein (HDL). These aldehydes promote cellular dysfuncttion under atherogenic stress and are levels in increased CKD. We previously used aldehyde scavenger, e.g., IsoLG scavenger - salicylamine (SAM) - to lessen lipoxidation-induced inflammation and presently investigate the impact of this treatment on kidney-injury driven acceleration of atherosclerosis.

Methods: 11 week old male apolipoprotein E-/- mice underwent 5/6 nephrectomy (SNx) or sham-operation (sham), then treatment with SAM (1g/L) or vehicle for 6 weeks. Extent and characteristics of atherosclerotic lesions were assessed; cultured THP-1 macrophages were used to examine effects of IsoLG modified HDL on macrophage inflammatory response.

Results: Compared to sham, SNx increased atherosclerosis. SAM reduced the atherosclerotic lesion area in SNx (121100 ± 217600 μm² vs 217600 ± 19890 μm², p<0.01), but had little effect in sham. Assessment of plaques revealed greater necrotic area in SNx than sham (9.4 ± 0.8% vs. 3.7 ± 1.2 %, p<0.01). SAM significantly lessened necrotic areas in SNx/SAM (6.2 ± 5.0%, p<0.01), and did not affect the macrophage area or collagen content. Amelioration in atherosclerosis in SNx was not accompanied by changes in body weight, blood pressure, serum cholesterol, triglycerides, or BUN. In vitro, compared
Concerning gene expression in PBMC, atherosclerotic subjects had significantly lower KLOTHO concentrations of KLOTHO and IL-6 were significantly lower in the atherosclerotic group compared to normal (0.363 ± 0.263 pg/mL). There was no correlation between PNs and CRP, phosphate, urea, urate, calcium, or urinary albumine excretion levels.

**Background:** Extracellular nucleosomes (in plasma) are complexes of DNA and histones that are released during cell death. In acute kidney injury, there is an increased release of nucleosomes with decreased nucleosome clearance. Nucleosomes mediate inflammatory and thrombotic responses and could serve as biomarkers in chronic kidney diseases. Microparticle-associated tissue factor (MP-TF) are released during cell death and mediate thrombosis.

**Methods:** The concentrations of PNs in ESRD patients (n = 90) and healthy volunteers (n = 50) were measured using the Cell Death Detection ELISA PLUS assay (Roche Diagnostics, Mannheim, Germany). MP-TF levels were measured using the ZYMUPHEN MP-TF kit (Hyphen BioMed, Neuville-sur-Oise, France). The levels of both PNs and MP-TF were also correlated with WBCs, RBCs, and platelets to determine their origin.

**Results:** In comparison to the plasma from healthy volunteers (6.74 ± 13.7 Arbitrary Units (AU)), the levels of PNs in ESRD patients were higher (15.5 ± 14.1 AU; p < 0.0001). Similarly, MP-TF levels were elevated in ESRD patients (3.0 ± 1.42 pg/mL; p < 0.001) compared to normal (0.363 ± 0.263 pg/mL). There was no correlation between PNs and MP-TF in ESRD patients (r = -0.077; p = 0.501). Moreover, there was no correlation between PNs and platelets (r = -0.067; p = 0.543) and RBCs (r = 0.083; p = 0.447). However, the PNs showed a positive correlation with WBCs (r = 0.223; p = 0.042). There was no correlation between MP-TF and WBCs (0.057; p = 0.632) and RBCs (r = -0.042; p = 0.722), but a positive correlation was observed between MP-TF and platelets (r = 0.237; p = 0.042).

**Conclusions:** PNs were elevated in ESRD patients, indicating an increased release of nucleosomes, suggesting increased cell death. The observed correlation between PNs and WBCs suggests that the detected PNs are derived from WBCs. A lack of correlation between PNs and MP-TF suggests that the MP-TF increase is independent of the pathogenesis responsible for abnormal PN generation in ESRD patients.

**Funding:** Other NIH Support - NHIIB

**TH-PO324**

**KLOTHO Expression in Different Vascular Territories and Its Relationship with Atherosclerosis**

**Ernesto Martin, Javier Donate, Angel Lopez-Castillo, Raúl Portas, Anabel Rodriguez, Sergio Rodriguez, Purificacion Cerro, Naya Pérez-Delgado, Carmen Moro, Juan F. Navarro-Gonzalez.**

**Univ Hospital Nuestra Señora de Candelaria (Santa Cruz de Tenerife).**

**Background:** The anti-aging factor Klotho has been related to protective effects on the vascular wall, while a decrease on its serum levels has been related with the presence and severity of coronary artery disease and an increased mortality in hemodialysis patients. The objectives of this study are (i) to determine the relationship between vascular expression of KLOTHO and the presence of atherosclerotic disease, and (ii) to assess potential differences in KLOTHO gene expression among different vascular territories.

**Methods:** Vascular tissue samples were collected from 44 patients with atherosclerotic disease under elective vascular surgery, and from 10 healthy organ donors (control group). Samples were obtained from different vascular territories: aorta (n=13), carotid (n=15) and femoral (n=16). KLOTHO gene expression levels were assessed by qPCR with TaqMan probes.

**Results:** In the overall group of patients with atherosclerotic disease, KLOTHO gene expression levels were significantly lower compared to healthy individuals [0.276 (-0.193 - 0.642) vs. 2.239 (0.017-2.756); p = 0.001]. Likewise, KLOTHO expression in every vascular territory was lower respect to controls (femoral, p<0.05; aorta and carotid, p<0.01). Within the group of patients affected of atherosclerosis, KLOTHO expression levels were significantly higher in the femoral territory respect to aorta [0.577 (0.29-0.93) vs. -0.053 (-0.17 - 0.52); p<0.01] and to carotid [-0.234 (-0.46 - 0.66); p<0.01], whereas there was no difference between the latter two regions.

**Conclusions:** The lower KLOTHO expression in patients with established vascular disease suggests a relationship between this factor and the pathophysiology of the atherosclerotic process. In addition, the differences observed in the expression of the KLOTHO gene among different vascular territories might suggest the existence of mechanisms of regulation dependent on the specific vascular territory.

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

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**TH-PO325**

**Expression of Klotho on Endothelial Derived Microparticles**

**Josefin I. G. Mörberg, Fariborz Mobarez, Kristina Lundwall, Hakan Wallen, Stefan H. Jacobson, Jonas Spaak.**

**Dept of Clinical Sciences, Danderyd Hospital, Karolinska Inst, Stockholm, Sweden.**

**Background:** Klotho is mainly expressed in the renal tubules, but also exists in a soluble form, where reduction is associated with renal disease, increased oxidative stress, endothelial dysfunction, and diffuse vascular calcification. Overexpression of Klotho promotes cardiovascular and renal protection. Endothelial derived microparticles (EMP) is considered a micro-biopsy of the endothelium. We investigated whether Klotho is found on endothelial cells in patients with myocardial infarction and renal failure, by measuring Endothelial derived microparticles.

**Methods:** Blood samples were collected from 30 patients (21 men, 9 women), after acute myocardial infarction. Patients were stratified according to renal function, above or below eGFR 60 ml. Cystatin C eGFR was 81±7 ml/min/m², and 34±14 respectively in the groups. EMP's were detected with antibodies towards CD144 (VE-cadherin), and also towards CD36E (E-selectin), a cell adhesion molecule expressed on cytokine activated endothelium. Klotho was identified on endothelial cells using a KLH conjugated polyclonal IgG antibody against human Klotho. All samples were analyzed using a Beckman Coulter Gallios flow cytometer and microparticles were defined as particles less than 1 µm in size.

**Results:** Our result indicate that Klotho is exposed on endothelial cells and on cytokine-activated vascular endothelium, (figure 1) without significant correlation with kidney function. There was no significant correlations between Klotho EMP levels and CRP, phosphatase, urea, urate, calcium, or urinary albumine excretion levels.
\textbf{TH-PO326}

\textbf{α-Klotho Alleviates LPS Induced Cardiorenal Syndrome Type 5} 
Chen Yu, Xi Liu. Dept of Nephrology, Tongji Hospital, Tongji Univ School of Medicine, Shanghai, China.

\textbf{Background:} Cardio-renal syndrome type 5 occurs when an overwhelming insult leads to the simultaneous development of acute kidney injury and acute cardiac dysfunction. The \( \alpha \)-klotho protein is a pleiotropic protein with a multitude of renal and extrarenal effects. Whether \( \alpha \)-klotho can alleviate cardiorenal syndrome type 5 is lack of research. We designed this study to evaluate the effect and mechanism of \( \alpha \)-klotho on cardiorenal syndrome type 5.

\textbf{Methods:} C57BL/6 mice were randomly assigned to four following groups: The CON group, the LPS group; the LPS+α-klotho (0.01mg/kg) group; and the LPS+α-klotho (0.02mg/kg) group. The dose of LPS is 10mg/kg. Plasma creatinine, NGAL, BNP and troponin was measured at 24hours after LPS treatment, as same as myocardial apoptosis, inflammation, oxidation stress and endoplasmic reticulum stress levels.

\textbf{Results:} The result showed that Klotho gene was highly expressed in kidney but undetectable heart tissue. LPS induced the reduction of the klotho expression in kidney as early as 6 hours after LPS injection. The \( \alpha \)-klotho protein (0.01–0.02mg/kg) reduced the levels of plasma creatinine, NGAL, BNP and troponin, and the protective effects were dose-dependent.

\textbf{Conclusions:} The \( \alpha \)-klotho protein ameliorated the cardiac injury and renal injury in cardiorenal syndrome type 5 induced by LPS. The mechanism included reducing myocardial apoptosis and oxidative stress, regulating inflammatory cytokines and improving endoplasmic reticulum stress levels.

\textit{Funding:} Government Support - Non-U.S.

\textbf{TH-PO327}

\textbf{p66Shc Mediates ET-1 Induced Intracellular Calcium Mobilization in Renal Resistance Arteries} 
Bradley S. Miller,1 Oleg Palygin,2 Alexander Staruschenko,2 Andrey Sorokin.1 1Medicine Div of Nephrology, Cardiovascular Center, Medical College of Wisconsin, Milwaukee, WI; 2Physiology, Medical College of Wisconsin, Milwaukee, WI.

\textbf{Background:} Increased renal perfusion pressure activates renal autoregulation mediated in part by vasconstriction of smooth muscle cells of preglomerular vessels, leading to reduction of blood flow to normal levels. The Dahl salt-sensitive (SS) rat model of hypertension is characterized by loss of renal vascular responsiveness upon increased dietary salt intake despite elevated levels of circulating Endothelin-1 (ET-1), a potent vasoconstrictor peptide. ET-1 mediates smooth muscle cell (SMC) contraction via elevated intracellular calcium signaling. In addition, ET-1 induction of p66Shc phosphorylation on serine 36 is essential for the promotion of mitochondrial oxidative stress, a potential factor in vascular dysfunction. The purpose of this study was to determine the role of p66Shc in ET-1 induced intracellular calcium mobilization in intact smooth muscle cells in isolated renal microvessels.

\textbf{Methods:} p66Shc knockout and p66Shc Ser36Ala substitution knock-in rats were generated on the SS genetic background using engineered Zinc Finger nucleases. Renal microvessels dissected from wild type SS rats.

\textbf{Conclusion:} p66Shc also reduced myocardial apoptosis and regulated the balance of proinflammation/anti-inflammation in both plasma and heart tissue. \( \alpha \)-klotho reduced oxidative stress and increased endoplasmic reticulum stress level in myocyte damage.

\textit{Funding:} NIDDK Support

\textbf{TH-PO328}

\textbf{Cholecalciferol Supplementation Improves Vascular Function in Non-Diabetic Chronic Kidney Disease Patients with Vitamin D Deficiency: A Self-Controlled Study} 
Ashok Kumar Yadav,1 Vivek Kumar,1 Manhpool Singhal,2 Vivekanand Jha.1 1Nephrology, PGIMER, Chandigarh, India; 2Radiodiagnosis, PGIMER, Chandigarh, India; 3George Inst for Global Health, New Delhi, India.

\textbf{Background:} Vitamin D deficiency is common and associated with mortality in chronic kidney disease (CKD) patients. Its supplementation might improve endothelial and vascular function in patients with CKD. We studied the influence of vitamin D supplementation on vascular function and inflammatory biomarkers in patients with non-diabetic CKD stage 3-4 and vitamin D deficiency.

\textbf{Methods:} In this self-controlled study, 31 patients with non-diabetic stage 3-4 CKD and vitamin D deficiency [serum 25(OH)D levels <20 ng/ml] were assessed at 0, 16, and 32 weeks. All patients received directly observed cholecalciferol supplementation (300,000 IU) at 16 and 24 weeks. Endothelium dependent brachial artery flow mediated dilatation (FMD), pulse wave velocity (PWV) and circulating biomarkers were analyzed at 0, 16 and 32 weeks. The primary outcome was change in FMD at 16 and 32 weeks.

\textbf{Results:} 25(OH)D levels remained similar to baseline at 16 weeks but significantly increased at 32 weeks (13.0±5.4, 15.7±9.8 and 34.7±15.2 ng/ml at 0, 16 and 32 weeks, respectively, p<0.0001). FMD, PWV and biomarkers were similar at 0 and 16 weeks (table 1). However, after cholecalciferol supplementation at 16 and 24 weeks, FMD increased significantly at 32 weeks (p<0.0001). Similarly, significant changes in 1,25(OH)D, IL-6, FGF-23 and PWV were seen at 32 weeks.

\textbf{Conclusions:} Cholecalciferol supplementation corrected vitamin D deficiency, improved FMD and PWV, and decreased serum levels of FGF-23 and IL-6 in subjects with non-diabetic CKD.

\textit{Funding:} Government Support - Non-U.S.

\textbf{TH-PO329}

\textbf{The Impact of Dietary Phosphate on Erectile Function in an Experimental Model of CKD} 
Mandy E. Turner, Melanie Wilson, Cynthia M. Pruss, Emilie C. Ward, Paul S. Jerominio, Bruno Svajger, Rachel M. Holden, Martin P. Petkovich, Michael A. Adams. Biomedical and Molecular Sciences and Medicine, Queen’s Univ, Kingston, ON, Canada.

\textbf{Background:} CKD patients are at a markedly increased risk of CVD and CVD-related mortality. Phosphate dysregulation and pathological consequences, such as vascular calcification(VC), are key to this increased CVD risk. Erectile dysfunction(ED) is one of the earliest predictors CVD and ~80% of CKD patients self-report ED. Erectile function is a complex process dependent endothelial and vascular health, both of which are negatively impacted by phosphate. In a model of CKD, we sought to determine the impact of increased dietary phosphate on the development of ED and VC.

\textbf{Methods:} CKD was induced in male Sprague-Dawley rats(N=51, 15 wks) for 5 weeks using a 0.5% PO 

\textbf{Baseline} & 16 weeks & 32 weeks & 32 weeks & 32 weeks \\
1,25(OH)D (ng/ml) & 22.3±13.9 & 21.4±20.2 & 0.974 & 40.1±18.9 & 0.001 \\
FGF-23 (pg/ml) & 82.7±58.5 & 70.3±50.5 & 0.151 & 48.9±45.6 & 0.005 \\
IL-6 (pg/ml) & 5.5±5.8 & 5.0±4.0 & 0.653 & 3.3±2.5 & 0.002 \\
E-selectin (ng/ml) & 57.9±25.2 & 54.2±22.0 & 0.281 & 51.6±18.0 & 0.581 \\
vWF (mU/ml) & 1128±166 & 1076±379 & 0.689 & 1225±253 & 0.103 \\
FMD (%) & 7.6±2.3 & 8.0±2.7 & 0.231 & 13.8±4.3 & <0.0001 \\
PWV (mmHg) & 7.9±1.4 & 8.0±1.3 & 0.092 & 7.3±1.3 & 0.005 \\

\textbf{Conclusions:} Cholecalciferol supplementation corrected vitamin D deficiency, improved FMD and PWV, and decreased serum levels of FGF-23 and IL-6 in subjects with non-diabetic CKD.

\textit{Funding:} Government Support - Non-U.S.
TH-PO330
Transcriptomic Analysis Reveals Molecular Mechanisms Underlying the Beneficial Effect of Lipoprotein-Apheresis (LA) in Blunting Atherosclerosis Progression in Familial Hypercholesterolemia
Simona Simone,1 Annarita Chieli,2 Maria Grazia Zenti,2 Matteo Accetturo,2 Paola Pontrelli,2 F. Rasco,2 Gianluigi Zaza,2 Antonio Lupo,1 Loreto Gesualdo,3 Giuseppe Grandaliano,3 Giovanni B. Pertosa.1 1 Univ of Bari, 2 Univ of Foggia, 3 Univ of Verona.

Background: LA is a potentially valuable treatment applied to conventional therapy-resistant hypercholesterolemic patients. Several clinical studies suggest that LA may reduce the recurrence of cardiovascular events, but the molecular mechanisms underlying this effect are still unknown. The aim of the study was to identify the modulation of peripheral blood mononuclear cell (PBMC) transcriptomic profile induced by LA.

Methods: The transcriptomic profile was evaluated in PBMCs isolated from 6 FH patients before and after LA by Microarray (Agilent Technologies). The results were evaluated by statistical (Genespring software) and functional pathway analysis (Ingenuity Pathway Analysis, IPA). The transcriptomic data were validated by real-time PCR in an independent testing-group (n=10).

Results: Using a fold-change (FC)=2, we demonstrated that LA modulates the expression of 240 genes. The top canonical pathways were: communication between innate and adaptive immune cells (p=0.0004), natural killer cell signaling (p=0.0004) and atherosclerosis signaling (p=0.0003). Many pro-inflammatory cytokines involved in the development and progression of the atherosclerotic process were significantly down-regulated: Interleukin 1 (IL-1 FC=-2.97), IL-6 (FC=-2.07), IL-8 (FC=-3.56) ed Amphiregulin (AREG FC=-3.5). Quantitative real-time PCR confirmed that IL-1 (-84%; p=0.0004), IL-6 (-69%; p=0.01), IL-8 (-75%; p=0.005) and AREG (-96% p=0.0002) were down-regulated after LA.

Conclusions: Our data suggest that LA may contribute to cardiovascular risk reduction through the modulation of different pathways involved in the progression of atherosclerotic disease and improvement of microcirculation. This observation might open new perspectives in the prevention of cardiovascular risk in patients with FH.

Funding: Government Support - Non-U.S.

TH-PO331
Adipose-Derived Mesenchymal Stem Cells (MSCs) from Human Atherosclerotic Renovascular Disease (RVD) Have Increased DNA Damage and Lower Angiogenesis as Compared with Normal Kidney Donors That Can Be Modified by Hypoxia
Ahmed Saad,2 Allan B. Dietz,3 Sandra Herrmann,2 LaTonya J. Hickson,2 Andre J. Van Wijnen,3 Lilach O. Lerman,2 Stephen C. Textor. Mayo Clinic.

Background: MSCs support angiogenic and immunomodulatory processes. Whether these properties are modified in older patients with RVD is not known. Hypoxic conditions modify functional and growth characteristics of MSCs and may affect their role in ischemic kidney tissue. We tested the hypothesis that MSCs from RVD patients differ from MSCs from healthy kidney donors, and that hypoxia changes their functional and molecular properties to promote angiogenesis.

Methods: MSCs obtained from adipose tissue of 11 patients with RVD (age =74.5 ±19.9) and 10 healthy subjects (age= 51.2±16.7) cultured under normoxia (20% O2) or hypoxia (1% O2) for 3-4 days. Expression of genes and microRNAs analyzed using RNA-sequenceing and RT-Quantitative PCR, H2AX and MSC migration using western blot. Sequestration of VEGF and HGF was quantified in supernatant using ELISA, and apoptosis using Annexin-V flow cytometry.

Results: MSCs from RVD patients proliferated normally, but exhibited increased DNA damage and reduced migration. VEGF protein secretion was lower in RVD MSCs (p= 0.05) while HGF was slightly higher. Both patterns were reversed during growth under hypoxic conditions.

Conclusions: Hypoxia upregulated expression of pro-angiogenic mRNAs in MSCs (VEGF, FGF, SPC and ANGPTLA) and downregulated expression of related miRNAs (e.g., miR-15a, miR-16, miR-93 and miR-424) whereas miR-210 was upregulated.

Funding: NIDDK Support

TH-PO332
Intraarterial Autologous Mesenchymal Stem Cells (MSC) Increase Renal Blood Flow and Preserve Kidney Function in Patients with Atherosclerotic Renovascular Disease (RVD)
Ahmed Saad,1 Sandra Herrmann,2 Alfonso Eirin,1 LaTonya J. Hickson,2 Michael A. Mckusick,2 Allan B. Dietz,1 Lilach O. Lerman,3 Stephen C. Textor,3 James Glocacker,2 Andre J. Van Wijnen. Mayo Clinic.

Background: Atherosclerotic RVD reduces renal blood flow (RBF), GFR and accelerates both hypertension and post-stenotic kidney (SK) tissue injury. Preclinical studies indicate that MSCs stimulate angiogenesis and modify immune function in experimental RVD. We tested the hypothesis that autologous MSCs would be safe and improve SK perfusion and function in a phase-I study of patients with RVD.

Methods: Adipose derived MSCs were collected from 14 RVD patients and expanded in platelet lysate media. Inpatient studies performed during fixed Na+ intake and ACE/ARB Rx before and 3 months after unilateral intra-arterial injection of 1.0-2.5 x 10^5/kg MSCs into the SK. Patients with RVD treated with standardized medical therapy alone (n=14), matched for age, severity of stenosis, and GFR, served as a control group. SK cortical perfusion and RBF were measured using multidetector CT, GFR by iothalamate clearance, and renal tissue oxygenation by BOLD-MRI at 3T.

Results: Age, GFR, and degree of stenosis did not differ between groups. MSC infusions were well-tolerated with no adverse effects. SK-RBF and cortical perfusion increased after 3 months (p<0.05). Fractional hypoxia (%D2=30 sec) decreased in MSC group. Iohalate SK-GFR remained stable during 3 months after MSC, but fell in the control group.

Conclusions: In this first-in-man study in 14 patients with atherosclerotic RVD, a single injection of MSCs into the SK increased cortical perfusion and RBF after 3 months. Increased perfusion was associated with reduction in tissue hypoxia and preserved GFR. Our results demonstrate the capability of MSCs to improve oxygenation and RBF in the human kidney in-vivo and support a potential role for MSCs in the management of ischaemic renal disease.

Funding: NIDDK Support

TH-PO333
Notch Signaling Mediates Indoxyl Sulfate-Induced Atherogenesis in Chronic Kidney Disease
Toshiaki Nakano,1 Mingxian Chen,2 Diego Vinicius Santinellli Pestana,1 Shunsuke Katsuki,1 Elena Aikawa,1 Masanori Aikawa.2 Dept of Medicine, Brigham and Women's Hospital, Boston, MA.

Background: Chronic kidney disease (CKD) increases cardiovascular risk, however, the mechanisms of atherogenesis in CKD remain obscure. We previously demonstrated that the Notch signaling ligand Delta-like-4 (Dll4) promotes macrophage activation. We investigated the causal role of the Dll4-Notch pathway in vascular inflammation in CKD.

Methods: We examined pro-inflammatory effects of indoxyl sulfate in human primary macrophages and C57BL/6 mice. To evaluate the role of Notch signaling in atherogenesis in CKD, we performed 5/6 nephrectomy in high-fed LDL receptor-deficient (Ldlr-/–) mice and administered Dll4 neutralizing antibody (Ab) or control IgG for 19 weeks (n=13-14/group).

Conclusions: In the present study, we investigated the role of the Dll4-Notch pathway in vascular inflammation in CKD. We previously demonstrated that the Notch signaling ligand Delta-like-4 (Dll4) promotes macrophage activation in human primary macrophages and C57BL/6 mice. To evaluate the role of Notch signaling in atherogenesis in CKD, we performed 5/6 nephrectomy in high-fat-fed LDL receptor-deficient (Ldlr-/–) mice and administered Dll4 neutralizing antibody (Ab) or control IgG for 19 weeks (n=13-14/group).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: [In vivo] In human macrophages, clinically relevant concentrations of indoxyl sulfate (0.5-1.0 mM) induced the expression of pro-inflammatory molecules IL-1β, TNFα, and MCP-1 and Notch-related genes (e.g., DI4, Notch-1, Hey2), which was suppressed by Notch inhibition with the γ-Secretase inhibitor DAPT (fig. A). [In vivo] Indoxyl sulfate administration in C57BL/6 mice (100mg/kg/day, 7 days) induced activation of peritoneal macrophages, which DI4 Ab treatment suppressed. In Ldlr−/− mice, ≥5/6 nephrectomy induced IL-1β, IL-6, Tnfa, and MCP-1 in splenic macrophages, and accelerated aortic atherosclerosis and calcification. DI4 blockade reduced the size of atherosclerotic lesions and macrophage accumulation as compared to IgG treatment (fig.B). DI4 Ab also suppressed aortic calcification as gauged by alkaline phosphate activity and molecular imaging of ostegenic activity (OsteoSense, fig.B).

Conclusions: DI4-Notch signaling mediates indoxyl sulfate-induced macrophage activation and promotes atherosclerotic plaque inflammation and calcification in CKD.

TH-PO334
Atherosclerosis a Circulatory Disease: The Pivotal Role of Primed Neutrophils
Evan Klieger,1 Shifra Sela,1 Ronit Geron,2 Galina Shapiro,3 Batya Kristal,3 Eliachar Research Laboratory, Galilee Medical Center, Nahariya, Israel; 2Nephrology, Galilee Medical Center, Nahariya, Israel; 3Bar-Ilan Univ Faculty of Medicine in the Galilee, Safed, Israel.

Background: Endothelial dysfunction and monocytes transmigration and differentiation, underlie the development of atherosclerosis. Increased counts and priming of circulating neutrophils are associated with atherosclerosis however, the role of neutrophils in the accelerated atherosclerotic process of hemodialysis (HD) patients is still unclear. We hypothesize that atherosclerosis is a circulatory disease, where peripheral primed neutrophils activate monocytes and endothelium concomitantly, at the blood-tissue interface. Our aims were to examine monocytes transmigration through endothelial layer and their post-transmigration activation, induced ex-vivo by primed neutrophils, separated from HD patients.

Methods: A unique ex-vivo co-culture system of 3 cell types was developed in this study, enabling interactions among: primary endothelial cells (HUVEC), monocytes (THP-1, cell line) and in-vivo primed neutrophils from HD and Healthy Controls (HC), in order to mimic the initiation of the atherosclerotic process. The interactions among these cells were examined at the cellular, protein and gene expression levels.

Results: Pre-exposed HUVEC to HD/HC neutrophils showed a significant monocytes transmigration yield, 120-170% above HC. Monocyte exposure to HD neutrophils induced pre- and post-transmigration activation compared to HC. When the 3 cell types were co-cultivated at the same time, MCP-1 protein levels released from HUVEC, activation markers on HUVEC (CD54, CXCL1) and monocytes (CXCR1, CCR2) were increased. We have found that when the 3 cell types were co-cultivated with HD neutrophils at the same time, monocytes transmigration yield decreased to 70% compared to HC due to adhesion-dependent transmigration of monocytes to HUVEC.

Conclusions: We conclude that peripheral primed neutrophils play a pivotal role in the initiation of the atherosclerotic process suggesting atherosclerosis as a circulatory disease. Primed neutrophils can be used as a mediator and a biomarker of atherosclerosis even before plaque formation.

TH-PO335
Cardiac and Inflammatory Biomarkers and Their Role in the Pathogenesis of Heart Failure in ESRD
Ryan McMillian,1 Vinod K. Bansal,2 Debra H. Connolly,1 Fared Khoury,1 Pathology, Loyola Univers Medical Center, Maywood, IL; 2Nephrology, Loyola Univers Medical Center, Maywood, IL.

Background: Heart failure (HF) is highly prevalent in patients with End-Stage Renal Disease with a prevalence of 40%. HF is characterized by left ventricular hypertrophy, diastolic and systolic left ventricular dysfunction and dysmyocardopathy. The purpose of this study was to determine the role of cardiac and inflammatory biomarkers in the pathogenesis of HF in ESRD patients.

Methods: Blood samples from maintenance hemodialysis patients were collected and stored at -70° C. Fifty plasma samples from healthy individuals were used as control. These samples were used to profile KIM-1, NT-pro-BNP, NGAL, and C reactive protein (CRP) in patients with ESRD compared to hemodialysis patients (n=23). Urine samples from these patients with ESRD, as compared to non-HF patients with ESRD, had significantly elevated NT-pro-BNP (P = 0.0194 | % change = 52.9) and KIM-1 (P = 0.0495 | % change = 58.5%). There were no differences found between age groups, except <60 y.o KIM-1 vs 60-69 y.o KIM-1. NT-pro-BNP in ESRD patients with HF was found to correlate with K+ (P = 0.033 | R = -0.39), Ca+ (P = 0.028 | R = 0.38), and Heparin anti Xa (P = 0.045 | R = 0.35). KIM-1 in ESRD patients with HF was found to correlate with Creatinine (P = 0.0175 | R = -0.41), EGFR (P = 0.008 | R = 0.45), Phosphate (P = 0.002 | R = -0.51), Intact PTH (P = 0.043 | R = -0.36), Calcium Phosphate Product (P = 0.002 | R = 0.92), and Vitamin D (P = 0.037 | R = 0.36).

Conclusions: Elevated plasma NT-pro-BNP and KIM-1 in all of the ESRD patients and ESRD patients with HF suggest that natriuretic peptides and KIM-1 may contribute to the pathogenesis of HF in ESRD patients. Elevated NT-pro-BNP further supports previous studies demonstrating NT-pro-BNP’s potential diagnostic and prognostic utility.

TH-PO336
Glomerular Hyperfiltration Is Associated with Elevated Urinary Mitochondrial-DNA Copy Number in African American Hypertensive Patients
Alfonso Finin,1 Ahmed Saad,1 John R. Woolard,2 Luis A. Juncos,2 Hai Tang,2 Amir Lerman,1 Lilach O. Lerman,1 Maya Clinic; 2Univ of Mississippi.

Background: Glomerular hyperfiltration may contribute to the high incidence of renal disease in African Americans essential hypertensive (AAEH) patients, but the precise mechanisms responsible for renal injury have not been elucidated. Mitochondria are important determinants of renal injury in hypertension, and increased levels of mitochondrial DNA (mtDNA) in the urine may indicate renal mitochondrial injury. We hypothesized that urine mtDNA copy numbers would be higher in AAEH compared to Caucasian essential hypertensive (EH) patients.

Methods: We prospectively measured systemic and urinary copy number of the mtDNA genes COX3 and ND1 by quantitative-PCR in Caucasian EH and AAEH patients during constant sodium intake and anti-hypertensive regimens, and compared them with healthy volunteers (HV) (n=23 each). Urinary mtDNA levels were corrected to the nuclear control gene RNAse-P and expressed as mtDNA/nDNA to identify mitochondrial-specific cellular damage.

Results: Blood pressure was similarly elevated in EH and AAEH, yet body mass index (BMI) and estimated glomerular filtration rate (eGFR) were higher and age lower in AAEH versus HV and EH (Table). Urinary (but not plasma) COX3 and ND1 were higher in EH compared to HV, and further elevated in AAEH patients (Figure). In AAEH patients, urinary COX3 and ND1 directly correlated with eGFR. In multivariate analysis, eGFR remained the only predictor of elevated urinary COX3 and ND1 levels.

Conclusions: Urinary fragments of the mitochondrial genome are elevated in AAEH patients and correlate with glomerular hyperfiltration. These results are consistent with mitochondrial injury that may aggravate renal damage and accelerate hypertension-related morbidity/mortality rates in AAEH.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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170A
and sepsis. An imbalance between TIE2 ligands, specifically an increase in antagonistic ANGPT2 and decrease in agonistic ANGPT1, is linked to vascular destabilization, increased leakage, and inflammation. We evaluated how augmentation of TIE2 activation, through genetic deletion of its inactivating phosphatase VE-PTP (PTPRB), affects renal function and blood pressure.

Using an inducible knockout mouse model, we induced deletion of VE-PTP in neonates and assessed potentialization of TIE2 autophosphorylation. Glomerular filtration rates (GFR) were determined by FITC-sinistin clearance while blood pressure (BP) values were measured by tail cuff plethysmography. Nitric oxide production was reduced in mice by blocking endogenous NO through a week-long administration on the drug L-NAME in drinking water.

**Results:** TIE2 phosphorylation is elevated in VE-PTP iKO mice versus control littermates. GFR increased 53.1±9% while systolic BP dropped 25.8±8% in VE-PTP iKO mice relative to control cohorts. AKT and ENOS phosphorylation were also higher in VE-PTP iKO mutant kidneys suggesting that increased NO production might underlie altered GFR and BP. Consistently, L-NAME treatment normalized GFR and BP values in VE-PTP iKO mutants to wild-type control levels.

**Conclusions:** Genetic loss of VE-PTP causes increased TIE2 activity leading to sustained AKT-dependent NO signaling and eventual rise in circulating levels of NO. Loss of VE-PTP thus promotes vasodilation and vascular compliance resulting in lower BP and enhanced renal blood flow and glomerular filtration. Targeted inhibition of VE-PTP therefore holds promise in maintaining renal function in conditions such as CKD.

**Funding:** Other NIH Support - RC1HL124120, Pharmaceutical Company Support - Eli Lilly & Company

**TH-PO338**

**Novel Mechanism for Cardiovascular Protective Effect of Vitamin D and ACE-Inhibitors in Chronic Kidney Disease: Correction of Impaired Cholesterol Efflux Induced by Plasma from Patients with Chronic Kidney Disease Nobuyuki (Bill) Miyawaki, Nicole Marie Siegert, Heather Anne Renna, Hirra A. Arain, Farah Daccueil, Joseph Mattana, Joshua De Leon, Allison B. Reiss. Medicine, Winthrop Univ Hospital, Mineola, NY.

In chronic kidney disease (CKD) and dialysis, ACE-inhibitors (ACEi) and Vitamin D (Vit D) reduce mortality/cardiovascular disease (CVD) risk while statins lose efficacy. Hence the atherosclerotic mechanism with advancing CKD likely differs from the general population. Macrophage lipid handling defect may be a pivotal proatherosclerotic factor in CKD. This study aims to detect changes in reverse cholesterol transport gene expression and foam cell accumulation in the setting of CKD in the presence and absence of Vit D or ACEi.

**Methods:** Following THP-1 human macrophage (10^5) incubation for 24h with pooled plasma from 5 CKD Stage 4-5 patients or with control media ± Vit D (calcitriol, 10^{-10} M), or ACEi (enalapril, 50 LM), mRNA was isolated and reverse transcribed. The resulting cDNA was subjected to quantitative real-time PCR using specific primers for ATP binding cassette transporter (ABCA1) and G1 (cholesterol efflux proteins). Foam cell quantification using Dil-acytetylated-LDL with VectaShield mounting medium was used.

**Results:** Plasma suppressed ABCA1 in macrophages while concurrent Vit D restored ABCA1 mRNA, increasing it by 44±2.8% (p<0.0001). Concurrent exposure to CKD plasma + ACEi increased ABCA1 dramatically by 148±4.9% (p<0.0001). ABCG1 expression did not increase (8.5±8.5%, nonsig) with Vit D, but increased 52±15% (p<0.0001) with ACEi. In control media, neither Vit D nor ACEi elicited significant response. In macrophages exposed to CKD plasma, foam cell accumulation decreased with addition of Vit D 54±22% (p<0.0001)

**Conclusions:** This is the first direct demonstration of an atheroprotective mechanism from Vit D and ACEi in the CKD milieu. ACEi and Vit D each promote cholesterol efflux with ACEi affecting ABCA1 and G1, while Vit D restored ABCA1 alone. Vit D reduced foam cell accumulation in a study in pig. Further studies of mechanism, synergy of Vit D + ACEi and cholesterol handling in CKD are planned. This novel insight may define viable therapeutic targets.

**Funding:** Private Foundation Support

**TH-PO339**

**Differential Role of Vascular Contractile Reactivity in Salt Wasting- and Salt Restriction-Induced Hypotension Saeed Alshahrani,1,2 Robert Rapoport,1 Manoocher Soleimani,1,3 Pharmacology and Cell Biophysics, Univ of Cincinnati, Cincinnati, OH; 1Nephrology and Hypertension, Univ of Cincinnati, Cincinnati, OH.

**Background:** While both salt wasting and salt restriction associated with NaCl-Cotransporter (NCC) dysfunction result in hypotension, whether decreased vascular contractility per se contributes to the hypotension in these models of volume depletion has not been entertained. This study investigated vascular contractility in mouse aorta in models of 1) sodium wasting due to double knockout (KO) of NCC and pendrin (the apical chloride/bicarbonate exchanger, ClHCO3-intercalated cells) and 2) NCC KO with salt restricted diet, both of which are associated with hypotension.

**Methods:** To determine vascular contractility, aorta was removed from 8-12 months male and female mice, and 4-5 mm ring segments placed in an isometric contractile apparatus under optimal resting tension of 3 g-force. Vessels were then challenged with maximal or near maximal agonist concentrations.

**Results:** Maximal contraction of aorta segments to KCl and phenylephrine in the NCC/pendrin double KO compared to wild type were decreased by 30% and 55%, respectively.

**Conclusions:** To these agents remained unaltered. In contrast, maximal contractions to KCl, and phenylephrine in NCC KO with and without salt restricted diet and sensitivity also remained unchanged.

**Funding:** VA Support

**TH-PO340**

**Role of AT1a Receptor in 2K1C Model of Renovascular Hypertension and Its Impact on Renal ACE2 and NEP Protein Expressions Nadia Grobe, Laale F. Alawi, Rucha Fadnavis, Khalid M. Elased. Pharmacology & Toxicology, Wright State Univ, Dayton, OH.

**Background:** Angiotensin (Ang) II is the major biologically active peptide of the renin angiotensin system (RAS). Elevated formation of Ang II contributes to initiation and progression of chronic kidney disease via its action as a vasoconstrictor through binding to the Ang II type 1 receptor (AT1R). Ang II is antagonized by the vasodilator Ang (1-7), partly generated by angiotensin converting enzyme 2 (ACE2) and nephrilysin (NEP). The two-kidney, one clip (2K1C) Goldblatt model is an experimental approach designed to mimic renovascular hypertension. We tested the hypothesis that renovascular hypertension in the 2K1C model is mediated by AT1AR and investigated its role on renal ACE2 and NEP.

**Methods:** For blood pressure (BP) measurements, a radiotransmitter probe was inserted into the left carotid artery of AT1,R knockout (KO) and wild type (WT) mice. 2K1C was induced by constricting the left renal artery using a shaped silver clip leaving a 0.12 mm gap for ischemic blood flow. Histochemistry, Immunofluorescence, Western blot, and RAS enzyme assays were used to study renal histology, protein expression and activity.

**Results:** At baseline, BP was significantly lower in KO compared to WT (90.4±8.4 mm Hg vs. 152±1.5 5.9 mm Hg, p<0.05). BP measurements revealed a significant increase of 46.1±6.8 mm Hg in 2K1C WT compared to 2K1C KO (145.3±12.9 mm Hg vs. 92.2±4.9 mmHg, p<0.05). Renal pathologies were exacerbated in the 2K1C model as revealed by a significant increase in mesangial expansion and renal fibrosis. Immunofluorescence demonstrated that ACE2 and NEP were mainly co-localized in the proximal and distal renal tubules. Western blot analysis showed renal ACE2 and NEP were significantly reduced in clipped 2K1C kidneys in both WT and KO compared to the unclipped kidneys or to sham controls. However, renal and urinary ACE2 activity was not altered by 2K1C.

**Conclusions:** Taken together, these results suggest that renovascular hypertension are mediated via AT1,R, and that the receptor has no impact on the decreased expression of renal ACE2 and NEP in renovascular hypertension.

**TH-PO341**

**Impact of Soluble Epoxide Hydrolase Inhibition on the Cardiovascular Consequences of Chronic Kidney Disease Dominique Guebre,1,2 Priya S. Roche,1 Mounid Haider1,2, Valerie Brunel,1,2 Vincent Richard,1,2 Jeremy Bellien,3 1Nephrology, Rouen Univ Hospital, Rouen, France; 2U1096, INSERM, Rouen, France; 3Biochemistry, Rouen Univ Hospital, Rouen, France.

**Background:** Cardiovascular (CV) events are the leading cause of morbidity-mortality in chronic kidney disease (CKD). Epoxyeicosatrienoic acids (EETs) are endothelium-derived metabolites of arachidonic acid, with vasodilatory, anti-inflammatory, natriuretic and antiproliferative properties. The aim of this project is to study, in experimental CKD, the cardiac impact of the pharmacological inhibition of soluble epoxide hydrolase (sEH), which degrades EETs.

**Methods:** 129Sv mice were subjected to 5/6 nephrectomy, and were assigned to t-AUCB, amiloride or placebo for 10 weeks. Echocardiography was performed before sacrifice. Hearts were weighed and histological analyses were performed to evaluate fibrosis. Vascular function was studied ex vivo on the mesenteric arterial. Sequential blood and urine tests were performed to assess kidney function.

**Results:** Following 5/6 Nx, mice developed CKD. The CV consequences were heart hypertrophy (heart weight/total length Nx vs Sham 7.9±0.3 vs 6.5±0.5 mg/mm, p<0.05), diastolic dysfunction (E/A ratio Nx vs Sham 1.29±0.05 vs 0.97±0.04, p<0.001) and diffuse fibrosis (Nx vs Sham 57.8±1.8 vs 1.8±1.8 %, p<0.001). t-AUCB significantly prevented left ventricular hypertrophy (t-AUCB 6.7±0.2 mg/mm, p<0.05 vs Nx), diastolic dysfunction (t-AUCB 1.12±0.04 vs 0.97±0.04, p<0.05 vs Nx), and diffuse fibrosis (t-AUCB 5.4±1.5 vs 11.8±2.8 %, p<0.05 vs Nx). t-AUCB treatment prevented the development of hypertension in this model.

**Conclusions:** Inhibition of sEH reduces the cardiac hypertrophy and diastolic dysfunction associated with CKD. These beneficial effects of inhibiting sEH hold a therapeutic potential in CKD patients to treat type 4 cardiovascular disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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TH-P0342

Rats with Adenine-Induced Chronic Renal Failure Develop Left Ventricular Hypertrophy with Selective Diastolic Dysfunction
Pavlos Kashoulis,1 Emman Shubbar,1 Lisa Nguy,1,2 Cecilia W. Guron,1 Gregor S. Guron.1 1Dept of Molecular and Clinical Medicine, Medicine, Sahlgrenska Academy at the Univ of Gothenburg, Sweden.

Background: Rats with adenine-induced chronic renal failure (ACRF) develop severe cardiac insufficiency and metabolic abnormalities characteristic of uremia. The aim of the present study was to analyze left ventricular (LV) morphology and function in rats with ACRF.

Methods: Male Sprague-Dawley rats received either chow containing adenine or were pair-fed an identical diet without adenine (controls, C). After 6 weeks rats were euthanized with isoflurane and cardiac function was assessed by echocardiography. At 12-13 weeks isoflurane-anesthetized rats were instrumented for measurements of aortic and LV pressures.

Results: Rats with ACRF showed an increase in mean arterial pressure (115±6 vs. 106±7 mmHg, p<0.05) and LV end-diastolic pressure (15±5 vs. 8±6 mmHg, p<0.05) vs. controls. Rats with ACRF had reduced early diastolic tissue Doppler velocities, enlarged left atrial diameter (4.8±0.8 vs. 3.5±0.4 mm, p<0.05) but increased cardiac output (211±66 vs. 149±24 ml/min, p<0.05). LV end-diastolic pressure was elevated in ACRF rats (15±5 vs. 8.1±1 mmHg, p<0.01). In the LV of ACRF animals there were statistically significant (p<0.05) increases in cardiomyocyte diameter, proliferation and apoptosis vs. controls.

Conclusions: Rats with ACRF develop LV hypertrophy, increased cardiomyocyte apoptosis, and diastolic dysfunction with preserved systolic function. These cardiac abnormalities resemble those in uremic patients making this a promising animal model for future studies of uremic cardiomyopathy.

TH-P0343

Disruption of Angiopoietin-TIE2 Signaling Causes Cystic Kidney Disease
Yaël Jenic-Kozlovsky,1 Rizaldy P. Scott, Benjamin R. Thomson, Shinji Ohtani, Ming Li, Gi H. Chung,2 Sue H. Wu,3 Susan E. Quaggin.1 Feinberg Cardiovascular Research Inst, Chicago, IL.

Background: The angiopoietin ligands ANGPT1 and ANGPT2, and their cognate receptor TIE2 are well recognized for their important roles in the development and remodelling of blood and lymphatic vessels. In this study, we sought to determine how angiopoietin-TIE2 signaling regulates the development and organization of the complex renal vasculature. Surprisingly, we found that loss of ANGPT1 and ANGPT2, or TIE2 causes cystic kidney disease.

Methods: Using a Cre-based inducible gene targeting strategy we deleted Ang1, Ang2, and Tie2 at mid-gestation or postnatally in the mouse in order to overcome null embryonic lethality.

Results: Compound ablation of Ang1 and Ang2, or Tie2 leads to a reduction of renal blood vascular density. Unexpectedly, mice lacking Ang1 and Ang2, or Tie2 develop renal cysts evident early as P10. These cysts are lined by myofibroblast-like cells. Cysts do not express epithelial, endothelial, or lymphatic markers. Vascular-specific deletion of these genes postnatally (P1-P3) does not lead to cysts suggesting that TIE2 signaling within late gestation is likely mitigating abnormal vascular development and cysts if perturbed. While investigating the lymphatic vasculature in the kidney using Prox1 reporter mice we discovered novel “hybrid” vessels that co-express lymphatic (Prox1) and blood vessel (CD31, CD34) markers, but not other classic lymphatic markers like Lyve1 and podoplanin.

Conclusions: Inactivation of AngPT1-TIE2 signaling affects the gross architecture and density of the renal vasculature, and a subsequent emergence of renal cysts. Newly identified novel hybrid vascular bundles in the kidney raises the question of whether such vascular remodeling is reminiscent of Schlemm’s canal defects in the eye, when ANGPT1-TIE2 signaling is absent. These findings highlight a hitherto unidentified link between attenuated angiopoietin-TIE2 signaling and the pathogenesis of renal cysts suggesting a potential therapeutic target that can be used to treat cystic kidney disease.

Funding: Other NIH Support - HL124120

TH-P0344

CPAP Treatment for Obstructive Sleep Apnea Improves the Heart Rate Variability Response to Angiotensin II
David Donald MacTavish Nicholl,1 Peter C. Halliday,1 David D. Manny,1 George Handley,2 Darlene Y. Solà,2 Sofia B. Ahmed.1 1Univ of Calgary, Calgary, AB, Canada; 2Healthy Heart and Vascular Health, Calgary, AB, Canada.

Background: Obstructive sleep apnea (OSA) is common in chronic kidney disease (CKD). Both conditions are associated with decreased heart rate variability (HRV) and increased renin-angiotensin system activity, each a risk factor for progression of kidney disease and cardiovascular disease. Surprisingly, we found that OSA exacerbated the link between attenuated angiopoietin-TIE2 signaling and the pathogenesis of renal cysts.

Methods: We performed haplotype analyses, methylation studies, chromatin immunoprecipitation (ChIP) analyses, immunoblotting, and CD177 expression studies in human hematopoietic stem cells, neutrophils, and HeLa cells.

Results: In our healthy cohort, 94% of 165 individuals showed a CD177+ neutrophil subset with a median size of 60 %. CD177+, but not CD177-, neutrophils, produced CD177 protein and mRNA. Haplotype analysis indicated parental-inherited mononucleic CD177 gene expression. Hematopoietic stem cells silenced one CD177 allele during neural differentiation. A HeLa cell model recapitulated key neutrophil findings of CD177+ expression. We hypothesized that the CD177 promoter drives expression of the CD177 gene.

Conclusions: We propose that epigenetic mechanisms are responsible for the two distinct CD177 neutrophil subsets.
Far Infrared Irradiation Inhibits Platelet Adhesion through the Induction of ADAMTS-13

Methods: Histologic changes and expressions of collagen IV, fibronectin, angiopoietin II (Ang II), Ang II type 1 receptor (AT1R), Ang II type 2 receptor (AT2R), prorenin receptor (PRR), Mas receptor (MasR), angiopoietin converting enzyme (ACE), ACE2, endothelial nitric oxide synthase (eNOS), NADPH oxidase 2 and 4 (NOX2 and NOX4), superoxide dismutase 1 and 2 (SOD1 and SOD2), silent information regulator T1 (SIRT1), peroxisome proliferator-activated receptor (PPAR) co-activator 1u (PGC-1u), and PPARa were measured in the thoracic aortas from 24-month-old C57BL/6 mice with or without resveratrol treatment.

Results: The aorta media thickness significantly decreased in the resveratrol-treated mice compared to the control mice (77.0±15.9 μm, P<0.001). The aortic expressions of collagen IV and fibronectin decreased in the resveratrol-treated mice compared with the control mice. Resveratrol treatment decreased the aortic expressions of Ang II, ACE, AT1R and PRR, and increased those of AT2R and MasR. The expressions of eNOS, SOD1, SOD2, PPARa, SIRT1, PGC-1u increased with resveratrol treatment, while the expression of NOX4 decreased.

Conclusions: The results suggest that resveratrol has protective effects on arterial aging by amelioration of oxidative stress and inflammation, which was associated with the reduction in the PRR-ACE-Ang II-AT1R axis and enhancement of the ATR2-MasR axis.

Funding: Government Support - Non-U.S.

Erythropoiesis-Stimulating Agent for Treatment of Anemia Alleviates Deterioration of Erythrocyte Deformability Associated with Chronic Kidney Disease

Methods: Methods: 173A

Results: Gli1+ progenitor cells were sorted and single cell multiomic analysis was performed. As VSMC marker expression increases, influential genes were CNN1,Tagln,CD140a and CD34. Tagln, a VSMC genes were differentially expressed between the clusters (ANOVA, p<0.0016): 32 genes of interest. Data was analyzed using the R package SINGuLAR Analysis Toolset.

Conclusions: In CKD rats, not only did Hb decrease but qualitative deterioration of deformability and stability in erythrocytes was also observed. These aspects were improved by therapeutic administration of C.E.R.A. The appropriate ESA therapy for anemia may contribute to a better understanding of the therapeutic benefits of ESA treatment in CKD-associated anemia.

Funding: NIH Support - NHLBI and K12 (Child Health Research Center Training Grant)

Single Cell Gene Expression of Adventitial Gli1+ MSC Indicates a Heterogeneous Pool of Myofibroblast and VSMC Progenitors

Methods: 1,3

Results: Fbn1E57K/E57K mice were hypertensive and developed arterial elongation, tortuosity and ascending aortic aneurysm. Mesenchymal markers were expressed in the smooth muscle and small arterioles. These data suggest that far infrared radiation inhibits platelet adhesion to endothelial cell through the induction of ADAMTS-13. Our results may provide information for further exploring the mechanisms of FIR in the prevention of thrombus formation.

Funding: Government Support - Non-U.S.
TH-P0352

Association of Vascular Injury Markers with Rate of GFR Decline in Type 2 Diabetes

Alexander Mohtadi, Olufemi B. Aina, Amcet Kumar, Candace D. Grant, Joseph Mattana, Shayan Shirazian. Winthrop-Univ Hospital.

Background: Urine microalbumin levels are the most commonly used biomarker for vascular injury and progression of chronic kidney disease (CKD) in patients with type 2 diabetes (T2DM). However, nonalbuminuric patients with T2DM and CKD are also prone to vascular injury and CKD progression, warranting study of additional biomarkers. This study examines the association between vascular injury markers and CKD progression in patients with T2DM and CKD.

Methods: This is a retrospective study of 40 subjects with T2DM and stage 3 CKD who had vascular injury marker testing including urine microalbumin to creatinine ratio (UACR), von-Willebrand factor antigen, high sensitivity C-reactive protein, uric acid and circulating endothelial cell (CEC) levels. CEC levels were tested by VeriCel® using an immune-magnetic bead based assay. The primary outcome, slope of estimated glomerular filtration rate (GFR) decline, was calculated in subjects with over 16 months of follow-up from vascular injury marker testing, and at least 3 measured creatinines separated by 3 months using a line of best-fit. Pearson correlations were performed between slope of eGFR decline and other demographic and clinical predictors including vascular injury markers.

Results: Of the original 40 subjects, 30 had sufficient follow-up data for slope of eGFR decline calculation. This group was 53.3% male, 70% Caucasian, 23.3% African American, 6.7% Asian, and had a mean age of 69.8±8.1 years, diabetes duration of 16.5±5.9 years, UACR of 393.5±896.1 mcg/mg, slope of eGFR decline of -1.5±2.45 mL/1.73m2/year, and median follow-up time of 23 months. UACR levels (r=-0.37, p=0.042) and hemoglobin A1C levels (r=0.35, p=0.018) negatively correlated with slope of eGFR decline. There were no significant correlations between slope of eGFR decline and other vascular injury markers.

Conclusions: In this pilot study, only urine microalbumin levels showed a significant negative correlation with slope of eGFR decline in patients with T2DM and stage 3 CKD over the median of 23 months of follow-up. Large prospective studies are needed to determine whether other vascular injury markers associate with eGFR decline in this population.

TH-P0353

IRE1 Activation Is Required for Collagen Secretion by Vascular Smooth Muscle Cells

Victor Tat, Jeffrey G. Dickhout. Dept of Medicine, Div of Nephrology, McMaster-Univ and St. Joseph’s Healthcare Hamilton, Hamilton, ON, Canada.

Background: Vascular stiffening is positively associated with both hypertension and aging and is a strong predictor of end-organ damage. Fibrotic remodeling of the extracellular matrix by vascular smooth muscle cells (VSMCs) contributes to the stiffening of conduit arteries such as the aorta. Activation of the IRE1 pathway within the unfolded protein response (UPR) results in adaptive programs that increase protein folding capacity. We hypothesize VSMCs transitioning to a collagen-secreting phenotype in response to TGFB1 require the activation of IRE1. Inhibition of this pathway is hypothesized to reduce collagen secretion and hence prevent the development of fibrosis in the aorta.

Methods: Aortic smooth muscle cells were isolated from Wistar-Kyoto rats. Small molecule inhibitors of the IRE1α endonuclease domain, 4μ8c and STF-083010, were used to block IRE1 activity. Collagen production was measured using a dot blot for Type I collagen and a Picrosirius red-based microplate assay. Markers of UPR activation and ERS were assessed with Western blot. Aortic rings were harvested from 5-7 week old WKY rats and cultured for 5 days in the presence of TGFB1 (5 ng/mL) and 4μ8c (30 μM). Arterial compliance was measured using a wire myograph.

Results: Inhibition of IRE1 endonuclease activity dose-dependently reduced the production of collagen by VSMCs in response to either L-ascorbic acid or TGFB1. 4μ8c blocked the splicing of the transcription factor XBP1 and prevented the induction of the collagen-folding chaperones GRP78, GRP94 and PDI by tunicamycin. Aortic rings incubated with TGFB1 had reduced compliance, which was improved by co-treatment with 4μ8c.

Conclusions: These results suggest that activation of the IRE1 pathway is required for the secretion of collagen by VSMCs, leading to vascular fibrosis in the aorta. It is hypothesized that IRE1 blockade will have similar antifibrotic effects in other tissues such as the heart, kidney, and lung, where increased collagen deposition is linked with impaired function. These effects should be studied in other tissues, as IRE1 activation in fibroproliferative diseases may be a novel target for the treatment of fibroproliferative diseases. Funding: CIHR MOP-133484.

Kidney Foundation of Canada Krescent New Investigator (Dr. Dickhout).

Funding: Government Support - Non-U.S.

TH-P0356

Aryl Hydrocarbon Receptor Signaling Is An In Vivo Targetable Antiatherothrombotic Pathway

Mostafa Belghamem,1 Moshe Shashar,2 Jamaica Siwak,1 Faisal F. Alouis,1 Anqi Zhang,1 Jean M. Francis,2 Joel M. Henderson,1 Vipul C. Chitalia.2 1Dept of Pathology, Boston Univ Medical Center; Boston, MA; 2Nephrology, Boston Univ Medical Center; Boston, MA; 3Metabolomics Core, Boston Univ Medical Center; Boston, MA.

Background: CKD is characterized by the retention of several solutes of which indoxyl sulfate (IS) is highly thrombogenic. It enhances thrombosis by activating AHR to increase tissue factor levels, a key procoagulant. Although AHR inhibitors (AHRIs) significantly suppressed thrombosis in an ex vivo model, there is a dearth of in vivo proof of AHR as an antiatherothrombotic. There are limitations to current CKD animal models in that they retain nephrotic glomerulonephritis and unrelated specific cangestations of IS and also fail to recapitulate the prothrombotic phenotype of human CKD.

Methods: We generated a uremic thrombosis model by combining IS administration along with the inhibition of its urinary excretion using Probencid (Prob) in C57Bl/6 mice. The protocol with high IS levels similar to stage 5 CKD was used. The effect of AHRI was examined in three groups: I) IS, II) IS + Prob, and III) IS + Prob + AHRI (CH223191 10 mg/kg IP). Plasma IS levels were measured on day 0, 2, and 5 using LC/MS, and the animals were subjected to ferric chloride-mediated carotid injury. The onset of thrombosis was defined after the reduction of blood flow to the background and time to thrombosis served as a primary end point.

Results: IS in water (4mg/ml) along with Prob IP (150mg/kg) twice daily for 5 days resulted in a significant increase in IS levels greater than stage 5 CKD patients. The IS levels remained significantly higher from day 2 onwards. The time to thrombosis was significantly lower in IS + Prob (315.9±163.3 sec) compared to Prob (673.7±395.6 sec), and was significantly prolonged with AHRI (655.7±342.8 sec), despite similar IS levels in group II and III (p=0.49).

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

Underline represents presenting author.
Conclusions: With the IS levels similar to stage 5 CKD patients, this first uronic thrombosis study in a murine model successfully recapitulates enhanced thrombotic phenotype in humans CKD. Validating IS as a thrombogenic uronic solute in vivo, the above observations confirm the in vivo druggability of AHRI as a novel class of antithrombotic.

TH-PO357
Disruption of Glomerular Permeability Barrier Increases Apolipoprotein AI (ApoAI) Ultrafiltration which Regulates Interstitial Lymphangiogenesis Jianyong Zhong,1 Haichun Yang,1 Yohei Tsuchida,1 Taiji Matsusaka,2 Agnes B. Fogo,3 Valentina Kon.1 1Vanderbilt Univ Medical Center, Nashville, TN; 2Molecular Life Science, Tokai Univ, Isehara-shi, Kanagawa, Japan.

Background: Lymphatics not only return fluids/lipoproteins from the periphery to the circulation but have critical pathophysiology/therapeutic roles in disease e.g., atherosclerosis, cancer, hypertension. Lipoproteins themselves appear to regulate lymphangiogenesis, however, little is known about lipoprotein modulation of the intrarenal lymphatic network. We examined ApoAI modulation of lymphangiogenesis in proteinuric kidney injury.

Methods: We studied Nphs1-hC25 mice (NEP25) expressing human C25 in podocytes which can be injured by immunotoxin, LMB2. Six weeks after LMB2, we assessed glomerular filtration, excretion of albumin and ApoAI, examined the intrarenal lymphatic network with podoplanin, localized endogenous ApoAI, and stained for lipoprotein transporters (scavenger receptor class B member 1, SRBI). In vitro, we examined lymphatic endothelial cells exposed to ApoAI with/without transporter blocker.

Results: Lymphatic endothelial cells exposed to ApoAI showed increased cell viability, lower migration, and reduced lymphangiogenesis compared to vehicle-exposed cells. Blocking SRBI with BLT1 reduced cell viability and promoted more migration than ApoAI alone. In vivo, NEP25 mice had glomerulosclerosis, albuminuria and increased ApoAI excretion. Podocyte injury also caused more tubulointerstitial injury and more ApoAI localized to tubular epithelial cells and interstitium. After injury, tubular cells showed more SRBI and VEGF-C, a powerful lymphangiogenic stimulus, compared to nonproteinuric mice. NEP25 mice had a dramatically more dense and complex lymphatic network than wild type mice. Lymphatic vessels expressed SRBI that co-localized with reabsorbed ApoAI.

Conclusions: Proteinuric glomerular injury leads to more ApoAI in the ultrafiltrate, greater reabsorption by the proximal tubules into the interstitium and more ApoAI uptake by lymphatic endothelial cells via SRBI. We conclude that tubular VEGF-C secretion and lymphatic ApoAI absorption promote renal lymphangiogenesis.

TH-PO358
Abnormalities in Cholesterol Flux Pathway Induced by Plasma from Patients with Chronic Kidney Disease Farah Daccueil, Allison B. Reiss, Nicolle Marie Siegert, Joseph Mattana, Iryna Voloshyna, Lora Kasselman, Joshua De Leon, Nobuyuki (Bill) Miyawaki. Medicine, Winthrop Univ Hospital, Mineola, NY.

Background: The mechanism underlying chronic kidney disease (CKD) as a major risk factor for atherosclerosis and cardiovascular disease (CVD) has not been elucidated. Lipid profile is less predictable of CVD risk and statins lose benefit with advancing CKD. This study aims to detect changes in cholesterol transport gene expression and to determine if such changes adversely affect macrophage lipid handling in CKD leading to atheromatous foam cell formation.

Methods: THP-1 human macrophages (10^6/ml) were incubated for 18h-24h with plasma from 9 CKD patients not on dialysis and non-renal transplant or 10 healthy control (HC) subjects. Post-incubation, mRNA was isolated and reverse transcribed to cDNA, and subjected to quantitative real-time PCR using specific primers for ATP binding cassette transporter (ABC)A1 (cholesterol efflux protein) and CD36, a scavenger receptor with the capacity to endocytose oxidized LDL). Foam cell quantification using Dil-acetylated-LDL and VectaShield mounting medium was used on 5 samples from each group.

Results: PCR analysis showed that ABCA1 mRNA was reduced by 28±5% (p<0.0001) while CD36 mRNA was decreased by 35±6% (p<0.0001) in macrophages exposed to CKD plasma as compared to HC. Increase in foam cell accumulation in macrophages exposed to CKD plasma by 36±11% as calculated to total fluorescence per cell corrected for total nuclei in frame (p=0.01).

Conclusions: A different mechanism of lipid dysregulation in CKD based on impaired efflux, through proatherogenic suppression of ABCA1, differs from our finding in autoimmune rheumatic diseases where, in addition to lowering of ABCA1, augmentation of CD36 influx was observed. In CKD, oxidized lipid uptake appears less dependent on macrophage CD36. Statins reduce lipid influx via down regulation of CD36 but low CD36 efflux, through proatherogenic suppression of ABCA1, differs from our finding in CKD. Further studies are indicated to determine if statin therapy can improve macrophage lipid handling in CKD.

TH-PO359
Atorvastatin Decreases Vascular Wall Inflammation following Arteriogenous Fistula Creation in a Murine Model Jie Cui,1,2 Harkamal Singh Hjaj,2 Chase Kessinger,2 Farouc Amin Jaffer.1 1Nephrology Div, Massachusetts General Hospital, Boston, MA; 2Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA; 3Center for Systems Biology, Massachusetts General Hospital, Boston, MA.

Background: The most common cause of AVF failure is inflammation-driven neointimal hyperplasia and thrombosis. Statins have well-recognized anti-inflammatory and anti-thrombotic properties. Here, we investigated whether statin therapy can improve murine AVF patency, and assessed the anti-inflammatory effects using in vivo nanoparticle-based molecular imaging.

Methods: AVFs were created using internal jugular vein and carotid artery (n=20). AVF blood flow was measured 15 minutes post-surgery. On day 6, an inflammatory cell targeted fluorescent nanoparticle, CLIO-VT680 (10mg/kg) was administered. 24 hours later, in vivo epifluorescence imaging was performed to visualize inflammatory response of the mobilized vein. In the statin treated group, 1.14mg/kg atorvastatin was administered daily. Changes in blood flows (BF) were compared in both statin treated (SG) and untreated control group (CG).

Results: AVF BF on day 0 and day 7 were similar between the SG and CG (p=0.05). The day 7 adventitial AVF inflammation signal (CLIO-VT680) assessed in vivo epifluorescence imaging was significantly lower in the SG compared to the CG (6.3±0.98 vs 3.4±0.2, p=0.002). There was a nonsignificant trend to increased BF’s from day 0 to day 7 in the SG compared to the CG (0.28 vs -0.33 ml/min, p=0.18).

Conclusions: Oral statin therapy decreases adventitial inflammation in experimental AVF as assessed by in vivo nanoparticle-based molecular imaging. There was a trend to improve AVF blood flow with statin therapy. Further studies are indicated to determine if statin therapy can improve AVF patency and maturation.

TH-PO360
Impact of HIV Infection on Arteriogenous Fistula Outcomes: A Retrospective Analysis Juan Camilo Duque Ballestero,1 Laisel Martinez,2 Adriana Dejman,2 Mawar Tabbara,2 Roberto I. Vazquez-Padron,3 Loy H. Salman.2 1Internal Medicine, Jackson Memorial Hospital / Univ of Miami, Miami, FL; 2Nephrology and Interventional Nephrology, Jackson Memorial Hospital / Univ of Miami, Miami, FL; 3Surgery, Jackson Memorial Hospital / Univ of Miami, Miami, FL.

Background: Multiple conditions have been associated to the elevated AVF failure rates. One of the influenced factors but less studied is the effect of the immunosuppression on the AVF vascular wall. In AVF, immunosuppression has been related with higher failure rates of newly created AVF in animal models.

Methods: This retrospective study assessed for the impact of HIV infection on one-stage and two-stage hemodialysis AVF outcomes. The study included 494 patients (HIV=42 patients) who underwent an AVF creation at the University of Miami/Jackson Memorial Hospital from 2008 to 2014. The effects of HIV on primary failure were determined using multivariate logistic regressions and Cox proportional hazard models adjusted for 10 clinical and demographic covariates.

Results: A positive predictors of primary failure are HIV infection (p=0.004) and previous AVF (p=0.002), but HIV does not correlate with primary patency after excluding primary failure rates. We could not find a correlation with any of the T-cell subsets counts (CD3, CD4, or CD8). In HIV patients a prior dialysis catheter is the only clinical factor that predisposes for AVF primary failure (p=0.012).

Conclusions: Our results suggest that immunosuppression might play a role in AVF outcomes. HIV infection show increased rate of AVF failure but this is not explained by the T-cell subsets counts and should be a different immunological relationship between AVF failure and vascular remodeling.

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

175A
Pro- and Anti-Inflammatory Factors and Vascular Stiffness in Chronic Hemodialysis Patients

Bonton Csiky,1,2 Attila Peti,3 Oroszla Lakatos,4 Endre Sulyok.3 1FMC Dialysis Center Pecs, Pecs, Hungary; 2Dept of Nephrology, Univ Medical School of Pecs, Pecs, Hungary; 3Faculty of Health Sciences, Univ of Pecs, Pecs, Hungary; 4Univ Medical School of Pecs, Pecs; 5Stifok Hospital, Hungary.

Background: In this cross-sectional study we addressed the accelerated arteriosclerosis in patients with chronic renal failure (CRF) on hemodialysis (HD) by measuring arterial stiffness parameters and attempted to relate them to pro- and inflammatory protective factors. Methods: 96 consecutive patients receiving regular HD were included in the study. 20 adult patients without major renal, cardiovascular or metabolic morbidities served as controls. Arterial stiffness parameters (carotid-femoral pulse wave velocity – PWV, aortic augmentation index) were measured by using applanation tonometry (SphygmoCor, AtCor Medical). In addition to routine laboratory tests 25(OH)vitamin D3, vitamin D3, α-Klotho, TNF-α, and TGF-β1 were determined by ELISA using commercially available kits (IBL International GmbH, Hamburg and BioVendol Laboratory Med. Inc Brno).

Results: Pro-inflammatory biomarkers (hsCRP, TNF-α and TGF-β1) were markedly elevated (p<0.01), while anti-inflammatory factors (fetuin-A: p=0.05, α-Klotho: p=0.01, vitamin D3: p=0.01) significantly depressed in CRF patients on HD when compared to control patients. PWV was significantly affected only by total cholesterol, fetuin-A and dialysis time. Multiple linear regression analyses revealed that several clinical and laboratory parameters were associated with pro- and anti-inflammatory biomarkers rather than arterial stiffness.

Conclusions: Our results provide additional information on the pathomechanism of accelerated atherosclerosis in patients with CRF but failed to document direct influence of pro- and anti-inflammatory biomarkers studied on the complex interplay between uremic milieu and vascular health.

TH-PO362

Morphological and Immunohistochemical Characterization of Thrombotic Microangiopathy (TMA) in Native and Transplanted Kidney Biopsies: A Multicenter Study

Jessica Schmitz,1 Wei Dai,1 Abedalrazag Ahmad Khalifa,1 Jan Menne,1 Ulrich Kunzendorf,1 Oliver Witzke,2 Hermann G. Haller,2 Hans Heinrich Kreipe,1 Jan H. Braesen,1 1Inst for Pathology, Hannover Medical School, Hannover, Germany; 2Nephrology, Hannover Medical School, Hannover; Germany.

Background: Thrombotic microangiopathy (TMA) is defined as microvascular endothelial injury and thrombosis, thrombocytopenia and MAHA, often affecting the kidney. Correct diagnosis of TMA in kidney biopsies is demanding since TMA may manifest without thrombi.

Methods: Using routine paraffin sections, accepted morphological criteria were analysed in TMA cases from the archives of the Institute for Pathology at Hannover Medical School in 163 kidney biopsies from the last three years.

Results: Patient (female 45%) age ranged from 4 to 81 (mean 47) years. 45% of TMA cases occurred in kidney transplants (KTXs), 53% of these revealed reaction (cellular 7%, humoral 34%, mixed 12%). Thrombi were identified in 71% of KTX TMA cases (glomerular 66%, collapse of capillary tuft (92%) and arterial intimal mucoid edema (arteries 78%, endothelial swelling (glomeruli 68%, arterioles 67%), thickened capillary walls (66%), collapse of capillary tuft (92%) and arterial intimal mucoid edema (arteries 78%, arterioles 47%). Most useful histological TMA criteria were fragmented red blood cells (glomerular 65%, arterioles/arteries 67%), fibrillar appearance of mesangium (66%), endothelial swelling (glomeruli 68%, arterioles 67%), thickened capillary walls (66%), collapse of capillary tuft (92%) and arterial intimal mucoid edema (arteries 78%, arterioles 47%). Grouping of well-characterized patients regarding the underlying cause for the TMA showed differences between morphological criteria comparing genetically (66%), collapse of capillary tuft (92%) and arterial intimal mucoid edema (arteries 78%, endothelial swelling (glomeruli 68%, arterioles 67%), thickened capillary walls (66%), collapse of capillary tuft (92%) and arterial intimal mucoid edema (arteries 78%, arterioles 47%). Grouping of well-characterized patients regarding the underlying cause for the TMA showed differences between morphological criteria comparing genetically.

Conclusions: One third of TMA cases do not display thrombi in kidney biopsies. Certain morphological criteria vary in their diagnostic value and differ between causes of TMA.

TH-PO363

Matrix Metalloproteinase-10 in Glomeruli of Aldosterone-Infused Systemic and Podocyte-Specific Guanylyl Cyclase-C Knockout Mice

Keisuke Osaki,1 Yukiko Kato,1 Naohiro Toda,1 Akira Ishii,1 Kiyoshi Morii,1 Moin Saleem,1 Taiji Matusuaka,1 Masashi Mukoyama,1 Motoko Yanagita,1 Hideki Yokoi,1 1Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 2School of Pharmaceutical Sciences, Univ of Shizuoka, Shizuoka, Japan; 3Academic and Children's Renal Unit, Univ of Bristol, United Kingdom; 4Dept of Molecular Life Sciences, Tokai Univ School of Medicine, Kanagawa, Japan; 5Dept of Nephrology, Kumamoto Univ Graduate School of Medical sciences, Kumamoto, Japan.

Background: Natriuretic peptide receptor/guanylyl cyclase-C (GC-C) signaling exerts renoprotective effects by eliciting natriuresis and reducing blood pressure. We previously reported that high salt-fed systemic GC-C knockout mice with aldosterone, uninephrectomy and high salt showed accelerated hypertension and severe glomerular injury with massive albuminuria. However, genes involved in glomerular injury are elusive.

Methods: By using microarray analysis, we compared gene expression in the glomeruli of systemic GC-C knockout mice and wild-type mice with aldosterone. Furthermore, we constructed podocyte-specific GC-C knockout mice to examine the role of GC-C in podocytes, and analyzed gene expression in systemic and podocyte-specific GC-C knockout mice.

Results: We identified 85 upregulated and 48 downregulated genes in GC-C knockout mice by more than 8-fold compared with wild-type mice. One of upregulated genes in GC-C knockout mice was matrix metalloproteinase-10 (MMP-10). Podocyte-specific GC-C knockout mice with aldosterone exhibited albuminuria by 13-fold, mesangial expansion and footprocess effacement compared to control mice with aldosterone. We confirmed that the expression of MMP-10 from the glomeruli in systemic and podocyte-specific GC-C knockout mice was 200 and 3 times higher than that from control mice by real-time PCR, respectively. Podocyte-specific GC-C knockout mice with aldosterone exhibited albuminuria, mesangial expansion and footprocess effacement. In vitro, the expression of MMP-10 was increased in podocytes as well as mesangial cells with TNF-α.

Conclusions: These results suggest that glomerular MMP-10 is increased in aldosterone-infused GC-C KO mice, and could play a role on inflammation during glomerular injury.

Funding: Government Support - Non-U.S.

TH-PO364

Gender-Dependent Hypertension-Induced Kidney Injury in Cystathionine γ Lyase Knock Out Mice: Amelioration by Sodium Hydrosulfide

Menne,1,2 Ulrich Kreipe,1 Jan H. Braesen,1 1Inst for Pathology, Hannover Medical School, Hannover, Germany; 2Nephrology, Hannover Medical School, Hannover; Germany.

Background: Hydrogen sulfide (H2S) is constitutively synthesized in the kidney by cystathionine γ lyase (CSE) and cystathionine β synthase (CBS). Although CSE knock out (KO) mice develop hypertension (HT) (Yang G et al, Science, 2008), whether they develop kidney injury is not known.

Methods: Male and female 2.5 to 4.5-month old wild type (WT) and CSE KO mice were randomized to receive water alone or 30 umoles/L of sodium hydrosulfide (NaHS, a source of hydrogen sulfide) in drinking water for 12 weeks (n=4-6 mice in each group).

Results: Compared to WT mice, male CSEKO mice had significantly higher blood pressure and albuminuria. NaHS robustly reduced the blood pressure and albuminuria in male CSEKO mice to WT levels (Systolic BP: WT water 114±19, WT NaHS 121±12, KO water 141±9, KO NaHS 122±8, p<0.05 ANOVA). Similar trends were seen in female CSEKO mice. However, the renal cortical contigent of HTGβ3, phospho-Smad3, collagen Iα2 and laminin was increased in male but not female CSEKO mice. NaHS restored these changes to normal. Renal cortical renin-angiotensin system assays in male CSEKO vs. WT mice showed higher Ang II, Ang III, AT1 receptor and low ACE2 levels; NaHS restored these changes to normal. Renal cortical renin-angiotensin system assays in male CSEKO vs. WT mice showed higher Ang II, Ang III, AT1 receptor and low ACE2 levels; NaHS restored these changes to normal. Renal cortical renin-angiotensin system assays in male CSEKO vs. WT mice showed higher Ang II, Ang III, AT1 receptor and low ACE2 levels; NaHS restored these changes to normal.

Conclusions: Other NIH Support

Funding: Other NIH Support - NIA, VA Support
Role of Adenosine A1 Receptor in Renal Afferent Arteriolar Constriction Induced by Hyperuricemia

Liu, Jin; Peng, Xiao; Huang, Qian; Hao, Jinling; Zhao, Li; Xue, Li; Cheng, Liming; Jinling Medical College, Nanjing, China; Peking University Health Science & Peking Union Medical College, Beijing, China; Physiology, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China.

Background: Hyperuricemia is a known independent risk factor of hypertension with prominent cortical vasoconstriction and renin activation. Adenosine A1 receptor (A1AR) play an important role in regulating the constriction of afferent arterioles (AA), known as a part of tubuloglomerular feedback. However, there is no direct pathogenic proof of A1as induction by uric acid and the role of A1AR has not been studied yet.

Methods: We investigated the effects of A1AR in AAs remodeling during hypertension induced by mild hyperuricemia in mice model. Renal arteriopathy was evaluated by α-SMA staining. The protein expression of adenosine receptors in mice kidney was detected. The direct role of A1AR in the AAs constriction induced by uric acid was observed by microperfusion technique and the diameter of AAs was monitored.

Results: Hyperuricemia induced by oxonic acid(OA) gavage effectively increased systemic blood pressure in WT mice, associated with an increase in total medial area of the renal arteriolar wall and up-regulated A1AR protein expression in renal tissues. The protein concentration of uric acid increased from 10-18 mol/L to 10-12 mol/L, the AA luminal diameter diminished from 10.03±1.85 μm to 8.49±1.69 μm (P<0.005, paired t-test). This constriction effect was abolished in A1AR mice(the average AA diameter increased from 10.46±1.00μm to 12.81±1.23μm, P<0.001), suggesting that uric acid induced hypertension possibly via directly activating AA constriction.

Conclusions: Adenosine A1 Receptor played an important role in renal afferent arteriolar constriction and remodeling induced by mild hyperuricemia. Funding: Government Support - Non-U.S.

Antihypertensive Effect of Thiazides Shifts from Salt Excretion to Vasorelaxation during Salt Restriction or Volume Depletion

Kahalari, Saeed; Zaidi, Zainab; White, Corey A.; Callahan, Robert E.; Division of Nephrology and Hypertension, Cardiovascular Research Institute and Div of Nephrology and Hypertension, Northwestern Univ, Chicago, IL.

Background: Thiazidaes, including hydrochlorothiazide (HCTZ), are specific inhibitors of the Na\(^+\)/Cl\(^-\) Co-transporter (NCC), and the most commonly used diuretic to treat mild hypertension. Both renal (natriuresis) and extra renal (vasorelaxation) mechanisms have been proposed as major mediators of blood pressure reduction by HCTZ but the circumstances under which the renal or extra renal mechanism predominates remain unknown.

Methods: Systemic blood pressure was monitored by intra-arterial catheter and computerized tail cuff in transgenic mice lacking NCC under varying conditions. Pendrin KO mice were used to ascertain the compensatory role of pendrin in salt reabsorption in response to HCTZ.

Results: Pendrin KO mice were the only group which showed enhanced salt excretion in response to HCTZ, with salt excretion increasing by ~30% in pendrin KO vs. WT mice (n=6, P<0.02). HCTZ and salt excretion decreased acutely with volume depletion, and significantly the systemic blood pressure only during salt restriction and without enhancing salt excretion. In volume depleted but not in volume repleted NCC/pendrin dKO mice, HCTZ caused dramatic reduction in systemic blood pressure from 72.13±5.1 at baseline to 51.06±6.6 mm Hg in dKO mice.
within 20 minutes of HCTZ administration (p>0.01 vs. baseline) with no significant effect in WT mice (p>0.5 vs. baseline) or in salt resuscitated NCC/pendrin dKO mice. There was no enhancement in salt excretion and no reduction in cardiac output in pendrin/NCC dKO mice. There was no enhancement in salt excretion and no reduction in cardiac output in pendrin/NCC dKO mice. The antihypertensive effects of HCTZ were abrogated in the presence of palmitoxine, a specific blocker of BK channel, which is upregulated in arterial vasculature of volume depleted mutant mice.

Conclusions: Thiazides reduce blood pressure predominantly via vasorelaxation during salt restriction/volume depletion; whereas, they enhance salt excretion during salt repletion state and specifically in conditions associated with pendrin inactivation.
Funding: VA Support

TH-PO370

1,2 Nephrology and Hypertension, Mayo Clinic; 2Cardiology, Mayo Clinic, Rochester, MN.

Background: Development of collateral circulation around a stenotic renal artery contributes to maintenance of renal blood flow (RBF) in the ischemic kidney. Stenotic kidney RBF is elevated in the metabolic syndrome (MetS) compared to lean pigs, but the underlying mechanism is unclear. We hypothesized that MetS increased collateral circulation around renal artery stenosis (RAS).

Methods: Unilateral RAS was induced using a coil (figure 1B) in 14 domestic pigs within 6 weeks of either an atherogenic (high-fat-fructose, MetS-RAS) or standard diet, which then continued for 10 more weeks. Pigs on standard diet served as controls (n=7 each group). At completion of diet, RBF, glomerular filtration rate (GFR), and the peri-stenotic collateral index (CI) were assessed in vivo using multi-detector computed tomodgraphy (CT). CI was assessed as the fractional vascular volume in the zone encompassing visibly discernible collaterals around the stenotic segment of the renal artery. The intrarenal microcirculation was examined ex vivo by micro-CT by the spatial density of microvessels, and renal fibrosis by trichrome staining.

Results: MetS-RAS developed obesity, dyslipidemia, and insulin resistance [figure 1A]. RBF and GFR were decreased in MetS-RAS, whereas their peri-stenotic CI’s were similar [figure 1B]. Conversely, intra-renal microvascular loss and fibrosis were greater in Met-S-RAS [figure 1C-D].

Conclusions: The unaltered collateral vessel formation in the stenotic MetS compared to lean kidneys argues against a major contribution of the collateral circulation to preservation of RBF, which might be secondary to hemodynamic factors in Met-S-RAS. Nevertheless, despite preserved RBF, the post-stenotic kidney shows microvascular loss, possibly due to MetS-induced fibrosis.

TH-PO371
Renal Nerves Mediate Increased Renal Vascular Resistance in Response to Moderate but Not Severe Elevation of Renal Venous Pressure in Rats Shereen M. Hamza, Xiaohua Huang, William A. Cupples, Branko Braam.

1 Medicine/Nephrology, Univ of Alberta, Edmonton, AB, Canada; 2Physiology, Univ of Alberta, Edmonton, AB, Canada; 3Physiology and Kinesiology, Simon Fraser Univ, Burnaby, BC, Canada.

Background: Heart failure (HF) often coincides with renal dysfunction, leading to significant and unexplained mortality, thus emphasizing the intricate connection between cardiac and renal systems. HF-induced elevation of central venous pressure translates to increased renal venous pressure (RVP) which may, in turn, impair renal function. We hypothesized that increases in RVP lead to increased renal vascular resistance (RVR) differentially in normal and renal systems. Objectives: (1) Determine the impact of selectively elevating RVP (10 or 20 mmHg) on renal hemodynamics, (2) Elucidate the contribution of renal nerves.

Methods: Blood pressure and RVP were assessed in anesthetized rats (300-400g, n=38). FITC-inulin was infused i.v. and urine collected to assess GFR, renal arterial blood flow (RBF) was directly measured. Rats were intact or subjected to bilateral renal denervation (RD). Following baseline measurements, RVP was selectively increased to either 10 or 20 mmHg by partial occlusion of the left renal vein for 20 min or not manipulated (time controls).

Results: Moderate elevation of RVP (1.1±0.3 to 11.3±0.4 mmHg, n=10) decreased RBF in intact rats with a concomitant increase in RVP (p<0.001, n=5). RD did not prevent a fall in RBF, but completely abolished the RVP increase (p<0.05, n=5). GFR remained unaltered in each group. Augmented RVP elevation (0.5±1.0 to 21.0±2.2 mmHg, n=12) similarly decreased RBF and increased RVR in intact rats (p<0.05, n=8), however, this was not prevented by RD (p>0.001, n=4). GFR dropped in both intact (1.2±0.1 to 3.0±0.1 mL/min, p<0.001) and RD (1.4±0.1 to 1.0±0.07 mL/min, p=0.001) rats.

Conclusions: Elevated RVP directly modulates renal hemodynamics, inducing significant reduction of RBF and GFR as well as a sustained increase in RVR, which appears to be differentially limited to renal nerves at moderate and high levels of RVP. SH and XH equally contributed to this work.

Funding: Private Foundation Support

TH-PO372
Transglutaminase Is a Critical Link between Inflammation and Hypertension Rennu Luo, 1,2,3 Dept of Nephrology, The First Affiliated Hospital of Dalian Medical Univ, Dalian, Liaoning, China; 2 Dept of Biochemistry and Molecular Biology, Univ of Texas Houston Medical School, Houston, TX; 3 Dept of Nephrology, Xiangya Hospital of Central South Univ, Changsha, Hunan, China.

Background: The pathogenesis of essential hypertension is multifactorial with different independent mechanisms contributing to disease. We have recently shown that TNF superfamily member 14, LIGHT (also known as TNFSF14), induces hypertension when injected into mice. Research reported here was undertaken to examine the role of transglutaminase (TGase) in LIGHT induced hypertension.

Methods: Six to eight mice for each group were infused with LIGHT by minipump. Recombinant mouse LIGHT (R&D Systems, Minneapolis) was delivered at a rate of 4ng/ day into mice for 14 days. Cystamine treated mice were provided drinking water containing 0.9 g/L cystamine dihydrochloride throughout the 14 days. Control mice were infused with saline. We collected urine and measured blood pressure at 0.5, 7, and 14 days. After treatment for 14 days, mice were sacrificed.

Results: Initial experiments showed that plasma and kidney TGase activity was induced by LIGHT infusion and was accompanied with hypertension and renal impairment. The increase in kidney TGase activity was correlated with increase in RNA for the tissue TGase isomor, termed TG2. Pharmacologically we showed that LIGHT-induced hypertension and renal impairment did not occur in the presence of cystamine, a well-known competitive inhibitor of TGase activity. Genetically we showed that LIGHT-mediated induction of TGase, along with hypertension and renal impairment, was dependent on IL-6 and endohedral HIF-1α. We also demonstrated that IL-6, endohedral HIF-1α and TGase are required for LIGHT induced production of angiostatin receptor agonistic autoantibodies, AT1, AA.

Conclusions: Thus, LIGHT induced hypertension, renal impairment and the production of AT1, AA requires TGase, most likely the TG2 isoform. Our findings establish TGase as a critical link between inflammation, hypertension and autoimmunity.

TH-PO373
Renal Cortex and Medulla Oxygenation during Chronic Angiotensin II Infusion in Conscious Rats Tonja Erman, 1,2 Maarten P. Koemen, Jaap A. Joles, 2 Ben Janssen, C.T.P. (Paul) Krediet.

1 Internal Medicine-Nephrology, AMC-UvA, Netherlands; 2 Nephrology & Hypertension, UMC Utrecht, Netherlands; 3Physiology and Pharmacology, Univ Bristol, United Kingdom; 4Pharmacology and Toxicology, Univ Maastricht, Netherlands.

Background: Angiotensin II (AngII) infusion persistently increases renal vascular resistance. We previously found reduction in renal cortical oxygenation during acute AngII (10 or 20 ng/kg/min) in conscious rats (TH-PO374). Experimental heart failure typically involves elevated free fatty acids and impaired renal oxygen delivery. Here we characterize chronic effects of AngII infusion on tissue oxygen levels of kidney cortex and medulla in conscious rats using telemetric pO2 recording.

Methods: Telemetric oxygen-sensitive carbon paste electrodes were implanted in Sprague-Dawley rats (250-300 g), either in cortical (n=7) or medulla (n=7). In vivo hyperoxia/hypoxia inhibition was performed weekly to test signal responsiveness. After recovery and baseline oxygen level assessment, 300ng/kg/min AngII was infused for 2 weeks. s.c. aspirin minipump (100mg/kg/d) was added to drinking water for 2 days. Blood pressure was monitored by telemetry in a separate group (n=5).

Results: Hyperoxia/hypoxia confirmed sensitivity for reproducibly detecting changes in tissue oxygen throughout the experiment. Upon hyperoxia, oxygen increased more in cortex than in medulla (peak change relative to baseline at 100% oxygen was 297±56% in cortex vs. 131±55% in medulla). There was sustained increase in blood pressure during AngII infusion (from 95±2 to 168±12mmHg, P<0.001). Renal oxygen decreased transiently during the first 20 hours of AngII infusion in both cortex and medulla. Losartan increased oxygen levels during the first 8 hours (peak change compared to 12 hours before losartan was 121±19% in cortex and 125±26% in medulla, P<0.05).

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

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Conclusions: Our data suggest that less oxygen reaches medulla than cortex during hypertension, possibly due to countercurrent vasa recta that enable oxygen shunting. Chronic AngII exposure at levels that induce hypertension only causes transient hypoxia in both cortex and medulla. This suggests renal adaptation to hypoxia by either altered metabolic demand due to decreased blood flow or increased efficiency of oxygen consumption.

Funding: Government Support - Non-U.S.

TH-PO374
Circadian Rhythm in Kidney Tissue Oxygenation Tonja Emans,1,2 Jaap A. Joles,1 C.T.P. (Paul) Krediet,1 Internal Medicine-Nephrology, AMC-UvA, Amsterdam, Netherlands; Nephrology & Hypertension, UMC Utrecht, Netherlands.

Background: Blood pressure, renal hemodynamics, electrolyte and water excretion all display diurnal oscillations. Disturbances of the renal circadian clock is involved in the pathogenesis of hypertension. Kidney oxygenation is dependent on oxygen delivery and consumption that in turn are regulated by renal hemodynamics and metabolism. We hypothesized that i) kidney oxygenation also demonstrates 24h periodicity, and ii) this periodicity is disturbed during angiotensin (AngII) infusion.

Methods: Telemetric oxygen-sensitive carbon paste electrodes were implanted in Sprague-Dawley rats (250-300g), either in renal medulla (n=7) or cortex (n=7). Rats were housed in a 12h light-dark cycle. Arterial pressure (MAP) was monitored by telemetry in a separate group (n=5). After 2 weeks of stabilization and recovery, hypertension was induced by s.c. osmotic minipumps containing 300ng/kg/min AngII. Both at baseline and during AngII 5 consecutive days were analysed for periodicity. The first 3 days of AngII were not analyzed.

Results: MAP was 97±2 mmHg during active dark phase and 94±2 mmHg during daytime (P<0.01). During the dark phase the oxygen levels increased to 106±2% in cortex and 104±4% in medulla (vs. baseline; P<0.05). During the light phase the oxygen levels decreased to 95±2% in cortex and 98±3% in medulla. Data was analysed for rhythmicity by curve fitting and 95% confidence intervals (rectangles in figure). During AngII rhythmicity for oxygenation was lost in cortex but not in medulla. There was a shift in MAP pattern.

Conclusions: We detected significant 24h periodicity in cortex and medulla oxygen based on curve fitting. Possibly oxygen levels in the kidney follow renal blood flow, which determines oxygen delivery and peaks in the active phase (at night) and troughs during the resting phase [Pons et al. AJP 1996:271:R1002]. Periodicity in cortex oxygen was disturbed by AngII, possibly by persistent vasoconstriction.

Funding: Government Support - Non-U.S.

TH-PO375
The Ablation of Dendritic Cells Prevents Hypertension and Enhances Natriuresis in Angiotensin II and High-Salt Diet Treated Mice Michelle. A. Araos,1 Daniel E. Hevia,1 Carolina E. Prado,1 Rodrigo Pacheco,1 Luis F. Michea,1 1Millennium Inst on Immunology and Immunotherapy, ICBM Facultad de Medicina, Univ of Chile, Santiago, Chile; 2Laboratory of Neuroimmunology, Fundación Ciencia & Vida, Santiago, Chile.

Background: Angiotensin II (AngII) and high salt diet (HS) cause hypertension, endothelial dysfunction and the upregulation of renal sodium transporters. Our previous studies showed that the ablation of Dendritic Cells (DCs) in mice prevented hypertension and the increased expression of renal sodium transporters. In the present study we evaluated if the ablation of DCs affects natriuresis.

Methods: We studied wild type (WT) mice and CD11c.DOG transgenic mice (CD11c) for the selective elimination of DCs by Diphtheria Toxin (DT) injection. WT and CD11c mice were divided into 3 groups: AngII+HS (AngII=1.042 μg/Kg/min+1% NaCl in drinking water), AngII+HS+DT (DT=8ng/g) and control. Blood pressure (BP) and urinary sodium were analyzed. At days 4 and 14, we made saline challenge tests to increase the levels of angiotensin 10-15 times more than the sodium intake. Kidney was analyzed by immunohistochemistry for renin and COX-2 containing cells.

Results: Kidney oxygenation in AngII+HS and AngII+HS+DT groups showed similar increase of SBP and MAP. However, the injection of DT prevented the increase of SBP in CD11c mice. Telemetric studies confirmed high BP of AngII+HS CD11c mice (PAM=144±1 mmHg; SBP=160±26 mmHg, day14) that was prevented by the ablation of DCs (PAM=92±7±20 mmHg and SBP=104±26 mmHg). The AngII+HS treatment increased 24h natriuresis (19.4±7.6 μEq/g BW) that was prevented by renal ablation of DCs for 5 days of treatment (36±7.9 μEq/g BW; n=5; P<0.05) in CD11c mice. Natriuresis after saline challenge test in AngII+HS mice was similar in WT and CD11c mice at day 4. However, the DT injection in CD11c mice increased natriuresis in 27% compared to the other AngII+HS groups (P<0.05). Aortic rings showed similar vascular reactivity and endothelial function in all AngII+HS groups.

Conclusions: The results suggest that DCs modulate tubular sodium reabsorption in response to AngII and high salt diet. FONDECYT1130550, IMII P09-016-F, BECA CONICYT 21130482.

Funding: Government Support - Non-U.S.

TH-PO377
Dietary Potassium Regulates Renal Kallikrein, Renin and Cyclooxygenase-2: Morphological Evidence Carlos P. Vio,1 Natalia A. Mendez,1,2 Daniela P. Salas,1 COX-2 cells was Alzondor,1,2 Universidad de Concepcion, Chile; 1Center for Aging and Regeneration, Dept Physiology, Pontificia Univ Catolica de Chile, Santiago, Chile; 2Inst of Anatomy, Histology, Pathology, Univ Austral de Chile, Valdivia, Chile.

Background: The importance of dietary potassium in health and disease is underscored compared with that placed on dietary sodium. Much effort has been placed on reduction of sodium intake and less on the adequate dietary potassium, although natural food contains 10-15 times more potassium than sodium. The benefits of a potassium-rich diet are known, and recent evidence showed that high potassium diet dephosphorylates NCC resulting in acute natriuresis. With the hypothesis that dietary potassium regulates renal sodium excretory hormonal systems at long-term, we studied the effect of high potassium diet on kallikrein (Kall), renin and cyclooxygenase-2 (COX-2).

Methods: SD male rats on a normal sodium diet received normal potassium (0.9%, NK) or high potassium diet (3%, HK) for 4 weeks. Urine was collected in metabolic cages for measurement of electrolytes and enzyme activities. Renal tissue was used to analyze kallikrein (Western blot) and mRNA (RT-qPCR) levels, and immunohistochemistry for morphometric analysis.

Results: Kall was restricted to connecting tubule cells, HK increased the Kall positive cells and renin mRNA levels (p<0.01). COX-2 containing cells were restricted to granular cells of the afferent arteriole; a HK diet decreased the number of renin secretory-like vesicles. Cell changes were associated with increased enzyme activity cell size and immunostaining area; cells were hypertrophied with increased Golgi and mitochondria. Kall was restricted to connecting tubule cells, HK increased the Kall positive

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

Underline represents presenting author.

179A
Conclusions: The increased renal kallikrein and decreased renin are consistent with the thiazide contribution to the natriuretic and renoprotective effect of potassium. Downregulation of COX-2 could be compensatory and requires further study.

Funding: Fondect 1130741, CONICYT PIA/Basal PBFB12, and CARE-SQM. Funding: Government Support - Non-U.S.

TH-PO378

Cyclooxygenase-2 Increases Its Expression by Recruitment of Neighboring Epithelial Cells from the Thick Ascending Limb of Henle Carlos P. Vio,1 Natalia A. Mendez,1,2 Carlos Cespedes,1 1Center for Aging and Regeneration, Dept Physiology, Pontificia Univ Catolica de Chile, Santiago, Chile; 2Inst Anatomy, Histology and Pathology, Univ Autoral de Chile, Valdivia, Chile.

Background: Cyclooxygenase-2 (COX-2) is an enzyme that contributes to regulation of renal function via local prostaglandins. We described its origin in a subset of cells from the thick ascending limb of Henle (TALc). COX-2 is regulated in physiological conditions by dietary sodium, glucocorticoids, postnatal development and a negative feedback loop mediated by PGE, EP receptor. COX-2 increases its expression along the axis of the TAL segment and we hypothesize that this follows a recruitment pattern.

Methods: We used renal tissue from a wide variety of conditions, some are new experiments such as SD adult rats with adrenalectomy (ADX), or treated with rofecoxib (rofecoxib), or with ACEi (ramipril), or AT1 blockers (ARBs, losartan), or EP3 antagonist (L-798106). Other tissue was obtained from our collection of stored tissue: microdissected neprhonips from treated rats, or early postnatal ages (5 to 15 days). The tissue was stained by immunohistochemistry, the levels of the enzyme quantified by its protein by Western (L-798106). Other tissue was obtained from our collection of stored tissue: microdissected neprhonips from treated rats, or early postnatal ages (5 to 15 days). The tissue was stained by immunohistochemistry, the levels of the enzyme quantified by its protein by Western blot and mRNA by RT-qPCR.

Results: A wide variety of stimuli produced the same pattern of recruitment of epithelial cells from TALc, with highest levels during early postnatal age, lowest levels in adult, increased in ADX, ACEi, ARBs or EP3 antagonist. This axil recruitment was confirmed in microdissected nephrons.

Conclusions: Regardless of the stimuli, when COX-2 increases, a recruitment phenomenon was observed. The recruitment phenomenon is rare, and the most studied is a similar recruitment observed with renin expression in the afferent arteriole. Both COX-2 and renin recruitment share similarities like regulation by sodium, postnatal development, ACEi and ARBs. Funding Fondect 1130741, CONICYT PIA/Basal PBFB12, SQM. Funding: Government Support - Non-U.S.

TH-PO379

TLR4/NFκB Inhibition Strongly Attenuated Renal and Vascular Injury in the Chronic NO Synthase Inhibition/Salt Overload Model Fernanda F.E. Zambom,1 Karin C. Oliveira,1 Victor F. Avila,1 Camilla Fancelli,1 Simone C.A. Arias,1 Flavia G. Machado,2 Claudia R. Senna,1 Vivian L. Viana,1 Denise M. Malheiro,1 Niels O.S. Camara,1 Roberto Zatz,1 Clarice K. Fujihara,1 1Univ de Sao Paulo, Brazil; 2Washington Univ.

Background: Chronic NO inhibition by Nω-nitroarginine methylster (NAME) combined with salt overload (HS) leads to severe hypertension (HT), albuminuria (ALB) and renal/vascular injury. The mechanisms of inflammation and tissue injury in this model remain poorly understood. We investigated the role of innate immunity in HS+NAME and the possible salutary effects of inhibiting NFκB with pyrroolidine dithiocarbamate (PDTC).

Methods: Male Munich-Wistar rats received oral NAME, 32 mg/kg/d, and HS (N=11), or HS+NAME+PDTC, 60 mg/kg/d (N=13). Rats given HS only were controls (N=12). After 4 wk, we assessed tail-cuff pressure (TCP, mmHg), ALB (mg/d), glomerular sclerosis (GS, %), glomerular ischemia (GI, %), arteriolar onion skin lesions (OSL, %), interstitial α-actin, collagen 1 (COL1, %), AngII+ cells and macrophages (MFs), cells/mm2. Renal content of IL1B (pg/mg), caspase-1 (Casp1), TLR4 and nuclear p65 (NFκB) was also measured (x HS).

Results: Expectedly, HS+NAME promoted severe HT, ALB and renal/vascular injury/ inflammation. Renal IL1B was increased along with activation of the TLR4/NFκB pathway. PDTC normalized renal IL1B and TLR4, reversed NFκB activation, prevented inflammation and strongly attenuated HT, ALB and renal injury.

Conclusions: Activation of the TLR4/NFκB pathway may promote, and its inhibition may reverse, renal injury in the chronic NOS inhibition model. The participation of other aspects of innate immunity, such as the Casp1/NLRP3 pathway, cannot be excluded. FAPESP/CNPq.

TH-PO380

The Effects of Pitavastatin on Renal Nitric Oxide System in Spontaneously Hypertensive Rats and Wistar-Kyoto Rats Gaizun Hu, Osamu Ito, Masahiro Kohzuki. Internal Medicine and Rehabilitation, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan.

Background: Clinical trials have demonstrated renoprotective effects of atorvastatin (ATV) and pitavastatin (PTV), which belong to the strong statins, are more potent than other statins. We reported previously that ATV attenuated the development of hypertension in SHR with increasing the endothelial and neuronal nitric oxide synthases (eNOS, nNOS) expressions in the kidney, inhibited the eNOS phosphorylation at serine1177 and of caspase-1 and strongly attenuated HT, ALB and renal injury.

Methods: Five-week-old, male SHR and WKY were given orally PTV (2mg/kg/day) or vehicle for 8 weeks. The renal eNOS, nNOS expressions and eNOS phosphorylation were examined by westernblot.

Results: PTV attenuated the hypertension (220 ± 8 vs. 177 ± 4 mmHg) and albuminuria(684 ± 66 vs. 398 ± 42 mg/day) without changing plasma total cholesterol or creatinine, but did not change the parameters in WKY. PTV tended to increase NO concentration in plasma both in SHR and WKY and significantly increased urinary NO excretion in WKY. PTV increased the renal eNOS and nNOS expressions in the medulla of SHR (eNOS, by 182% and 186%, nNOS, by 315% and 194%), PTV increased the renel eNOS and nNOS expressions in the cortex and inner medulla of WKY (by 181% and 45%, nNOS by 45% and 125%). PTV significantly stimulated the eNOS phosphorylation at serine1177 in the inner medulla (98%) and inhibited the eNOS phosphorylation at threonine495 in the medulla of SHR (50% and 58%). PTV also enhanced the eNOS phosphorylation at serine1177 in the medulla (30% and 158%) and inhibited eNOS phosphorylation at threonine495 in inner medulla of WKY (39%).

Conclusions: PTV attenuates the development of hypertension and albuminuria in SHR, PTV increases the expressions, and activates the eNOS phosphorylation in the kidney of both in hypertensive and normotensive rats. The antihypertensive and renoprotective effects of PTV may be mediated in part by an upregulation of NO system in the kidney. Funding: Pharmaceutical Company Support - Kowa Pharmaceutical Company, Government Support - Non-U.S.

TH-PO381

Role of Angiotensin II Type 1b (AT1b) in Renal Injury in the DOCA-Salt Hypertension Model Using AT1a Deficient Mice Atsuko Shibagaki,1 Takeshi Sugaya,1 Daisuke Ichikawa,1 Kenjiro Kimura,1 Yugo Shibagaki.1 1The Div of Nephrology and Hypertension, Dept of Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki City, Japan; 2Dept of Anatomy, St. Marianna Univ School of Medicine, Kawasaki City, Japan; 3JCHO Tokyo Takanawa Hospital, Tokyo, Japan.

Background: Genetic null mice of AT1a receptor have been used to study the functional role of AT1a receptors in the kidney. After the identification of the single human AT1 receptor, AT1b receptors were reported to be more related to myogenic response in vascular smooth muscle than AT1a receptors. The aim of this study is to reveal the role of the AT1b receptor on myogenic vasoconstriction in pressure-dependent renal injury.

Results: Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>TCP (mmHg)</th>
<th>ALB (mg/d)</th>
<th>GS%</th>
<th>GI%</th>
<th>OSL%</th>
<th>CIC%</th>
<th>MIN%</th>
<th>AngII</th>
<th>IL1B</th>
<th>p65</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS N=15</td>
<td>149±2</td>
<td>209±4</td>
<td>147±12*</td>
<td>37±8*</td>
<td></td>
<td></td>
<td></td>
<td>2±1</td>
<td>1.4±0.3</td>
<td>2±3</td>
</tr>
<tr>
<td>HS+NAME+PDTC</td>
<td>174±4</td>
<td>376±5</td>
<td>4±1±10*</td>
<td>0.7±0.3*</td>
<td></td>
<td></td>
<td></td>
<td>2±1*</td>
<td>1.8±0.5</td>
<td>2±3</td>
</tr>
</tbody>
</table>

Means±SE;p < 0.05 vs HS, *p < 0.05 vs HS+NAME

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

Underline represents presenting author. 180A
Methods: Female AT1a deficient (AT1a−/−) mice were subjected to left nephrectomy and were divided into three groups; the DOCA group received systemic DOCA (0.75 μg/kg·min−1) using tablets and were provided with drinking water containing 1% NaCl for 28 days. We used losartan as a blocker of all AT1 receptors. The DOCA group, was but was not reduced by the losartan treatment. Expansion of the mesangial matrix and increase in urinary albumin induced by DOCA-salt tend to be slightly prevented by the losartan treatment. Glomerular size and urinary albumin excretion were provided with only tap water.

Results: Systolic blood pressure was significantly increased on day 28 in the DOCA group, but was not reduced by the losartan treatment. Expansion of the mesangial matrix and increase in urinary albumin induced by DOCA-salt tend to be slightly prevented by the losartan treatment. Glomerular size and urinary albumin excretion were provided with only tap water.

Conclusions: The AT1β receptor might contribute to myogenic vasoconstriction of afferent arterioles in the DOCA-salt hypertension model using AT1a deficient mice.

TH-PO383
Renal Afferent Peptidergic Neurons – What Are They Like?

Tatiana Dritting1, Kristina Rodionova1, Sonja Loosen1, Christian Ott1, Roland E. Schmiedt1, Kerstin U. Aman1, Roland Vegeen1

1Medical Dept 4, Univ of Erlangen, Erlangen, Bavaria, Germany; 2Nephropathology, Univ of Erlangen, Erlangen, Bavaria, Germany.

Background: Renal afferent nerves comprise a complicated neuro-paracrine regulatory system influencing the sympathetic nervous system. We tested the hypothesis that the activity of renal afferent neuronal units is primarily altered by inflammatory processes in cardiovascular disease.

Methods: In rats, hypertension was induced by unilateral clipping of one renal artery (2K1C1 model), normorenal as well as nephritic animals. Neurons (anti-Thy-1) and were examined by i.v. injection of 1.75 mg/kg BW Thy-1 antibody. Retrograde labelling (DiI) identified renal afferent neurons in the dorsal root ganglion (DRG) (Th11-L2). Patch clamp recordings, i.e. current clamp allowed to clamped neurons as highly active or “tonic” with sustained action potential (AP) firing versus low active or “phasic” (<3 APs) upon current injections. Electrophysiological parameters and AP properties were determined in all experimental groups, proteinuria and renal morphology for all kidneys.

Results: In normorenal hypertension (mean arterial pressure: 173±12 mmHg) only neurons with projections to the clipped kidneys showed a significant decrease in tonic firing (30.6% [23/75]), the non-clipped kidney showed an unaffected proportion of tonically firing neurons (67.5% [50/74], p<0.05) compared to controls. There was no increase in blood pressure (BP) in nephritic animals. Rats with nephritis exhibited albuminuria (61±6 μg/24h), infiltration of macrophages in the interstitium (26 ± 4 cells/high-power field) and glomeruli (3.7±0.6 cells/glomerular cross-section). In 2K1C1 hypertension, renal inflammation occurred mainly in the glomeruli and interstitium of the nonstenotic kidneys, in clipped kidneys signs of inflammation were significantly less.

Conclusions: Inflammation (and hypertension) may play less important roles for the decreased activity pattern of afferent renal nerves in cardiovascular disease. Rather altered perfusion occurring in a clipped kidney with renal stenosis and likely also present the decreased activity pattern of afferent renal neurons in cardiovascular disease. Rather altered perfusion occurring in a clipped kidney with renal stenosis and likely also present altered perfusion occurring in a clipped kidney with renal stenosis and likely also present altered perfusion occurring in a clipped kidney with renal stenosis.

Funding: Other NIH Support - Deutsche Forschungsgemeinschaft

TH-PO384
Fexofenast Supresses High-Salt-Induced Hypertension and Renal Damages in Dahl Salt-Sensitive Rats

Takahiro Miura, Akihiro Sakuyama, Masahiro Kohzuki, Osamu Itou

1Dept of Internal Medicine & Rehabilitation Science, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan.

Background: Several clinical studies reported that fexofenast (Fx), a xanthine oxidase (XO) inhibitor, has anti-hypertensive and renal protective effects. However, their mechanisms are not elucidated. We studied whether Fx affects the blood pressure and renal damages in Dahl salt-sensitive (Dahl-S) rats fed a high-salt diet (HS).

Methods: Eight-week-old, male Dahl-S rats were divided into three groups, normal salt diet (0.6% NaCl) group, HS (8% NaCl) group and HS-Fx (1 mg/kg/day, po) group. Every 2 weeks, 24 hours urine sample was collected, and the systolic blood pressure (SBP) was measured every week by tail-cuff method. After 8 weeks, the kidney was removed for XO activity measurement, Western blot analysis, and histologic analysis.

Results: HS intake significantly increased the SBP, urinary protein (UP), plasma creatinine (Cr), uric acid (UA) and urinary H2O2 excretion. Fx significantly improved the HS intake-induced hypertension, renal dysfunction and oxidative stress (SBP 209±16 vs. 174±6 mmHg, UP 324±54±0.3 vs. 162±40±9 mg/dl, Cr 0.41±0.3 vs. 0.29±0.01 mg/dl, UA 1.67±0.21 vs. 0.83±0.06 mg/dl, urinary H2O2 483±84.74 vs. 339±7±278 mmol/day, P<0.01 respectively, HS group vs.HS-Fx group). HS intake increased the XO activity and expression in the renal cortex, outer medulla, and inner medullary tubules (5 μg/g tissue) and inner medullary thick ascending limbs. Immunohistochemical analysis showed that HS intake increased the XO expression in the proximal tubules and outer medullary interstitial. HS intake significantly increased index of glomerular sclerosis (IGS), desmin-positive area of glomeruli, relative interstitial volume (RIV) and ED-1 infiltration, and Fx significantly suppressed the HS-induced renal damages.

Conclusions: Fx suppresses the HS-induced hypertension and renal damages in Dahl-S rats. Fx may have anti-hypertensive and renal protective effects in patients with salt-sensitive hypertension.

Funding: Pharmaceutical Company Support - Teijin Limited, Government Support - Non-U.S.
-effects on salt transporters of the distal nephron. This study was designed to investigate the impact of hypertensive disease and systemic sclerosis on glomerular injury and localization of renal cell adhesion molecules and to prevent development of hypertension in TIDM, and possibly T2DM, variants.

**Funding:** Private Foundation Support

**TH-PO390**

**Response of Renal Podocytes to High Hydrostatic Pressure: Pathophysiological Cascade in a Model of Malignant Hypertension**

Ramzia Abu Hamad,1,2 Moshe Stark,1 Yafit Hachmo,1 Fadia Hassan,1 Keren Doenys-Barak,1,2 Shai Efrati.1,2

**Research & Development Unit, Assaf-Harofeh Medical Center; 2Nephrology Div, Assaf-Harofeh Medical Center.**

**Background:** Renal injuries induced by increased intraglomerular pressure coincide with podocyte detachment from the glomerular basement membrane. We investigated the pathophysiologic cascade responsible for podocyte detachment and the cascade’s relationship with renal cells.

**Methods:** Rat renal mesangium and podocytes were exposed to high hydrostatic pressure to H2O to simulate malignant hypertension. In some cultures, podocytes were placed in milieu of mesangial cells pre-exposed to pressure, or treated with excessive angiotensin-II, TGF-β1 or cAMP agonists. The resultant detachment, apoptosis and podocyte expression of adhesion proteins, podocin and integrin-β1, were evaluated.

**Results:** Pressure resulted in increased angiotensin-II production. Via AT1 receptors, this reduced the expression of podocin (54±3.6 vs. 84±8.15; p<0.05) and integrin-β1 (271±1.3 vs. 55±8±10.5; p<0.05), and culminated in detachment of viable and apoptotic podocytes. Mesangial cells, pre-exposed to pressure, resulted in a greater increase in angiotensin II production than podocytes exposed to pressure (2999.5±580 vs. 367±14.1; p<0.05/g/ml). The massively increased concentration of angiotensin by mesangium, together with increased TGF-β1 production (20.5±4.5 vs. 84±30; p<0.05), resulted in increased apoptosis, and considerable detachment of non-viable apoptotic podocytes, with no change in adhesion protein expression.

**Conclusions:** Malignant hypertension induces podocyte detachment by autocrine and paracrine effects. In direct response to pressure, podocytes increase angiotensin-II production. This leads, via AT1 receptors, to structural changes in the manifestation of adhesion proteins, culminating in detachment of viable podocytes.Further, the adjunct mesangial cells respond to pressure by increasing angiotensin-II and TGF-β, production, leading to massive apoptosis and detachment of non-viable podocytes.

**TH-PO391**

**Functional Alterations in the Glomerular Filtration Barrier in Rats Infused with Angiotensin II**

Omran Bakouden,1 Churu Sharma,2 Nima Nalin,1 Subramanian Dhansukar,1 Abderrahim Nemmar.1

**Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates Univ, Al Ain, Abu Dhabi, United Arab Emirates; 2Pharmacology and Therapeutics, College of Medicine and Health Sciences, United Arab Emirates Univ, Al Ain, Abu Dhabi, United Arab Emirates.**

**Background:** Chronic infusion of angiotensin II leads to progressive hypertension and podocyte injury, however, the effect of chronic angiotensin infusion on the glomerular perm-selectivity have been less well characterized. In this study we evaluated the changes in the glomerular filtration barrier caused by chronic angiotensin II infusion.

**Methods:** Male Wistar rats (n = 5) were fitted with an osmotic minipump and infused with angiotensin II was infused for 7 days at 200 ng/kg/min. The glomerular sieving coefficient was measured for polydisperse inert ficoll molecules with a radius of 10-90 Å. Ficoll is a neutral polysaccharide that is not significantly reabsorbed by proximal tubules, which enables its use for determination of the filtrate-to-plasma concentration ratios for a broad spectrum of molecular radii (10-90 Å).

**Results:** The glomerular sieving coefficient for Ficoll was significantly increased in rats following the chronic angiotensin II infusion, and to prevent development of hypertension in TIDM, and possibly T2DM, variants.

**Conclusions:** Chronic infusion of angiotensin II leads to progressive hypertension and podocyte injury, however, the effect of chronic angiotensin infusion on the glomerular perm-selectivity have been less well characterized. In this study we evaluated the changes in the glomerular filtration barrier caused by chronic angiotensin II infusion. The sieving coefficient increased 1.6 fold for ficoll-20 Å, two-fold for ficoll-35 Å, six-fold for ficoll-50 Å, and ten-fold for ficoll-70 Å.

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

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Conclusions: Angiotensin II infusion severely impairs the glomerular perm-selectivity to cause a ten-fold increase in the urinary leakage of large molecular weight molecules in the size range of IgG and IgM proteins.

Funding: Government Support - Non-U.S.

TH-PO392

Effect of Diet-Induced Vitamin D Deficiency on Renal Sodium Transporter Expression and Oxidative Stress Weverton M. Luchi,1 Renato Crajona,1 Antonio C. Seguro,1 Adriana C.C. Girardi.1 1Nephrology, Medical School Univ of São Paulo; 2Federal Univ of Espírito Santo, Brazil.

Background: Vitamin D Deficiency(VDD) has been linked to hypertension in experimental and clinical studies. Thus, we aimed to test the hypothesis that high blood pressure in VDD rats is associated with altered expression of sodium transporters along the nephron.

Methods: Wistar rats were fed for 30 days with a vitamin D-free(VDD) or standard diet(control). Blood Pressure(BP) was measured by tail cuff plethysmography. The expression of sodium transporters and intrarenal Renin-Angiotensin System(RAS) were evaluated by immunoblotting. In combination to vitamin D deficiency, renal expression of angiotensinogen(AGT) were determined by ELISA. Intrarenal redox status were analysed by the ratio of thiobarbituric acid reactive substances and glutathione levels(TBARS/GSH).

Results: Compared to controls, VDD rats had lower serum levels of 25(OH)D (48.0±2.5 vs. 4.2±1.0ng/mL, p<0.01) and higher BP(153±2 vs. 119±3mmHg, p<0.01). Urinary flow and sodium excretion were not affected by VDD, but it slightly reduced GFR. VDD rats exhibited higher expression of NKCC2 in medulla(147±12 vs.100±10%, p<0.05) and cortex(157±12 vs.100±10%, p<0.05). No significant changes were observed in cortical levels of NHE3, NCC, NCC phosphorylated at Thr 53 and in cortical and medullary a, β and γ ENaC subunits between groups. However, the levels of NHE3 phosphorylated at Ser 552 were higher in cortex of VDD rats(200±12 vs.100±11%, p<0.01). Renin expression was only markedly elevated in the medulla of the VDD rats(207±28 vs.100±25%, p<0.05). Higher expression of cortical AGT(160±18 vs.100±19%,p<0.05) and urinary AGT/Cr ratio(0.35±0.08 vs.0.12±0.01ng/mg;p<0.05) were found in VDD rats. Angiotensin II concentration was higher in cortex(1.22±0.04 vs.0.60±0.07;p<0.01) and medulla(2.32±0.15 vs.1.55±0.10ng/g;p<0.01) of the VDD group. Also, VDD rats showed higher TBARS/GSH ratio in cortex[11±5.00 vs.18±0.4±0.01] and medulla[6±0.5 vs.3±0.3; p<0.01].

Conclusions: These data suggest that VDD leads to altered renal sodium handling and high BP by upregulating NKCC2 coupled with intrarenal RAS activation and oxidative stress. CNPq

TH-PO393

Sexual Dimorphism in the Diabetic Kidney in Response to ACE2 Down-Regulation and ANGII Infusion Sergi Clotet-Freixas,1 Maria Jose Soler,1 Vanesa Palau,1 Lidia Anguiano,1 Marta Rebull,1 Javier Gimeno,1 Julio Pascual,1 Marta Riera.1 1Nephrology, Hospital del Mar-Institut Hospital del Mar d’Investigacions Mèdiques, Barcelona, Spain; 2Pathology, Hospital del Mar-Institut Hospital del Mar d’Investigacions Mèdiques, Barcelona, Spain.

Background: Loss of ACE2 exacerbates hypertension in ANGII-infused male mice. Sex influence on the effects of ACE2 deletion in diabetic(DB) mice with ANGII-induced hypertension has not been studied.

Methods: We evaluated wild-type(WT)and ACE2KO streptozotocin(STZ)-infused female and male mice. At week of follow-up, minipumps for ANGII infusion were implanted. Kidney/body weight(K/W/BW), heart/body weight(H/W/BW), systolic blood pressure(SBP), urinary albumin excretion(UAE), glomerular area(GA), glomerular tuft area(GTA), mesangial area(MA), podocyte number(%POD), circulating(c) and renal(r) ACE, TGF-β1, and collagen I expression, than females.

Results: OSL and NFκB activation develop. We further investigated the role of innate immunity (InIm) in this model.

Methods: Male newborn rat pups received PDTC or no treatment (C) for 20 d, under different nutritional conditions: standard (NS) and high sodium (HS). PDTC promoted mesangial expansion and podocyte loss in the context of ACE2 deficiency(tissue effect).

Conclusions: Our results suggest a sexual dimorphism in relation to the role of ACE2 in diabetic and hypertensive kidney disease. Loss of ACE2 exacerbated ANGII-induced hypertension,albuminuria and cardiac, renal and glomerular hypertrophy in diabetic females(hemodynamic effect). In diabetic males,ANGII promoted mesangial expansion and podocyte loss in the context of ACE2 deficiency(tissue effect).

TH-PO394

Role of Innate Immunity in a Model of Malignant Hypertensive Nephropathies Victor E. Avila,1 Orestes Foresto-Neto,1 Simone C.A. Arias,1 Camilla Fanelli,1 Lisieney C.T. Rempel,1 Mariliza V. Rodrigues,1 Claudius R. Sena,1 Vivian L. Viana,1 Denise M. Malheiro,1 Jose E. Krieger,1 Niels O.S. Camara,1 Roberto Zatz,1 Clarice K. Fujihara,1 União de São Paulo, Brazil.

Background: NFKB inhibition by PDTC during rat lactation (PDTClac) promotes moderate hypertension (HT) with no apparent renal injury. With salt overload (HS) and high sodium diet, HT, glomerulosclerosis (GS), oniom-skin renal artherosclerosis lesions (OSL) and NFKB activation develop. We further investigated the role of innate immunity (InIm) in this model.

Methods: Male newborn rat pups received PDTC or no treatment (C) for 20 d, under different nutritional conditions: Standard (NS) and high sodium (HS). HS was reached within 70 minutes. IRA NS had no effect. Tonically suppressed RSNA (CAP) was transiently but completely unmasked by systemic (IV) administration of BK, P<0.01. IRA BK was associated with short lived (1-2 sec) increases of RSNA (up to 13.3±2.4µV*sec; P<0.001). IRA BK was associated with a ten-fold increase in the urinary leakage of large molecular weight molecules in the size range of IgG and IgM proteins.

Results: Even without renal injury, Casp1 was upregulated in PDTClac, whereas TCP correlated with M0 and IL1β, suggesting incipient InIm activation. Expectedly, HS enhanced HT, renal injury/inflammation and the renal content of IL1β, TLR4 and nuclear p65. Even with a moderate injury, IL1β and TLR4 expression decreased, suggesting both inflammatory and TLR4/NFKB activation.

Conclusions: InIm is activated early in PDTClac, perhaps reflecting incipient vascular injury. HS enhances InIm, aggravating HT and renal/vascular injury. InIm may be an important mediator of renal injury by HT. FAPESP/CNPq.

Funding: Government Support - Non-U.S.

TH-PO395

Bimodal Action of Intrarenal Affenter Stimulation by Bradykinin on RSNA: Tonic Inhibition after Short Excitation Martin Hindermann,1 Tilman Ditting,1 Kristina Rodionova,1 Sonja Loosen,1 Christian Ott,1 Roland E. Schmieder,1 Kerstin U. Amann,2 Roland Veelken,2 1Dept of Nephrology and Hypertension, Friedrich-Alexander-Universität, Kempten, Germany; 2Dept of Nephrology, Friedrich-Alexander-Universität, Erlangen, Germany.

Background: Renal affenter nerves (RANs) play an important role in the modulation of renal sympathetic nerve activity (RSNA). We recently reported tonic sympatho-inhibitory action due to intrarenal affenter nerve stimulation by the TRPV1 agonist capsaicin. However, some studies indicate sympatho-excitatory RANs, stimulated by Bradykinin (BK). Since BK is known to augment TRPV1 effects we hypothesized that intrarenally applied BK would rather inhibit than excite RSNA.

Methods: 3 groups of anesthetized rats (n=8, each) were equipped with arterial and venous catheters for blood pressure (BP) and heart rate (HR) recording and drug application; left sided renal arterial catheter for intrarenal administration (IRA) of Bradykinin (BK, group 1) or the TRPV1 agonist capsaicin (CAP, pos. control; group 2) to stimulate RANs (CAP 3.3, 6.6, 10 and 33*10⁶ M; 30 to 60 minutes; BK 10⁻⁵ M). IRAs were reached within 70 minutes. IRA NS had no effect. Tonically suppressed RSNA (CAP) was transiently but completely unmasked by systemic (IV) administration of the NK₁-blocker (1.6±0.5 to 8.6±2.9µV*sec; P<0.001 (BK); 1.0±0.2 to 6.1±1.5µV*sec; P<0.01 (CAP)). IRA BK was associated with short lived (1-2 sec) increases of RSNA (up to 13.3±2.4µV*sec; P<0.01).

Conclusions: IRA BK was associated with short lived (1-2 sec) increases of RSNA (up to 13.3±2.4µV*sec; P<0.01).
Conclusions: The effect of intrarenal BK was similar to CAP. Thus, the net effect of intrarenal stimulation of RANs by BK is sympatho-inhibitory in nature. To the similarity of NK1,-blocker effects indicates a common final pathway of intrarenal afferent stimulation. However, the nature of the short-lived BK induced RSNA increases remains unclear. Nocteptive effects or differential central processing are possible.

**TH-PO396**

**MicroRNA-122 Regulates Aldosterone Production by Targeting KCNJ5 in Aldosterone-Producing Adenomas**

**Kang-Yung Peng, Vincent Wu**

*Dept of Internal Medicine, National Taiwan Univ, Taipei, Taiwan.*

**Background:** It has been identified that 40%-60% of aldosterone-producing adenoma (APA) patients carry somatic mutations in KCNJ5 gene. These KCNJ5 mutations lead to reduced K^+/-Na^+ channel selectivity in vitro and result in increased calcium influx and expression of genes promoting aldosterone synthesis. In this study, we investigate the role of miR-122 in the pathogenesis of APA through targeting KCNJ5.

**Methods:** The expression level of miR-122 in APA and cultured adrenal cells were validated by using quantitative reverse transcriptase polymerase chain reaction (qPCR). Radioimmunobass (RIA) was used to measure the aldosterone concentration in the culture supernatants. Liposome-mediated transfection of miR-122 inhibitor was constructed into HAC15 human adenocortical cells. The expression of KCNJ5 was assessed by immunoblotting and qPCR.

**Results:** Our data showed that KCNJ5 protein was upregulated in APAs compared with peri-tumor tissue. Besides, the upregulated ratio of KCNJ5 in APAs tissues than their counterpart with KCNJ5 mutations were much higher than APA tissues without KCNJ5 mutations. miR-122 was chosen based on its possible functions, and target prediction by multiple algorithms. The expression of miR-122 was down-regulated in APA when compared to the adjacent non-tumor tissues (p = 0.0207). In cultured HAC15 cells, miR-122 inhibitor augmented aldosterone synthase (CYP11B2) and promoted aldosterone production.

**Conclusions:** Our findings suggest that miR-122 may mediate some of hyperaldosterone in aldosteronism, in part via regulating KCNJ5 expression. The novel results add another dimension to accumulating evidence regarding further development of new therapies and diagnosis in APA.

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

**TH-PO397**

**Trend Toward Lower Exosomal Thiazide-Sensitive NaCl Co-Transporter Expression after Renal Denervation in Resistant Hypertensive Humans**

**Olivier Bonny,**

1 Candice Stoudmann, 2 Fanny Durusel, 3 Marc P. Maillard, 1 Johannes Loefing, 1 Grégoire Wuerzner. 1 Service of Nephrology, Lausanne Univ Hospital, Lausanne, Switzerland; 2 Dept of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; 3 Inst of Anatomy, Univ of Zurich, Zurich, Switzerland.

**Background:** The renal sympathetic nervous system is implicated in most forms of hypertension. It has recently been shown in animals that norepinephrine activates the thiazide-sensitive NaCl cotransporter (NCC), which participates to sodium retention in the distal part of the nephron (DCT). However, no data are available in humans. Now, we used human urinary exosomes from timed urine collection before and after renal denervation (RDN) and investigated the acute effect of renal denervation on NCC abundance and phosphorylation.

**Methods:** Baseline 24 hours blood pressure and sodium excretion were measured before RDN. Timed urines were collected the morning before and the morning after renal denervation. Exosomes were freshly isolated by ultracentrifugation and stored at -80°C. NCC abundance and phosphorylation were analyzed by Western blot. Detection of TSG101 and NCC abundance and phosphorylation were analyzed by Western blot. Detection of TSG101

**Results:** Thirteen patients (7 women/6 men) with proven resistant hypertension and an estimated GFR > 60 ml/min/1.73m² were included in the study. Mean age was 58 ± 2.7 years, mean body mass index was 32.9 ± 4.5 kg/m², mean daytime systolic and diastolic blood pressure were respectively 146 ± 17 mmHg and 87 ± 12.5 mmHg. In the isolated urinary exosomes, the levels of total and phosphorylated NCC normalized to TSG101 varied considerably, but showed a trend towards lower expression levels post-denervation, but without reaching significance though.

**Conclusions:** Thus, RDN may reduce total NCC abundance and phosphorylation and urinary exosome analysis may represent a mean to monitor the acute effects of RDN. Additional studies are necessary confirm these initial observations and to assess the long term effects of RDN on renal NCC and possibly other renal transport proteins involved in blood pressure control.

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

**TH-PO398**

**A Novel Chronic Kidney Disease Mouse Model with Hypertension**

**Jin Wei,**

1 Jie Zhang, 1 Gensheng Zhang, 2 Shaohui Wang, 1 Lei Wang, 1 Jacentha Lynn Burgs, 2 Ruisheng Liu. 1 Molecular Pharmacology & Physiology, Univ of South Florida, Tampa, FL; 2 Tampa General Hospital.

**Background:** Chronic kidney disease (CKD) affects 26 million American adults and may eventually develop into end-stage renal disease. Hypertension is a leading cause and a common consequence of CKD. Subtotal nephrectomy is a widely used low-nephron CKD model. This model creates hypertension in rats, however, the mouse model exhibits strain-dependent outcomes following subtotal nephrectomy. In particular, C57BL/6 mice are normotensive. The goal of the present study is to create a new CKD model with low nephron numbers and hypertension in C57BL/6 mice.

**Methods:** The reduction of renal mass was performed by ligating either upper (LU) or lower (LL) branches of the renal artery in the left kidney plus a nephrectomy (UX) of the right kidney. The mean arterial pressure was measured with a telemetry system and glomerular filtration rate (GFR) was measured in conscious mice.

**Results:** Eight weeks after surgery, there was no significant difference in body weight among LU, LL, and control mice. The left kidney weight decreased by 22.7% in LU group (184.3 ± 12.9 mg), and by 22.1% in LL group (185.7 ± 13.2 mg) compared with control mice (238.4 ± 19.1 mg). Both LU and LL mice had a significant decrease in GFR. In LU (128.4 ± 23.7 µl/min) and LL (144.7 ± 23.9 µl/min) compared with the control mice (193.7 ± 13.9 µl/min). Plasma creatinine increased from 0.08 ± 0.01 to 0.18 ± 0.02 mg/dl in LU group; from 0.09 ± 0.01 to 0.17 ± 0.03 mg/dl in LL group; and from 0.08 ± 0.03 to 0.11 ± 0.02 in controls (r=4 group, p < 0.05 vs control). The MAP increased and remained elevated at 131.5 ± 12.7 mmHg in LU and 126.8 ± 11.4 mmHg in LL mice. The MAP in control mice did not change (n=3 group, p > 0.05 vs control). Proteinuria increased from 2.7 ± 0.3 to 8.1 ± 3.4 mg/24h in LU; from 2.3 ± 0.9 to 6.7 ± 3.1 mg/24h in LL; and from 2.5 ± 0.9 to 2.7 ± 0.7 in control mice (n=4 group, p < 0.05 vs control). Glomerular injury score was 1.4 ± 0.4 in LU mice, 1.2 ± 0.5 in LL mice, and 0.2 ± 0.1 in controls.

**Conclusions:** In summary, we developed a new CKD model with low-nephron and hypertension by a combination of ligation in renal artery branch and UX in C57BL/6 mice.

**Funding:** NIDDK Support

**TH-PO399**

**Screening for HLA Linear Epitopes Using Personalized Peptide Array: A Feasibility Study of Alloantibody Specificity in Transplantation**

**Jing Jin, Pan Liu, Tomokazu Souma, Andrew Z. Wei. Dept of Medicine - Nephrology, Northwestern Univ, Chicago, IL.**

**Background:** HLA molecules are highly polymorphic cell receptors, posing a major obstacle to the success of organ transplantation. The allorecognition of mismatched donor HLA directly contributes to chronic rejection. DNA typing for HLA is widely used in the clinic and one of the most important challenges is to determine which mismatched transplants will fare well and which should be avoided. Therefore it is desirable to specify antibody reactivity to individual mismatched epitopes.

**Methods:** We use peptide antigens of donor sequences to probe for antisera specificity in kidney transplant subjects. A large custom panel of 15-residue HLA peptides was synthesized in an array format following one of the two designs: a standard array of a fixed panel of peptides or personalized arrays. The standard array contains 420 peptides derived from a predetermined set of HLA-DQ allogeneic antigens. The personalized arrays that each includes donor-derived peptides of HLA-A, B, C, DQ and DR sequences were separately synthesized for individual transplant subjects. These arrays were used to probe pre- and post-transplant patients' sera for alloantibodies against the peptide antigens.

**Results:** The array method detected distinct antigen patterns among transplant subjects and revealed epitope-levels of specificity largely in accordance with the Luminex single-antigen results. Collective mapping of alloantibody epitopes in five kidney transplant patients revealed a highly antigenic "hotspot" of reactive epitopes in HLA-DQ/B1 across individual patients and their allelic variants, provided donor-recipient mismatch(es) present within this ~15 amino acid segment.

**Conclusions:** The peptide arrays robustly detected de novo antibodies following transplantation, directly revealing epitope-levels of antibody specificity associated with HLA mismatches. The array method also showed superior sensitivity to the Luminex single-antigen assay. Collectively, our pilot study proved the feasibility of personalized design to achieve high-resolution detections of linear HLA epitopes associated with distinct donor-recipient mismatches.

**Funding:** Private Foundation Support

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

Underline represents presenting author.

**184A**
Anti-Fibrotic MicroRNA Strategies in a Mouse Model of Chronic Renal Allograft Dysfunction Celina Schauerte,1 Song Rong,2 Michael Mengel,3 Hermann G. Haller,2 Thomas Thum,1 Johan Lorenzen,1,2 1Instit of Molecular and Translational Therapeutic Strategies (IMTTS), Hannover Medical School, Germany; 2Dept of Nephrology & Hypertension, Hannover Medical School, Germany; 3Dept of Laboratory Medicine & Pathology, Univ of Alberta, Canada. 

Background: Pro-fibrotic microRNA-21 (miR-21) is upregulated in chronic allograft dysfunction (CAD), which is characterized by fibrotic remodeling, renal injury and chronic inflammation. This study investigates miR-21 inhibition as a therapeutic approach in an evaluated murine model of CAD.

Methods: Allogenic kidney transplantation (KTx) was performed from male C57BL/6 into CBA/Ca females. Recipients were treated at day 1 and day 7 either with LNA-nc (control) or LNA-21 (inhibitor of miR-21) (20mg/kg bw, ip). Kidneys were analyzed 6 weeks after KTx, e.g. by qRT-PCR, PAS-, Picrosirius Red- and immunostaining. In vitro assays were performed in renal fibroblasts (NRK49F) and macrophages (RAW264.7).

Results: We documented increased expression of fibrosis (ESMA, ColI, Col3, FSP-1) and inflammation (IL-6) markers in KTx kidneys which were rescued by miR-21 inhibition. Moreover, Picrosirius Red staining and BANFF scoring (ci and ct) revealed significantly less fibrosis and injury development due to miR-21 inhibition. Besides, allografts of LNA-21 treated mice showed less infiltrated T-cells (CD3) and macrophages (F4/80) visualized by immunostaining. In vitro we found LPS-activated macrophages to produce and secrete high levels of IL-6. IL-6 activates the transcription factor STAT3, which has a putative binding site in the miR-21 promoter. We hypothesize, that inhibiting macrophages produce IL-6 which affects resident renal cells causing fibrosis and injury processes. Culture assays revealed a crosstalk between fibroblasts and resident renal cells with increased expression levels of miR-21, primary miR-21, IL-6 and CTG in fibroblasts. Similar results were observed due to IL-6 treatment of fibroblasts. Furthermore, EMSA verified IL-6 mediated activation of STAT3 in fibroblasts.

Conclusions: MiR-21 antagonism could reduce allograft rejection due to less inflammation and fibrosis and suggests a new essentially needed anti-fibrotic treatment strategy against CAD.

Role of Brain-Derived Neurotrophic Factor in Chronic Cyclosporine Nephropathy Long Ye Zhang, Shang Guo Piao, Ji Zhe Jin, Can Li. Nephrology, YanBian Univ Hospital, YanJi, JiLin, China.

Background: Increasing evidence suggests that Brain-derived neurotrophic factor (BDNF) induces a variety of psychiatric and neurological disorders. However, the role of BDNF in the kidney has yet to be determined. The present study examined the expression of BDNF and tropomyosin-related kinase (Trk) receptors in the kidney in a rat model of chronic cyclosporine A (CsA) nephropathy.

Methods: SD rats were maintained on a low-salt diet and treated daily for four weeks with vehicle or CsA. Basic parameters, histology (tubulointerstitial fibrosis and apoptosis), concentration of the pro-inflammatory stress marker HSP-70, and expression of BDNF and Trk receptors (TrkB and TrkC) were compared between groups. The effect of vasopressin infusion on the urine-concentrating ability was examined by measuring the expression of AQP-2 and BDNF and urine profiles in normal and CsA-treated rats.

Results: Compared with the vehicle-treated rats, rats given CsA showed renal insufficiency, increased urine volume and number of apoptotic cells, decreased urinary osmolality, and tubulointerstitial fibrosis. Immunohistochemistry showed that BDNF and Trk receptors TrkB and TrkC were constitutively expressed in the collecting duct of corticomedullary and medulla in vehicle-treated rats. This was confirmed by immunofluorescent staining. Treatment with K-ATPase-α1, AQP-1, and AQP-2. By contrast, the expression of these receptors (TrkB and TrkC) were compared between groups. The effect of vasopressin infusion on the urine-concentrating ability was examined by measuring the expression of AQP-2 and BDNF and urine profiles in normal and CsA-treated rats.

Conclusions: Compared with the vehicle-treated rats, rats given CsA showed renal insufficiency, increased urine volume and number of apoptotic cells, decreased urinary osmolality, and tubulointerstitial fibrosis. Immunohistochemistry showed that BDNF and Trk receptors TrkB and TrkC were constitutively expressed in the collecting duct of corticomedullary and medulla in vehicle-treated rats. This was confirmed by immunofluorescent staining. Treatment with K-ATPase-α1, AQP-1, and AQP-2.

Targeting Histone Deacetylase in Renal Tubular Epithelial Cells Reduces T Cell-Mediated Inflammatory Responses Byconvgoo Woo Kim, Sunwoo Kang, Tae Hee Kim, Yeong Hoon Kim. Div of Nephrology, Dept of Internal Medicine, Inje Univ Busan Paik Hospital, Busan, Republic of Korea.

Background: More studies are focusing on renal tubular epithelial cells (RTECs) as a new target to restore inflammatory environment as clarifying their immune regulatory function. Here, we investigated whether histone deacetylases (HDACs) are activated during T cell-mediated inflammation and their blockade is able to reduce inflammatory responses.

Methods: Human renal proximal tubular epithelial cell line HK-2 was cultured in the presence of recombinant IFN-γ (20 U/ml) plus TNF-α (5 ng/ml). The HDAC activity was determined on the expression levels of acetylated H3 and α-tubulin by immune blot assay. To determine the functional activity of HDAC inhibitor SB939, we analyzed the immune stimulatory phenotype of HK-2 cells such as class II MHC molecule, CD80, CD86, and CD40 by flow cytometry. In addition, the culture supernatants were used for measurement of cytokines and chemokines by ELISA assay.

Results: We found that HDAC activity was markedly increased in HK-2 cells by treatment of IFN-γ/TNF-α within 12h. Treatment of pan-HDAC inhibitor SB939 in HK-2 cells completely prevented HDAC activity increased by IFN-γ/TNF-α treatment. SB939 treatment significantly inhibited up-regulating CD40 expression but not MHC class II, CD80, and CD86. In addition, MCP-1 was significantly inhibited more than IL-6 and TNF-α by treatment of SB939 in HK-2 cells. Therefore, our study suggests that HDAC inhibitor has a therapeutic potential for the treatment of acute renal inflammatory diseases such as allograft rejection in transplantation.

Funding: Clinical Research Support
TH-PO405
High Dose Belatacept Is Diabetogenic and Toxic to Pancreatic Islet Cells

Background: Belatacept is a promising immunosuppressant for replacing calcineurin inhibitors in kidney transplantation, but its side effect is not fully studied. We evaluated whether belatacept is diabetogenic at therapeutic dose.

Methods: Three experimental groups were established: Belatacept (1.2mg/kg) or control (0mg/kg) were chosen based on previous animal studies that 2mg/kg of belatacept is effective in preventing acute rejection in rats. Belatacept was administered intravenously via tail vein on a weekly basis for 4 weeks in rats, and VH group rats received a saline via tail vein injection on the weekly basis for 4 weeks. Each dose weight, urine volume, and water intake were measured daily according to the IPITT. The diabetogenicity of belatacept was evaluated by intraperitoneal glucose tolerance test (IPGTT) and area under the curve for glucose (AUCg) calculated by trapezoidal estimation. Pancreatic beta cells were isolated from experiment animals then AO/PI staining, which was examined via fluorescence microscope and glucose-stimulated insulin secretion (GSIS) were performed in isolated beta cells.

Results: After four weeks, there is no significant difference in body weight, water intake and 24hr-urine volume between control and belatacept-treated groups. Belatacept 1mg/kg and 2mg/kg treatment increased AUCg from the values obtained during the IPITT, which was not statistically significant. However, received-4mg/kg of belatacept group showed significantly increased blood glucose level at 30 min compared with VH group. Consistently, AO/PI staining showed PI-positive cell death were increased in belatacept 1mg/kg and 2mg/kg treatment groups. However, only treatment with belatacept 4mg/kg significantly increased PI-positive cell death compared with VH group. GSIS also showed a high dose of belatacept significantly decreased insulin secretion.

Conclusions: Our preliminary study clearly defines that belatacept (therapeutic dose) increased blood glucose level gradually and diabetogenic at the high dose. Further evaluation is needed to confirm diabetogenicity of belatacept in clinical practice.

Funding: Clinical Revenue Support

TH-PO406
Addition of a DPP-IV Inhibitor to Metformin Decreases Siroliimus-Induced Oxidative Stress and Improves Mitochondrial Respiration in Pancreatic Islet Cells

Background: The guideline for the management of new-onset diabetes after transplantation recommends metformin (MET) as a first-line drug, and the addition of a second-line drug is needed in case of inadequate glycemic control. The influence of oxidative stress and apoptotic cell death was evaluated by serum and pancreas tissue. An in vitro study was also performed by INS-1 cells. Pancreas beta cell death and production of ROS were evaluated by INS-1 cells. At the subcellular level, mitochondrial respiration was also evaluated in INS-1 cells.

Results: In an animal model of SRL-induced DM, MET treatment improved pancreatic islet function. The influence of oxidative stress and apoptotic cell death was evaluated by serum and pancreas tissue. An in vitro study was also performed by INS-1 cells. Pancreas beta cell death and production of ROS were evaluated by INS-1 cells. At the subcellular level, mitochondrial respiration was also evaluated in INS-1 cells.

Results: In an animal model of SRL-induced DM, MET treatment improved mitochondrial islet function and attenuated oxidative stress and apoptotic cell death. The addition of a DPP-IV inhibitor to MET improved these parameters more than MET alone. An in vitro study showed that SRL treatment increased pancreatic beta cell death and production of ROS, and pretreatment of ROS inhibitor or p38MAPK inhibitor effectively decreased SRL-induced islet cell death. Exendin-4 (EXD), a substrate of DPP-IV, or MET significantly improved cell viability and decreased ROS production compared with SRL treatment, and combined treatment with the two drugs improved both parameters. At the subcellular level, impaired mitochondrial respiration by SRL was partially improved by MET or EXD, and much improved further after addition of EXD to MET.

Conclusions: Our data suggest that addition of a DPP-IV inhibitor to MET decreases SRL-induced oxidative stress and improves mitochondrial respiration. This finding provides a rationale for the combined use of a DPP-IV inhibitor and MET in treating SRL-induced DM.

Funding: Clinical Revenue Support

TH-PO407
Regulation of IFNγ Production by IL-10 May Predict Functional Outcome in Chronic Antibody-Mediated Rejection
Hatty A.A, Douthwaite, Hannah E. Wilkinson, The Dorling Group. MRC Centre for Transplantation, King’s College London, London, United Kingdom.

Background: Kidney transplants do not last for the natural lifespan of most recipients. The single biggest cause of renal allograft failure is chronic rejection (CR). Surprisingly little is known about the mechanisms that underpin CR. HLA antibodies are important but multiple lines of evidence indicate that it is the immune interactions between donor alloantibodies, CD4+ T and B lymphocytes that underpin CR. Th1 effector CD4+ T cells, which produce interferon-gamma (IFNγ), mediate chronic rejection. Regulation of Th1 cells by IL-10 is essential, as unchecked IFNγ production results in severe tissue damage and death. We demonstrated that ELISPOT patterns (detecting indirect CD4+ T cell alloresponses) are significantly associated with functional outcome after renal transplantation.

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

Underline represents presenting author.

186A
Long Term Renal Allograft Survival and Inhibitory KIR Receptors

Raj K. Sharma, Swayam Prakash, Suraksha Agarwal. Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, UP, India.

Background: NK cell is regulated by KIR like inhibitory and activating cell surface receptors. We evaluated allelic diversity of KIR3DL1/3DS1 and its effect on human HLA-Bw4 ligand affinity on long term transplant outcome.

Methods: KIR3DL1/3DS1 allelic diversity was examined in 100 transplant cases and 100 controls. All samples were positive for KIR3DL1 or/and KIR3DS1 and possessed HLA-Bw4 ligand. PCR-SSP was used to determine incidence of KIR3DL1/3DS1 genes and sequence based typing method evaluated the pattern of KIR3DL1/3DS1 allelic distribution. HLA class I typing was performed using PCR-SSP kits. Quantification of KIR3DL1/3DS1 mRNA expression was done by qRT-PCR with GAPDH as the housekeeping gene.

Results: We observed presence of 84 KIR3DL1/3DS1 alleles in the north Indian cases and 72 in controls. 3 KIR3DL1 alleles with incidence > 1% were noted. For KIR3DL1*010101, no-risk (OR=0.37, p=0.072) association was observed with increased mRNA expression among ABMR (Fold change=1.48±0.32, p=0.031), and antibody mediated chronic rejection (Fold change=1.12±0.15, p=0.042) cases. Risk was found for KIR3DS1*049N (OR=5.16, p=0.0001) and KIR3DS1*1301 (OR=4.27, p=0.0001). Both KIR3DS1*049N and KIR3DS1*1301 showed a decreased mRNA level. Looking at the ligand affinity, 3DS1*0101/HLA-Bw4+ (OR=2.12, p=0.012) and 3DS1*049N/HLA-Bw4+ (OR=3.42, p=0.001) combinations showed subdued susceptibilities. Kaplan-Meier survival analysis performed on a 15 year follow-up data revealed highest overall survival of 11 years for KIR3DL1*010101/HLA-Bw4 (cumulative survival=65%). Less prolonged survival of 10 years for 3DS1*0101/HLA-Bw4+ (cumulative survival=36%) and 8 years for 3DS1*049N/HLA-Bw4+ (cumulative survival=18%) combinations. Inhibitory ligands transmitted via KIR3DL1 induces the ITIM motifs giving rise to inhibitory signaling in KIR positive cells. Inhibition leads to higher T cell response due to protection of T cell from activation induced death.

Conclusions: Survival of renal allograft depends on presence of inhibitory KIR receptors. Suppressing KIR3DS1 like activating NK cell surface receptors may improve long term survival of kidney allografts.

Effect of Inflammation on Intracellular Concentration of Tacrolimus

Hua Lin,1 Chih-Jen Cheng,1,2 Shih-Hua P. Lin,1 Cathay General Hospital, 1National Defense Medical Center; 2Tri-Services General Hospital.

Background: Hypercapnic Acidosis Attenuates Ischemia-Reperfusion Injury Associated Acute Kidney Injury in Rats

Ming-Tso Yan,1 Chih-Jen Cheng,1,2 Shih-Hua P. Lin,1 Cathay General Hospital; 2National Defense Medical Center; 2Tri-Services General Hospital.

Background: Hypercapnic acidosis (HCA) preconditioning was suggested to attenuate ischemia-reperfusion (IR) injury of brain and lung, and underlying mechanism is uncertain. No study has assessed renoprotective effect of HCA preconditioning on renal IR injury. Here we investigate the effect and mechanism of HCA preconditioning on renal IR injury. We determined by immunoblot.

Methods: Adult Sprague-Dawley rats are randomly exposed to humidified gas containing either FICO2 of 5% or room air only for 30 minutes before sham operation or clamping renal artery for 30 minutes. Three or 24 hours reperfusion followed. Urine, blood and kidney tissue were obtained for biochemistry and histology. Protein level was determined by immunoblot.

Results: Histologically, less IR-related tubulointerstitial injury, leukocyte infiltration and tubular cell apoptosis were disclosed after HCA preconditioning. Functionally, HCA administration preserved renal function after IR injury. Renal blood flow was increased by better concentrating ability as well as low serum creatinine and urea nitrogen. Circulating TNF-α, interleukin (IL)-1β and IL-6 levels in response to IR is suppressed significantly in HCA group. HCA preconditioning demonstrated anti-apoptotic effect by downregulating TRAF6-ASK1-p38/JNK pathway and reducing the cleavage of caspase 3 and PARP. HCA also suppressed NF-kB pathway to achieve anti-inflammatory effect and enhanced anti-stress ability by raising expression of heat shock protein 70 and heme oxygenase-1.

Conclusions: These results suggest that protective effect of HCA preconditioning on renal IR injury may be mediated by complex mechanisms including anti-apoptosis, anti-inflammation and anti-stress.

ARTICLES OF INTEREST

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

187A
Development of Experimental Model of Renal Thrombotic Microangiopathy in Rat: Allogeneic Bone Marrow Transplantation Takafumi Kamenitsu, Yusuke Okabayashi, Michiko Aoki, Yusuke Kajimoto, Kiyotaka Nagahama, Akira Shimizu. The Dept of Analytic Human Pathology, Nippon Medical School, Bunkyo, Tokyo, Japan.

**Background:** The thrombotic microangiopathy (TMA) after bone marrow transplantation (BMT) is a severe complication that carries a high risk of renal dysfunction. In TMA after BMT, total body irradiation, use of immunosuppressants and chronic graft-versus-host-disease (GVHD) have been proposed as risk factors in inducing endothelial cell injuries and causing TMA. The skin, gut and liver are well-known primary target sites in GVHD. In our previous study, the kidney was a primary target organ of acute GVHD after BMT. In TMA after BMT, the involvement of the kidney is not well-understood. We are focusing on the pathogenesis of TMA after BMT affecting the kidney.

**Methods:** We induced TMA in irradiated BN rat by transplanting BM cells from allogeneic Lewis rats without immunosuppression. For chimerism analysis, FCM was performed. We examined the clinical and pathological characteristics of TMA in several organs including kidney at 9 months after BMT.

**Results:** Almost all blood cells were replaced by the donor cells. Mild to moderate GVHD in the skin, gut and liver was developed at 9 months after BMT. The serum creatinine levels were mildly increased. Renal pathology at 9 months after BMT showed the increase of number of collapsed and sclerotic glomeruli with endothelial cell injuries in all rats. In addition, in half of the rats, renal TMA developed, that were characterized by the glomeruli with mesangiolysis, double contour of the GBM with widening of subendothelial spaces, and the fibrin exudation in the glomerular capillaries. Exudative lesions in small arteries were also seen. These renal findings were quite similar to renal TMA after BMT in humans. RT-PCR showed that mRNA levels of Th2 cytokines are strongly expressed than Th1 cytokines in glomeruli.

**Conclusions:** We have developed the animal models of renal TMA after BMT in rats. In this model, renal TMA is accompanied with mild to moderate GVHD in the skin, gut and liver. These findings may be indicated that renal TMA after BMT is one of the findings of chronic GVHD in the kidney. Further studies are also needed to assess the mechanism of TMA after BMT.

Drug Repurposing: In Vitro Validation of In Silico Predicted Transcriptomic Changes in Primary Human Mesangial Cells Induced by Calcineurin Inhibitor FK 506 Constantin Aschenbrenner, Andreas Heinzel, Judith Sanzenauer, Peter Oberbauer. 1Dept of Nephrology, Medical Univ of Vienna, Vienna, Vienna, Austria; 2Emergentec Biodevelopment GmbH, Vienna, Austria.

**Background:** Network-based drug repurposing is an emerging area in systems pharmacology utilizing Omics derived network-based models of disease pathophysiology and drug mechanism of action (MoA) in order to identify new indications for established drugs. The calcineurin-inhibitor FK 506 shows positive potential effects in a set of diseases outside the area of transplantation.

**Methods:** A FK 506 MoA molecular model was constructed using two published transcriptional datasets and a set of molecular features affected by FK 506 based on a literature mining approach. This model was screened against an in-silico library of ~2000 pharmacology utilizing Omics-derived network-based models of disease pathophysiology and drug mechanism of action (MoA) in order to identify new indications for established drugs. The calcineurin-inhibitor FK 506 shows positive potential effects in a set of diseases outside the area of transplantation.

**Results:** A set of 222 transcripts mapping to 284 unique protein coding genes were found deregulated. Pathway enrichment analysis identified the TGF-β signaling pathway (p-value: 0.0210) and a set of cell adhesion molecules (p-value: 0.0217) as relevant. Although TGFβ1 was upregulated (1.32 fold), also one major inhibitor of the TGFβ signaling cascade, SMAD7, was upregulated (1.31 fold). Other drug targets in the context of diabetes and DN as JAK2 (0.81 fold) and DPP4 (0.76 fold) were downregulated. On the other hand, NOX4 and EDN1 were both significantly upregulated being detrimental for DN.

**Conclusions:** Our in-silico drug screening approach identified DN as one of the key candidates showing interference on a molecular level with FK 506. In an in-vitro experiment we could validate the effect of FK 506 on TGFβ signaling as well as other drug targets currently being addressed in clinical practice or trials. A set of predictive markers might guide the use of FK 506 in DN thus identifying those patients potentially benefiting from a low-dose tacrolimus treatment.

**Funding:** Government Support - Non-U.S.
Diabetes Mellitus, Obesity: Basic-Experimental – 1

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

**Underlines represent presenting author.**

189A
of diabetic rats was markedly increased and closely correlated with increased LDLr protein expression, compared with the controls. However, these change was significantly inhibited by a nonselective inhibitor of COX-2, Aspirin.

**Conclusions:** Dysregulation of LDLr pathway contributes to podocyte injury in diabetic nephropathy, which might be mediated through the increased COX-2 expression.

**TH-PO425**

Mulglycoside of *Tripterygium wilfordii* Hook.f. Attenuates Podocyte Damage in Diabetic Nephropathy Rats via Regulating mTORC1 Signaling Pathways, Compared with Ramapycin Ge Nai, Yiyan Han, Yan Nan, Ning Univ of Chinese Medicine; Ningjing Drum Tower Hospital, The Affiliated Hospital of Ningjing Univ Medical School.

**Background:** Mulglycoside of *Tripterygium wilfordii* Hook.f. (GTW) has been applied extensively for treating podocyte injury in patients with early diabetic nephropathy (DN) in China. Activation of mTORC1 plays a critical role in podocyte damage under hyperglycemia, which can be realized by the combined actions of Akt activation and AMPK inhibition. This study thus aimed to investigate effects and mechanisms in vivo of GTW on podocyte lesion, compared with ramapycin (RAPA) as an mTORC1 inhibitor, by regulating Akt/mTORC1 or AMPK/mTORC1 signaling activities.

**Methods:** Rats were randomly divided into 4 groups, the sham-operated group, the GTW-treated group, the vehicle-group given and the RAPA-treated group, and sacrificed at week 8 after the injection of DN by 2 consecutive intraperitoneal injections of streptozotocin (STZ) with an interval of 1 week following unilateral nephrectomy. Daily oraladministration of GTW, RAPA and saline were started after the second injection of STZ until sacrifice.

**Results:** The results indicated that, after p-Akt was up-regulated and p-AMPK was down-regulated respectively, mTORC1 signaling pathways were concurrently activated in kidneys of the DN model rats. GTW, similar to RAPA, markedly regulated the protein expressions of p-Akt, p-AMPK, p-mTOR and p-T70S kinase in kidneys, and ameliorated albuminuria, foot process effacement, podocyte loss and glomerulosclerosis. In addition, the recuperative protein expressive levels of podocin and CD2AP and the rasied protein expression, compared with the controls. However, these change was significantly inhibited by a nonselective inhibitor of COX-2, Aspirin. 1 – 100.01% compared to the WT controls. In vitro, PMID-427 decreased apoptosis of cultured podocytes by 72±17% in hyperglycemic conditions and by 30±9% when exposed to CPT. The decreased apoptosis was associated with 70-90% decrease in ROS production. A significant 1.7 fold increase in fatty acid oxidation was also observed.

**Conclusions:** Global PDEF deficiency results in worsening of glomerular lesions in the STZ-induced mouse model of diabetes A short fragment of PDEF derived from its active epitope has a marked protective effect in vitro. This peptide attenuates ROS, and increases fatty acid oxidation in podocytes and may have therapeutic potential for diabetic kidney disease.

**TH-PO426**

TRIM72-Containing Microvesicles Protect Podocyte in Diabetic Nephropathy via TWIST Pu Duann, Haichang Li, Elias A. Lianos, Pei-Hui Lin, Medicine, OSU Wexner Medical Center, Columbus, OH; Surgery, OSU Wexner Medical Center, Columbus, OH; Medicine/Nephrology Div, Rutgers RWJ Medical School, New Brunswick, NJ; DHLRI, OSU Wexner Medical Center, Columbus, OH.

**Background:** Glomerulosclerosis is the major kidney complication in diabetes. GBM thickening caused by disrupted ECM homeostasis, is a prominent feature in DN with hyperglycemia, which can be realized by the combined actions of Akt activation and AMPK inhibition. We previously reported a glocuse intolerance phenotype with a TRIM72-null transgenic mice. TRIM72 loss of function was associated with 70-90% decrease in ROS production. A significant 1.7 fold increase in fatty acid oxidation was also observed.

**Methods:** The results indicated that, after p-Akt was up-regulated and p-AMPK was down-regulated respectively, mTORC1 signaling pathways were concurrently activated in kidneys of the DN model rats. GTW, similar to RAPA, markedly regulated the protein expressions of p-Akt, p-AMPK, p-mTOR and p-T70S kinase in kidneys, and ameliorated albuminuria, foot process effacement, podocyte loss and glomerulosclerosis. In addition, the recuperative protein expressive levels of podocin and CD2AP and the rasied protein expression, compared with the controls. However, these change was significantly inhibited by a nonselective inhibitor of COX-2, Aspirin. 1 – 100.01% compared to the WT controls. In vitro, PMID-427 decreased apoptosis of cultured podocytes by 72±17% in hyperglycemic conditions and by 30±9% when exposed to CPT. The decreased apoptosis was associated with 70-90% decrease in ROS production. A significant 1.7 fold increase in fatty acid oxidation was also observed.

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**TH-PO427**

Pigment Epithelium Derived Factor (PEDF) Is Protective for Podocytes, and Global Genetic Ablation Exacerbates Glomerular Lesions in Mice with STZ-Induced Diabetes Minhao Ye, Olga V. Volpert, Jan A. Wysocki, Daniel Battle. Div of Nephrology and Dept of Urology, Northwestern Univ, Feinberg School of Medicine, Chicago, IL.

**Background:** Pigment Epithelium Derived Factor (PEDF) encoded by SERPINF1 gene is a multifunctional protein that has anti-angiogenic and cytoprotective activities. It has been reported that PEDF protein levels are reduced in the kidneys of rodents with experimentally induced diabetes and 44mer PEPF fragment may be renoprotective. We used SERPINF1 KO mice to examine the impact of global PEDF deficiency on kidney pathology and tested a short PEDF fragment for protective effects in cultured podocytes.

**Methods:** The potential protective effects of a novel PEDF peptide PMID-427 was tested in cultured podocytes exposed to high glucose or genotoxic stress (cisplatin, CPT). Podocyte apoptosis was measured by TUNEL assay and ROS levels were assessed using DHR fluorescent dye. Metabolic activity was evaluated in cells exposed to control vehicle and PMID-427 using Seahorse analyzer in the presence of free drug fatty acids (Palmitate).

**Results:** Twelve weeks after diabetes induction by STZ, SERPINF1 KO mice showed a significant increase in mesangial matrix (2.8±0.14 vs. 1.2±0.14 arbitrary units, p<0.01) and ~20% decrease in podocyte counts (8.2±0.04 vs. 9.7±0.2 podocytes/glomerulus, p<0.01) compared to the WT controls. In vitro, PMID-427 decreased apoptosis of cultured podocytes by 72±17% in hyperglycemic conditions and by 30±9% when exposed to CPT. The decreased apoptosis was associated with 70-90% decrease in ROS production. A significant 1.7 fold increase in fatty acid oxidation was also observed.

**Conclusions:** Global PEDF deficiency results in worsening of glomerular lesions in the STZ-induced mouse model of diabetes A short fragment of PDEF derived from its active epitope has a marked protective effect in vitro. This peptide attenuates ROS, and increases fatty acid oxidation in podocytes and may have therapeutic potential for diabetic kidney disease.

**TH-PO428**

Mitochondrial Dynamic Alterations Mediated by P66Shc Signaling Promotes Diabetes-Induced Tubular Cell Injury and Apoptosis Ming Zhan, Yiashal S. Kanwar, Lin Sun. Medicine, Ningbo First Hospital, Zhejiang Univ, China; Pathology, Northwestern Univ; Medicine, Second Xiangya Hospital, Central South Univ, China.

**Background:** Renal tubular injury is an early characteristic of diabetic nephropathy (DN), mitochondrial damage and the adaptor protein p66Shc-mediated oxidative stress are both critical during diabetic tubular cell injury and death, their correlation is unclear.

**Methods:** We investigate mitochondrial morphological changes in renal tissues from DN and MCD patients, and explore the involvement of p66Shc-mediated mitochondrial dynamic alterations and cell apoptosis in human renal tubular cells.

**Results:** Elongated mitochondria became fragmented in renal tubules of patients with DN, compared with the control group. The levels of mitochondrial shaping proteins Drp1 and Fis1 were increased and Mfn1 decreased in DN tissues, these changes were accompanied with the elevation of p66Shc level and oxidative stress. In HK-2 cells, alterations in mitochondrial dynamics and its related protein levels was observed under HG ambiene, together with upregulation of p66Shc and phosphorylated p66Shc at Ser36. Notably, siRNA knockdown of p66Shc alleviated HG-induced mitochondrial fragmentation and apoptosis. Knockdown of negative Ser36 p66Shc mutant in HK-2 has marginal similar effects.

**Conclusions:** Clinical evidence of mitochondrial fragmentation in human diabetic nephropathy was presented in our study. P66Shc activation and phosphorylation mediated mitochondrial dynamic alterations through regulating mitochondrial shaping proteins, and leading to tubular oxidative injury and apoptosis via p66Shc/Mfn/Bak pathway under HG ambiene.

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

**TH-PO429**


**Background:** Obesity-related glomerulopathy (ORG) is an emerging complication of the obesity epidemic. However, the underlying molecular mechanisms through which obesity may cause renal injury are not well understood. Potential mechanisms include metabolic maladaptive pathways, lipid accumulation, podocyte hypertrophy and dysfunction, adipokine dysregulation, oxidative and inflammatory stress.

**Methods:** To obtain insight into molecular mechanisms underlying obesity-induced kidney injury we studied metabolic target gene expression in amplified mRNA of laser captured microdissection (LCM) isolated glomeruli and tubules. We studied FFPE renal biopsies of patients with clinical and pathological established obesity- related...
glomerulopathy (OR), compared to normal kidneys. We also investigated lipid content and markers of podocyte injury and hypertrophy (Immunohistochemistry analysis of GLEPP1/WT1).

Results: OR manifests a benign course with slow eGFR deterioration compared to DN. Glomerular surface area was markedly enlarged in OR and was accompanied by significant decreases in the podocyte marker and genes with only limited compensatory podocyte hypertrophy. There was marked lipid accumulation in both glomeruli and tubules.

The most prominent difference in lipid metabolism gene expression was down-regulation of fatty acid β oxidation genes in both glomerular and tubulointerstitial fractions, possibly secondary to the increased transport of nuclear genes involved in mitochondrial respiration (PGC1α) and decreased expression of adiponectin receptors 1 and 2. Furthermore, increased were observed in genes contributing to cholesterol and triglyceride uptake (CD36) and decreases in cholesterol efflux (ABCA1) with a parallel decrease of liver X receptor alpha (LXRα). We also observed increased regulatory element binding protein-2 (SREBP-2) mRNA content, mainly in the tubular fraction.

Conclusions: The major finding of this study is that lower expression of the mitochondrial respiratory pathway and defective regulation of lipid metabolism pathways involved in obesity-induced kidney injury.

Funding: NIDDK Support

TH-PO430


Background: Elevated blood pressure (BP) was frequently observed in subjects with midlife weight gains and in obese mice. Elevated mitochondrial dysfunction is associated with obesity induced BP elevation. Previously we and others have shown that an EET agonist (EET-A), reduced adiposity and ROS resulting in normalization of BP by uncoupling mitochondrial mechanisms. We hypothesized that EET-A may attenuate BP in mice fed high caloric diet intake by recruiting Pgc1a-HO-1 that resulted in restoring mitochondrial function and fusion.

Methods: C57/B16 mice at the age of 5 weeks, fed a HF diet that for 24 wks. When all mice had established pre-diabetic stage (12-wks), EET-A was administered intraperitoneally, 1.5 mg/100g BW. (Blood was collected, glucose and visceral fat and renal tissues were harvested, HO-1, NKKC2, ENaC, NCC, insulin receptors, PGC1α Mito-fusion protein markers and VO2 consumption were determined in group: A) Control, B) HF, C) HF-EET-A and D) EET-A-L-PGC1α (sh). Results: Renal PGC1α, HO-1, pAMPK, and mitochondrial fusion protein Mfn1/2, and Opal were decreased in obese mice and restored by EET-A treatment. VO2 consumption were impaired in control obese mice compared to mice treated with either EET-agonists or vehicle solution p<0.05. A HF diet increased levels of Na1 co-transporter (NCC) but not type 2 Na-K co-transporter (NKK2C) or epithelial Na channel-alpha subunit ENaC while treatment with EET-A decreased NCC expression (p<0.05) that was associated with normalization of BP. Electron transport and mitochondrial citrate carrier (p<0.05) were lowered in mice fed a HF diet compared to EET-A.

Conclusions: EET-A restores cortical NCC channel function is associated with recruitment of PGC1α-HO-1, mitochondrial Mfn1/2 and Opal 1, mitochondrial function that is associated with normalization of BP. Pharmacological targeting mitochondrial fusion proteins may restore the release of HO-1 and antiinflammatory activity via decrease bilirubin that may be a promising therapy in prevention of renal function and amelioration of hypertension.

Funding: Other NIH Support - National Institutes of Health grants HL-34300 (NGA)

TH-PO431

Acute Mitochondrial Response to High Glucose Exposure in Primary Renal Cells Studied with Super Resolution Microscopy Limina M. Nilsson,1 Lena Scott,1 Jacopo Maria Fontana,1 Liang Zhang,1 Kristoffer Bernhem,1 Hjalmar Brismar,2 Anita Aperea,1 Karolinska Inst, Stockholm, Sweden; 2Royal Inst of Technology, Stockholm, Sweden.

Background: Hyperglycemia is a major cause of diabetic complications. Many aspects of mitochondrial dysfunction are reported in studies of experimental diabetic nephropathy. Yet, little is known about the immediate mitochondrial response to high glucose (HG) in primary renal cells.

Methods: Acute response of primary renal cells, proximal tubule cells (RPTC), mesangial cells (MC) and podocytes, to HG (15-20mM) exposure was studied with immunocytochemistry, TUNEL stain, Stimulated Emission Depletion (STED) and Stochastic Optical Reconstruction (STORM) microscopy.

Results: First we compared the 8 h response to HG in RPTC and MC, which express both Glut transporters and SGLT2 or 1 respectively, and in podocytes which only express GluT1. We observed significant increase in apoptotic index in RPTC and MC but not in podocytes, associated with an increased expression of apoptotic factor Bax and decreased expression of anti-apoptotic factor Bcl-xL. Next we used STED to visualize initiation of apoptosis in RPTC exposed to HG. In control cells, Bax in inactive form was found in cytoplasm, while Bcl-xL was found on mitochondria. After 6 h of HG, clusters of active Bax was found on mitochondria, while Bcl-xL remained on mitochondria. STORM revealed progressive co-localization between Bax and the voltage–dependent anion channels (VDAC) in approximately 10% of cells. Bax–VDAC interaction permitted an uncontrolled mitochondrial calcium influx, marking the point of no return in the apoptotic process.

Previously we have described how ouabain/Na-K-ATPase signaling exerts an anti-apoptotic effect. Here we show that this signal halts initiation of the apoptotic process.

Conclusions: We conclude that exposure to glucose in concentrations not uncommon in poorly controlled diabetes promptly initiates an apoptotic process in SGLT expressing renal cells and would require preventive anti-apoptotic treatment.

Funding: Private Foundation Support

TH-PO432

Apoptosis Signal-Regulating Kinase 1 (ASK1) Pathway Activation in Diabetic Kidney Disease (DKD) Patients and db/db eNOS−/− Mice John T. Liles,1 Haichun Yang,2 Ted Sullivan,1 Erik G. Huntzicker,1 Dorothy French,1 Agnes B. Fogo,2 David G. Breckenridge,1 1Gilead Sciences, Inc, Foster City; 2Vanderbilt Univ Medical Center, Nashville.

Background: ASK1 is a serine/threonine kinase activated by pathological oxidative stress that drives renal inflammation, apoptosis, and fibrosis via the downstream MAPK kinases p38 and c-Jun N-terminal kinase (JNK). GS-4997 is a selective ASK1 inhibitor in clinical development for the treatment of DKD. We quantified p38 activation (p-p38) in kidney biopsies from patients with DKD and renal ASK1 activation (p-ASK1) and p-p38 levels in the db/db eNOS−/− model of DKD. A selective ASK1 inhibitor was used to determine the role of ASK1 in p38 activation and progressive GFR decline in db/db eNOS−/− mice.

Methods: p-p38 levels in renal biopsy tissue from patients with DKD (n=10) and healthy subjects (n=7) were determined by IHC. Slide images were analyzed with Delfin Developer XD and expressed as an H-Score that quantifies intensity and distribution. Masson’s trichrome, PAS, and H&E stains were done to assess fibrosis and morphology. 10 week old db/db eNOS−/− mice were treated with a structural analog of GS-4997 (GS-144217) or vehicle for 8 weeks (n=8-10). Endpoints included p-p38 and p-ASK1 in kidney lysates, histology, and GFR by inulin-FITC clearance.

Results: Compared to normal subjects, p-p38 levels were significantly elevated in DKD biopsies (144 ± 49 vs 15 ± 9 H-Score, p=0.00001). In glomeruli with mild to severe mesangial expansion, p-p38 expression was prominent and localized to mesangial cells, podocytes, and parietal epithelial cells. Tubule epithelium and areas of interstitial fibrosis/ inflammation also had prominent p-p38. p-p38 staining was similarly distributed in kidneys of db/db eNOS−/− mice. Treatment of db/db eNOS−/− mice with an ASK1 inhibitor suppressed p-p38 (80% <p=0.05) and p-p38 by 94% (p=0.00095), and decreased albuminuria, glomerulosclerosis, and GFR decline (365: 31 vs 212: 21 ml/min, p=0.0007) compared to vehicle.

Conclusions: p-p38 is elevated in the glomerulus and tubulointerstitium of patients with DKD. A selective ASK1 inhibitor strongly suppresses p-ASK1 and p-p38 levels and halts GFR decline in db/db eNOS−/− mice.

Funding: Pharmaceutical Company Support - Gilead Sciences, Inc.

TH-PO433

Involvement of Endoplasmic Reticulum Stress, Autophagy, and Apoptosis in Advanced Glycation End Products-Induced Glomerular Mesangial Cell Injury Chih-Kang Chiang,1,2 Shing-Hwa Liu,1 1Graduate Inst of Toxicology, National Taiwan Univ; College of Medicine, Taipei, Taiwan; 2Dept of Integrated Diagnostics & Therapeutics, National Taiwan Univ Hospital, Taipei, Taiwan.

Background: Advanced glycation end-products (AGEs)-induced mesangial cell death is one of major causes of glomerulosclerosis in diabetic nephropathy. Both endoplasmic reticulum (ER) stress and autophagy are adaptive responses in cells under environmental stress and participate in the renal diseases. The role of ER stress and autophagy in AGEs-induced mesangial cell death is still unclear. Here, we investigated the effect and mechanism of AGEs on mesangial cells.

Methods: Mouse mesangial cells (MCs) were obtained from Food Industry Research and Development Institute. MCs were treated with AGEs to evaluate the cell viability by MTT assay and flow cytometry. The protein expressions were measured by Western blot analysis. Furthermore, MCs were treated with 3-Methyladenine (3MA), siATG5 and 4-phenylbutyric acid (4PBA) to study the influence of autophagy and ER stress.

Results: AGEs dose-dependently decreased mesangial cell viability and induced MCs apoptosis. AGEs also induced ER stress signals (GRP78, IRE1α, eIF2α, ATF4, and CHOP) in a time- and dose-dependent manner. Inhibition of ER stress with 4PBA significantly inhibited the activation of eIF2α and CHOP signals and reversed AGEs-induced apoptosis. AGEs also significantly activated LC3 cleavage, decreased p62 expression, and increased Atg5 expression in a time- and dose-dependent manner, which indicated the autophagy induction in mesangial cells. Inhibition of autophagy by Atg5 siRNA transfection aggravated AGEs-induced MCs apoptosis. Moreover, ER stress inhibition by 4PBA significantly reversed AGEs-induced autophagy inhibition (Atg5 siRNA) did not influence the AGEs-induced ER stress-related signals activation. These results suggest that AGEs induce MCs apoptosis via an ER stress-triggered signaling pathway. The Atg5-dependent autophagy plays a protective role in AGEs-induced MCs apoptosis. It may offer a new strategy against AGES toxicity in the diabetic kidney.

Funding: Government Support - Non-U.S.
Modification of Renal Macrophage Signaling via MCP-1 Inhibition Reduces Albuminuria in Diabetic Nephropathy in Mice
Daphne Thomas-Japelj,1 Margien G.S. Boels,2 Angela Koudijj,1 Cristina Avramut,1 Wendy Sol,1 Gangqi Wang,1 Annemarie Van Oeveren-Riedtijd,1 Anton Jan Van Zonneveld,3 Hetty C. de Boer,4 Johan Van der Vlag,5 Cees van Kooten,1 Dirk Eulbergh,6 Bernard van den Berg,1 Tom J. Rabelink,1 JUMC, Netherland; 2RadboudUMC, Netherlands; 3NOXXON Pharma AG, Germany.

Background: Recently, inhibition of the pro-inflammatory chemokine monocyte-macrophage chemotactic protein 1 (MCP-1) with Emapticap was found to reduce albuminuria in patients with type 2 diabetic nephropathy (DN). MCP-1 regulates inflammatory cell recruitment and differentiation of macrophages. Pro-inflammatory macrophages express chemokine L (CTSL), which activates heparanase (HPSE), thereby degrading heparan sulphates, one of the components of the glomerular endothelial glycocalyx (GEG). Presence of GEG is essential to prevent albuminuria. Therefore, we hypothesized that MCP-1 inhibition reduces albuminuria via influencing macrophage function, resulting in reduced HPSE activity and restoration of GEG.

Methods: DN was induced in 6 weeks old ApoE-KO mice with STZ (5x 60mg/kg) and a high cholesterol diet (0.15%). At week 18 mice were treated for 4 weeks with mouse specific MCP-1 inhibitor mNOX-E36 (20mg/kg, s.c.) or control Spiegelmer. Cationic ferritin (CF) binding to the GEG was imaged using transmission electron microscopy. Glomeruli were analysed for F4/80, CTSL and HPSE protein expression. Macrophages were isolated from the kidney with FACS and ex vivo cytokine production was measured.

Results: Treatment with mNOX-E36 attenuated albuminuria, without changes in blood glucose and blood pressure. This was accompanied by reduced CTSL and HPSE expression and increased binding of CF to the GEG. The number of glomerular macrophages did not change upon treatment. However, functional ex vivo analysis showed a reduced LPS-induced IL-6/L-10 ratio, demonstrating an anti-inflammatory phenotype.

Conclusions: MCP-1 inhibition by mNOX-E36 decreases albuminuria in diabetic apoe-KO mice. The accompanied anti-inflammatory phenotype of macrophages and GEG restoration, suggest that MCP-1 inhibition attenuates albuminuria in DN by restoration of the GEG via polarization of renal macrophages.

Funding: Other NIH Support - Dutch Kidney Foundation

**TH-PO435**

The Role and Mechanism of Alternatively Activated Macrophage in Renal Fibrosis of Diabetic Mice
Ning Su, Jiang Zongpei. Dept of Nephrology, The Sixth Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong Province, China.

Background: The effect and mechanisms of alternatively activated macrophage (M2) on renal fibrosis in diabetic mice has not been elucidated.

Methods: M2 macrophages (F4/80+/CD206+ double positive cells) and the accumulation of fibronectin in the kidney were observed in diabetic C57BL/6J mice after eight weeks of diabetic melius with intraperitoneal injection of streptozocin. Liposome-encapsulated clodronate (LC), the specific scavenger of macrophages was used to treat the diabetic mice by intraperitoneal injection (10µl/1g bodyweight) twice one week from the third to the eighth week to investigate the effect of M2 on renal fibrosis. Furthermore, Raw 264.7 cells were induced to M2 phenotype with high glucose concentration (30mmol/L) and TGF-β1 (5ng/ml). The special inhibitor of Smad2 (SB431542) and Erk (U016) were used to investigate the mechanism involved in the process of M2 differentiation.

Results: M2 macrophages in kidney were eliminated and the accumulation of fibronectin was improved in those diabetic mice treated with LC. Furthermore, the activation of Smad2 and Erk were all involved in the transformation of M2 macrophage, and not only the inhibitor of Smad2 but also Erk partially inhibited the process of M2 macrophage. However, no crosstalk between the Smad2 and Erk signal pathway was found in this process.

Funding: Other NIH Support - Dutch Kidney Foundation

**TH-PO436**

De-Nitrosylation of Laminin 521 in Diabetic Nodular Glomerulosclerosis
Alda Tufro, Qi Li, Pablo A. Ortiz-Pineda. Pediatrics/Nephrology, Yale Univ, New Haven, CT.

Background: We showed that glomerular basement membrane laminin 521 is nitrosylated in normal glomeruli. Laminin S-nitrosylation, a reversible post-translational modification controlled by nitric oxide availability and by VEGF-A in mouse kidneys and podocytes. Laminin 521 is increased in glomerular nodules observed in experimental diabetic nephropathy (DN) and likely involved in the pathogenesis of nodular glomerulosclerosis. We examined α5 and β2 laminin S-nitrosylation function in podocytes and DN.

Methods: We assessed S-nitrosylation (SN0) of α5- and β2-laminin using dual immunohistochemistry, biotin switch assay and proximity link assay in tissue and cultured cells. Kidneys from normoglycemic and T1D mice with mild DN and advanced DN were compared. SNO-α5-laminin and SNO-β2-laminin, secretion of each laminin chain, and cell migration were evaluated in human podocytes exposed to medium with normal glucose, high glucose, or mannitol.

Results: We determined that α5- and β2-laminin are S-nitrosylated in kidneys from non-diabetic mice and from mice with mild DN, whereas SNO-α5-laminin and SNO-β2-laminin decrease dramatically in advanced DN, inversely correlating with glomerular nodules. Podocytes cultured in normal glucose or mannitol medium express abundant SNO-α5-laminin and SNO-β2-laminin, while podocytes exposed to high glucose showed minimal SNO-α5-laminin and SNO-β2-laminin, as assessed by 3 independent methods. This SNO-α5-laminin and SNO-β2-laminin decrease was associated with several fold increase in α5- and β2-laminin secretion to the medium, which was abolished by nitric oxide (NO) donors. Wound assays showed that podocyte migration is impaired when α5-laminin and β2-laminin is S-nitrosylated by high glucose, and that NO donors rescue this migration defect.

Conclusions: De-nitrosylation of α5-laminin and β2-laminin leads to increased laminin secretion by podocytes, impairs their migration and contributes to development of glomerular nodules in advanced diabetic nephropathy. Nitric oxide donors reverse the podocyte increased SNO-α5-laminin and β2-laminin secretion and migration defect induced by high glucose. The inherent S-nitrosylation reversibility implies that this pathogenic mechanism may be a therapeutic target in DN.

Funding: NIDDK Support

**TH-PO437**

Periostin-Binding DNA Aptamer Attenuates Diabetic Nephropathy-Induced Renal Fibrosis
Seonghun Kim,1 Jae Eun Um,1 Hae-Ryong Yun,2 Boyoung Nam,3 Seung Hyeok Han,2,12 Dept of Internal Medicine, College of Medicine, Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ, Seoul, Korea; 2Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Diabetic nephropathy is the major cause of chronic kidney disease, and is associated with progressive renal fibrosis. Recently, accumulation of periostin, an extracellular matrix, was shown to be implicated with renal fibrosis. Aptamers, a novel oligonucleotide which binds to specific target molecules, have been proved to have higher binding affinity without developing the common side effects of antibodies. In addition, the costs of aptamer productions are cheaper than small molecules making them a promising pharmaceutical candidate. This study was aimed to examine the therapeutic role of periostin-binding DNA aptamers (PA) on renal fibrosis under diabetic conditions.

Methods: In vitro, immortalized mouse distal convoluted tubule cells (mDCTs) were exposed to TGF-β1 (5 ng/ml) to induce fibrosis with or without PA (100µmol/l). In vivo, C57BL/6 mice were intraperitoneally injected with saline (C group, N=16) or streptozocin (50mg/kg/d) (DM group, N=16). Eight mice from each group were treated with PA (500µg/kg/d). mRNA and protein expressions of periostin, fibronectin, collagen type I (coll-I) in mDCTs and mouse kidney were examined by real-time polymerase chain reaction and western blot analysis, respectively. Immunohistochemistry (IHC) was conducted with renal tissues.

Results: In vitro, TGF-β1 treatment significantly up-regulated periostin, fibronectin and collagen type I expression, and treatment significantly ameliorated the TGF-β1-induced fibronectin and coll-I expressions (P < 0.05). In vivo, fibronectin and coll-I was significantly up-regulated in kidney samples of diabetic mice (P < 0.05). IHC staining revealed that the number of fibronectin and coll-I (+) cells were significantly higher in diabetic mice (P < 0.05). These increases were clearly ameliorated by PA treatment (P < 0.05).

Conclusions: These findings suggest that inhibition of periostin using a DNA aptamer could be a potential therapeutic strategy against renal fibrosis in diabetic nephropathy.
TH-PO438
Susceptibility of Renal Fibrosis in Early Diabetes Shuqin Mei,1,2 Qingqing Wei,1 Man J. Livingston,2 Changlin Mei,1 Zheng Dong,1 1Shanghai Changzheng Hospital, Shanghai, China; 2Augusta Univ, Augusta, GA; 1Augusta Univ, Augusta, GA; 1Shanghai Changzheng Hospital, Shanghai, China; 2Augusta Univ, Augusta, GA.

Background: The diabetic complication in kidneys is traditionally characterized as pathological alterations in glomerular. However, tubulo-interstitial fibrosis (TIF) frequently occurs earlier than glomerular pathology in diabetic kidney disease (DKD). It is largely unclear how TIF is induced in DKD. We hypothesize in diabetes, renal tubulo-interstitial is predisposed to fibrogenesis and, upon stress, is highly sensitive to the development of TIF. To test this possibility, we examined renal fibrosis induced by unilateral ureteral obstruction (UUO) in diabetic models.

Methods: Two diabetic mouse models were tested: (1) Akita model. C57BL/6-Ins min mice (Akita) mice were monitored to detect diabetic hyperglycemia at ~6-7 weeks of age and then were subjected to UUO along with matched wild-type littermate mice. The mice were sacrificed 7 and 14 days later for analysis. (2) STZ model. Mice were injected with 50mg/kg body-weight of STZ for 5 consecutive days at the age of 4 weeks. After verification of hyperglycemia 2-3 weeks, the mice were subjected to UUO for 7 or 14 days. For tissue analysis, Masson staining was used to detect collagen deposition and TUNEL staining was used to examine kidney injury. Fibrotic proteins were analyzed by immunoblotting. For hyperglycemia 2-3 weeks, the mice were subjected to UUO for 7 or 14 days. For tissue analysis, Masson staining was used to detect collagen deposition and TUNEL staining was used to examine kidney injury. Fibrotic proteins were analyzed by immunoblotting. For in vitro study, mouse tubular BUMPT cells were incubated with high or normal glucose media under hypoxia for 48, 72, and 96h to examine pro-fibrotic changes.

Results: UUO induced higher fibronectin and α-SMA expression after 7 and 14 days in Akita and STZ-induced diabetic mice than non-diabetic mice. Consistently, Masson staining showed more collagen deposition in Akita and STZ-induced mice. TUNEL staining showed more apoptosis after UUO in Akita and STZ-induced mice. In cultured BUMPT cells, hypoxia induced fibronectin accumulation, which was significantly higher in high glucose cells than that in the normal glucose group.

Conclusions: The results suggest that diabetes sensitizes kidney tissues and renal tubular cells to fibrosis. Hyperglycemia exposure appears to contribute to this sensitivity.

TH-PO439
Aerobic Exercise(EXE) Reduce Proteinuria, Fibrosis and Renal Inflammatory Factors, in Diabetic Rats Rodolfo Rossoeto Rampaso, Rafael DaSilva Luiz, Kleiton Augusto Santos Silva, Luciana Jorge, Edson Andrade Pessoa, Mario Luis Ribeiro Cesaretti, Nestor Schot. Nephrology Div, Escola Paulista de Medicina/UNIFESP, Sao Paulo, Brazil.

Background: We evaluated the role of EXE in controlling the progression of diabetic nephropathy as proteinuria, fibrosis, inflammatory factors, and thus, its possible renoprotective effects.

Methods: Wistar rats divided into 4 groups (n=8): Sedentary controls (SED), Diabetes+/−Sedentary (DM-SED), Diabetes+/−Exercise (DM-EXE) and Exercise+/−Controls (EXE). DM was induced with streptozotocin, 50mg/kg i.v. EXE was done on treadmill 60min/day/3 days/week/1 week. Weekly it was measured the Maximal Exercise Test(MEtest). Fibrosis,Glycemia 24h post training(glycemiapt), creatinine clearance/(EXE). DM was induced with streptozotocin, 50mg/kg i.v. EXE was done on treadmill 60min/day/5 days/week/3 weeks. It was weekly measured the Maximal Exercise Test(MEtest). Fibrosis,Glycemia 24h post training(glycemiapt), creatinine clearance/(EXE).

Results: The MEtest was better in DM/Sedentary compared to DM-EXE (p<0.05) and to a similar extent by treatment with 3mg/kg PDE4I or losartan/lisinopril (all p<0.05) in all groups of db/db mice. All these changes were improved significantly by the PDE4I therapy could be a treatment for patients with DKD. 7Seven week treatment with a PDE4I in a robust model of DKD, at a dose that did not reduce hyperglycemia, ameliorated the functional and pathologic features of DKD to an extent similar to that achieved with ACE inhibitor/ARB therapy. Therefore, PDE4I therapy could be a treatment for patients with DKD.

Funding: Pharmaceutical Company Support - Takeda Pharmaceutical Company

TH-PO440
Enhanced Expression of Two Isoforms of Matrix Metalloproteinase-2 in Diabetic Nephropathy Sang Hoon Song,1 Eun Young Seong,1 Dong Won Lee,2 Soon Bong Lee,1 Ihm Soo Kwak,1 David H. Lovett.2 1Internal Medicine, Pusan National Univ School of Medicine, Busan, Korea; 2Internal Medicine, Univ of California San Francisco, San Francisco, CA.

Background: We recently reported on the enhanced expression of two isoforms of matrix metalloproteinase-2 (MMP-2) in human renal transplantation delayed graft dysfunction. The present study aimed to assess the conventionally employed full length MMP-2 (FL-MMP-2) and a novel intracellular N-Terminal Trimmed isoform (NTT-MMP-2) generated by oxidative stress-mediated activation of an alternate promoter in the MMP-2 first intron. This generates an intracellular, enzymatically active MMP-2 isoform that induces mitochondrial injury.

Results: In db/db, renal cortical expressions of the isoforms was increased (FL-MMP-2, 1.8-fold vs. NTT-MMP-2, over 7-fold). Isoform-specific immunohistochemical staining revealed low levels of the FL-MMP-2 isoform in controls, while NTT-MMP-2 was not detected. There was a modest increase in diffuse epithelial cell staining for FL-MMP-2 in STZ mice. In contrast, NTT-MMP-2 was intensely expressed in a basolateral pattern. FL-MMP-2 and NTT-MMP-2 transcript expression were both significantly elevated in renal biopsies of human diabetic nephropathy (12-fold and 3-fold, respectively). NTT-MMP-2 expression correlated with tubular atrophy.


TH-PO441
Treatment with a Novel Phosphodiesterase-4 Inhibitor Reduces Diabetic Kidney Disease in eNOS +/- db/db Mice Honvyu Zhang,1 Jharna Saha,2 Takenori Matsuo,3 Masatoshi Hazama,2 Frank C. Brosius,3 1Univ of Michigan; 2Takeda Pharmaceutical Company.

Background: Phosphodiesterase (PDE) 4 is expressed in immune, nonrenal cells and in tubular epithelia in the kidney. Inhibition of PDE4 can reduce inflammation in multiple conditions. However, little is known about PDE4 effects in the pathogenesis of diabetic kidney disease (DKD). Recent findings suggest that PDE4 inhibitors may ameliorate DKD both by lowering blood glucose levels and perhaps by other mechanisms. Therefore, we determined whether a novel specific PDE4 inhibitor (PDE4I) ameliorated the DKD phenotype and compared it to combined losartan/lisinopril treatment in a type 2 diabetic model, the C57BLKS eNOS +/- db/db mouse.

Methods: db/db and db/+ eNOS +/- mice were bred in our animal facility. Mice received either the PDE4 inhibitor (3 or 10mg/kg), losartan/lisinopril (30mg/kg and 20mg/kg, respectively) or equal volume of vehicle (0.5% methylcellulose) daily by gavage between 18 and 25 wks of age (n=8/group). Urine, blood samples and kidney tissues were obtained from each animal at 26 wks.

Results: At 26 wks all groups of diabetic mice had elevated blood sugar and glycosylated hemoglobin values which were reduced by 10mg/kg PDE4I but not by 3mg/kg PDE4I when compared to vehicle-treated db/db eNOS +/- mice. Albuminuria, mesangial matrix and tubulointerstitial fibrosis were increased and podocyte density was reduced (all p<0.05) in all groups of db/db mice. All these changes were improved significantly (p<0.03) and to a similar extent by treatment with 3mg/kg PDE4I or losartan/lisinopril. Conclusion: Seven week treatment with a PDE4I in a robust model of DKD at a dose that did not reduce hyperglycemia, ameliorated the functional and pathologic features of DKD to an extent similar to that achieved with ACE inhibitor/ARB therapy. Therefore, PDE4I therapy could be a treatment for patients with DKD.

Funding: Pharmaceutical Company Support - Takeda Pharmaceutical Company

TH-PO442

Background: Diabetic nephropathy (DN) is one of the major microvascular complications in patients with diabetes mellitus (DM), and leads to chronic kidney diseases and end-stage renal failure. Phosphodiesterase (PDE) 4 is an enzyme class that selectively hydrolyzes cAMP and activates various cellular events such as inflammatory and fibrotic mechanisms. Therefore, we determined whether a novel specific PDE4 inhibitor (PDE4I) interfered with immune and inflammatory control in T2DM patients (Wouters et al. 2012). Based on these unique mechanisms of action, our novel and selective PDE4I is expected to show a protective effect in DN.

Methods: Male uninephrectomized db/db mice (UnN-db/db) and KKA/e mice were used as diabetic mouse models. After 8-week repeated dose, glycosylated hemoglobin (GHB), plasma ACE and creatinine were measured. Additionally, matrix metalloproteinases (MMP-2 and MMP-9) and extracellular superoxide dismutase (ECOD) were measured by western blotting.

Conclusions: Treatment with a novel PDE4 inhibitor (PDE4I) significantly reduced proteinuria and inflammation in T2DM diabetic mice, while a novel selective PDE4 inhibitor (PDE4I) could be a treatment for patients with DKD.

Funding: Pharmaceutical Company Support - Takeda Pharmaceutical Company
glucose (PG) and urinary albumin/creatinine ratio (UACR) were measured. In vitro study, anti-fibrotic effect of the PDE4i was evaluated in human embryonic kidney 293FT cells. The treatment with BMS002 resulted in a marked reduction in in vitro proliferation of fibroblasts and fibroblast-like cells. In addition, BMS002 also inhibited renal macrophage infiltration and oxidative stress. These effects were observed in a dose-dependent manner, suggesting that BMS002 has potential therapeutic effects.

**Conclusions:** These studies indicate that BMS002 prevents against GFR decline and attenuates renal fibrosis in mouse models of diabetic nephropathy, suggesting that BMS002 has the potential to improve renal function and protect against diabetic kidney disease.
Renoprotective Effects of Dipeptidyl Peptidase Type 4 Inhibitor Linagliptin in Glucagon Like Peptide 1 Receptor Knockout Mice with 5/6 Nephrectomy Berthold Z. Bocher,1,2,3 Ahmed A. Hasan,1 Karoline von Websky,1,4 Christoph Reichetzeder,1 Jinglu Guo,1 Oleq Tsypkryan,2,3 Thomas Klein,2
1Univ of Potsdam, Potsdam, Germany; 2Inst für Laboratoriumsmedizin IFL, Berlin, Germany; 3Medical College of Hunan Normal Univ, Changsha, China; 4Charité-Universitätsmedizin, Berlin, Germany; 2Boehringer Ingelheim Pharma Gmbh & Co. KG, Biberach, Germany.

Background: Dipeptidyl peptidase (DPP)-4 inhibitors were reported to have beneficial effects in experimental chronic kidney disease (CKD) models. The underlying mechanisms are not completely understood. Many studies suggested that these renoprotective effects are mediated via the glucagon like peptide-1 (GLP-1r) GLP-1 receptor pathway. To challenge this hypothesis we investigated the renal effects of DPP-4 inhibitor linagliptin (LIN) in delaying CKD progression in GLP-1 receptor knockout (GLP-1r-) mice with 5/6 nephrectomy (5/6 Nx).

Methods: The mice were allocated to the following groups: sham + placebo (PBO); 5/6Nx + PBO; 5/6Nx + LIN; sham + GLP-1r-; PBO; 5/6Nx + GLP-1r- + LIN + PBO and 5/6Nx + GLP-1r- + LIN and the treatment period was 12 weeks.

Results: LIN led to a significant decrease in plasma DPP-4 activity and a significant substantial increase of plasma active GLP-1, which was more pronounced in mice than wild-type mice. Moreover, 5/6 nephrectomy caused the development of renal interstitial fibrosis and glomerulosclerosis and increased plasma cystatin C levels in wild-type and GLP-1r- mice and these effects were counteracted by LIN treatment. In addition, proteins were separated from kidney tissues and subjected to liquid chromatography/mass spectrometry (LC/MS-MS). After mass spectrometry-data acquisition, spectra were analyzed and 298 signals were differentially regulated among the groups, with 150 signals specific to LIN treatment. The identification of the amino acid sequences of the peptides corresponding to these signals were differentially regulated among the groups, with 150 signals specific to LIN treatment. In addition, proteins were separated from kidney tissues and subjected to liquid chromatography/mass spectrometry (LC/MS-MS). After mass spectrometry-data acquisition, spectra were analyzed and 298 signals were differentially regulated among the groups, with 150 signals specific to LIN treatment. The identification of the amino acid sequences of the peptides corresponding to these signals, by means of tandem mass spectrometry, is currently going on.

Conclusions: The beneficial renal effects of 5/6 nephrectomy cannot solely be attributed to the GLP-1r/1 GLP-1 receptor pathway, highlighting the importance of other signaling pathways influenced by DPP-4 inhibition.

Funding: Pharmaceutical Company Support - Ironwood Pharmaceuticals Inc

Prolyl Hydroxylase Inhibitor Decreases Albuminuria and Improves Glucose and Lipid Metabolism in a Mouse Model of Type 2 Diabetes Shinni Tanaka,1 Tetsuhiro Tanaka,1 Mai Sugahara,1 Hisako Saito,1 Kenji Fukui,2 Yu Ishimoto,1 Reiko Inagi,1 Masaomi Nagakura,1 1Div of Nephrology and Endocrinology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan; 2Biological and Pharmacological Laboratories, Central Pharmaceutical Research Inst, Japan Tobacco Inc., Osaka, Japan.

Background: Although prolyl hydroxylase (PHD) inhibition was reported to have important beneficial effects in several kidney disease (especially acute kidney injury) models, the effect of long-term PHD inhibition on diabetic kidney disease remains unclear. We examined the effects of the specific PHD inhibitor, JTZ-951 (Japan Tobacco Inc., Japan), in a mouse model of type 2 diabetes.

Methods: Four-week-old male BTBR ob/ob mice were divided into the vehicle and JTZ-951 groups. JTZ-951 (0.005%; in feed) was administered from 4 weeks of age until euthanasia at 22 weeks.

Results: During the study period, body weight and blood glucose level tended to be lower in the JTZ-951 group (HbA1c: 8.9±0.3 vs 8.2±0.2%) with comparable feed intake between the groups. JTZ-951 caused transient and mild polycystinopathy with an increase in plasma erythropoietin level (9.3±3.7 vs 21.0±2.4 IU/mL) but did not affect plasma VEGF levels. PHD inhibition significantly decreased urinary albumin at 16 and 22 weeks (4.8±0.7 vs 1.9±0.4 and 5.9±1.3 vs 2.3±0.5 mg/mgCr, respectively). At euglycemia, GFR and kidney weight were comparable between the groups while PHD inhibition significantly decreased the epididymal white adipose tissue weight (1901±110 vs 1315±88 mg), total cholesterol (260±26 vs 164±19 mg/dL) and plasma insulin (6.0±1.0 vs 2.8±0.5 ng/mL) levels and increased plasma adiponectin levels (9.8±0.5 vs 15.8±1.4 ng/mL). Histological studies showed the glomerular tuft area, mesangial expansion, podocyte density, peritubular/interstitial fibrosis, collagen IV, fibrotic gene expression in kidney and white adipose tissue, as well as kidney histology displays metabolic properties by reducing blood glucose level. In healthy volunteers, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant adverse effects (SAEs). Similarly, PBI-4050 was well tolerated in chronic kidney disease (CKD) patients with no SAEs observed at 800 mg. PBI-4050 is presently in Clinical Phase 1 (normal tissue/organ toxicity (NTOT)) associated with metabolic syndrome. Preliminary data from this open-label phase showed that PBI-4050 significantly reduced glycated hemoglobin (HbA1c, -0.7), and biomarkers (IL-18, resistin, and peroxin-3) from the first 12 enrolled patients. This study examined the effect of PBI-4050 in leptin-deficient ob/ob mice, a model of type 2 diabetes with renal fibrosis.

Methods: ob/ob mice (6 weeks old) were treated with vehicle or PBI-4050 (100 and 200 mg/kg, oral once a day) from day 1 through 105. Blood glucose, pro-inflammatory/lipid fibrotic gene expression in kidney and white adipose tissue, as well as kidney histology were examined.

Funding: Government Support - Non-U.S.


Background: PBI-4050 is a first-in-class novel orally active compound which displays anti-inflammatory/antibiotic activities via a novel mechanism of action. PBI-4050 also displays metabolic properties by reducing blood glucose level. In healthy volunteers, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant adverse effects (SAEs). Similarly, PBI-4050 was well tolerated in chronic kidney disease (CKD) patients with no SAEs observed at 800 mg. PBI-4050 is presently in Clinical Phase 1 (normal tissue/organ toxicity (NTOT)) associated with metabolic syndrome. Preliminary data from this open-label phase showed that PBI-4050 significantly reduced glycated hemoglobin (HbA1c, -0.7), and biomarkers (IL-18, resistin, and peroxin-3) from the first 12 enrolled patients. This study examined the effect of PBI-4050 in leptin-deficient ob/ob mice, a model of type 2 diabetes with renal fibrosis.

Methods: ob/ob mice (6 weeks old) were treated with vehicle or PBI-4050 (100 and 200 mg/kg, oral once a day) from day 1 through 105. Blood glucose, pro-inflammatory/lipid fibrotic gene expression in kidney and white adipose tissue, as well as kidney histology were examined.

Funding: Government Support - Non-U.S.

Novel sGC Stimulator 1W-1701 Prevents the Progression of Diabetic Nephropathy when Administered in Combination with Enalapril in the ZSF1 Rat Model Jaime L. Masferger,1 Courtney Shea,1 Elisabeth Lonie,1 Guang Liu,1 Albert Profy,2 George Todd Milne,1 Mark G. Currie,1 1Pharmacology, Ironwood, Cambridge, MA; 2Tobacco Inc., Osaka, Japan.

Background: In diabetic nephropathy, elevated reactive oxygen species and reduced nitric oxide (NO) availability contribute to endothelial dysfunction and disease progression. Soluble guanylate cyclase (sGC) stimulators enhance NO signaling and increase the formation of cyclic guanosine monophosphate. Previous studies have shown the capacity of sGC stimulators to lower proteinuria and improve glomerular filtration rate, and exert renoprotective and positive metabolic effects. This study assessed the effects of 1W-1701, a novel sGC stimulator in clinical development, in the ZSF1 model of diabetic nephropathy.

Methods: Male ZSF1 rats were implanted with radiotelemetry transmitters (abdominal aorta and left femoral vein). After receiving enalapril (20 mg/kg) for 10 days, the rats were treated with 1W-1701 (20 mg/kg). Plasma and urine were collected during the study.

Results: After the initial 10 days, treatment with enalapril-only reduced mean arterial pressure (MAP) by 5/+1 mmHg compared with untreated rats; this effect was increased with 1W-1701 (≥40% compared to untreated rats). Urinary protein creatinine ratio (UPCR) increased to 27.5%/±3 by day 10 and to 5±1 /±3 by week 10. Enalapril-only treatment UPCR increased to 33% compared to untreated control. Enalapril + 1W-1701 reduced UPCR by 54% and 96% at the 10 and 30 mg/kg doses, respectively.

Conclusions: 1W-1701 in combination with enalapril demonstrated efficacy reducing blood pressure and proteinuria in the ZSF1 rats. This preclinical study suggests the sGC stimulator 1W-1701 could be beneficial in preventing the progression of diabetic nephropathy when added to the standard of care.

Funding: Pharmaceutical Company Support - Ironwood Pharmaceuticals Inc
Results: In oral glucose tolerance test, PBI-4050 slightly improved glucose metabolism. Compared to vehicle (water), 200 mg/kg PBI-4050 orally administered reduced white adipose tissue of PBI-4050 treated animals compared to control-ob/ob mice. Further characterization of the activity of PBI-4050 in ob/ob mice by quantitative RT-PCR analysis of pro-fibrotic markers demonstrated that PBI-4050 reduced β-SMA, fibronectin, CTGF, MCP-1, and MMP-2 expression in kidney. Furthermore, histomorphometry analysis was performed on kidneys and PBI-4050 was shown to reduce collagen deposition in glomeruli as determined by Picro Sirus staining.

Conclusions: Taken together, these results suggest that PBI-4050 offers the potential as a novel therapy for diabetes, diabetic nephropathy, and pro-inflammatory/pro-fibrotic markers in kidney and white adipose tissue.

TH-PO452
PBI-4050 Protects against Renal Fibrosis and Improves Pancreatic Function in High Fat Diet db/db Mouse Model

Background: PBI-4050, a novel first-in-class orally active compound which is currently in a phase II clinical trial, significantly reduced glycated hemoglobin (HbA1c) after 12 weeks of treatment in patients with type 2 diabetes and metabolic syndrome with elevated HbA1c despite anti-hyperglycemic treatment. In the present study, we examined whether PBI-4050 affected high fat diet (HFD)-induced triglycerides, insulin and adiponectin levels and the development of renal fibrosis induced by HFD in db/db mice.

Methods: db/db mice were fed with a HFD and received vehicle (water) or PBI-4050 (200 mg/kg/day) by daily gastric gavage from 6 to 21 weeks of age.

Results: High fat diet induced an increase in triglycerides and a decrease in adiponectin levels in serum which were significantly improved by PBI-4050 treatment. PBI-4050 increased serum insulin which correlated with the improvement of β-cell function observed by immunohistochemistry analysis. Kidney function was also improved by PBI-4050 treatment as shown by a decrease in hyperfiltration measured by increased inulin clearance. Furthermore, expression of IL-6, Collagen I, CTGF, MCP-1, and iNOS in kidney were downregulated by PBI-4050 treatment.

Conclusions: These studies suggest that PBI-4050 improves insulin production and β-cell function and survival, and prevents renal fibrosis in association with regulation of pro-fibrotic biomarkers in HFD obese db/db mice.

TH-PO453
Oral Treatment with PBI-4547, a Novel Anti-Diabetic and Anti-Fibrotic Compound, Reduces Blood Glucose and Renal Fibrosis in ob/ob Mice

Background: Type 2 diabetes is a major health problem worldwide. Adiponectin has been shown to play important roles in the regulation of energy homeostasis and insulin sensitivity, and its low level is predictive of future development of diabetes. PBI-4547 is an orally active compound that displays anti-fibrotic activities via a novel mechanism of action. This study examined the effect of PBI-4547 in leptin-deficient ob/ob mice, a model of type 2 diabetes with renal fibrosis.

Methods: ob/ob mice (6 weeks old) were treated with vehicle or PBI-4547 (10 and 50 mg/kg/d, oral once/day) from day 1 through 105. Blood glucose, white adipose tissue (WAT) histology, kidney pro-inflammatory/fibrotic gene expression, as well as serum adiponectin levels were examined.

Results: In oral glucose tolerance test, PBI-4547 increased glucose metabolism. Serum cholesterol and triglyceride levels were also reduced by PBI-4547. Serum level of adiponectin was reduced in ob/ob non-treated mice and strongly increased in PBI-4547-treated mice. Histomorphometry analysis performed on WAT indicated that PBI-4547 treatment reduced fibrosis, inflammatory cell infiltration and adipocyte size. Further characterization of the activity of PBI-4547 by quantitative RT-PCR analysis of pro-fibrotic markers in the kidney demonstrated that PBI-4547 reduced β-SMA, fibronectin, CTGF, MRC-1, MCP-1 and MMP-2 expression. Moreover, PBI-4547 reduced collagen deposition in glomeruli as determined by Picro Sirus staining.

Conclusions: Taken together, these results suggest that PBI-4547 offers the potential as a novel therapy for diabetes, diabetic nephropathy, and obesity by reducing blood glucose levels, reducing pro-inflammatory and pro-fibrotic markers in kidney, and by increasing serum adiponectin to regulate energy homeostasis.

TH-PO454
Effects of LCZ696 on Blood Pressure and Renal Injury in Type 2 Diabetic OLETF Rats with Overt Proteinuria

Background: In the present study, we aimed to examine the effect of LCZ696, an angiotensin receptor-neprilysin inhibitor, on blood pressure and renal injury in type 2 diabetic Otsuka-Long-Evans-Tokushima-Fatty (OLETF) rats with overt proteinuria.

Methods: In OLETF rats, vehicle (n=10), valsartan (30 mg/kg/day, n=10), LCZ696 (68 mg/kg/day, n=9) or valsartan plus hydralazine (3 mg/day, n=10) was treated from 56 to 80 weeks of age.

Results: At baseline (56-week-old), diabetic OLETF rats showed hypertension, overt proteinuria, glomerular injury (glomerular PAS positive area) and tubulointerstitial fibrosis (GTW), but no renal glycemic accumulation (13±3 versus 18±6 CD68+ cells/field, p<0.01). mRNA expression of cytokines (IL-6 and TGF-β1), chemokines (CCL2) and pro-fibrotic (fibronectin) genes in the kidney were attenuated in diabetic mice treated with SA versus control diabetic mice (p<0.05).

Conclusions: Treatment with sodium acetate provided partial protection against the development of diabetic nephropathy in mice with STZ-induced diabetes. Dietary manipulation of the microbiome warrants further exploration in the prevention and management of diabetic nephropathy.

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

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Novel Immunomodulatory Cytokine Offers Multi-Pronged Protection from Type-2 Diabetic Nephropathy (T2DN)  
Rahul Sharma, 1  
Stresa Mrema, 1  
Saleh Mohammad, 1  
Poonam R. Sharma, 2  
Mark D. Okusa. 1  
1Div of Nephrology, Department of Medicine, Univ of Virginia, Charlottesville, VA; 2Dept of Biomedical Engineering, Univ of Virginia, Charlottesville, VA.

Background: While inflammation contributes to T2DN pathogenesis, regulatory T (Treg) cells are protective. We developed a novel cytokine (IL233) bearing IL-2 and IL-33 activities in a single molecule, IL233 promotes Treg and protects mice from acute kidney injury and lupus glomerulonephritis (Sharma R et al, Kidney week 2015). We investigated whether IL233 will enhance Treg, inhibit inflammation and protect from T2DN.

Methods: Male BTBR.Cg-Lpr/Lps  (Ob) mice were treated with saline or IL233 (3pmoles/g) daily for 5-5 weeks or 10-12 weeks of age. Body weight, fasting blood glucose, glucose tolerance, kidney function (urinary albumin creatinine ratio, ACR; mean±SEM) were analyzed. Spleen, kidneys and visceral fat were analyzed by flow cytometry and histology at necropy.

Results: Compared to controls, treatment of 4-5wk old Ob mice with IL233 induced a 2x increase in Treg as measured in the blood, which persisted for ~ 4 months in lymphoid organs (1.5x) and adipose tissue (2.3x) upon necropy. IL233 treated Ob mice had lower proteinuria (ACR: 29.4±4 mg/acr at necropy) than controls (ACR: 133±35 mg/g). IL233-treatment also inhibited diabetes (lower blood glucose and normalization of glucose tolerance) and obesity (lower body and adipose tissue weights) in the Ob mice. Kidney histology of control Ob mice showed leukocytic infiltration and mesangial expansion, which was inhibited in the IL233 treated mice. IL233 treatment of the 10-12 weeks old Ob mice also resulted in lower proteinuria (2.4x higher ACR in controls vs IL233-treated). This was accompanied with lower blood glucose starting two weeks post treatment and persisting until the end of study, when the control mice had to be euthanized. Along with increasing Treg, IL233 also enhanced Treg’s ability to produce IL-10.

Conclusions: The novel cytokine IL233 containing the activities of IL-2 and IL-33 bears therapeutic potential as it protects genetically obese mice from T2DN, by regulating Treg and obesity, as well as by preserving kidney function using suitable animal models that mimic the human pathology of diabetic nephropathy and hyperglycemia. Due to the polygenic origin of diabetes, therapeutic approaches must target multiple signaling pathways. The membrane metallo-endopeptidase (MME) activates peptide hormones and generates bioactive peptides distributed throughout the body. MME knockout mice developed dyslipidemia and hyperglycemia, however its receptor knockout mice are poorly understood. The combinations of renal effects of MME in diabetic nephropathy and hyperglycemia remain unexplored.

Methods: We established a high-fat diet (HFD)-fed medaka model that mimics human diabetic nephropathy and hyperglycemia. By using this model, we performed shotgun proteomics, western blot, and subcellular immunohistochemical analysis and discovered the MME down-regulation in the kidney. We applied genetics to confirm the MME involvement in diabetic nephropathy and hyperglycemia in medaka and mouse models. Furthermore, we confirmed the relevant role of MME in diabetic human kidney specimens. Finally, we evaluated whether this model could be used for drug screening.

Results: We demonstrated that 1) MME is down-regulated in HFD-fed medaka kidney by shotgun HPLC-ESI-MS/MS, western blot, and subcellular immunohistochemical analysis, 2) MME knockdown in medaka and mouse adults resulted in diabetic nephropathy and hyperglycemia, 3) MME protein subcellular downregulation is confirmed in the glomeruli specimens from human patients with diabetes, 4) treatment with Telsimurtan, omega-3-PUFAs, and metformin prevented diabetic nephropathy and hyperglycemia induced by HFD-fed medaka.

Conclusions: These data implicate that our new animal models will highlight novel therapeutic targets suitable for preventing diabetic nephropathy and resulted in decreased kidney function in response to hyperglycemia. In summary, these discoveries will lead to identification of highly specific therapeutic targets against human CKD.

Funding: Private Foundation Support

Lacking Fructokinase-A Exacerbates Renal Injury in Streptozotocin-Induced Diabetic Mice  
Tomoko Obara, 1 Takoji Ishimoto, 1 Takahiro Hayasaki, 1 Miho Ueda, 1 Hideyuki Kimura, 1 Keisuke Watanabe, 1 Richard J. Johnson, 2 Seiichi Doke, 1 1Dept of Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Aichi, Japan; 2Renal Diseases and Hypertension, Univ of Colorado Denver, Aurora, CO.

Background: Ketohexokinase (KHK), a primary enzyme for fructose, exists as two isoforms, KHK-C and KHK-A. We have reported that endogenous fructose and its metabolism produced by polyol pathway activation in diabetes may have a deleterious role in the pathogenesis of diabetic nephropathy using mice lacking both isoform KHK-A and KHK-C. KHK-C has higher affinity for fructose compared to KHK-A. Although both isoforms express in proximal tubule, the role of KHK-A is not yet elucidated. The aim of this study is to determine the role of KHK-A in the development of diabetic nephropathy in mice.

Methods: Male wild-type mice, KHK-A knockout mice, and KHK-A/C knockout mice (lacking both isoforms) were used. Diabetes was induced by intraperitoneal injections of streptozotocin (50 mg/kg/day, 5 days). Body weight, blood glucose were measured regularly. At 18 weeks, urine and blood samples and kidney tissues were collected. Kidney injuries were assessed for proteinuria, urinary NGAL, serum creatinine, and histology. Gene and protein expressions related to inflammation, fibrosis, oxidative stress, and polyol pathway enzymes were analyzed.

Results: The level of blood glucose was similar among three genotypes during study period. However, diabetic KHK-A knockout mice showed significant increase of urinary NGAL, renal dysfunction, glomerular hypertrophy, and tubular injuries accompanied by increased HIF1α expression, inflammatory cytokines and macrophage infiltration (F4/80 staining) compared to diabetic KHK-A/C knockout mice. While diabetic wild type mice also showed increase of urinary NGAL, the degree of renal injury, inflammation, fibrosis and pyogranuloma was significantly less than diabetic KHK-A knockout mice. Similarly both isoforms, KHK-A and KHK-C, showed increased inflammatory cytokines.

Conclusions: Kidney injury in streptozotocin-induced diabetes was exacerbated in mice lacking KHK-A, but is prevented in mice lacking both isoforms, KHK-C and KHK-A. These results suggest that KHK-A has an important role in attenuation of endogenous fructose-related kidney injury in diabetic mice.

Inhibition of YAP Activity Ameliorates Diabetic Nephropathy  
Jianchun Chen, Ming-Zhi Zhang, Raymond C. Harris. Medicine, Vanderbilt Univ, Nashville, TN.

Background: Yes-associated protein (YAP) is a transcriptional regulator modulated by the Hippo signaling pathway that controls the balance of cell proliferation, cell differentiation and cell death to define organ size, as well as to mediate fibrotic injury. Activation of YAP leads to nuclear translocation and interaction with the TEA domain (TEAD) family of transcription factors. The current studies investigated the effect of YAP and pharmacologic inactivation of YAP-TEAD interactions on development of diabetic nephropathy (DN).

Methods: We utilized a model of accelerated DN (STZ-eNOS-/-). Diabetic mice were treated for 20 weeks with vehicle or verteporfin (100 mg/kg, every other day), a porphyrin derivative that is used clinically as a photosensitizer for neovascular macular degeneration and that inhibits YAP-TEAD interactions.

Results: At 20 weeks of diabetes, verteporfin significantly decreased albuminuria (ACR: 232.7 ± 40.3 vs 365.0 ± 31.8 μg/mg, P < 0.05 vs. n = 7) and glomerulosclerosis index (0.74 ± 0.03 vs. 0.96 ± 0.06, P < 0.01, n = 7). It also decreased podocyte loss (15.83 ± 0.40 vs. 12.54 ± 0.60 podocytes/glomerulus, P < 0.005, n = 7) as well as decreasing kidney macropage infiltration and increasing M2 markers including arginase 1 and YM-1. Immunoblotting showed that DN increased expression of the YAP-TEAD target genes CTGF and amphiregulin, which were inhibited in verteporfin. Immunostaining demonstrated higher CTGF expression in podocytes from vehicle-treated mice than in verteporfin-treated mice. Immunoblotting also indicated that verteporfin inhibited expression levels of markers of dedifferentiation and fibrosis, including TGF-β, p-SMAD2-3, a-SMA, smail-1, Kim-1, and vimentin and collagen I.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Conclusions: Inhibition of YAP-TEAD activation ameliorates injury in a model of experimental diabetic nephropathy, suggesting an important role for this pathway in development of diabetic kidney injury and indicating that it may be a target for therapeutic intervention.

Funding: NIDDK Support, VA Support

TH-PO462

p66Shc Knockout Prevents Development of Diabetic Nephropathy in Streptozotocin-Treated Dahl Salt-Sensitive Rats Bradley S. Miller, Shoshana R. Blumenthal, Kevin D. Wright, Andrey Sorokin. Medicine, Medical College of Wisconsin, Milwaukee, WI.

Background: One of the main pathophysiological mechanisms, which are responsible for the kidney damage associated with diabetic nephropathy (DN), is the generation of reactive oxygen species (ROS) by mitochondrial electron transport system. The purpose of this study was to test whether adaptodor protein p66Shc, a redox protein capable of promoting of mitochondrial ROS generation, is the cause of renal damage in streptozotocin-treated Dahl Salt-Sensitive (SS) rats.

Methods: p66Shc rat knockout and rats with a knock-in Ser36Ala substitution in p66Shc were generated using engineered Zinc Fingert Nucleases (ZFN) and, in case of knock-in, also a template plasmid containing the desired mutation. Diabetes was induced in the SS control and mutant rats by an injection of streptozotocin (STZ). Hyperglycemia, excessive urination, body weight, albuminuria and display of renal pathologies, typical for patients with DN, was evaluated for the time period of twelve weeks after treatment.

Results: Following STZ injection SS rats develop hyperglycemia, excessive urination, albuminuria and other renal pathologies which accompany the progression of DN in patients. Both, p66Shc knockout and introduction of the mutation into p66Shc mutant, which incapacitated its translocation to mitochondria, prevented the development of DN in our rat model.

Conclusions: Adaptor protein p66Shc plays the primary role in the progression of DN in a STZ-triggered rat model of diabetes. The Ser36Ala substitution in p66Shc, which disables the phosphorylation-mediated mitochondrial translocation of p66Shc, is sufficient to prevent increase of albuminuria after treatment with STZ. Thus, the rat experimental model of DN provides novel opportunities for identification of new molecular targets and confirmation of previously identified molecules for therapeutic intervention in DN. The inhibiting of mitochondrial translocation of p66Shc could be considered as an efficient therapeutic strategy to combat DN.

Funding: NIDDK Support

TH-PO463

Role of P2Y2 Receptor in Adipogenesis and Metabolism Yue Zhang,1 Carolyn M. Ecelbarger,2 Christa E. Müller,1 Anna U. Brandes,3 Tao Liu,1 Lisa Lesniewski,1 Bellakonda K. Kishore.1 1Univ of Utah & VA Medical Center, Salt Lake City, UT; 2Georgetown Univ, Washington, DC; 3Univ of Bonn, Bonn, Germany.

Background: Previously we reported that genetic deletion of P2Y2 receptor (R) confers significant resistance to the development of high-fat diet (HFD)-induced obesity, without reducing the food intake or causing steatorrhea. To understand the mechanisms involved in this protection, we investigated adipogenesis, lipid tolerance, energy metabolism and feeding behavior in mice treated with P2Y2-R antagonist (PPARγ agonist) to the culture medium. UCP1 mRNA expression was used as an index of browning.

Methods: Preadipocytes from KO or WT mice were induced to mature in vitro in the absence or presence of ACR-118925 to block P2Y2-R. Intraperitoneal lipid tolerance test (ILT) was conducted in KO and WT mice. Metabolic Phenotype of KO and WT mice. Metabolic Phenotype of KO and WT mice. Metabolic Phenotype of KO and WT mice.

Results: When induced in vitro, preadipocytes derived from KO mice did not mature as robustly as those from WT mice, as assessed by the accumulation of lipid droplets (oil red staining). Blockade of P2Y2-R in preadipocytes derived from WT mice prevented their maturation in a dose-dependent manner. Under basal conditions KO mice had significantly higher serum triglycerides and showed impaired lipid tolerance as compared to WT mice. Metabolic profiling revealed significantly increased VO2 and energy production and decreased RER (respiratory exchange ratio) in KO mice vs. WT mice. When browning was induced, UCP1 mRNA expression was significantly higher in the inguinal fat of KO mice or adipocytes derived from KO mice vs. WT mice.

Conclusions: These results suggest that P2Y2-R plays a significant role in the development of diet-induced obesity by promoting maturation of adipocytes, altering adipocyte lipid metabolism, and by negatively impacting browning of fat and thereby energy metabolism. Thus, targeting P2Y2-R may be a viable strategy to prevent or treat diet-induced obesity.

Funding: NIDDK Support, VA Support

TH-PO464

Longitudinal Characterization of Glomerular Filtration Rate of the Naïve ZSF1 Rat Robin E. Haimbach, Li-Jun Ma, Maarten Hock, Shilpy Pinto, Xiaoyan Zhou. Dept of Cardiometabolic Diseases, Merck & Co., Inc., Kenilworth, NJ.

Background: The obese ZSF1 rat exhibits many features of metabolic syndrome in humans and is widely used as a translational model of diabetic nephropathy. However, the glomerular filtration rate (GFR) changes over time have not been fully characterized. Therefore we evaluated FITC-sinistrin as a method to determine GFR and to characterize changes in GFR in ZSF1 rats with disease progression.

Methods: Male lean and obese ZSF1 rats were used for GFR measurements every 1-5 weeks from the age of 5 to 50 weeks old. GFR was measured using the plasma clearance of FITC-sinistrin as a marker of glomerular filtration rate (GFR). A 22-gauge intraperitoneal vein was cannulated with a 27-gauge intraperitoneal catheter (mounted detector (Mannheim Pharma & Diagnostics). In order to determine the robustness of FITC-sinistrin GFR measurement, additional groups of aged male ZSF1 rats (43-48 weeks old) were studied to compare the sensitivity and variability of FITC-sinistrin GFR with that of estimated GFR by creatinine clearance.

Results: Between 5 and 11 weeks of age, significant kidney hyperfiltration occurred ranging from a 22-45% increase compared to the lean ZSF1 control. After 15 weeks of age, we observed a progressive decrease in GFR until week 25 in both obese and lean rats. After week 25, the obese ZSF1 rats showed an increased rate of decline in kidney function compared to the lean ZSF1. Between 45-50 weeks, the ZSF1 obese rat displayed a sustained GFR decrease of ~50% compared to the lean. GFR values were replicated in three cohorts for the respective age groups of lean and obese rats. FITC-sinistrin GFR compared to creatinine clearance provides a 1.8-3.3x greater effect size that provides a more sensitive method to detect changes in GFR.

Conclusions: Data from these studies show that FITC-sinistrin GFR measurement is a more robust measurement of GFR than creatinine clearance in the ZSF1 rat. Consistent with the classical manifestation of early stage human diabetic nephropathy, the hyperfiltration phase of diabetic nephropathy in the male ZSF1 rat occurs at an early age (5-11 weeks old), with the obese ZSF1 GFR decline outpacing the lean ZSF1 GFR decline after 25 weeks of age.

Funding: Pharmaceutical Company Support - Merck & Co., Inc.

TH-PO465

A New Model for Diabetic Nephropathy: A Hyposia-Induced Antioxidant Metallothionein-3 BACTG Mice Yumi Takiyama,1 Ryoshi Bessho,1 Takahiko Nakahara,2 Masakazu Haneda.1 1Department of Medicine, Asahikawa Medical Univ, Asahikawa, Hokkaido, Japan; 2Industry-Academia-Government Collaboration Promotion Center, Nara Medical Univ, Nara, Japan.

Background: Metallothionein (MT) is a cysteine-rich protein with low molecular weight, and an antioxidant against the toxicity of metals, ischemia, and ROS. MT3 is one of the four MTs, which is originally cloned as a neuronal growth inhibitory factor from brain and is decreased in Alzheimer’s brain. We have recently found that MT3 is a target for Hyposia Inducible Factor-1 and MT3 protein expression is increased in tubular cells in diabetic nephropathy (DN). In addition, we found four putative hypoxia response elements containing the consensus sequence (A/G)CGT within the MTM gene, not in mouse. The purpose of this present study was to reveal the pathophysiological potential of MT3 in DN.

Methods: In this study, we generated transgenic mice, harboring a 40-kb bacterial artificial chromosome (BAC) expressing human MT3 mRNA and protein to generate humanized BAC transgenic mice (MT3 BACTG). By inducing hypoxic condition in vivo, we used streptozotocin-induced diabetic or aged MT3 BACTG mice.

Results: Aged transgenic mice which overexpress MT3 in renal tubules showed the nodular glomerulosclerosis like Kimmelstiel-Wilson lesion, capsular drop and doughnut glomerular lesion. Humanized MT3 BACTG mice propose a new model for the study of DN.

Conclusions: Overexpressed MT3 in tubular cells in BACTG mice complicates peritubular capillary dilatation accompanied with the swelling endothelial cells which caused narrowing capillary lumen. Multiple low-dose streptozotocin injections induced moderate hyperglycemia, histological mesangial expansion and an accumulation of hyaline material in collapsing glomerular segments without glomerular hypertrophy. The glomerular nodule in transgenic mice was negative for phosphotungstic acid-hematoxin stain. Electron microscopy showed no electron dense deposits in mesangial lesion with thickening of the glomerular basement membranes and podocyte process effacement.Intriguingly, endothelial cell marker CD31 staining showed peritubular capillary dilatation accompanied with the swelling endothelial cells which caused narrowing capillary lumen. Multiple low-dose streptozotocin injections induced moderate hyperglycemia, histological mesangial expansion and an accumulation of hyaline material in collapsing glomerular segments without glomerular hypertrophy.

Funding: Government Support - Non-U.S.

TH-PO466

Myostatin, a New Mediator of Inflammation and Tissue Injury in Diabetic Nephropathy (DN) Giacomo Garibotto, Daniela Verzola, Samantha Milanese, Francesco Amasolo, Francesca Varini, Ambra Chiri, Daniela Piicco, Francesca Costigliolo, Chiara Barisone. DIMI, Genoa Univ and IRCCS AOI San Martino-IST, Genoa, Italy.

Background: Myostatin (MSTN), a structurally-related member of the TGFβ superfamily, acts as negative regulator of tissue growth and promotes fibrosis/atrophy. Although initially described as a negative regulator of muscle growth, MSTN has been found in other tissues, including the kidney in pigs. In humans, MSTN participates to the

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

Underline represents presenting author.

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HIIT can be a time-efficient strategy to a non-pharmacological treatment to minimize other diabetic symptoms as polyuria, polydipsia and sarcopenia. These data suggests that capacity, prevent the lower glomerular function (showed by the proteinuria) and attenuate of 1 minute (90% of maximal effort test) intersected with 10 periods of low intensity.

MSTN could be a new mediator of inflammation and injury in DN.

Our data indicate that MSTN is expressed in the human kidney and overexpressed in DN. Diabetic mielius induces MSTN in PTECs. In vitro, MSTN slows cell proliferation and induces inflammatory changes. The above reported data suggest that MSTN could be a new mediator of inflammation and injury in DN.

TH-PO467

High Intensity Interval Training (HIIT) Prevent Proteinuria in STZ Diabetic Rats
Natália Lopes Reinecke, Rafael DaSilva Luz, Rodolfo Rosseto Rampsao, Waldemar S. Almeida, Nestor Schor. Medicine/Nephrology. UNIFESP, São Paulo, São Paulo, Brazil.

Background: The benefits of physical exercise on Diabetes are already well known, however, the insertion of these patients on a regular physical training program is still a challenge. The increasing prevalence of obesity in diabetes means that time remains one of the most commonly cited barriers to regular exercise participation. HIIT, which involves repeated bursts of vigorous exercise interspersed with periods of rest, has been demonstrated to have potential metabolic benefits in Diabetic or pre-diabetic subjects, even requiring a lower commitment time than the current recommendation of exercise for this population. However, the effects of HIIT on renal function of diabetic rats have yet no been studied. The aim of this study was to examine the effects of low-volume HIIT on renal function and physical capacity in STZ Diabetic rats.

Methods: 8-Wistar rats were submitted to HIIT following a protocol: 10 bouts of 1 minute (90% of maximal effort test) intersected with 10 periods of low intensity walking (50% of maximal effort test), 3 days/week, 8wk total. Diabetes was induced by a single injection (50mg/kg i.v.). Animals were divided into three groups 6 to 8 animals/group: Sedentary Control (SC), Sedentary Diabetic (SD) and Diabetic HIIT (DHIIT).

Results: HIIT improved the exercise capacity as shown by the higher maximal velocity reached in the exercise test (37.1±1.55v.s 25.2±2.7 min/m) in DHIIT vs SD (p<0.001). HIIT also prevented the increased proteinuria caused by Diabetes in comparison to SD (9.9±6 vs 19.6±1.9 mg/dL/24h, p<0.05), respectively with no difference between DHIIT vs SD, (9.9±6 vs 19.6±1.9 mg/dL/24h, p<0.05). The lower hemoglobin seen in the dRTA/SAO group may reflect the lower glomerular function (showed by the proteinuria) and attenuate other diabetic symptoms as polyuria, polydipsia and sarcopenia. These data suggests that HIIT can be a time-efficient strategy to a non-pharmaceutical treatment to minimize Diabetes complications.

Funding: Government Support - Non-U.S.

TH-PO468

Bias and Imprecision in Net Acid Excretion Predictions
Lynda A. Frassetto, Tanushree Banerjee. 1UCSF; 2Sunshine U.

Background: Diet contains to the body’s net acid or base load. Several equations using diet cation, anion and protein content have been developed to help estimate whether specific foods would be an acid or base containing and tested against the current gold standard, 24 hour net acid excretion (NAE), since measuring NAE requires a research lab. NAE has also been shown to correlate with urinary acid, organic acid and ion markers (UPRAL). How well equations or UPRAL predict any one individual’s actual NAE has not been evaluated.

Methods: Retrospective analyses of studies where NAE and UPRAL were reported for samples of urine following both an acid and alkali dietary consumption were included. They also contained individual dietary data pertinent to estimating net endogenous acid production (NEAP). Estimate NEAP according to Frassetto (F), Remer/Manz (R), and Lemann (L) were computed in their usual manner. Bland-Altman technique was used to compute the average difference between NEAP equations to NAE during the acid-consuming and alkali consuming diets. All statistical analyses were completed using XLStat.

Results: The equations were too imprecise for NAE for any individual, although the accuracy of NEAP-R at a group level was reasonable for the acid-forming diets. Similar consumption diets. All statistical analyses were completed using XLStat. Bland-Altman technique was used to compute the average difference between NEAP and NAE during the acid-consuming and alkali-consuming diets. All statistical analyses were completed using XLStat.

TH-PO469

Genotype, Phenotype Correlations in Distal Renal Tubular Acidosis

Background: Distal renal tubular acidosis (dRTA) has been characterized by an inability of α-intercalated cells in the distal nephron to secrete H+ ions. Mutations leading to dRTA have been found in the anion-exchanger 1 (AE1), and V-ATPase subunits. AE1 mutations may be autosomal dominant or recessive, and dRTA has been described in compound heterozygotes who also have the AE1 red cell disorder Southeast Asian Ovalocytosis (SAO). We sought to compare biochemical and hematological data among different genetic groups.

Methods: We compared patients with mutations in AE1 or V-ATPase subunits at our institution. Phenotypic data was collected including baseline electrolytes, hematological results, and urine tests.

Results: Ten-sixty patients had a gene mutation known to cause dRTA; 5 were due to V-ATPase subunit mutations, 19 were due to AD AE1 mutations and 2 were AE1 autosomal dominant or recessive, and dRTA has been described in compound heterozygotes who also have the AE1 red cell disorder Southeast Asian Ovalocytosis (SAO). We found that serum bicarbonate was significantly lower in the dRTA/SAO group: 17 versus 23.5 and 22.4 mmol/L in the V-ATPase subunit and AD AE1 groups respectively (P = 0.02). There was a trend towards both AE1 groups having a lower creatinine excretion than the V-ATPase subunit group: 0.12 versus 2.16 mmol/L (p = 0.053). The dRTA/SAO group had a hemoglobin of 111±1 g/l which was significantly lower than the other two groups: 128 and 140 g/l (p = 0.034). The serum creatinine in the V-ATPase group was 75±6±14, which was significantly lower than the SAO and the AD AE1 groups; 124 and 112, respectively (p = 0.04).

Conclusions: The lower hemoglobin seen in the dRTA/SAO group may reflect sub-clinical hemolysis known to occur in this group. Both the AE1 groups together had significantly worse GFR than the V-ATPase group; the trend towards lower serum bicarbonate and lower citrate excretion also suggests a more severe systemic acidosis. Acidosis may be both a factor contributing to deteriorating GFR, or a consequence. It has been suggested that V-ATPase subunit mutations cause a more severe phenotype than AE1 mutations; these data suggest that this might not always be the case and further work is required to elucidate this.

TH-PO470

Association of Serum Bicarbonate Levels with a Novel Marker of Serum Calcification Propensity
Jessica B. Kendrick, Emily Decker, Andreas Pasch, Zhiying You, Michel Chonchol. 1Univ of Colorado Denver; 2Denver Health & Hospital; 3Univ of Bern.

Background: Acid retention in patients with chronic kidney disease (CKD) results in increased production of angiotensin II, aldosterone and endothelin-1, all of which can directly and indirectly induce vascular calcification. However, the relationship between serum bicarbonate levels and serum calcification propensity has not been comprehensively explored with urinary calcium and ion markers (UPRAL).

Results: We measured serum bicarbonate levels and serum TCa in 128 patients with CKD stage 3-4. TCa was measured using a Nephelostat nephelometer (BMG Labtech, Offenburg, Germany). Multiple linear regression was used to examine the association between serum bicarbonate levels and TCa.

Conclusions: The mean (SD) age and eGFR was 58.1 ± 12.4 years and 33.1 ± 10.2 ml/min/1.73m2, respectively. Mean (SD) serum bicarbonate and TCa levels were 22.9 ± 2.9 mEq/L and 223.4 ± 46.8 min, respectively. Higher serum bicarbonate was associated with higher TCa.

TH-PO480

Typical acid forming diets Alkali supplementation

<table>
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<th>95% CI for the bias</th>
<th>Limits of Agreement</th>
<th>Bias</th>
<th>95% CI for the bias</th>
<th>Limits of Agreement</th>
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<tr>
<td>NEAP vs NAE (mEq/d)</td>
<td>40</td>
<td>-0.7</td>
<td>-7.5 to 5.9</td>
<td>-41.7</td>
<td>40.2</td>
<td>-6.6</td>
</tr>
<tr>
<td>NEAP vs NAE (mEq/d)</td>
<td>55</td>
<td>11.3</td>
<td>5.2 to 17.4</td>
<td>-32.9</td>
<td>35.5</td>
<td>15.1</td>
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<tr>
<td>NEAP vs NAE (mEq/d)</td>
<td>53</td>
<td>6.3</td>
<td>0.5 to 12.2</td>
<td>-35.7</td>
<td>47.9</td>
<td>19.4</td>
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</table>

Conclusions: Both dietary NEAP estimates and UPRAL are more precise for group as opposed to individual NAE estimates, and results differ depending on the diet acid or base load. Researchers may wish to collect both NEAP as well as UPRAL data when doing dietary acid experiments.

Funding: Clinical Revenue Support
Acute Regulated Expression of Pendrin in Human Urinary Exosomes (UEs) Ganesh Pathare,1,2 Nasser Dhayat,1 Nilufar Mohhebi,1 Carsten A. Wagner,1 Daniel G. Fuster,1,2 1Div of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Univ Hospital of Bern, Switzerland; 2Inst of Biochemistry and Molecular Medicine, Univ of Bern, Switzerland; 1Div of Nephrology, Univ Hospital of Zurich, Switzerland; 2Inst of Physiology, Univ of Zurich, Switzerland.

Background: Regulation of pendrin upon chronic acid-base changes has been well studied in the rodent kidney. However, impact of acute acid-base changes on pendrin expression and subcellular localization is unknown. Furthermore, there is a paucity of data on the regulation of pendrin in the human kidney. Here we studied effect of acute acidosis, alkalosis or sodium chloride loading in humans on pendrin expression in urinary exosomes (UEs).

Methods: After acute NH4Cl (100 mg/kg) or equimolar alkali NaHCO3 (157 mg/kg) or NaCl (110 mg/kg) loading in fasting individuals, urinary exosomes were isolated from hourly collected spot urine samples. Pendrin and the housekeeping UE protein alix were detected by immunoblotting. UE pendrin expression was normalized to alix expression. Results: Acute NH4Cl loading (n=8) elicited a systemic acidosis with a drop in urinary pH and an increase of urinary NH4+ excretion. Nadir urinary pH was achieved 5 hrs after NH4Cl loading. UE pendrin expression was first significantly reduced after 3 hrs, lowest UE pendrin levels were observed after 4 hrs. In contrast, after acute equimolar NaHCO3 loading (n=8), urinary and blood pH rose rapidly and urinary NH4+ excretion decreased. Densiometric analysis of immunoblots revealed rapid upregulation of UE pendrin expression already after 1 hr of NaHCO3 loading. However, UE pendrin levels returned to baseline after 2 hrs. To analyze the effect of acute NaCl loading, we administered an oral equimolar amount of NaCl to healthy individuals (n=7). Urinary Na+ and Cl- excretion increased significantly and rapidly after NaCl loading. Urinary pH, blood pH and urinary ammonia were unaltered throughout the experiment. Compared to baseline levels, UE pendrin abundance fell and was significantly lower at 3 hrs after NaCl loading.

Conclusions: Acute acid, alkali or chloride loading significantly alter UE pendrin expression in human UE within a few hours.

Funding: Government Support - Non-U.S.

TH-PO472

Urinary Exosomes Analysis of Renal Tubular Transporters in Patients with Acute and Chronic Hypokalemia Chih-Chien Sung,1 Sung-Sen Yang,2 Shih-Hua P. Lin.1 1Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; 2Graduate Inst of Medical Science, National Defense Medical Center, Taipei, Taiwan.

Background: Urinary exosomes contain membrane and cytosolic proteins from each renal epithelial cell type and has been used as an index of renal tubular transporter expression in primary aldosteronism or renal tubular disorders. Urinary exosome analysis of renal sodium (Na+) and potassium (K+) associated transporters in hypokalemia patients has not been studied. We aim to evaluate renal Na+ and K+ transporters expression in patients with acute and chronic hypokalemia.

Methods: We have collected timed spot urine from 19 hypokalemia patients including thyrotoxic periodic paralysis with acute hypokalemia (TPP, n=6), Gitelman with acute hypokalemia and 2.5±0.4 mmol/L in GS. In TPP patients, only NHE3 abundance and Maxi-K significantly increased.

Conclusions: Urine exosomes could evaluate the renal Na+ and K+ transporters expression in hypokalemia. Acute hypokalemia may not affect expression in distal Na+ transporters but affect ROMK, not Maxi-K, in response to hypokalemia. Chronic hypokalemia with NCC defect could activate upstream NHE3 and downstream ENaCβι with concomitant increased ROMK and Maxi-K expression in response to flow.

TH-PO473

Identification of a CACNA1S-Specific Missense Mutation in a Three Generation Pedigree with Hypocalcemic Periodic Paralysis Martin Russwurm, Andreas Hofmeister, Joachim Hoyer, Ivica Grgic. Nephrology, Philips-Univers Marburg, Marburg, Germany.

Background: Hypokalemia is an electrolyte imbalance that is not only common, but can also be debilitating and life-threatening to a patient if not addressed appropriately. Mechanisms that may lead to hypokalemia include decreased intake, increased losses via sweat, urine or the GI tract, and disproportionate translocation into cells. A rather rare cause (~1:100,000) of recurrent, modest to severe hypokalemia with accompanying muscle weakness is a neuromuscular disorder known as hypocalcemic periodic paralysis (HypoPP). HypoPP is related to a skeletal muscle channelopathy of either the voltage-activated sodium channel Na1,1,4, encoded by SCN4A, or the L-type calcium channel Ca1,1,1, encoded by CACNA1S. We suspected the disease in an otherwise healthy 26-year-old male carpenter with no family history of hereditary disorders, who presented to the emergency room with flaccid quadriparesis and a serum potassium of 2.3 mmol/L.

Methods: We extracted the patient’s genomic DNA and designed primers to specifically amplify and study the S4 voltage-sensor domains of Na1,4 and Ca1,1,1. DNA from HeLa cells was used as control template.

Results: Sequencing and alignment identified a heterozygous single nucleotide exchange (G to A) at position 1583 of the CACNA1S gene (chromosome 1q31-32), predicting an amino acid switch at position 528 from highly conserved arginine to histidine (R528H). To test the hypothesis of a de-novo mutation in this index case, we obtained and analyzed the DNA from the patient’s first and second degree relatives. Interestingly, we found the same pathological single nucleotide polymorphism (SNP) in the patient’s mother and maternal grandmother, although they have never had symptoms characteristic of HypoPP including sudden onset of profound muscle weakness or hypokalemia.

Conclusions: In conclusion, we have identified a new pedigree with autosomal-dominantly inherited HypoPP in central Germany. The possibility of missing or incomplete clinical manifestation of HypoPP has to be considered. The causal relationship between gender and HypoPP penetrance remains unclear and needs further investigation.

Funding: NIDDK Support

TH-PO474

Association of Potassium Values with Mortality: Data from a Metropolitan Safety-Network Hospital David T. Gilbertson,1 James B. Wetmore,2 Wendy L. St. Peter,1 Charles A. Herzog,1,2 1Chronnic Disease Research Group, Minneapolis Medical Research Foundation, Hennepin County Medical Center, Minneapolis, MN; 2Univ of Minnesota, Minneapolis, MN.

Background: Extremes of serum potassium (K) levels have been associated with adverse outcomes. We examined the association between K values with mortality in patients hospitalized at a metropolitan safety-net hospital.

Methods: We obtained K values for all patients hospitalized over a 1-yr period (July 2014-June 2015) and analyzed the association between K level, and variability, with in-hospital mortality. We also assessed the % of patients with K > 5.0 overall and by comorbidity: Diabetes Mellitus (DM), Chronic Kidney Disease (CKD), and Congestive Heart Failure (CHF).

Results: 17,317 hospitalizations with K values were included. The mean age was 50.2 yrs, 57.3% of patients were male, 47.7% white, 33.7% black; for comorbidities, 25.9% had DM, 14.1% CKD, and 6.2% CHF. The distribution of K <3.5, 3.5<5<5.6, and >61, was 7.9%, 88.7%, 3.1%, 0.3%, respectively. There was a U-shaped relationship between K and mortality, with the lowest risk between 3.5 and 5.0 mEg/L (see figure). The % of patients with K > 5.0 for patients with DM was 4.0%, CKD 6.4%, CHF 6.0%, compared to 0.9% among patients without any of the three comorbidities (all p < 0.001). For the association between K standard deviation (for each increase of 0.1) and in-hospital mortality, the odds ratio was 1.19 (p < 0.001).

Funding: Government Support - Non-U.S.
Conclusions: Although both low and high K values were associated with an increased risk of mortality, risk of death increased once potassium exceeded 5.5 mEq/L and increased markedly thereafter. Increasing variability in K was also associated with mortality. The comorbid conditions of DM, CKD, and CHF are all associated with increased serum K levels. More intense efforts targeted to prevent severe hyperkalemia in pts with DM, CKD, and CHF may be warranted.

TH-PO475
Serum Potassium and the Risk of Adverse Outcomes: A CKD Prognosis Consortium Meta-Analysis

Kunihiro 2

Background: Potassium levels outside the normal range may be dangerous. We evaluate the continuous relationship between potassium and all-cause mortality, cardiovascular mortality, and end-stage renal disease in 21 international cohorts.

Methods: We used Cox regression followed by random-effects meta-analysis to assess the relationship between baseline potassium (spline term with knots at 3.5, 4, 4.5, 5, and 5.5 mmol/L) and adverse outcomes, adjusted for age, sex, race, diabetes, systolic blood pressure, anti-hypertensive medications, cardiovascular disease, heart failure, total cholesterol, body-mass index, smoking, eGFR and albuminuria. We tested for effect modification by levels of eGFR (60+, 30-59, and <30 ml/min/1.73 m²) and adverse outcomes across a range of eGFR.

Results: There were 418,999 participants with both eGFR and albuminuria across 11 general population, 2 high cardiovascular risk, and 8 CKD cohorts followed for an average of 5 years. Mean baseline potassium was 4.2 mmol/L. Average age was 55 years; 54% were female, and 6% were black. Average eGFR was 83 ml/min/1.73 m², 19% had albuminuria, and 44% were on antihypertensive medications. The relationship between potassium and all-cause mortality demonstrated higher risk outside of the 3.5-5.5 mmol/L range (Figure). Compared to a reference of 4.2 mmol/L, the adjusted hazard ratio for all-cause mortality was 1.27 (95% CI: 1.12-1.45) at 5.5 mmol/L and 1.36 (95% CI: 1.17-1.57) at 3.2 mmol/L. Risk relationships were similar for cardiovascular mortality and end-stage renal disease. Associations were similar but slightly attenuated in persons with lower eGFR.

Conclusions: Potassium levels both above and below the normal range are associated with adverse outcomes across a range of eGFR.

Figure 1 (representative patient)

In 5 patients we calculated the slope of K as a function of temperature, which revealed a linear relationship.

Table 1. Correlation coefficient calculated from the slope of K and Temperature during rewarming. Patients also received variable amounts of K supplementation.

<table>
<thead>
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Conclusions: Marked hypothermia produces hypokalemia due to a shift in the distribution of K between extracellular and intracellular compartments possibly by slowing down cellular K exit via K⁺ channels. The increase in K and the linear relationship between K and temperature during rewarming suggests the dominance of the K+ channels (exit pathway) over the Na,K-ATPase (entry pathway) by reactivation of temperature dependent K+ channels. The hyperkalemia encountered suggests that K⁺ supplementation should be minimized during rewarming.

TH-PO477
Long-Term Sodium Zirconium Cyclosilicate Treatment in Patients with Hyperkalemia: Interim Analysis of an Open-Label Phase 3 Study

Bruce S. Spinowitz, 1 James A. Tumlin, 2 Edgar V. Lerma, 3 Wajej Y. Qunibi, 4 Bhupinder Singh, 5 Jose A. Menoyo, 6 Philip T. Lavin, 6 Henrik S. Rasmussen, 7 Steven Fishbane, 3 New York Presbyterian, Queens and Weill Medical College of Cornell Univ; 5Univ of Tennessee College of Medicine; 6Univ of Illinois at Chicago College of Medicine, Advocate Christ Medical Center; 7Univ of Texas Health Science Center at San Antonio; 8ZS Pharma; 9Boston Biosciences Research Foundation; 1Hofstra Northwell Health School of Medicine.

Background: Sodium zirconium cyclosilicate (ZS-9) is a non-absorbed, selective cation trap that binds potassium (K) throughout the GI tract.

Methods: This ongoing, open-label, single-arm Phase 3 trial enrolled adult patients (pts; N=751) with hyperkalemia (HK; K⁺ ≥5.1 mEq/L). Pts received ZS-9 10g TID for 24–72 h (induction phase). Pts who achieved normokalemia (K⁺<3.5–5.0 mEq/L) received ZS-9 5g/d for ≤12 mo (maintenance phase).

Results: As of Dec 7, 2015, 751 pts were enrolled and 436 pts had completed 6 mo of treatment; 64.6% were on RAASI and 34.4% had heart failure. During the induction phase, 99.3% of pts achieved normokalemia and mean K⁺ declined from 5.6 mEq/L at baseline to 4.7 mEq/L at maintenance phase start. Mean K⁺ for all pts was 4.7 mEq/L during the maintenance phase. Among pts treated for ≥6 mo (n=436; figure), mean K⁺ was 4.7 mEq/L and 99% of pts had mean K⁺ ≤5.1 mEq/L over mo 3–12; results were similar for pts treated for ≥9 mo (n=287). The most common AEs across all treated pts were constipation (5.0%), peripheral edema (7.6%), and worsening hypertension (HTN; 8.2%); rates did not increase over time with increasing duration of exposure to ZS-9. No pts discontinued study drug due to edema or HTN.

Figure. Mean K⁺ in Pts Treated ≥6 Mo (n=436).

Conclusions: Marked hypothermia produces hypokalemia due to a shift in the distribution of K between extracellular and intracellular compartments possibly by slowing down cellular K exit via K⁺ channels. The increase in K and the linear relationship between K and temperature during rewarming suggests the dominance of the K⁺ channels (exit pathway) over the Na,K-ATPase (entry pathway) by reactivation of temperature dependent K⁺ channels. The hyperkalemia encountered suggests that K⁺ supplementation should be minimized during rewarming.

TH-PO476
Hypothermia Induced Hypokalemia and Recovery during Rewarming: Risk for Hyperkalemia

Khaled Boobes, Daniel Batlle, Tanya Tocharoen Tang, Robert M. Rosa. Nephology, Northwestern Univ, Chicago, IL.

Background: Induced hypothermia is a commonly recommended intervention to improve neurological outcome in patients who have survived prolonged cardiac resuscitation. Different degrees of hypothermia are currently used (91.4-96.8°F). Hypothermia, however, can produce hypokalemia and can be associated with rebound hyperkalemia during the rewarming phase.

Methods: We obtained retrospective data on 74 patients who underwent hypothermia after cardiac arrest of whom 64 developed hypokalemia (range 1.9-3.5 mEq/dL). We then excluded for this analysis who did not survive the rewarming phase.

Results: Hyperkalemia (defined as K⁺ ≥5.0 mEq/dL) developed in 47 out of the 74 patients. Of those, 18 had a K⁺ ≥6.0 mEq/dL and 5 had K⁺ ≥7.0 mEq/dL.
Conclusions: These initial findings indicate that normokalemia was maintained with daily ZS-9 dosing in pts treated for ≥6 mo. Safety data is presented from all treated pts through Dec 7, 2015.

Funding: Pharmaceutical Company Support - ZS Pharma

TH-PO478

Effect of Sodium Zirconium Cyclosilicate Treatment for Hyperkalemia on Blood Pressure in a Long-Term Open-Label Phase 3 Study  

Pablo E. Pergola,1 Bruce S. Spinowitz,2 Peter A. McCullough,2 Bhupinder Singh,3 Jose A. Menoyo,4 Philip T. Lavin,5 Henrik S. Rasmussen,5 Steven Fishbane,6  

1Renal Associates PA, San Antonio, TX; 2New York Presbyterian, Queens and Weill Medical College of Cornell Univ, Flushing, NY; 3Baylor Univ Medical Center, Dallas, TX; 4ZS Pharma, San Mateo, CA; 5Boston Biostatistics Research Foundation, Framingham, MA; 6 Hofstra Northwell Health School of Medicine, Great Neck, NY.

Background: Sodium zirconium cyclosilicate (ZS-9) is a non-absorbed, selective cation trap that binds potassium (K+) in exchange for H+ and Na+. This interim analysis assessed the effects of ZS-9 on blood pressure (BP) in a 12-month study in patients (pts) with hyperkalemia (HK).

Methods: This ongoing, open-label, single-arm Phase 3 trial enrolled adult patients (pts, N=751) with HK (K+ ≥5.1 mEq/L). Pts received ZS-9 10g TID for 24–72 h (induction phase). Pts who achieved normokalemia (K+ 3.5–5.0 mEq/L) received ZS-9 5g daily for ≤12 mo (maintenance phase).

Results: As of Dec 7, 2015, 751 pts were enrolled; 82.6% with hypertension (HTN), 34.4% with heart failure and 64.6% on RAASi. During the induction phase, 99.3% of pts achieved normokalemia and mean K+ declined from 5.6 mEq/L at baseline to 4.7 mEq/L at start of maintenance phase. There were no clinically meaningful changes in mean systolic and diastolic BP nor in related variables like body weight over time for all treated patients and those who completed 12 mo of treatment (n=155; figure). The most common AEs were constipation (5.0%), peripheral edema (7.6%), and worsening HTN (8.2%); rates did not increase over time with increasing duration of exposure to ZS-9. No discontinuation study drug due to edema or HTN. Figure. Mean BP Over Time.

Conclusions: These initial findings indicate no clinically meaningful changes in BP were observed with daily ZS-9 treatment of HTN. Safety data is presented from all treated pts through Dec 7, 2015.

Funding: Pharmaceutical Company Support - ZS Pharma

TH-PO479

Aldosterone, Renin and Blood Pressure during Patiromer Treatment of Hyperkalemia in CKD  

Matthew R. Weir,1 Martha Mayo,2 Dahlia Garza,2 Natalie Panov,2 Lilla S. Simon,2 Charles Du Mond,2 Lance Berman,2 George L. Bakris.3 1Univ of Maryland School of Medicine, Baltimore, MD; 2Relypsa, Inc., Redwood City, CA; 3Univ of Chicago Medicine, Chicago, IL.

Background: Patiromer is a sodium-free, non-absorbed potassium binder approved for the treatment of hyperkalemia (HK). In in vitro studies, patiromer was shown to bind about half of the oral medications tested. Recent studies in healthy volunteers indicate that there may be a much lower potential for pharmacokinetic interactions with patiromer. We retrospectively evaluated the potential for adverse pharmacodynamic (PD) effects on 3 antihypertensive drugs that showed in vitro binding and were most frequently used in patiromer clinical trials.

Methods: Safety data were pooled from 4 patiromer trials, (2 HK treatment studies in CKD patients and 2 HK prevention studies in HF). Patiromer was initiated at total daily doses of 8.4-33.6 g (divided BID). In patients on stable doses of oral antihypertensive drugs (AHDs) of interest at baseline (amlodipine [AM], furosemide [FUR], and metoprolol [MP]), objective measures of PD effects, ie changes in systolic and diastolic blood pressure (SBP/DBP), and AHD dose increases, were evaluated during the first 4 weeks after patiromer initiation.

Results: Overall 666 patients were treated with patiromer in the clinical trials; hypertension was present in 97.3%. Of these, 512 were receiving oral AHDs of interest at baseline: AM (n=227), FUR (n=227) and MP (n=58). Mean ± SD SBP at baseline, at week 4 and change from baseline to week 4 are shown (Table). An oral AHD dose increase was required in 1 patient each in the AM and MP groups and in 5 patients in the FUR group.

Conclusions: No evidence of adverse systematic BP effects of oral AHDs were observed after the initiation of patiromer in clinical trials for the prevention or treatment of hyperkalemia.

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

Underline represents presenting author.

202A
Blood Pressure Statistics/Parameter Amlodipine Furosemide Metoprolol
Baseline N 227 227 58
SBP (mm Hg) Mean (SD) 146.3 (15.4) 143.1 (7.9) 146.4 (20.3)
DBP (mm Hg) Mean (SD) 80.1 (11.2) 80.5 (11.6) 81.5 (9.9)

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Funding: Pharmaceutical Company Support  2Rypsy, Inc.

TH-PO481

Profound Hypokalemia and Generalized Paralysis following the Chronic Ingestion of Large Amounts of Ibuprofen

Ogurevi Olaode,1 Paul Zamudio, Nand K. Wadhwa, Edward P. Nord, Rajeev B. Patel, Wilfred Lieberthal, Medicine, Stony Brook Medicine, Stony Brook, NY.

Background: The effects of an acute overdose with the non-steroidal anti-inflammatory drug (NSAID) Ibuprofen are well described, and include oliguric AKI, alterations in mental electrolyte abnormalities have been described previously. Most of these cases are due to acute overdoses of Ibuprofen. There are sparse reports of Ibuprofen abuse causing profound hypokalemia and generalized paralysis. The present case is the first report in the medical literature of recovery from Ibuprofen overdose with profound hypokalemia and generalized paralysis.

Methods: The patient was a 48 year old man who presented with profound muscle weakness for 10 days prior to presentation. He was taking 10-12 tablets (600mg/tablet) of Ibuprofen every 4-6 hours almost daily for about one year for back pain. He was fully oriented with normal vital signs. The only notable finding on exam was severe muscle weakness and an inability to lift his extremities or sit up. Laboratory data on admission: Serum electrolytes: BUN 68mg/dL, creatinine 3.84 mg/dL, sodium 123 mmol/L, potassium <1.5 mmol/L, chloride 78 mmol/L, bicarbonate 7 mmol/L (anion gap 38 mmol/L). Calcium 8.1 mg/dL, phosphorus 5.4 mg/dL, magnesium 2.7 mg/dL. Plasma beta-hydroxybutyrate 0.6 mmol/L. L-lactate 2.4 mmol/L. D-lactic acid undetectable. Toxicology screen negative. Urine electrolytes: pH 5.5, sodium 80 mmol/L, potassium 118 mmol/L, chloride 56 mmol/L. The patient was given potassium intravenously (IV) and orally. When his potassium exceeded 2.0 mmol/L, an IV infusion of sodium bicarbonate was started. Two days after admission the BUN was 45 mg/dL and creatinine 3.1 mg/dL. The serum sodium was 141 mmol/L, the bicarbonate 20mmol/L and the anion gap 16 mmol/L. When the patient was seen in renal clinic 2 months later after discharge his BUN was 31 mmol/L, his creatinine 2.6 mg/dL and his electrolytes were normal.

Conclusions: There are sparse reports of Ibuprofen abuse causing profound hypokalemia and generalized paralysis. In this case, a patient with normal renal function and a urine pH >6.0, suffering from renal tubular acidosis. By contrast, the severe life threatening hypokalemia and metabolic acidosis in this case, was associated with a large anion gap of undefined cause and a urine pH of 5.5. To the best of our knowledge, no cases of Ibuprofen abuse with these electrolyte abnormalities have been described previously.

TH-PO482

Dietary Salt Induces Catabolism in Humans

Kento Kitada,1 Natalia Rakova,2 Steffen Daub,1 Tetyana Pedchenko,1 Yahua Zhang,1 Friedrich C. Luft,1 Jens Titze.1 Div of Clinical Pharmacology, Vanderbilt Univ Medical Center, Nashville, TN; 2Experimental and Clinical Research Center, Charité Medical University, Berlin, Germany.

Background: The concept that increasing salt intake elevates fluid intake and urine volume originates from short-term experiments in humans exposed to extremes in salt intake. In the first ultra-long term sodium and water balance study performed in man, we found that high salt intake induced a catabolic state with increased metabolic water formation that accompanied the excretion of dietary salt by renal concentration. We hypothesized that salt induces energy-intense urea generation, which is accumulated in the renal medulla and provides with the osmotic driving force necessary to concentrate the urine and excrete dietary salt without osmotic diuresis.

Methods: We fed male mice (C57/B6) a low-salt diet (<0.1%NaCl) with tap water (LSD) or a high-salt diet (4%NaCl) with 0.9% saline to drink (HSD) for 4 consecutive weeks, followed by 2 weeks of pair-feeding to match energy intake in both groups. We studied the effects of high-salt intake on osmolyte and water balance and urea generation.

Results: HSD increased urea content and urea transporter expression in the renal medulla, resulting in reduced urea osmolyte excretion. Retaining urea osmolytes, HSD mice preserved their urine concentration ability despite excess Na and Cl osmolyte excretion, thereby preventing osmotic diuresis. HSD induced arginase-driven urea production in liver and skeletal muscle, but not in the kidney. Metabolomic analysis revealed corticosterone-driven free amino acid wasting in muscle to provide liver with nitrogen for urea generation. The energy-intense nature of urea osmolyte generation resulted in a catabolic state with exploitation of stored energy fuels and ketogenesis.

Conclusions: Na metabolism cannot be understood without investigation of urea metabolism. The biological pattern of dietary salt excretion includes urea osmolyte generation and accumulation in the kidney to the urine and prevent salt-driven water loss by osmotic diuresis. The resulting reprioritization of energy metabolism for energy-intensive urea production may explain muscle wasting in patients with Na overload.

Funding: Other NIH Support  RO1 HL118579-01

TH-PO484

The Relationship of Tissue Sodium Concentration to Cardiovascular Indices in Advanced Chronic Kidney Disease

Nicos Mitides,1 Damien J. McHugh,2 Jane Alderdice,1 Paul E. Brenchley,1 Geoff J.M. Parker,2 Sandip Mitra,1 1Manchester Academic Health Science Centre; 2Centre for Imaging Sciences of the Univ of Manchester.

Background: Body sodium (Na) balance is considered to be an important determinant of cardiovascular (CV) risk. Chronic kidney disease (CKD) is considered to be a salt sensitive state. However the role of Na tissue accumulation in influencing CV parameters in CKD has not been investigated.

Methods: The relationship of tissue Na concentration to CV indices was investigated using a 3T Magnetic Resonance (MR) scanner & a dual-tuned 1H/23Na coil. We acquired 23Na MR images of the lower legs of 6 healthy volunteers (HV) and 7 CKD stage 5 patients (eGFR<15 ml/min, not yet on dialysis) and calculated Na concentration in the muscle and subcutaneous (SC) tissue using calibration saline phantoms placed under the leg. Participants underwent simultaneous measurement of their CV status using pulse wave velocity (PWV), 24hr ambulatory Blood Pressure monitoring (ABPM), skin auto-fluorescence & sublingual dark field capillaroscopy.

Results: The MR derived Na concentrations (mmol/L) for CKD participants were higher than HV. This difference was more pronounced in the SC tissue (CKD 26.3±9.4, HV 18.1±3.5, p<0.05) than in the muscle (CKD 24.3±6.0, HV 22.6±3.0, p=0.19). The mean ABPM measurements (mmHg) for the entire cohort was systolic 127±12.5, diastolic 79.8±8.6 and mean arterial pressure (MAP) (95.8±9.6). Muscle Na concentration showed a positive correlation with ABPM derived systolic (p=0.02), diastolic (p=0.02) and MAP (p=0.02). Both Na concentration for muscle and SC tissue correlated with capillaroscopy measurements of endothelial glycoxidation with the former exhibiting a positive association with the thickness of the Perfused Boundary Region of large size capillaries (p=0.02) and the latter with Red Cell width (p=0.01).

Conclusions: Our results indicate that CKD leads to higher tissue accumulation of salt. Both SC and muscle Na concentrations are linked to microvascular injury and the muscle Na accumulation is closely linked to hypertension.

Funding: Clinical Research Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
TH-PO485

Syndrome of Inappropriate ADH versus Reset Osmostat: Blind Spots in Classification and Evaluation of Hyponatremia

Hormoz Dara Dastoor,1 Chandra Mauli Jha,2 Ken J. Donaldson,3 Thalakunte Muniraju,4 Sanra Abouchacra,1 Hatem Mohyeldin Ebed,4 1Div of Nephrology, Rahba Hospital; Johns Hopkins International, Abu Dhabi, United Arab Emirates; 2Div of Nephrology, Burjeel Hospital, Abu Dhabi, United Arab Emirates; 3Div of Nephrology, Dumfries and Galloway Royal Infirmary, Dumfries, United Kingdom; 4Div of Nephrology, Al Noor Hospital, Abu Dhabi, United Arab Emirates.

Background: We present a case diagnosed as SIADH on the basis of current classification of Hypotonic Hyponatremia. However, further evaluation including measurement of Vasopressin levels revealed the diagnosis as Reset Osmostat and a careful classification of Hypotonic Hyponatremia is needed.

Methods: Case A 72-year-old lady presented with nausea and euvolemic hyponatremia with Plasma Sodium 121 mmol/l, urine osmolality 162 mosm/kg. On the basis of prevalent diagnostic algorithm she was diagnosed to have SIADH and Fluid restriction raised her Pn+ to 130 mmol/l. However measured ADH levels at time of admission was found to be <0.1 pg/ml (normal 0.7-3.8 pg/ml) suggesting near absence of ADH. The patient had either Reset Osmostat or Age related inability to excrete Free Water with Primary Polydipsia.

Results: We find the current diagnostic algorithm of hyponatremia leads to a false diagnosis of SIADH.

Conclusions: Using a diagnostic approach of combining the pathophysiology of hyponatremia and measurement of Urine Osmolality, we have been able to accurately diagnose pathologies which have been mistakenly labelled as SIADH. These include Residual Water Permeability, Reset Osmostat and Age related Hyponatremia, and Diagnosis of SIADH in euvolemic hyponatremic patients with urinary Na<100 mosm/l appears to be faulty causing over diagnosis of SIADH.

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TH-PO486

Is the Fall in Serum [Glu] in Response to a Rise in Serum Glucose ([Glu]) Affected by Prevaling [Glu]? Why Philip Goldwasser,1 Andrea Roche-Recinos,2 Robert H. Barth.1 1Medicine, VA NY Harbor Heathcare System, Brooklyn, NY; 2Medicine, SUNY Downstate, Brooklyn, NY.

Background: [Na] falls (ANA) as [Glu] rises ([Glu]), but the slope of this effect (ANAGlu) may vary. Theory predicts the slope should shallower as [Glu] increases (Robin ‘79; Moran ‘85), but one post hoc study found it steepen when [Glu] exceeded 400 mg/dL (Hiller ‘99). Changes in total protein (TP), hemoglobin (HB) and bicarbonate (ICO2)—which often accompany ANA—are cause bias in [Na] measured by either the indirect (diluted) method (INa), in chemistry (chem) panels, or the direct method (dNa), in gas panels. Prior estimates of ANA dNa didn’t account for these biases. We recently defined linear corrections for them in 772 paired chem and gas panels, obtained up to 19 min. apart (median: 4 min.), retrospectively collected from our critical care units [NDT ‘15; ASN Nov ‘15].

Methods: To test whether [Glu] itself influences ANA dNa, we classified each pair, by the mean of its chem and gas [Glu], into one of 4 subgroups: A) ≤100 mg/dL; B) 101-150 mg/dL; C) 151-200 mg/dL; D) >200 mg/dL. Next, defining ANA as [Glu] and ANA as [Na] - dNa, we estimated the effect on ANA of [Glu] by regressing, adjusting for TP, HB and ICO2, in the subgroups and the entire cohort. Data changes on the balance of the Na, K and water were unavailable.

Results: In the entire cohort, mean [Glu] ranged from 40 to 1043 mg/dL, and ANA from -189 to 164; ANA was +2.4 ± 0.4 [SE] mEq/L per 100 mg/dL of [Glu] (p < 0.1). The subgroup slopes varied from -1.4 to -5.1, but pairwise comparison of the 4 slopes yielded only one difference of even borderline significance (C vs D: p < 0.05, unadjusted for multiple comparisons).

TH-PO487

Hyponatremia in the Emergency Department, Role of Prescription Medications

Gudrun Sigurdardottir,1 Petur S. Gunnarsson,1,2 Anna Ingibjorg Gunnarsdottir,2 Elin Ingibjorg Jacobsen,3 Runolfur Palsson,1,2 Olafur S. Indridason.2 1Univ of Iceland; 2Landspati - the National Univ Hospital of Iceland, Reykjavik, Iceland.

Background: Commonly prescribed medications have been associated with development of hyponatremia. We examined the frequency of hyponatremia, defined as serum sodium (SNa) ≤135 mEq/L in patients visiting a University Hospital emergency department (ED) and its relationship to medication use.

Methods: This was a retrospective study of all patients >18 years, who visited the ED in 2014. SNa levels and other clinical data were obtained from the electronic medical records. Information on drugs dispensing for subjects with hyponatremia and matched controls drawn from ED patients with normal SNa levels, was obtained from the National Pharmaceuticals Database of the Directorate of Health. Patients were matched on age, sex, creatinine and diagnoses of hypertension, diabetes, coronary artery disease, COPD, malignancy and psychiatric disorders. Kaplan-Meier method was used for survival analysis and the log-rank test to compare groups.

Results: In total, 40,365 individuals had 58,137 ED visits. SNa was measured at 26,474 visits of 19,159 patients, with hyponatremia present at 2,287 (3.9%) visits of 1,785 (4.4%) patients, of whom 62.5% were women. Frequency of hyponatremia increased with age and was 12.8% in patients >70 years. Compared with the control group, more patients with hyponatremia had filled a prescription for thiazides (25.6% vs 19.6%, p<0.001), amiodarone (11.0% vs 7.4%, p<0.001), aldosterone antagonists (8.7% vs 5.5%, p<0.001), proton pump inhibitors (0.7% vs 0.1%, p<0.001), carboxamide and hydantoins (2.7% vs 0.8%, p<0.001), ACE inhibitors (16.9% vs 14.0%, p=0.04) and tricyclic antidepressants (6.2% vs 4.8%, p=0.048). No difference was observed for SSRIs (21.7% vs 23.1%, p=0.74) or SNRIs (13.3 vs 13.8%, p=0.86). One-year survival was 78.3% (95% CI, 76.3-80.2%) in the hyponatremia patients compared with 84.6% (95% CI, 82.9-86.4%) in the control group (p<0.001).

Conclusions: Hyponatremia is common in the ED, especially among older individuals and is associated with increased mortality. Thiazides, aldosterone antagonists and proton pump inhibitors are likely causative agents in many patients.

TH-PO488

Severe Hyponatremia in the Hospital Setting: Incidence, Etiology and Outcome

Arni H. Geirsson,1 Runolfur Palsson,1,2 Kristinn Sigvaldason,1,2 Olafur S. Indridason.1 1Landspati - The National Univ Hospital of Iceland; 2Univ of Iceland, Reykjavik, Iceland.

Background: Severe hyponatremia can be a devastating disorder and its management is frequently very challenging. The aim of this study was to investigate the incidence, etiology and outcome of severe hyponatremia, defined as serum sodium (SNa) <120 mEq/L in a metropolitan area in Iceland.

Methods: This was a retrospective study that included all patients >18 years of age with SNa <120 mEq/L at the University Hospital in Reykjavik, in 2005-2014. Patients were identified in the electronic database of the Department of Clinical Biochemistry and clinical data were extracted from medical records. Incidence was calculated per hospital admission and per 100,000 population of the greater Reykjavik area. Changes in incidence were evaluated by poisson regression.

Results: A total of 350 patients suffered 619 episodes of severe hyponatremia. Median age was 74 (range, 23-98) years and 76% were females. The average annual incidence was 2.49/1000 admissions, increasing from 1.69/1000 to 2.59/1000 over the study period (p=0.007). The average population incidence was 41/1000,000/yr, without a significant change during the study period (p=0.59). The etiology of severe hyponatremia was considered to be SIAD in 205 cases (33.1%), volume depletion in 153 (24.3%) and a thiazide diuretic in 141 patients (22.8%), 113 (80.1%) of whom were women. Intensive care was required in 102 cases (16.5%). Eighty patients (12.9%) had acute hyponatremia and 24 (3.9%) received emergency treatment with 3% saline. The in-hospital mortality was 9%. Five patients experienced neurologic complications following correction of SNa. Thirty patients (2.1%) had SNa <105 mEq/L, of whom 2 died and 5 could not be discharged/discharged to their home.

Conclusions: The frequency of severe hyponatremia is increasing in hospitalized patients and most commonly occurs in females and older individuals. Intensive care management is often needed and the mortality rate is substantial. Since thiazide diuretics are a common cause of severe hyponatremia, a more cautious use of these agents is warranted in patients at increased risk, such as elderly women.
The Association between Serum Sodium Levels at Hospital Admission and Outcomes among 2.7 Million Hospitalized Patients

Background: Hyponatremia is the most common electrolyte disturbance in hospitalized patients. While studies have addressed its association with selected outcomes, few included a large cohort of hospitalized patients. In this study, we examined the association of serum sodium at hospital admission with subsequent outcomes.

Methods: We extracted data from the Cerner Health Facts database. We included the index hospital admission defined by the first inpatient encounter of any patient between 2000 and 2014 that met the following inclusion criteria: age ≥18 years and serum sodium levels drawn during 24 hours before admission. ICD-9 codes were used to identify the comorbidities. Logistic regression models were used in the analysis.

Results: 2.7 million patients were included in this analysis. 14.7% of patients had serum sodium (Na) <135 mEq/L. The prevalence of Na <135 mEq/L increased with age. Adjusting for age, sex, and race, patients with diabetes mellitus, end stage renal disease, cirrhosis, lung cancer, adrenal insufficiency, and HIV were associated with a higher likelihood of Na <135 mEq/L. After adjusting for age, sex, race, and the Deyo Charlson Comorbidity Index, a serum Na across a range of 115 to <135 had a higher likelihood of in-hospital mortality compared to Na of 140 to 145 mEq/L (p<0.001). Similar trends were observed between Na and discharge to hospice. More research is needed to study other outcomes associated with hyponatremia.

Conclusions: Hyponatremia (Na <135 mEq/L) is common in patients who present to the hospital and is independently associated with outcomes such as in-hospital mortality and discharge to hospice. More research is needed to study other outcomes associated with hyponatremia.

Funding: Other NIH Support - Clinical and Translational Science Center (CTSC) Award

Association of Hyponatremia with Impaired Cognition

Background: Hyponatremia is a common finding in older adults and is linked to attention deficits, gait disturbances, and risk of falls. However, the association of hyponatremia with cognition in older adults is currently unknown. We hypothesized that hyponatremia would be associated with cognitive impairment and risk of cognitive decline in asymptomatic, community-dwelling older men.

Methods: 5,376 men aged >65 years who were enrolled in the Osteoporotic Fractures in Men (MrOS) study were included in this analysis. Multivariable logistic regression was used to examine the association between baseline serum sodium levels and the odds of both prevalent cognitive impairment (cross-sectional analysis; modified mini-mental status [3MS] score <80 or Trail Making Test Part B score >1.5 S.D. above the mean [>223.4 sec]) and decline incident cognitive impairment (prospective analysis [n=3,667]; follow-up 3MS score of <80 or decline of >5 points, or change in Trails B time >1 S.D. above mean change in completion time [>45.1 sec]).

Results: Mean age was 74±6 years with a mean serum sodium level of 141±3 mEq/L. After adjustment demographics, education, co-morbid conditions, smoking, alcohol, body-mass index, estimated glomerular filtration rate, physical activity, and quality of life measures, serum sodium was associated with prevalent cognitive impairment (quartile 1 [126-140 mmol/L] vs. quartile 4 [143-153 mmol/L]: OR 1.49, 95% CI 1.15-1.92). For incident cognitive impairment (median follow-up of 4.6 years), quartile 3 (142-143 mmol/L) was associated with lower odds of cognitive impairment vs. quartile 4 (143-153 mmol/L; adjusted OR 0.77, 95% CI 0.61-0.96), with no difference in quartile 1 (126-140 mmol/L) vs. quartile 4 (adjusted OR 0.95, 95% CI 0.77-1.18).

Conclusions: In asymptomatic, community-dwelling older men, hyponatremia was associated with prevalent but not incident cognitive impairment.

Funding: Other NIH Support - NIA and NIAMS

The Association between Serum Sodium Levels at Hospital Admission and Outcomes among 2.7 Million Hospitalized Patients

Background: Hyponatremia is a well-known factor for adverse clinical outcomes, the impact of postoperative hyponatremia in urology remains unclear.

Methods: We examined the incidence, risk factors, and outcomes of postoperative hyponatremia in urologic surgery. Patients with events of postoperative sodium level lower than 135 mEq/L within 7 days after surgery were included in our study group, and the others in the control group. Primary outcomes were postoperative all-cause mortality and end-stage renal disease (ESRD) progression, defined by the start of dialysis or newly diagnosed stage 5 chronic kidney disease (eGFR <15ml/min/1.73m²). The secondary outcome was the worsening of the long-term renal outcome, including ESRD progression and serum creatinine doubling/eGFR halving from baseline, occurring 1 month or more after surgery.

Results: The medical records of 9,449 cases of bladder, prostate, ureter, and kidney surgery were collected. Incidence of postoperative hyponatremia was 16.5% (1,562,449). Postoperative hyponatremia mostly developed in patients with high-risk perioperative characteristics. Moreover, postoperative hyponatremia was related to both mortality (adjusted HR 1.46, 95% CI 1.02-2.21, P = 0.04) and ESRD progression (adjusted HR 1.31, 95% CI 1.07-1.62, P = 0.008). The secondary outcome was also related to the electrolyte imbalance in prostate (adjusted HR 1.78, 95% CI 1.21-2.62, P = 0.003), ureter (adjusted HR 1.83, 95% CI 1.07-1.13, P = 0.03), and kidney (adjusted HR 1.22, 95% CI 1.01-1.49, P = 0.04). Surgery. However, this relationship was not observed in bladder surgery cases (adjusted HR 1.09, 95% CI 0.83-1.45, P = 0.54).

Conclusions: Postoperative hyponatremia was a common electrolyte imbalance after urologic surgery, especially in patients with high-risk perioperative status. Postoperative hyponatremia was an important predictor of both mortality and adverse renal outcome in major urologic operations.
November 27, 2016
Fluid, Electrolyte, Acid-Base Disorders
Poster/Thursday

TH-PO493
Hyponatraemia in Cancer Patients Treated with Immune Checkpoints’ Inhibitors: Is Adrenal Impairment the Cause? Laura Cosmai, 1 Wanda Liguigli, 1 Camillo Porta, 1 Maurizio Gallieni, 1 Marina Foramitti, 1 Fabio Malberti, 1
1Nephrology, Istituti Ostipalieri, Cremona, Italy; 2Oncology, Istituti Ostipalieri, Cremona, Italy; 3Oncology, IRCCS San Matteo Univ Hospital Foundation, Pavia, Italy; 4Nephrology, San Carlo Borromeo Hospital, Milan, Italy; 5Nephrology, Istituti Ostipalieri, Cremona, Italy; 6Nephrology, Istituti Ostipalieri, Cremona, Italy.

Background: Immune checkpoints’ inhibitors such as Ipilimumab and Nivolumab are more and more commonly used to treat patients (pts) with different solid cancers (e.g. melanoma, lung cancer and kidney cancer).

Methods: We have observed 7 pts who developed hyponatraemia during treatment with Ipilimumab-Nivolumab (Nivolumab within a randomised clinical trial) treated in metastatic kidney cancer, n = 6) or Ipilimumab monotherapy (for melanoma, n = 1).

Results: Of the 7 pts observed, 1 had a grade 4, 3 a grade 2, and 2 a grade 1 hyponatraemia. The patient with grade IV was hospitalized (serious adverse event was urgent hyponatraemia. The patient with grade IV was hospitalized (serious adverse event was urgent hyponatraemia. The patient with grade IV was hospitalized (serious adverse event was urgent hyponatraemia. The patient with grade IV was hospitalized (serious adverse event was urgent hyponatraemia). The patient with grade IV was hospitalized (serious adverse event was urgent hyponatraemia). The patient with grade IV was hospitalized (serious adverse event was urgent hyponatraemia).

Conclusions: Hyponatraemia is a relatively frequent event during treatment with immune checkpoint inhibitors; its pathogenesis is unknown, but a drug-induced adrenal impairment/infammation could be postulated and the efficacy of steroids in one of our cases do support this hypothesis.

TH-PO494
Predicators of Rapid Correction of Hyponatraemia Caused by the Syndrome of Inappropriate Secretion of Antidiuretic Hormone during Treatment with Tolvaptan Jesse H. Morris, 1 Rachel E. Crawford, 1 Denise O. Kelley, 2 Nicole Bohn, 3 Bhavna Bhasin, 3 Paul Niestert, 4 Juan Carlos Velez, 4 1Nephrology, Dept of Nephrology, University of South Carolina, 2Dept of Pharmacy, Wake Forest Baptist Medical Center, 3Dept of Pharmacy, UF Health Jacksonville, 4Dept of Clinical Pharmacy and Outcomes Sciences, Medical University of South Carolina, 5Dept of Public Health Sciences, Medical University of South Carolina.

Background: Tolvaptan can correct hyponatraemia caused by SIADH rapidly, thus carrying a risk for central pontine demyelination. We hypothesized that clinical and/or lab parameters predict the likelihood of rapid correction of SIADH-induced hyponatraemia during treatment with tolvaptan.

Methods: Data were extracted from hyponatraemic [serum sodium (sNa) ≤ 130 mmol/L] adults with SIADH treated with tolvaptan (1st dose 15 mg) at 3 university hospitals between 2010 and 2015. Those who also received po/i.v. sodium or demeclocycline were excluded. The ability of baseline parameters to predict the change in sNa was assessed by Spearman correlation and a multivariate linear regression analysis.

Results: A total of 22 patients entered the analyses. Mean baseline sNa was 121.2 ± 8.4 mmol/L and the mean rise in sNa over the first 24 hrs was 8.4 ± 12.0 mmol/L. Linear correlation of sNa > 12 or ≥ 8 mmol/L 24 hrs increased in 27% and 36% of the cases, respectively. Change in sNa over 24 hrs significantly correlated with baseline sNa (r=0.75, p=0.001), blood urea (r=0.76, p=0.001) and eGFR (r=0.58, p=0.011). The variation in 24 hr sNa, although its effect did not reach significance (p=0.10). Four out of 4 patients with baseline sNa <120 mmol/L and BUN < 7 mg/dL corrected their sNa > 12 mmol/L 24 hrs (mean rise in sNa 17.8 mmol/L 24 hrs).

Conclusions: Baseline sNa is significantly predictive of the magnitude of response to tolvaptan therapy for SIADH, and a lower baseline sNa may also be predictive. We would consider changing tolvaptan in patients with particularly low sNa (<120 mmol/L) and low BUN (< 7 mg/dL).

TH-PO495
Use of Salt Tablets in the Treatment of Mild-to-Moderate Hyponatraemia due to Syndrome of Inappropriate Antidiuresis Ittikorn Spanuchart, 1 Thomas Aldan, 2 Hidecine Watanabe, 1 Dominic Chow, 3 Roland C.K. Ng, 3 1Univ of Hawaii Internal Medicine Residency Program; 2Univ of Hawaii John A. Burns School of Medicine.

Background: Hyponatraemia is the most common electrolyte disorder with significant morbidity and mortality. However, the effectiveness of salt tablets in treating this disorder has never been systematically examined. In this retrospective cohort study, we examined the effectiveness of salt tablet treatment in correcting mild-to-moderate hyponatraemia.

Methods: Eighty-three patients with hyponatraemia on fluid restriction, and laboratory values of urine osmolality >100 mosm/kg and urine sodium >30 mEq/L, who did not correct with normal saline infusion, were studied. Patients who had received salt tablets and fluid restriction as compared to those on fluid restriction alone. The primary outcome was the change in serum sodium at 48 hours.

Results: There were 41 patients in the non-salt treated group (NS) and 42 patients in the salt-treated group (ST). The median serum sodium before treatment was (NS) 129 mEq/L (IQR: 125-131.5) and (ST) 124 mEq/L (IQR121-129). The ST patients tended to be older (p=0.019), female (p=0.049), lower weight (p=0.039), and have lower initial serum sodium (p=0.005). The serum sodium after 48 hours of treatment increased significantly more in the salt tablets (S) than with fluid restriction (NS) alone (p=0.014). The change in serum sodium remained significant with S even after adjustment for age, gender, weight and initial serum sodium. The length of stay was longer in the S group (p=0.006). When the analysis was confined to more refractory patients (urine osmolality >500 mosm/kg), S (8 patients) vs NS (5 patients), treatment with salt tablets resulted in a significant increase in serum sodium (p=0.004) compared with fluid restriction alone. Adverse effects such as congestive heart failure and severe hypertension were not different in the two groups.

Conclusions: Use of salt tablets in the treatment of mild-to-moderate hyponatraemia due to syndrome of inappropriate antidiuresis is effective. Further studies of a prospective, randomized nature should be done to confirm these data.

TH-PO496
Salt Taste Thresholds and Salt Preference in Patients with Chronic Kidney Disease According to Stage: A Cross-Sectional Study Jie Wan, 1,2,3 Hyosang Kim, 4 Soon Bae Kim. 1Internal Medicine, 2Nephrology, 3Asan Medical Center, Seoul, Republic of Korea.

Background: Increased salt thresholds may affect the adequate control of oral salt intake and subsequent high blood pressure. This study was performed to evaluate the differences in salt taste thresholds among normal controls and non-dialysis chronic kidney disease (CKD) patients according to the stage and to evaluate the relationship between salt taste thresholds and salt preference in the mean spot urine sodium.

Methods: This cross-sectional study enrolled 456 patients with nondialysis CKD who visited Asan Medical Center (Seoul, Korea) more than three times and underwent spot urine sodium measurement at each clinic visit. We averaged the three most recent spot urine sodium concentrations and used this “mean spot urine sodium” value to estimate sodium intake. In addition, 74 normal controls were enrolled and their one-time spot urine sodium was measured. We evaluated the detection and recognition thresholds, salt preference, and salt usage behavior (via questionnaire) in CKD patients and normal controls.

Results: The detection thresholds of the stage 3a, 3b, 4 and 5 CKD patients and the recognition thresholds of the stage 4 and 5 patients were lower than those of normal controls. Estimated glomerular filtration rate (eGFR), salt usage behavior, and salt preference significantly correlated with the mean spot urine sodium in CKD patients. Age, sex, the detection and recognition thresholds, and serum zinc did not show a relationship with the mean spot urine sodium.

Conclusions: The detection and recognition thresholds were increased and salt preference and the salt usage behavior score were decreased in CKD patients. eGFR, salt preference, and the salt usage behavior score independent are correlated with the mean spot urine sodium.

TH-PO497
Endothelin Induces Aquaresis in Man via an AQP2-Independent Mechanism Robert W. Hunter, 1 Centre for Cardiovascular Science, Univ of Edinburgh, United Kingdom.

Background: Endothelin-1 (ET-1) receptor antagonists show promise in the treatment of chronic kidney disease. Their use is complicated by salt / water retention. Whereas in animal models ET-1 receptors cause natriuresis and aquaresis, with collecting duct ET-1bA inhibiting the activation of AQP2 channels, the pathogenesis of fluid retention with ET antagonists in man is not known. We aimed to determine the effect of ET-1 on water transport in the human collecting duct.

Methods: We conducted a 2-phase randomised, double-blind, placebo-controlled crossover study in 10 healthy volunteers. After sodium restriction, subjects received either intravenous placebo or the inactive ET-1 precursor, big ET-1, in an escalating dose (up to 360μmol/min). We prepared urinary extracellular vesicles (uEVs) by ultracentrifugation and analysed them using immuno2X (Milipore).

Results: Big ET-1 infusion increased plasma concentration and urinary excretion of ET-1. Fractional excretion of ET-1 rose from 0.6 to 2.4% and urine ET-1/creat from 0.05 to 0.29μg/mmol. Big ET-1 caused a fall in heart rate (~6 beats/min) but no change in other measures of systemic hemodynamics or in GFR. Fractional excretion of sodium increased by ~0.5%. There was no change in urine flow rate. Big ET-1 increased free water clearance (5.5±0.6 vs 4.1±0.4 μl/min, p<0.05) and the abundance of AQP2 in uEVs.

Conclusions: In man, ET-1 increased AQP2 excretion in uEVs (a proxy for AQP2 density in the collecting duct apical membrane). ET-1 stimulates pituitary AVP release, a
TH-PO498
Tolvaptan Increases Renal Water and Sodium Excretion More Than Furosemide in Patients with Congestive Heart Failure Complicated by Advanced Chronic Kidney Disease
Naoto Tomigonja, Keisuke Kida, Takaaki Suwa, Satoshi Satoh, Satoshi Sato, Tetsu Inomata, Naoki Sato, Yugo Shibagaki, 1 Div. of Nephrology and Hypertension, St. Marianna Univ, Japan; 2 Div. of Cardiology, St. Marianna Univ; 3 Dept of Cardio-angiologo, Kitasato Univ; 4 Cardiology and Intensive Care Unit, Nippon Medical School Masushia-Kosugi Hosp; 5 Div of Cardiology, Niigata Minami Hospital.

Background: Tolvaptan (TLV) is known to increase electrolyte-free water clearance. However, TLV actions on renal electrolytes including sodium (Na+) excretion and its consequences are less well understood in congestive heart failure (CHF) patients with CKD. This subanalysis investigated the effect of add-on TLV compared to furosemide (FUR) on both free water and electrolyte clearance in patients with CHF complicated by advanced CKD.

Methods: The Kanagawa Aquases Investigators Trial of TLV on HF Patients with CHF (KANTO) was a multicenter, open-label, randomized, and controlled prospective clinical study. Eighty-one Japanese patients with congestive HF and residual signs of congestion despite oral FUR treatment (≥40 mg/day) were recruited. They were randomly assigned to a 7-day treatment with either add-on 540 mg/day FUR or ≤15 mg/day TLV. However, 31 patients dropped out during the study and 16 patients had missing data resulting in 17 patients in each group. Free water and electrolyte excretion were compared before and after therapy between the two groups.

Results: As expected, free water clearance was significantly higher in the add-on TLV group than in the add-on FUR group (0.25±0.07 vs. -0.01±0.04 mEq/ml, P=0.001). However, electrolyte clearance was also higher in the add-on TLV group than in the add-on FUR group (0.06±0.06 vs. -0.08±0.07 mEq/ml, P=0.185). It was mainly because ΔNa excretion was significantly higher in the add-on TLV group than in the add-on FUR group (13.8±10.9 vs. -16.2±12.0 mEq/ml, P=0.040), since ΔK+ excretion was lower in the add-on TLV group than in the add-on FUR group (6.7±2.2 vs. 4.8±1.1 mEq/ml, P=0.014).

Conclusions: Add-on TLV may have an effect to increase both renal water and Na excretion in CHF patients with advanced CKD to a greater degree than add-on FUR.

TH-PO500
A Gain of Function NKCC2 Mutation in a Patient with Chronic Cyclic Edema
Mihbri K. Nguyen, 1 Alejandro Rodriguez-Gama, 2 Erika Moreno, 2 Theresa L. Nilson, 1 Gerardo Gamba, 1 Iratu Kurtz, 1 David Geffen School of Medicine, UCLA, Los Angeles, CA; 2 Molecular Physiology Unit, INCMSNZ-HU, UNAM, Mexico City, Mexico.

Background: We report a 20 y o female with a complex medical history significant for chronic cyclic edema, who has a homozygous R116H substitution in the SLC12A2 gene.

Methods: Expression/phosphorylation of NKCC2 was assessed by Western blot in proteins extracted from transiently transfected HEK-293 cells with wild-type and mutant NKCC2-R116H that were exposed to control and different osmolar conditions.

Results: Basal phosphorylation of the same wild-type mouse was found to be similar to add-on TLV-R116H.

Conclusions: Since phosphorylation of NKCC2 stimulates its transport activity, the R116H mutation in our patient appears to represent the first gain of function NKCC2 mutation ever reported.

Funding: Private Foundation Support

TH-PO501
Gender Difference in Thiazide Sensitive Na-CI Cotransporter Activity and Expression in Wild Type and Angiotensin Type 1a Receptor (AT1a) Deficient Mice
Chi Li, 1 Ryo Hatanao, 1 Lei Yang, 1 Shuhua Xu, 1 Akira Kikuchi, 2 Yasuyuki Sakai, 1 C. & M. Physiology, Yale Univ, School of Medicine, New Haven, CT; 2 Physiology and Biophysics, Weill Medical College of Cornell Univ, New York, NY.

Background: Thiazide sensitive Na-Ci cotransporter (NCC) mediates the majority of NaCl absorption in the distal tubule. Alteration of NCC directly affects salt and water balance and blood pressure. We studied gender differences in NCC activity and expression in WT and AT1a receptor knockout (KO) mice.

Methods: Renal clearance experiments were performed on both male and female WT and KO mice. Urine volume (UV), GFR, absolute (ENA) and fractional (FENa) Na excretion were measured and compared at peak changes after a bolus injection of hydrochlorothiazide (HCTZ; 30mg/kg). NCC mRNA expression was examined by Q-PCR; total NCC (tNCC) and phosphorylated NCC (pNCC) were examined by Western blotting.

Results: The fractional increases of UV, ENa and FENa by HCTZ were 8.3- vs. 5.3-fold; 13.5- vs. 9.5-fold; 0.33- vs. 0.26-fold in female, compared to male respectively (P>0.05). In separate experiments, the rate of dephosphorylation was monitored following cell swelling (known to inhibit NCC2). The phosphorylation of NCC in WT at 10, 20 and 30 min decreased from 1±0.01 to 0.8±0.05, 0.8±0.05 and 0.8±0.09 respectively.

Conclusions: The NCC2 dephosphorylation is precluded by the R116H mutation. Since phosphorylation of NCC2 stimulates its transport activity, the R116H mutation in our patient appears to represent the first gain of function NKCC2 mutation ever reported.

Funding: Private Foundation Support

TH-PO502
Impaired Renal Electrolyte Reabsorption in Moesin-Deficient Mice
Kotoku Asano. 1 College of Pharmaceutical Sciences, Ritsumeikan Univ, Kusatsu, Shiga, Japan.

Background: ERM (erlin, radixin, and moesin) proteins have important roles in organization of actin cytoskeleton, communication between the two through their interactions with protein components of the cell membrane, and in growth and division of cells. We have previously reported that ezrin plays important roles in the regulation of membrane localization of Na+ dependent phosphate transporter (NaPi2a) and scaffolding protein NHERF1 in the proximal tubules. However, physiological roles of ezrin and moesin in the kidney are still unclear. In the present study, we have investigated the physiological functions of radixin and moesin in the kidney using knockout mice.

Methods: To investigate the renal functions in male radixin (Rdxr) and moesin (Moesin) knockout mice, these mice were housed in metabolic cages and monitored following cell swelling (known to inhibit NCC2). The phosphorylation of NCC in WT at 10, 20 and 30 min decreased from 1±0.01 to 0.8±0.05, 0.8±0.05 and 0.8±0.09 respectively.

Conclusions: We conclude that in WT higher NCC expression in females correlates with activity; the gender-specific difference in activity is absent in AT1a−/− mice. The findings are consistent with less reliance on the renin-angiotensin system for BP maintenance in females. Funding: NIDDK Support

TH-PO503
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for the measurement of urinary excretion of electrolytes. These mice were sacrificed to
assess the effect of tacrolimus on the renal mRNA and protein expression of calcium-transport proteins: the apical transient receptor potential cation channel-V (TRPV5) and basolateral plasma membrane Ca2+ ATPase (PMCA) and basolateral sodium-calcium exchanger (NCX1). Regulatory proteins including: cytosolic Ca2+ binding protein calcibindin-D (D28k), calcineurin and calcinerin were also investigated. Male C57BL/6J mice of 6-8 weeks age were treated with vehicle or tacrolimus (2mg/kg/day/ I.P) for 2 weeks. Quantification of mRNA expression was determined by qPCR and protein levels were quantified by Western blotting. Values are presented as mean fold changes relative to controls ± S.E.M.; statistical significance was calculated using
unpaired t-test.

Results: FK506 significantly increased renal mRNA expression of TRPV5 (1.48±0.11, p<0.01); mRNA expression of the other transport-proteins: PMCA1, PMCA4 and NCX1, was not significantly different. FK506 significantly decreased mRNA expression of D28k (0.60±0.10, p<0.05), but changes in calcinerin was not observed. Furthermore, FK506 caused no change in the expression of TRPV5 but significantly increased the protein levels of PMCA (3.02±0.24, p<0.0001) and NCX1 (2.76±0.27, p<0.001). Although the protein abundance of the regulatory proteins: D28k and Cax, showed no significant difference after FK506 treatment, a decreasing trend post-FK506 treatment was observed in D28k.

Conclusions: These data are not compatible with FK506 induced hypercalciuria arising from altered calcium transporter levels in the distal convoluted tubule. The increase in the protein abundance of PMCA and NCX1 may be due to the removal of the inhibitory effect of calcineurin and dysregulated protein kinase C signalling.

TH-PO503

Urokinase-Type Plasminogen Activator Is Not Required for Edema Formation in Experimental Nephrotic Syndrome

Jasminka, 1,2
Leeds Teaching Hospitals, United Kingdom; 3Fresenius Medical Care, Elizabeth
1,2
Peter 1Heartlands Hospital, United Kingdom; 2Leeds Teaching Hospitals, United Kingdom; 3Fresenius Medical Care, Germany.

Background: Edema formation in nephrotic syndrome is thought to arise from increased urinary excretion of electrolytes. These mice were sacrificed to

Results: Our results suggest that moesin, but not radixin, plays an important role in the regulation of sodium reabsorption in the TAL, possibly due to the regulation of membrane localizations of NCC2.

Conclusions: Although BCM data should be used with caution in patients that differ significantly from the population used to develop the models, these results suggest that the device can be used in children.

TH-PO506

The Effect of Tacrolimus on Distal Renal Calcium Transporter Expression

Methods: This study investigated the effect of tacrolimus on the renal mRNA and protein expression of calcium-transport proteins: the apical transient receptor potential cation channel-V (TRPV5) and basolateral plasma membrane Ca2+ ATPase (PMCA) and basolateral sodium-calcium exchanger (NCX1). Regulatory proteins including: cytosolic Ca2+ binding protein calcibindin-D (D28k), calcineurin and calcinerin were also investigated. Male C57BL/6J mice of 6-8 weeks age were treated with vehicle or tacrolimus (2mg/kg/day/ I.P) for 2 weeks. Quantification of mRNA expression was determined by qPCR and protein levels were quantified by Western blotting. Values are presented as mean fold changes relative to controls ± S.E.M.; statistical significance was calculated using unpaired t-test.

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TH-PO507
The Effect of Sodium Nitrite Infusion on Renal Variables, Brachial and Central Blood Pressure during Enzyme Inhibition by Allopurinol, Enalapril or Acetazolamide in Healthy Subjects: A Randomized, Double-Blinded, Placebo-Controlled, Cross-Over Study
Jeppe B. Rosenback, Erling B. Pedersen, Jesper N. Bech. Univ Clinic in Nephrology and Hypertension, Dept of Medical Research, Regional Hospital West Jutland and Aarhus Univ, Denmark.

Background: Sodium nitrite (NaN3) causes vasodilatation, presumably by enzymatic conversion to nitric oxide (NO). Several enzymes with nitrite reducing capabilities have been discovered in vitro, but their relative importance in vivo has not been investigated. We aimed to examine the effects of NaN3 on hemodynamics, fractional sodium excretion (FENa), free water clearance (CH2O), and urinary excretion rate (UER) of cyclic guanosine monophosphate (cGMP) and nitrite and nitrate (NOx). Subjects were urine and orally water-loaded throughout the examination day.

Results: After 90-120 min of NaN3 infusion, we observed an increase in FeNO, heart rate, UER of NOx, and a decrease in Ceu, UER of cGMP, and brachial systolic BP irrespective of pretreatment. We observed a consistent trend towards a reduction in central systolic BP which was only significant after allopurinol. An increase in GFR was only observed after placebo.

Conclusions: This study shows a BP lowering and natriuretic effect of NaN3 regardless of preceding enzyme inhibition. GFR was increased by NaN3 infusion, when no enzymes were inhibited the decrease in UER of cGMP indicates little or no conversion of nitrite to NO, thus the effect of NaN3 does not seem to be mediated by NO generation.

Funding: Government Support - Non-U.S.

TH-PO508
Generation of p62/SQSTM1 (p62) KO Cell Lines Using CRISPR/Cas9 -The Role of WNK1 Regulation by Changes of Extracellular Potassium Concentration - Yutaro Mori,1 Shiranto Manda1,1 Takayasu Mori,1 Eisei Sohara,1 Tatematsu R1, Shinichi Uchida.1 1Dept of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan; 2Div of Nephrology, Tachuiora Kyodo General Hospital, Tachuiura, Ibaraki, Japan.

Background: We reported that KLHL3 binds to WNK4 and Cullin3 (CUL3) and ubiquitinate WNK4 and that the impaired WNK4 ubiquitination and degradation cause human hypertensive disease through the activation of WNK-OSR1/SPAK-NCC cascade. We also discovered that p62/SQSTM1 (p62), an autophagic adaptor protein, binds to WNK4-KLHL3 complex and is degraded together by selective autophagy. However, the physiological role of autophagic degradation of WNKs remained to be determined. Here, we generated p62 knockout (KO) cell lines by using CRISPR/Cas9 system and investigated the physiological role of selective autophagy in WNKs degradation.

Methods: We generated p62 KO HEK293T cell lines by using CRISPR/Cas9 system and p62 KO HEK293T cells were incubated with 5mM NaN3 for 4h.

Results: We designed the guide RNA targeting the exon 3 of p62 gene. We transfected HEK293T cells with the guide RNA expression vector and Cas9 vector. By single colony isolation after transfection, some hetero or homo KO cell lines were obtained. We confirmed that expressed WNK4 and KLHL3 protein level was dramatically increased in p62 KO cells. In wild-type HEK293T and COS7 cells, exposure to low potassium induced increased WNK1 expression, and high potassium medium decreased. However, in p62 KO and KD cells, WNK1 changes were partially canceled compared with wild-type.

Conclusions: We succeeded the generation of p62 KO cell lines. We confirmed that p62 degraded WNK4-KLHL3 complex by selective autophagy. Furthermore, this degradation system may regulate WNK expression under changes of extracellular potassium concentration.

TH-PO509
Three-Layered Proteomic Analysis of MAGED2 Signaling
Markus M. Rinsch1, Malte P. Bartram,1 Thomas Benzing,1 Robert A. Fenton,2 Martin Könhoff,2 Bodo B. Beck.1 1Internal Medicine, Univ Hospital Cologne, Cologne, Germany; 2Dept Biomedicine, Aarhus Univ, Aarhus, Denmark; 3Univ Children's Hospital, Philips Univ Marburg, Germany; 4Human Genetics, Univ Hospital Cologne, Cologne, Germany.

Background: Loss of function mutations in the X-chromosomal MAGED2 gene were recently discovered as a novel cause for X-linked antenatal Bartter’s syndrome and polyhydramnios. The antenatal Bartter’s syndrome was severe but completely resolved within a few weeks after birth. Staining of a fetal kidney from a patient with a truncating mutation in MAGED2 revealed decreased total and apical abundance of the NKCC2 and NCC protein. Cell culture studies demonstrated impaired maturation of the NKCC2 and NCC protein in the absence of MAGED2.

Methods: To investigate the function of MAGED2 in an unbiased manner, we performed a three-layered proteomic analysis. First, we analyzed the interactome of native MAGED2 in HEK293T cells. We also analyzed the interactome of wild-type (WT) and mutant (R446C)-MAGED2 when overexpressed in HEK 293T cells. Finally, we analyzed the effect of MAGED2 knockout on the proteome and phosphoproteome.

Results: We performed an initial interactomic analysis of MAGED2 naturally expressed in HEK293T cells using two different antibodies. We found that MAGED2 interacts with the nuclear proteins NAP1L1, NAP1L2, and the stimulatory G-protein Galphai (gene symbol: GNAS). Next, we expressed tagged WT- and R446C-MAGED2 in HEK293T cells. The R446C mutant was not stable as compared to the WT MAGED2. In interactomic analysis, both WT- and R446C-MAGED2 were found to interact with NAP1L1 and NAP1L2. MAGED2 WT, but not R446C-MAGED2 interacted with GNAS and Hsp40. Cell culture studies confirmed the involvement of MAGED2 in controlling G-protein coupled receptor signaling. Proteomic and phosphoproteomic analyses of cells with MAGED2 knockout demonstrated that several candidate proteins and substrates are controlled by MAGED2.

Conclusions: Our analyses suggest that MAGED2 could be a modulator of GNAS function. During renal development, sensitivity of adenylate cyclase increases. To understand the transient phenotype, the role of MAGED2 in controlling cAMP signaling in the distal nephron needs to be elucidated in greater detail.

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

TH-PO510
Free Vitamin D May Be Altered during Chronic Kidney Disease
Delia Bischohra, Marie-Christine Carlier, Laetitia Koppe, Mathilde Nouvier, Maurice Laville, Beritille Pommer, Denis Fouque, Solernei Pelletier. Univ de Lyon, Lyon, France.

Background: Most chronic kidney disease (CKD) patients suffer from 25OHD vitamin D (25OHD) deficiency, which might contribute to adverse health outcomes. Because vitamin D binding is altered during CKD, it has been proposed that serum free 25OHDi vitamin D better reflects vitamin D metabolism than total 25OHDi vitamin D. We aim to evaluate whether serum free 25OHDi vitamin D varies regarding the different stages of CKD, in comparison with total 25OHDi vitamin D.

Methods: We prospectively assessed 34 CKD patients during a glomerular filtration rate measurement (GFR) by inulin clearance. We measured serum free 25OHDi vitamin D by ELISA (DiaSource, Leuven, Belgium) and total 25OHDi vitamin D by immunoluminometry (DiaSorin, Italy).

Results: Patients were aged 54.7±13.6 yr, 44% were males. Mean GFR was 59±26 ml/ min/1.73m2, serum total 25OHDi vitamin D was 59.9±27.5 mg/ml and serum free 25OHDi vitamin D was 1.96 mg/ml. We found a strong association between free 25OHDi vitamin D and total 25OHDi vitamin D (r=0.88, p<0.001). There was no correlation between free 25OHDi vitamin D and GFR below 60 ml/min/1.73m2 significantly declined with GFR decrease (r=-0.34, p=0.048). Of interest, the ratio free/total 25OHDi vitamin D strongly decreased with the decline of kidney function (r=-0.55 p<0.001). We did not find any relationship between free 25OHDi vitamin D and measures of mineral metabolism.

Conclusions: This pilot study suggests that vitamin D bioavailability may be reduced in advanced CKD. The serum level of total 25OHDi vitamin D may indeed mask low free 25OHDi vitamin D and inadequate correction of vitamin D deficiency. Free 25OHDi vitamin D may represent a new target for treatment adaptation.

TH-PO511
Effect of Vitamin D Therapy on CKD-MBD Biomarkers in CKD: A Post Hoc Analysis of the PACE Study
Stuart M. Sprague,1 Ying Zhou,1 Mark D. Faber,1 Rosemary Coyne.1 NorthShore Univ HS-Univ of Chicago; 2Henry Ford Hosp; 3Washington Univ.

Background: PACE, a 24 week randomized study comparing calcitriol (Calci) and paricalcitol (Pari) in CKD stage 3 & 4. Both Calci and Pari similarly decreased PTH, with minimal effects on Ca and Phos. Few studies have evaluated the effect of VDRA therapy on other mineral biomarkers in CKD. Therefore, a post hoc analysis of biomarkers was performed in a subgroup of subjects at baseline and week 24.

Methods: PACE, an open label, active comparator, multi-center, parallel group, phase 4 study of Pari vs Calci for suppression of PTH in CKD stages 3 & 4. Of the 110 original subjects, serum was available for 76 (38 in each group) for analysis of FGF23, sclerostin, bone specific alkaline phosphatase (BSAP), tartrate resistant acid phosphatase (TRAP), stimulated osteocalcin (OC), and 1,25 vitamin D (1,25D). The effect of therapy on their serum levels were analyzed.

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

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Results:

<table>
<thead>
<tr>
<th></th>
<th>Calci</th>
<th>Pari</th>
<th>Calci vs Pari</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>0.34±0.07</td>
<td>&lt;0.001</td>
<td>0.36±0.07</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>-0.68±0.07</td>
<td>&lt;0.001</td>
<td>-0.84±0.07</td>
</tr>
<tr>
<td>1,25D (pg/mL)</td>
<td>4.95±5.59</td>
<td>0.416</td>
<td>21.84±6.20</td>
</tr>
<tr>
<td>FGF23 (R/U mL)</td>
<td>184.4±45.2</td>
<td>0.001</td>
<td>190.8±44.4</td>
</tr>
<tr>
<td>BSAP (μg/L)</td>
<td>-3.69±2.96</td>
<td>0.0007</td>
<td>-2.96±2.97</td>
</tr>
<tr>
<td>TRAP (ng/mL)</td>
<td>-1.08±0.20</td>
<td>0.0001</td>
<td>-0.73±0.20</td>
</tr>
<tr>
<td>OC (ng/mL)</td>
<td>-16.40±8.95</td>
<td>0.087</td>
<td>-17.38±9.70</td>
</tr>
<tr>
<td>Sclerostin (pg/mL)</td>
<td>88.2±31.5</td>
<td>0.008</td>
<td>152.3±135.1</td>
</tr>
</tbody>
</table>

*Log transformed

**Conclusions:** Calci and Pari had comparable actions on biomarkers of bone activity, including significant increases in Ca, FGF23, and sclerostin, with significant suppression of bone turnover markers PTH, TRAP, BSAP, and a trend toward reducing OC. Pari, but not Calci, significantly increased 1,25D. Except for the difference between Calci and Pari on 1,25D, there was no differential effects on multiple biomarkers of these agents in a 6-month prospective clinical trial treating SHPT in patients with CKD.

**Funding:** Pharmaceutical Company Support - AbbVie

TH-PO512

Modified-Release Calcidiol Is Effective in African-American and Non-African-American Patients with Stage 3-4 CKD, Secondary Hyperparathyroidism and Vitamin D Insufficiency

Stuart M. Sprague,1 Stephen A. Strugnell,2 Joel Z. Melnick,1 Martin P. Petkovich,1 Charles W. Bishop.2

1NorthShore Univ HealthSystem, Evanston, IL; 2OPKO Health, Miami, FL; 3Queen’s Univ, Kingston, ON, Canada.

**Background:** Current treatments for vitamin D insufficiency (VDI) and related secondary hyperparathyroidism (SHPT) in stage 3-4 CKD may influence bone turnover pathways. Here we examined the efficacy of oral modified-release calcidiol (MRC) for treating VDI and SHPT.

**Methods:** Two identical, randomized, double-blind, placebo-controlled trials were conducted in 429 subjects (138 AA, 291 non-AA) with stage 3 or 4 CKD. MRC treated to 60 μg/d, as needed, to lower plasma iPTH. Changes in plasma iPTH, serum 25(OH)D, and 1,25(OH)D levels were measured.

**Results:** MRC increased mean serum 1,25D levels by 16 pg/mL in AA subjects, and by 25.2% (139 to 104 pg/mL) in non-AA subjects (p < 0.05 for both relative to placebo). MRC reduced mean plasma iPTH by 15.7% (from 153 to 129 pg/mL) in AA subjects, and from 20.3 to 69.6 ng/mL in non-AA subjects (p < 0.001); levels in placebo-treated subjects declined slightly. MRC reduced mean plasma iPTH by 15.2% (from 153 to 129 pg/mL) in AA subjects, and from 20.3 to 69.6 ng/mL in non-AA subjects.

**Conclusions:** MRC was effective for correcting VDI and reducing iPTH in both AA and non-AA subjects with stage 3-4 CKD.

**Funding:** Pharmaceutical Company Support - OPKO Health

TH-PO513

Cholecalciferol Supplementation and MBD-Related Parameters in Hemodialysis Patients - A Randomized Controlled Trial

Yoshitsugu Hamano,1 Takayuki Hamano,1 Yusuke Sakaguchi,1 Akhiro Shimomura,2 Yoshitaka Isaka.1

1Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 2Univ of California Irvine.

**Background:** Prior studies have shown that vitamin D receptor activators (VDRA) reduce albuminuria beyond the placebo effect, and that the anti-albuminuric response to VDRA treatment is not Calci, significantly increased 1,25D. Except for the difference between Calci and Pari on 1,25D, there was no differential effects on multiple biomarkers of these agents in a 6-month prospective clinical trial treating SHPT in patients with CKD.

**Funding:** Pharmaceutical Company Support - OPKO Health

TH-PO514

Impact of Genetic Variants in DBP, CYP2R1, CYP24A1, and VDR on Serum 25-Hydroxyvitamin D Levels and Cholecalciferol Supplementation in Hemodialysis Patients

Yoshitsugu Hamano,1 Takayuki Hamano,1 Yusuke Sakaguchi,1 Akhiro Shimomura,2 Yoshitaka Isaka.1

1Osaka Univ Graduate School of Medicine; 2Univ of California Irvine.

**Background:** Genetic variants in vitamin D-related genes have been linked to serum 25(OH)D levels and the effect of cholecalciferol (VD3) supplementation. However, still unclear whether these findings can be extrapolated to hemodialysis population where vitamin D deficiency is frequently observed.

**Methods:** This is a post-hoc analysis of a double-blind RCT of VD3 supplementation in MHD patients. A total of 96 patients were randomly assigned to either twice-weekly 3,000 IU VD3, monthly VD3 (equivalent to 9,000 IU/week), twice-weekly placebo, or monthly placebo. Of those, 89 (93%) provided informed consent to this gene study. We put each generic variant in DBP (rs7041, rs12512651, and rs2282679), CYP2R1 (rs10741465) and rs2066793), CYP24A1 (rs2209314), and VDR (rs11568820) into multivariate linear regression model with adjustment for age, sex, and season of blood draw ignoring the administration intervals.

**Results:** Baseline serum 25(OH)D levels were median 11 (8–14) ng/mL. The T allele at rs11568820 was associated with 1.12 (95%CI, 1.01–1.24) times higher serum 25(OH)D levels per allele while alleles in the other candidate variants did not show significant association. Median (IQR) change in serum 25(OH)D levels was 2.0 (1.0–5.1) ng/mL in the group and 3.5 (8.4–18.8) ng/mL in the VD3 group at Month 3, and none of genetic variants did not significantly modify the effect of VD3 on serum 25(OH)D levels.

**Conclusions:** Patients with the T allele at rs11568820 had slightly lower serum 25(OH)D levels but the effect of VD3, supplementation was not modified by these genetic variants in MHD patients.

**Funding:** Pharmaceutical Company Support - Molecular Physiological Chemistry Laboratory, Inc., Private Foundation Support

TH-PO515

Baseline 25-Hydroxyvitamin D Level and the Anti-Albuminuric Response to Vitamin D Receptor Activation in Patients with Chronic Kidney Disease

Maarten A. de Jong,1 Charlotte A. Keyzer,1 Fenna van Breda,1 Marc G. Vervoort,2 Gozewijn Dirk Lavermans,1 Marc H. Hemmelder,1 Wilbert M. Janssen,1 Hiddo Jan Lambers Heerspink,1 Stephen J.L. Bakker,1 Gerjan Navis,3 Martin H. De Bore,1 Div of Nephrology, UMC, Groningen, Netherlands; 2Dept of Nephrology, VUmc, Amsterdam, Netherlands; 3Dept of Internal Medicine, ZGT, Almelo, Netherlands; 4Dept of Internal Medicine, MCL, Leeuwarden, Netherlands; 5Dept of Internal Medicine, Martini Hospital, Groningen, Netherlands; 6Dept of Pharmacology, UMC, Groningen, Netherlands.

**Background:** Vitamin D receptor activators (VDRA) reduce albuminuria beyond RAAS-blockade; it is unclear whether this effect is similar among vitamin D sufficient and deficient individuals. We studied whether baseline 25(OH) vitamin D status determines the anti-albuminuric response to VDRA treatment.

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

Underline represents presenting author.
**TH-PO516**

**Effect of Vitamin D Receptor Activation and Sodium Restriction on FGF23 Propensity and Fibroblast Growth Factor 23: The Virtue-CKD Trial**


**1**Div of Nephrology, UMCG, Groningen, Netherlands; 2Dept of Nephrology, VUMC, Amsterdam, Netherlands; 3Dept of Pathology, UMCN, Groningen, Netherlands; 4Div of Nephrology, Inselspital, Bern, Switzerland.

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

**Background:** Vitamin D receptor activators (VDRA) reduce albuminuria but also increase FGF23 levels and vascular calcification. To address whether these effects are linked, we studied the effect of VDRA on FGF23 and calcification propensity in relation to its efficacy (i.e. albuminuria reduction).

**Methods:** This is a posthoc analysis of a double-blind, randomized, cross-over trial (NTR2898) in patients with stage 1-3 CKD (eGFR 67±22) and albuminuria >300 mg/d, treated with ramipril (10 mg/d) throughout plus four 8-week study periods: VDRA (paricalcitol, 2 µg/day, PARI), or placebo (PLAC) combined with a regular (LS, 50 mmol/d Na+) or low-sodium (LS, 50 mmol/d Na+) diet. Patients >95% VDRA compliant were included (N=34) and 25(OH)D as mean±SD. Compliance to PARI was >95% in all patients.

**Results:** Plasma 25(OH)D was 21.2±9.1 ng/mL during LS+PLAC and did not change between study periods (P>0.90). Notably, the changes in FGF23 (LS+PLAC) were 25(OH)D dependent: with LS+PARI (1177[715;1939]mg/d), but increased FGF23 (113[79;137] to 140[104;185] RU/mL, P=0.01 vs PLAC). There was no association between baseline albuminuria and the anti-albuminuric effect of PARI during LS (r=0.03, P=0.01) or LS (r=0.10, P=0.52). Similar findings were in regression models adjusted for baseline albuminuria and FGF23 rU/mL: (LS: stb=0.22, P=0.25; LS: stb=0.11, P=0.63).

**Conclusions:** The anti-albuminuric response to VDRA is independent of baseline albuminuria, suggesting that VDRA therapy should not be restricted to vitamin D-deficient patients.

**TH-PO517**

**FGF23 and Inflammatory Markers Blood Levels Decrease with Paricalcitol and Atorvastatin Combined Treatment in Hemodialysis Patients with Tunnelled Central Venous Catheters: The SPENARC Study (NCT 1820767)**

Ricardo Mouzo, Valter Ruggiero Lombardi, Jose Carlos Diez Baylon, Herless Rodrigo Avelanedas Campos, Fernando Simal, Jose Panagia De la Riva, Ana Tierra, Jorge Estfan Kasabiyi, Carmen Perez Nieto.

1Nephrology, Hospital El Bierzo, Ponferrada, Leon, Spain; 2Laboratory, CODEBL, A Coruña, Spain; 3Hemodialysis Unit, PONFEDIAL, Ponferrada, Leon, Spain; 4Nephrology, Hospital El Bierzo, Leon, Spain.

**Background:** The aim of the current study was to evaluate the effect of different oral treatments, paricalcitol (P), paricalcitol plus atorvastatin (P+A), and atorvastatin (A) alone on FGF23 and pro-inflammatory cytokines/oxidative stress blood markers.

**Methods:** Patients (age 71 ±16) in Hemodialysis (HD) treatment 3 times per week for 48 ±64 months were randomized to a 12 weeks period study. Group 1 (n=10) was treated with P; Group 2 (n=11) was treated with P+A; Group 3 (n=9) received A alone. Blood samples were collected two weeks before treatment (T0), and during T12 (T2). During T12, patients treated with P+A (n=11) were treated with P; patients treated with P (n=10) were treated with P+A. A diminution in IFN-γ, IL-1β, IL-2 and IL-5 was also noted, mainly in Groups 1 and 2, and also as in COX-2 p=0.012 (T0 vs T12).

**Results:** It was well known that the administration of vitamin D analogues to HD patients was associated with improved survival despite an increase of FGF23 serum levels. This apparent paradox is not observed in our CT where the combined treatment with P+A to HD patients reduces FGF23 levels and elicits an early and significant decrease of inflammation and oxidative stress. These results could be of interest in the approach to atherosclerotic disease in HD patients.

**Funding:** Pharmaceutical Company Support - Abbvie

**TH-PO518**

**Let-7 and microRNA-148 Regulate Parathyroid Hormone Levels in Secondary Hyperparathyroidism**

Idlo Z. Bakker, Maarten A. de Jong, Josep Leví, Yosef Levi, Gerald Wasserman, Tallay Naveh-Manuy, Nephrology, Hadassah Hebrew Univ Medical Center, Jerusalem, Israel.

**Background:** Secondary hyperparathyroidism (SHP) commonly complicates chronic kidney disease (CKD) and associates with morbidity and mortality. MicroRNA (miRNA) are small RNAs that regulate gene expression. Parathyroid specific deletion of Dicer that mediates the final step of miRNA maturation showed that miRNA are essential for the increase in serum PTH during both acute and chronic hypercalcemia, uremia and the hyperplastic process in SHP.

**Methods:** We profiled miRNAs in parathyroid from SHP models and CKD patients by miRNA deep-sequencing. We demonstrated the function of specific miRNA using antagonizing oligonucleotides in vivo in normal and CKD rats and in vitro in parathyroid organ cultures.

**Results:** miRNA deep-sequencing showed that human, rat and mouse parathyroids share similar profiles. Parathyroids from SHP and normal rats segregated based on their miRNA expression profiles, and a similar finding was observed in humans. We identified specific parathyroid miRNAs that were dysregulated in experimental SHP, including miR-29, miR-21, miR-148, miR-30 and miR-141 (up-regulated) and miR-10, miR-125 and miR-25 (down-regulated). Importantly, inhibition of the parathyroid abundant let-7 family increased PTH secretion in normal and CKD rats, as well as in parathyroid organ cultures. Constitutive inhibition of the up-regulated miR-148 family prevented the increase in PTH in CKD rats and decreased secreted PTH in parathyroid cultures.

**Conclusions:** The evolutionary conservation of abundant miRNA and their regulation in SHP indicates their importance for parathyroid function and the development of SHP. Specifically, let-7 and miR-148 antagonism modified PTH secretion in SHP, and let-7 and miR-148 in parathyroid organ cultures. Our findings suggest a role for miRNA in parathyroid physiology and disease. They may be utilized for therapeutic interventions aimed at altering PTH expression in diseases such as osteoporosis and SHP.

**TH-PO519**

**The Down-Regulated Vitamin D Receptor Involves in the Parathyroid Glands Hyperplasia via Nuclear Factor-κB Pathway Activation**

Sen Kan, Qian Zhang, Minmin Zhang, Jing Chen. Div of Nephrology, Huashan Hospital, Fudan Univ, Shanghai, China.

**Background:** Vitamin D receptor (VDR) plays a key role in the parathyroid gland (PG) hyperplasia of secondary hyperparathyroidism (SHPT). However, the mechanism is still unclear. Our study aimed to explore the role of nuclear factor-kappa B (NF-κB)-pathway in parathyroid hyperplasia, and the correlation between VDR and NF-κB pathway in growth of parathyroid.

**Methods:** Parathyroid gland samples obtained from hemodialysis patients who accepted the parathyroidectomy surgery were divided into diffuse hyperplasia and nodular hyperplasia according to the H.E staining. Sham-operated rats were fed with the normal diet. 5,6-nitroenemopritides were fed with a high phosphate diet and treated with NF-κB inhibitor PDTC or calcitriol. Rats were sacrificed to collect the blood and parathyroid samples after 3 months. The expressions of PCNA, VDR, and activation of NF-κB pathway were detected in the rats treated with NF-κB pathyway in parathyroid and in the sham-operated group. The expressions of PCNA, VDR and activation of NF-κB pathway in the rats treated with NF-κB inhibitor or calcitriol were detected in the 5,6-nitroenemopritides fed rats and the rats treated with calcitriol. The expressions of PCNA, VDR and activation of NF-κB pathway in the rats treated with NF-κB inhibitor or calcitriol were detected in the 5,6-nitroenemopritides fed rats and the rats treated with calcitriol. The expressions of PCNA, VDR and activation of NF-κB pathway in the rats treated with NF-κB inhibitor or calcitriol were detected in the 5,6-nitroenemopritides fed rats and the rats treated with calcitriol.

**Results:** The activation of NF-κB pathway was significantly increased in nodular hyperplasia PGS than diffuse PGS in SHPT patients (P<0.05), the activated NF-κB p65 positive cell were (32.2±5.9)% and (59.5±5.9)% respectively. 5,6-nitroenemopritides rats fed with high phosphate diet showed a notable reduced serum PTH, down-regulated expression of PCNA and activation of NF-κB pathway in parathyroid in vivo in vitro, implying roles for these miRNA in SHP. Our studies show that let-7 members restrict PTH secretion, while miR-148 members promote secretion. In CKD, the expression of parathyroid let-7 and the increase in miR-148 members would contribute to the development of SHP. Our findings suggest a role for miRNA in parathyroid physiology and disease. They may be utilized for therapeutic interventions aimed at altering PTH expression in diseases such as osteoporosis and SHP.
TH-PO520

Hypermethylation of the CaSR and VDR Genes in the Parathyroid Glands in Chronic Kidney Disease Rats with High Phosphate Diet
Taketo Uchiumi, Sakoko Kamejima, Ichiro Okhidoko, Takashi Yokoo. Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.

Background: Chronic kidney disease (CKD) disrupts mineral homeostasis and its representative pathosis is defined as secondary hyperparathyroidism (SHPT). SHPT occurs during the early course of progressive renal insufficiency, and is associated with mortality and cardiovascular events. SHPT causes reduction of calcium-sensing receptor (CaSR) and vitamin D receptor (VDR) in the parathyroid glands during CKD. However, the precise mechanism of CaSR and VDR reduction is largely unknown.

Methods: CKD was induced through two-step 5/6 nephrectomy, then CKD rats and sham-operated rats were maintained for 8 weeks on diets containing 0.7% phosphorus (normal phosphate) or 1.2% phosphorus (high phosphate). In gene expression analysis tagman probes were used for quantitative real-time polymerase chain reaction. CaSR and VDR protein expressions were analyzed using immunohistochemistry. DNA methylation analysis was performed using a restriction digestion and quantitative PCR.

Results: CaSR and VDR mRNA were reduced only in CKD rats fed the high phosphorus diets (CKD HP), then CaSR and VDR immunohistochemical expressions were compatible with gene expression assay. SHPT was observed only in CKD HP rats. Furthermore, CKD HP rats showed the hypermethylation in CaSR and VDR genes; however, the percentage methylation of both genes was low.

Conclusions: Although CaSR and VDR hypermethylation was demonstrated in PTGs of CKD HP rats, the extent of hypermethylation was insufficient to support the relevance between hypermethylation and down-regulation of gene expression because of the low percentage of methylation. Consequently, our data suggest that mechanisms, other than DNA hypermethylation, were responsible for the reduction in mRNA and protein levels of CaSR and VDR in PTGs of CKD HP rats.

TH-PO521

Intact Parathyroid Hormone Is Associated with Increased Risk of Death But Not Fragility Fracture in Patients with Chronic Kidney Disease
Alex R. Chang, Amanda Young, Ion D. Bucaloiu, James E. Hartle, Morgan Grams. Geisinger Health System; Johns Hopkins Univ.

Background: We evaluated the association between iPTH with risk of incident fragility fracture for secondary hyperparathyroidism and fragility fractures. Little is known about the relationship between intact parathyroid hormone (iPTH) and adverse outcomes in CKD patients.

Methods: Patients with chronic kidney disease (CKD) are at increased risk for secondary hyperparathyroidism and fragility fractures. We evaluated the association between intact parathyroid hormone (iPTH) and adverse outcomes in CKD patients.

Results: Median values (interquartile range) of eGFR and iPTH were 40.8 (30.0-50.2) ml/min/1.73m² and 59 (38-94) pg/ml, respectively. The prevalence of iPTH ≥ 130 pg/ml (twice the upper limit of normal range) was 4.3%, 7.8%, 28.8%, and 62.7% in patients with SHPT undergoing parathyroidectomy (PTX) from a very high iPTH condition to another where hormone levels drop dramatically. The effects of PTX in bone tissue are poorly studied, especially in osteocyte-expressed proteins, such as fibroblast growth factor-23 (FGF23), dentin matrix protein 1 (DMP1), matrix extracellular phosphoglycoprotein (MEPE), sclerostin, receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG), which regulate remodeling and especially bone mineralization. Studies that evaluated bone biopsies (BB) after PTX showed low remodeling and impaired bone mineralization. The aim of this study is to characterize bone expression of FGF23, DMP1, MEPE, sclerostin, RANKL and OPG and analyze their correlations with histomorphometric analysis results of BBs of patients with SHPT pre and post PTX.

Methods: We studied 10 patients with SHPT undergoing pre bone biopsy and at 6 to 12 months after PTX. We assessed histomorphometry and osteocyte-expressed proteins by immunohistochemistry.

Results: After PTX, there was significant increase in sclerostin expression 3.91 ± 2.76 vs10.3 ± 3.14 % (p<0.001) and of OPG (0.88 (1.73-0.3 vs 1.91 (0.53-16.13) % / p<0.002). Percentage change of MEPE was inversely correlated with the time interval for mineralization (MTL) (r=0.73 / p<0.02) and directly with bone formation rate (BFR/BS) (r=0.73 / p<0.02). After PTX, six patients showed worsen mineralization and significant increase in OPG expression [1.1 (0.83-0.3) vs 2.3 (1.2-10.7) % / p<0.03].

Conclusions: Significant changes in expression of bone proteins (sclerostin, OPG and MEPE) that can potentially compromise mineralization were observed after PTX.

TH-PO522

Parathyroidectomy Effects on Bone Mineralization in Patients with Chronic Kidney Disease and Secondary Hyperparathyroidism
Geovanna Oliveira Pires, André L. Teixeira, Ivone Braga de Oliveira, Melissa Fernanda Pinheiro Santos, Luciene dos Reis, Wagner Dominguez, Aluizio B. Carvalho, Rosa M.A. Moyes, Yanda Jorgetti, Nephrology Div, Univ of Sao Paulo, Sao Paulo, SP, Brazil; Nephrology Div, Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; Medicine Master Degree Program, Univ Nove de Julho (UNINOVE), Sao Paulo, SP, Brazil.

Background: Secondary hyperparathyroidism (SHPT) is a complication of chronic kidney disease (CKD) which compromises skeletal integrity, since excessive parathyroid hormone (PTH) increases remodeling, especially resorption, and decreases bone mineral density, increasing the risk of fractures. Patients with SHPT undergoing parathyroidectomy (PTX) go from a very high PTH condition to another where hormone levels drop dramatically. The effects of PTX in bone tissue are poorly studied, especially in osteocyte-expressed proteins, such as fibroblast growth factor-23 (FGF23), dentin matrix protein 1 (DMP1), matrix extracellular phosphoglycoprotein (MEPE), sclerostin, receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG), which regulate remodeling and especially bone mineralization. Studies that evaluated bone biopsies (BB) after PTX showed low remodeling and impaired bone mineralization. The aim of this study is to characterize bone expression of FGF23, DMP1, MEPE, sclerostin, RANKL and OPG and analyze their correlations with histomorphometric analysis results of BBs of patients with SHPT pre and post PTX.

Methods: We studied 10 patients with SHPT undergoing pre bone biopsy and at 6 to 12 months after PTX. We assessed histomorphometry and osteocyte-expressed proteins by immunohistochemistry.

Results: After PTX, there was significant increase in sclerostin expression 3.91 ± 2.76 vs10.3 ± 3.14 % (p<0.001) and of OPG (0.88 (1.73-0.3 vs 1.91 (0.53-16.13) % / p<0.002). Percentage change of MEPE was inversely correlated with the time interval for mineralization (MTL) (r=0.73 / p<0.02) and directly with bone formation rate (BFR/BS) (r=0.73 / p<0.02). After PTX, six patients showed worsen mineralization and significant increase in OPG expression [1.1 (0.83-0.3) vs 2.3 (1.2-10.7) % / p<0.03].

Conclusions: Significant changes in expression of bone proteins (sclerostin, OPG and MEPE) that can potentially compromise mineralization were observed after PTX.

TH-PO523

Surgical Parathyroidectomy Confers a Survival Advantage in Chronic Kidney Disease Patients - Results of the Largest Meta-Analysis
Goldsmith David Goldsmith, Muguel Apatrini, Dimitri Cristian Sirtopel, Ionut Nistor, Dragos Scipiecau, Adrian Cavic, Guy’s and St. Thomas’ Hospitals, London, United Kingdom; Parhon Hospital, Iasi, Romania.

Background: Secondary hyperparathyroidism (SHPT) leads to progressive enlargement of parathyroid glands, and increasingly “autonomous” parathormone (PTH) secretion. Vitamin-D therapy is the usual treatment, but if refractory, patients have traditionally then had surgical parathyroidectomy (SPTX). We aimed to assess the impact of PTX in SHPT patients.

Methods: A systematic review and meta-analysis was conducted on observational and randomized controlled trials (RCTs) in adults with CKD/ESRD that evaluated the role of PTX in determining clinical outcomes. We studied CKD/ESRD patients who had undergone parathyroid surgery. The surgery itself could be (1) total parathyroidectomy with or without parathyroid transplantation, (2) total parathyroidectomy with auto transplantation, or (3) subtotal parathyroidectomy.

Results: 12 cohort observational studies, comprising 23,731 participants were included in the final analysis. The follow-up period varied between 12 and 360 months. Compared with medical treatment, parathyroidectomy significantly decreased all-cause mortality (RR 0.68 [95% CI, 0.58 to 0.78], p<0.001) in 5 observational studies that included almost 10,000 patients.

Conclusions: Surgical parathyroidectomy confers a survival advantage in chronic kidney disease patients.

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

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Table 1. Adjusted Hazard Ratios of Fracture and Mortality by Intact PTH Category

<table>
<thead>
<tr>
<th>Intact PTH Category</th>
<th>Fracture Mortality</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>RR (per 1000 Pp)</td>
<td>95% CI</td>
</tr>
<tr>
<td>&lt;15 pg/ml (n=124)</td>
<td>3.12</td>
<td>1.35 (0.90-2.02)</td>
</tr>
<tr>
<td>15-65 pg/ml (n=256)</td>
<td>25.8</td>
<td>REF</td>
</tr>
<tr>
<td>≥ 65 pg/ml (n=949)</td>
<td>24.9</td>
<td>1.10 (0.82-1.58)</td>
</tr>
</tbody>
</table>

Abbreviations: IPTH (incidence fractures), PTH (person-years), adjHR (adjusted hazard ratios)
*Adjusted for age, sex, race, smoking status, eGFR, albuminuria, blood pressure, body mass index, cardiovascular disease, medications affecting the bone (corticosteroids, diuretics, anti-psychotics, estrogens, testosterone, calcium, vitamin D, and calcium/magnesium)

Funding: NIDDK Support
Conclusions: This is the largest and most comprehensive meta-analysis of SPTX reported to date. We show that there is clinically significant beneficial effect of PTX on all-cause and CV mortality in CKD patients with SHPT. The immediate need now is for a well-conducted, independent RCT comparing surgical PTX with cinacalcet therapy examining mortality, major morbidity, to mental and physical health, quality of life, and pharmaco-economics.

TH-PO524

Downregulation of ABCG2, a Urate Exporter, by Parathyroid Hormone Enhances Urate Accumulation in Secondary Hyperparathyroidism

Takashi Watanabe,1,1 The Jikei Univ; 2Tokai Univ; 3Wakayama Medical Univ; 4St. Luke’s International Hospital; 5Ono Pharmaceutical Co., Ltd., Osaka, Japan.

Background: Hyperuricemia occurs with increasing frequency among patients with secondary hyperparathyroidism. However, the molecular mechanism by which serum parathyroid hormone (PTH) regulates serum urate levels remains unknown.

Methods: Secondary hyperparathyroidism (SHPT) model rats were created by feeding a high phosphorus diet (Ca 0.6%, P 1.2%) to the 5/6 renal nephrectomy rats. In vitro experiments were performed to investigate the effect of PTH on ABCG2 expression in Caco-2 cells.

Results: We show that, in rats with SHPT, serum urate levels are increased and urate excretion in the intestine and kidney is decreased, presumably due to the downregulation of the intestinal and renal membrane expression of a urate exporter ABCG2. These effects were predicted by the administration of the calcimimetic PTH suppressor, cinacalcet, indicating that PTH downregulates ABCG2 expression. In Caco-2 cells, the plasma membrane expression of ABCG2 was directly downregulated by PTH (1-34) and its mRNA level remained unchanged, but an inactive PTH derivative (13-34) had no effect, suggesting a posttranscriptional regulatory system acting through the PTH receptor. Additional clinical studies showed, as observed in an animal study, that treatment with cinacalcet resulted in significant reductions in serum urate levels together with decreases in PTH levels in SHPT patients who were undergoing dialysis.

Conclusions: PTH downregulates ABCG2 expression on plasma membrane, and thereby suppresses intestinal and renal urate excretion, and that the effects of PTH can be prevented by a cinacalcet treatment.

TH-PO525

Etelcalcetide (ONO-5163/AMG 416) Influences Bone Metabolism and Exhibits Stable Pharmacodynamics

Keitaro Yokoyama,1 Masafumi Fukagawa,2 Takashi Shigematsu,3 Tadao Shigematsu,4 Toru Manyama,5 Dept of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto Univ, Kumamoto, Japan; 2Dept of Nephrology, Akebono Clinic, Kumamoto, Japan; 3Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan.

Background: Exhibits Stable Pharmacodynamics. Etelcalcetide (ONO-5163/AMG 416) Influences Bone Metabolism and

Results: Etelcalcetide dose-dependently decreased the levels of TRACP-5b and intact FGF-23 after multiple dosing (Fig 1). However, the daily fluctuations of intact PTH and corrected Ca after the multiple dosing did not vary largely compared with the levels after the initial dose (Fig 2).

Conclusions: If unstable fluctuations of pharmacodynamic parameters are observed, the timing for assessment of efficacy and safety needs to be considered. Although etelcalcetide influenced bone metabolism, marked daily fluctuations of pharmacodynamic parameters did not occur. Therefore, it may not be necessary to consider the timing for its assessment.

TH-PO526

Etelcalcetide (ONO-5163, AMG 416), an Intravenously Available Agonist of the Calcium-Sensing Receptor, Effectively Controls Plasma Parathyroid Hormone Levels in a Rat Chronic Renal Insufficient Model with Secondary Hyperparathyroidism

Masakazu Konno,1 Kazutosune Harada. ONO Pharmaceutical Co., Ltd., Osaka, Japan.

Background: Secondary hyperparathyroidism (SHPT) is a complication of chronic kidney disease and end stage renal disease that results in defective Ca and P homeostasis, thereby persistently elevated levels of parathyroid hormone (PTH) in blood caused by the ongoing release of excess amounts of PTH from enlarged parathyroid glands. Currently, we have developed the first intravenously available CaSR agonist etelcalcetide (ONO-5163 or AMG 416). The objectives of these studies were to elucidate in vivo pharmacological profile and in vivo PTH lowering activity of etelcalcetide in rat 5/6 nephrectomized (5/6 Nx) model of chronic renal insufficiency with SHPT.

Methods: To determine in vivo activity, cells stably expressing human CaSR and parent cells were treated with etelcalcetide, and the intracellular Ca concentration was measured using Fura-2-AM dye. Also, the primary cultured rat parathyroid cells were treated for 24 hours with etelcalcetide, and the PTH concentrations in culture supernatant were measured. To determine in vivo activity, nine-week-old male 5/6 Nx rats were fed a special diet (10% phosphorus) to induce SHPT. Following 3 weeks on the special diet, 5/6 Nx rats were intravenously single injected with etelcalcetide (0.3, 1, 3 mg/kg). Blood were sampled predose and at 1, 6, 24, 48 hours after dosing and the plasma PTH and the serum Ca were measured.

Results: In vitro, etelcalcetide increased the intracellular Ca concentration in stably expressing human CaSR with EC50 of 0.53 μmol/L. No signaling activity was observed in parent cells. Etelcalcetide also suppressed PTH secretion from the primary cultured rat parathyroid cells with EC50 of 0.36 μmol/L. Furthermore, in vivo, etelcalcetide dose-dependently suppressed circulating levels of plasma PTH and subsequently serum Ca in rat 5/6 Nx with SHPT. Reductions of PTH and Ca were reversible.

Conclusions: We have identified etelcalcetide as a novel calcimimetics with a potent PTH lowering efficacy via CaSR-agonistic activity. Etelcalcetide will provide a new therapeutic option for the SHPT patients that may improve compliance and pill burden.

TH-PO527

Interim Analysis of a Multicenter Single-Arm Extension Study to Describe the Long-Term Safety of Eitelcalcetide (AMG 416) in the Treatment of Secondary Hyperparathyroidism in Subjects with Chronic Kidney Disease on Hemodialysis

Kevin J. Martin,1 Geoffrey A. Block,1 Sunfá Cheng,1 Botond Csáky,1 Hongjie Deng,1 K. Adi Ntoso,2 Rainer Oberbauer,3 Mariano Rodriguez,4 Dennis L. Ross,5 Glenn Matthew Cherto,6,7 St. Louis Univ SOM, St. Louis, MO; 8Denver Neph, Denver, CO; 9Agena; 10FMC Hungary, Budapest, Hungary; 11Penn Neph Assoc, Philadelphia, PA; 12Med Univ of Vienna, Vienna, Austria; 13Univ of Cordoba, Cordoba, Spain; 14KS Neph Physicians, Wichita, KS; 15Stanford SOM, Palo Alto, CA.

Background: Etelcalcetide is a novel IV calcimimetics shown to decrease parathyroid hormone (PTH) in 3 26-week (wk) phase 3 (P3) trials, with sustained efficacy in a 52-wk open label extension (OLE) trial. This follow-on OLE further characterizes the long-term safety of etelcalcetide.

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

Underline represents presenting author.

213A
Methods: Subjects (subj) enrolled from previous OLEs stayed on the same dose; subj from the 33 trial of etelcalcetide vs cinacalcet had a 4-wk washout. Etelecalcetide was titrated by 2.5mg or 5mg to a max of 15mg, at a frequency based on the site’s standard of care to achieve PTH ≥2x to ≤9x the upper limit of normal (ULN). Primary endpoint was subj incidence of adverse events (AEs). Secondary endpoints were (1) PTH ≥2x to ≤9x the ULN and (2) previous P:ULN at months (M) 6, 12, 18.

Results: 902 subj enrolled; mean time on drug was 391 days. Mean dose/session at M6, M12, M18 was 5.1, 5.3, and 5.0 mg. 82% and 41% had AEs and serious AEs (SAEs), respectively. 4% had AEs that led to stopping drug. Most common AE (>10%) was blood Ca decreased (decr) (25%); most common SAEs (≥2%) were pneumonia (4%) and sepsis (2%). Most common AEs leading to stopping drug were blood Ca decr, nausea, vomiting-4 subj each. The secondary endpoints and additional analyses results are:

<table>
<thead>
<tr>
<th>M6</th>
<th>M12</th>
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<tr>
<td>PTH ≥2x and ≤9x ULN</td>
<td>515/767 (67%)</td>
<td>434/591 (72%)</td>
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<tr>
<td>P ≤ULN</td>
<td>288/379 (39%)</td>
<td>197/333 (37%)</td>
</tr>
<tr>
<td>PTH ≥2x and ≤9x ULN AND P ≥3.5 and ≤5.5 mg/dL</td>
<td>211/716 (30%)</td>
<td>194/520 (31%)</td>
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<tr>
<td>PTH ≥2x and ≤9x ULN AND P ≥3.5 and ≤5.5 mg/dL, normal corrected Ca</td>
<td>151/701 (22%)</td>
<td>154/516 (30%)</td>
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Conclusions: (1) No new safety findings with additional long-term treatment; (2) using real-world PTH targets achieved sustained reductions in PTH and P.

Funding: Pharmaceutical Company Support - Amgen

TH-PO528

The Evaluation of the Safety and Efficacy with Etelecalcetide (ONO-5163/AMG 416: A Novel Intravenous Calcimetic) on Secondary Hyperparathyroidism (SHPT) for 52 Weeks in Japanese Hemodialysis Patients

Kazuhiko Uchiyama,1 Hiroshi Sato,2 Yuko Nakayama,3 Tomoaki Takahashi,4 Hidenori Suzuki,5 Shozo Funata,6 Koichi Kato,7 Yosuke Yamada,8 Katsunori Shoda,9 Koichi Sato,9 Ryohei Yoneda,9 Toshihito Hara,10 Enku Yoshihara,11 Jongmin Lee,12 Shigeki Omata,12 Tetsuhide Nakamura13,14

Background: Etelecalcetide had decreased serum intact PTH (iPTH) in Japanese HD patients with SHPT for a 12-week. We designed the 52-week, phase III, multicenter, open-label, single-arm study to evaluate the long-term safety and efficacy of etelcalcetide. Methods: We prescribed etelcalcetide intravenously at 3 times/week for 52 weeks.on all HD subjects with the both of serum iPTH ≥240 pg/mL and corrected calcium (cCa) level ≥8.4 mg/dL. The initial dose was 5 mg, followed by individual adjustment to dose of 2.5–15 mg to achieve Japanese serum iPTH target of 60–240 pg/mL.

Results: 191 subjects were enrolled, of whom 83.8% completed the 52-week treatment. The mean iPTH decreased (decr) (25%); most common SAEs (≥2%) were pneumonia (4%) and sepsis (2%). Most common AEs leading to stopping drug were blood Ca decr, nausea, vomiting-4 subjects each. The secondary endpoints and additional analyses results are:

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</table>

Conclusions: In clinical practice, the PTH level motivating initiation of cinacalcet therapy is frequently higher than recommended targets, including levels above 1000 pg/mL. Future research is needed to understand the impact of delaying calcimimetic treatment.

Funding: Pharmaceutical Company Support - Amgen

TH-PO529

Treatment with Cinacalcet Reduces Oxidative Stress in Hemodialysis Patients with Secondary Hyperparathyroidism

Marcin Adamczak,1 Piotr Kuczera,1 Grzegorz Machnik,2 Boguslaw Okopieć,3 Andrzej Wieczek.1

1Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland; 2Dept of Internal Medicine and Clinical Pharmacology, Medical Univ of Silesia, Katowice, Poland.

Background: It is known well that oxidative stress is one of the factors contributing to the increased mortality in patients with chronic kidney disease (CKD). Cinacalcet is used in the treatment of secondary hyperparathyroidism (SHPT). The purpose of this prospective clinical study was to assess the influence of treatment with cinacalcet on the oxidative stress in patients on hemodialysis with SHPT.

Methods: In 58 hemodialysed patients with sHPT plasma Advanced Oxygenation Products (AOPP) and total antioxidant capacity – ImAnOx (TAS/TAC) and serum antioxidant capacity (ImAnOx) significantly increased from 260 (251-270) µmol/l to 272 (264-280) µmol/l; p<0.047. After 6 months of treatment a significant, positive correlation as found between ImAnOx and the dose of cinacalcet (r=0.30; p<0.02). The also change of plasma ImAnOx during treatment with cinacalcet significantly correlated with the dose of cinacalcet ≥0.35; p<0.01. No significant correlations were found between plasma AOPP concentrations and ImAnOx and PTH, nor their changes in time.

Conclusions: 1. 6-month treatment with cinacalcet reduces oxidative stress in maintenance hemodialysis patients with sHPT 2. This beneficial effect seems to be related rather to the direct action of cinacalcet than to the decrease of serum PTH concentration.

Funding: Government Support - Non-U.S.

TH-PO530

Cinacalcet Initiation at Varying Parathyroid Hormone (PTH) Levels

Paul Dlugiewicz,1,2 Diane Reams,1,2 Kerry Cooper,1 Abhijit V. Kshirsagar,1 Brian D. Bradbury,3 Amgen Inc., Thousand Oaks, CA; 2Univ of North Carolina, Chapel Hill, NC.

Background: Despite evidence of the effectiveness of cinacalcet in managing secondary hyperparathyroidism (SHPT) related biochemistries, PTH levels are increasing over time, possibly due to delays in treatment initiation. We sought to describe real-world PTH levels and trajectories leading up to cinacalcet initiation.

Methods: Using patient-level data from a large dialysis provider merged with data from the USRDS, we identified adult new users of cinacalcet (2007-2011) from Part D prescription claims. We estimated the mean ± standard deviation of PTH levels (same assay throughout follow-up period) and the distribution across PTH categories: 150-300, 301-600, 601-900, and > 900 pg/mL. We also assessed PTH trajectories in the 12 months prior to cinacalcet initiation.

Results: We identified 21,786 patients who initiated cinacalcet during our study period. Overall, PTH levels increased steadily in the 12 months leading up to initiation of cinacalcet. We observed varying patterns of increasing versus decreasing PTH levels prior to the initiation of cinacalcet (Figure 1a). We also observed substantial variability in PTH levels at the time of cinacalcet initiation (Figure 1b).

Funding: Pharmaceutical Company Support - Amgen Inc.

TH-PO531

Disparate Actions of Paricalcitol and Cinacalcet on Parathyroid Oxyphil Cell Content in Patients with Chronic Kidney Disease

Cynthia S. Ritter, Brent W. Miller, Alex J. Brown, Eduardo Slatopolsky.1

1Div of Nephrology, Washington Univ School of Medicine, St. Louis, MO.

Background: Parathyroid (PT) oxyphil cell content increases in patients with uremia. This increase is more even enhanced in patients receiving treatment with the calcimimetic cinacalcet and/or calcitriol for hyperparathyroidism (HPT). Previously, we reported that oxyphil cells have significantly more calcium-sensing receptor (CaSR) than chief cells, supporting the hypothesis that the CaSR and, likewise, calcimetics are involved in the transdifferentiation of a chief-to-oxyphil cell type. Here, we compared the effect of the vitamin D analog paricalcitol (which is less calcemic than calcitriol) and cinacalcet on the oxyphil content in uremic patients to investigate further the genesis of oxyphil cells.

Methods: We analyzed archived H&E-stained sections of PT tissue from 28 CKD patients who underwent parathyroidectomy (PTX) for secondary HPT. Patients received the following treatment for HPT prior to PTX: no treatment (n=7), cinacalcet (n=8), paricalcitol (n=8), and cinacalcet+paricalcitol (n=5). Tissue from 4 “normal” subjects was examined. Each tissue section was digitally captured in its entirety using serial images (200x) and analyzed using Image-Pro Plus software. Oxyphilic areas were circumscribed, the area calculated and reported as % of total area of tissue for each patient.

Conclusions: Of particular interest, treatment of patients with paricalcitol does not stimulate genesis of oxyphil cells. Because the function of the oxyphil cell is not known, the question remains as to whether the genesis of oxyphil cells is favorable or unfavorable to the patient. Nevertheless, the finding two conventional treatments for HPT have disparate effects on parathyroid composition, and perhaps function, is provocative and may be useful when evaluating future drugs for HPT.

Funding: Pharmaceutical Company Support - Abbott Laboratories
Calcium Sensing Receptor Genotype and Response to Cinacalcet
Sharon M. Moe, Brian S. Decker, Leah Wetherill, Dongbiai Lai, Safia Abdalla, Jing Long, Matteo Vatta, Tatiana Foroud, Glenn Matthew Chertow 1  2
1 Indiana Univ, Indianapolis, IN; 2 Stanford, Stanford, CA.

Background: The calcimimetic cinacalcet is a calcium sensing receptor (CASR) allosteric activator, and thus polymorphisms in CASR may alter the drug therapeutic response. Genetic mutations in CASR are known to lead to diseases of mineral metabolism. We tested the hypothesis that single nucleotide polymorphisms (SNPs) in CASR alters the biochemical response to cinacalcet.

Methods: We analyzed DNA samples in the EVOLVE trial (Evaluation Of Cinacalcet Hydrochloride (HCl) Therapy to Lower CardioVascular Events (EVOLVE)), a randomized trial of 5,291 patients with secondary hyperparathyroidism on a background of usual care (calcitriol or analogues and binders). 49% of subjects in EVOLVE consented to DNA collection, and 1,852 samples were of adequate quality to be genotyped for 18 known CASR polymorphisms. All SNPs were in Hardy-Weinberg equilibrium in the European American (EA, N=1,086) and African American (AA, N=413) samples; these groups were assessed separately. The association of SNPs with baseline and change from 0 to 20 weeks in calcium, phosphorus, PTH and FGF23 was determined using PLINK.

Results: There was modest association of baseline PTH and bone alkaline phosphatase levels with CASR SNPs in the EA population (all p<0.04), but not in the AA population. In contrast, there was a modest association of baseline calcium, and FGF23 levels with CASR SNPs (all p<0.03) in the AA, but not in the EA, sample. The only CASR SNP that showed association with percent reduction in PTH after adjustment for significant covariates was rs1393199 in the EA sample (p = 0.042). Among placebo-treated patients, those with genotypes CC or CT rs1393199 had higher percent change in PTH relative to individuals with AA genotype. Cinacalcet-treated patients had approximately equal percent change in PTH, irrespective of genotype.

Conclusions: SNPs in CASR are only modestly associated with baseline CKD-MBD laboratory tests with different clinical phenotypes in EA and AA populations. Only one SNP was associated with change in PTH at 20 weeks in the EA population. This association was not seen in patients treated with cinacalcet.

Funding: NIDDK Support, Pharmaceutical Company Support - Amgen

ILI-6 knockout mouse by an adjuvant high phosphorus diet given for 3 w. FGF23 mRNA levels were analyzed by qRT-PCR in calvarial tissue, UMR106 cells and osteoblast cells, demonstrating a direct effect of IL-6 to increase FGF23 expression. Uremic IL-6 knockout mice had an impaired increase in serum FGF23 and calvarial FGF23 mRNA levels in adrenomedullin induced chronic kidney failure, compared to the marked increase in uremic wild type mice, indicating that IL-6 is also necessary for the increased FGF23 of prolonged uremia.

Conclusions: Serum IL-6 levels increase in follicle induced AKI and this precedes the increases in FGF23. DEX prevents the increase in FGF23 expression in AKI. Hyper-IL-6 acts directly on bone cells to increase FGF23. IL-6 is essential for the increased FGF23 serum levels in chronic kidney failure. Therefore, IL-6 is an important mediator of the high levels of FGF23 in both acute and chronic uremia.

TH-PO535
WNK Pathway Regulates Osteostestinal FGF23 Secretion
Olga Andrukhova, Sibel Ada, Yeliz Toluay, Dario Alesssi, Reinhold Erben 1  2
1 Dept of Biomedical Sciences, Univ of Veterinary Medicine Vienna, Vienna, Austria; 2 MRC Protein Phosphorylation & Ubiquitylation Unit, Univ of Dundee, Dundee, United Kingdom.

Background: With-no-lysine kinases (WNK) are key regulators of intracellular trafficking of ion transporters such as the Na+-Cl co-transporter (NCC) in the kidney. Chronic activation of the WNK signaling pathway by activation of the renin-angiotensin-aldosterone system (RAAS) and/or by genetic defects leads to increased renal sodium reabsorption and hypertension. We previously reported that FGF23 signaling activates WNK4 and that FGF23 and aldosterone signaling interact in the kidney.

Methods: To better understand the mechanisms underlying this crosstalk, we used cell lines of 3 (KLH3, KLH3R528H) knock-in Mutant mice in which lack of the KLH3-mediated degradation of WNKs results in a constantly activated WNK signaling pathway. In patients, this loss-of-function mutation in the RING ligase family member KLH3 leads to pseudohyppocalciteronism type II (PHAI).

Results: As expected, KLH3R528H/+ mutants exhibited a PHAI-like phenotype with hyperkalemia, hypernatremia and increased phosphorylation of NCC in the kidney. Surprisingly, KLH3R528H/− mutants also showed increased serum levels of FGF23 and increased abundance of total and phosphorylated WNK1 and NCC protein in bone. Isolated primary osteoblasts from KLH3R528H/− mutants secreted increased amounts of FGF23 in the medium as compared to wild-type (WT) cells, indicating that activation of WNK signaling in osteoblasts results in a cell autonomous increase in FGF23 secretion. Treatment of mutant osteoblasts with the WNK pathway inhibitor closantel (0.3 μM) normalized the enhanced secretion and mRNA expression of FGF23. To confirm the involvement of WNK in the physiological regulation of FGF23 secretion, we treated WT osteoblasts with aldosterone (10 nM/ml) alone or in combination with closantel. Aldosterone increased WNK phosphorylation in WT osteoblasts, demonstrating that aldosterone activates WNK signaling in osteoblasts. However, the aldosterone-induced increase in FGF23 mRNA and protein expression was abrogated by co-treatment with closantel.

Conclusions: Taken together, we identified WNK signaling as a novel regulator of FGF23 secretion in osteoblasts.

TH-PO536
Klotho Does Not Have FGF23 Independent Functions in Mineral Homeostasis
Olena Andrukhova, Jessica Bayer, Ute Zetz, Reinhold Erben
Dept of Biomedical Sciences, Univ of Veterinary Medicine Vienna, Vienna, Austria.

Background: Fibroblast growth factor-23 (FGF23) is a bone-derived hormone regulating vitamin D production and mineral homeostasis by signaling through a FGF receptor (FGFR1)/αKlotho (Klotho) complex. Whether Klotho has FGF23-independent effects on mineral homeostasis is a controversial issue.

Methods: Here, we aimed to shed more light on this controversy by comparing male and female triple knockout mice with simultaneous deficiency in Klotho and Vitamin D receptor (VDR), (FGF23/Klotho/VDR) with double (FGF23/VDR and Klotho/VDR) and single FGF23, Klotho and VDR mutants. Ablation of vitamin D signaling is known to rescue the severe phenotype of FGF23and Klotho single mutants. To prevent hypocalcemia in VDR mutants, all mice were kept on a diet enriched with calcium, phosphate and lactose.

Results: As expected, 4-week-old FGF23 and Klotho knockout mice were hypercalcemic and hyperphosphatemic, whereas VDR, FGF23/VDR and Klotho/VDR mice on rescue diet were normocalcemic and normophosphatemic. Mineral homeostasis did not differ between 4-week-old FGF23 and FGF23/VDR or double FGF23/VDR or Klotho/VDR knockout mice. Three-mo-old male and female FGF23/VDR and Klotho/VDR compound mutants were characterized by hyperphosphatemia, hyperkalemia, increased serum PTH as well as renal Ca and sodium (Na) wasting. Notably, 3-mo-old FGF23/Klotho/VDR triple knockout mice were indistinguishable from double FGF23/VDR and Klotho/VDR compound mutants in weight, serum Na, Ca, P, K, PTH as well as urinary Ca and Na excretion. Protein expression analysis revealed increased membrane abundance of
the Na-P-cotransporter NPT2a, and decreased expression of the Na- and Ca-transporting molecules NCC and TRPV5 in kidneys of FgF23/Klotho/VDR, FgF23/VDR, and Klotho/VDR mice, relative to WT and VDR mice, but no differences between triple and double knockouts. Similarly, bone mineral density remained unchanged in 4-wk-old and 3-mo-old FgF23/Klotho/VDR mice compared with FgF23/VDR and Klotho/VDR mice.

Conclusions: In conclusion, our data suggest that the main physiological function of FGF23 in vivo is its role as co-receptor for FgF23 signaling.

TH-PO537
Excessive FGF23 Drives Progression of Chronic Kidney Disease in Mice via Partially Klotho-Independent Activation of WNK Signaling
Olena Andrushkova, Svetlana Slavic, Jessica Bayer, Reinhold Erben.
1Dept of Biomedical Sciences, Univ of Veterinary Medicine Vienna, Vienna, Austria;
2MRC Protein Phosphorylation & Ubiquitylation Unit, Univ of Dundee, Dundee, United Kingdom.

Background: It is currently unclear whether elevated circulating fibroblast growth factor-23 (FGF23) causes maladaptive pathological effects in chronic kidney disease (CKD). Here, we analyzed the role of FgF23 and its co-receptor Klotho in the pathogenesis of CKD in mice by a dual approach, using genetic loss-of-function together with pharmacological inhibition models.

Methods: CKD was induced by 5/6 nephrectomy in 3-month-old wild-type (WT) mice, vitamin D receptor (VDR) mutant mice, FgF23/VDRΔ−/Δ (FgF23/VDR), and Klotho/VDRΔ−/Δ (Klotho/VDR) compound mutant mice. All mice were kept lifelong on a rescue diet enriched with calcium, phosphorus, and lactate to prevent secondary hyperparathyroidism in VDR mutant mice. Sham-operated (SHAM) mice served as controls. In addition, SHAM and CKD WT, VDR, and Klotho/VDR mice were treated with low dose anti-FG23 antibody (anti-FGF23Ab, 50 µg per mouse, two times per week) over 8 weeks.

Results: In our in vivo models, we found that high circulating concentrations of intact FGF23 activate Klotho dependent and independent with no-lysine kinase (WNK) signaling pathways in the kidney, contributing to volume overload, hypertension, hypercalcemia, cardiac dysfunction, and vascular calcification in CKD mice. Using Western blotting analysis as well as 2-photon microscopy of live 200-µm-thick renal slices prepared from WT and Klotho/VDR mice and treated with recombiant FGF23, we uncovered a novel Klotho-independent FGF23 action in the kidney, leading to FGF3 receptor 3-α and WNK1/4-mediated stimulation of distal renal tubular Ca2+ and Na+ uptake.

Conclusions: In conclusion, our study identified excessive FGF23 signaling as a major disease-modulating factor in CKD progression, promoting vascular calcification and volume overload.

TH-PO538
Oral Sodium Ferrous Citrate (Fe2) Reduces the Serum Fibroblast Growth Factor 23 Levels of Maintenance Hemodialysis Patients to the Same Extent as Ferric Citrate (Fe3) Sonoo Mizuiri, Yoshiko Nishizawa, Kazuomi Yamashita, Shigehiro Doi, Takao Masaki, Kenichiro Shigemoto.
1Ichiyokai Harada Hospital; 2Hiroshima Univ Hospital.

Background: Iron deficiency stimulates FGF23 transcription. It was reported that ferric citrate hydrate (Fe3) reduces the serum FGF23 levels of iron-deficient chronic kidney disease (CKD) patients. However, ferrous citrate hydrate is an iron-based phosphate binder and might reduce serum FGF23 levels via actions other than increasing iron stores. This study aimed to determine whether oral ferrous (Fe2) iron reduces the serum FGF23 levels of iron-deficient maintenance HD (MHD) patients.

Methods: Thirty-one MHD patients with iron deficiency were enrolled in this study. The exclusion criteria included the use of intravenous or oral iron or iron-based phosphate binders within 8 weeks. The patients’ iron stores and their serum FGF23, phosphate, calcium (Ca), intact parathyroid hormone (iPTH), albumin, and C-reactive protein (CRP) levels were examined at the baseline and after 3 months' treatment with sodium ferrous citrate.

Results: The patients’ transferrin saturation values (13.8±0.8 vs. 38.8±4.4%, P<0.0001) and serum iron (37.4±2.3 vs. 94.6±11.3 µg/dl, P<0.0001) were significantly increased after 3 months' treatment, as were serum ferritin levels (37.6±4.4 vs. 114±5.7 µg/l, P<0.0001). The iron status was associated with changes in SLR (ß=-0.13, p<0.001) and CRP (ß=0.18, P<0.001). In multivariable analysis, serum iron (ß=-0.15, p<0.001) and transferrin saturation (ß=0.18, p<0.001) were independent risk factors for mortality and allograft loss. To date, the interplay between FGF23, iron metabolism and red blood cell dynamics has not been fully evaluated.

Conclusions: Hemodialysis patients given protocol IV FCM demonstrated a fall in iron and rise in FGF23, changes not evident with IS. This suggests a differential effect of IV iron according to formulation, and different effects to people with normal renal function.

Funding: Pharmaceutical Company Support - Partial financial support for this investigator-initiated study was provided by Vifor Pharma Australia through an unrestricted grant

TH-PO540

Background: Fibroblast growth factor 23 (FGF23) regulates phosphate and vitamin D homeostasis. In renal transplant recipients (RT), an elevated level of FGF23 is an independent risk factor for mortality and allograft loss. To date, the interplay between FGF23, iron metabolism and red blood cell dynamics has not been fully evaluated.

Methods: Plasma C-terminal FGF23 was measured with enzyme-linked immunosorbent assay in stored plasma samples. Statistical analyses were performed using univariable linear regression followed by stepwise backward linear regression.

Results: We included 593 stable RTR (age 52±12 years, 53% males at 80±6.4 years after Tx). Median [IQR] FGF23 was 140 (95-219) RU/ml, ferritin was 160 (81-287) µg/l, EPO was 174 (120-245) U/L, and mean cFGF was 47±16 ml/min/1.73m2. In univariable and multivariable analysis, eGFR (ß=-0.39, P<0.001), phosphate (ß=0.23, P<0.001), EPO (ß=0.22, P=0.001), ferritin (ß=0.16, P=0.001), CRP (ß=0.13, P<0.001), and PTH (ß=0.12, P=0.001) (model R2=0.44) were identified as independent determinants of FGF23 (Table 1). Moreover, a significant interaction between EPO and hemoglobin on FGF23 was noted (p<0.02).

Conclusions: We identified serum ferritin and EPO levels as major, potentially modifiable independent determinants of serum FGF23, alongside of the known association with phosphate homeostasis. EPO was positively associated with FGF23 independent of kidney function suggesting that anemia and/or EPO resistance may play a role in the association. Furthermore, since iron status and FGF23 are inversely associated, correction of iron deficiency may be a promising target to reduce FGF23 levels in an attempt to improve outcome.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Elevations in FGF23 Precede Abrogation of Either Phosphate or Iron Homeostasis in a Mouse Model of Renal Insufficiency

Jackie A. Fretz,1 Tracy Nelson,2 Xuqi Li,1 Karin Finberg,1 Orthopaedics and Rehabilitation, Yale School of Medicine, New Haven, CT;1Pathology, Yale School of Medicine, New Haven, CT.

Background: Phosphate and iron metabolism are linked intimately through the phosphatonin FGF23. Iron status is inversely correlated to the level of circulating FGF23, and variation in iron status in individual patients correlates with decrements in FGF23. Development of anemia during chronic kidney disease is a multifactorial process, but the exact mechanisms driving its development during the early stages of renal function decline are still not completely understood.

Methods: To better understand these early events regulating the early dysfunction of iron bioavailability, phosphate balance and FGF23 we employed targeted deletion of the transcription factor Early B cell Factor 1 (Ebf1) from the kidney stromal progenitors (using Foxd1Cre). This results in a developmental abrogation of outer cortex development, and avascular kidneys with glomerulosclerosis, phosphate wasting, elevations in FGF23, and anemia. We profiled the sequential presentation of indicators of renal dysfunction (NGAL, albuminuria, hematuria, TGFβ), phosphate imbalance (PTH, 1,25(OH)2D3, serum phosphate, phosphaturia), and regulators of iron bioavailability and transport (hepcidin, transferrin, erythrocyte counts, Epo, and splenic erythropoiesis) to understand the events that initiate and drive abrogation of the phosphate, iron, FGF23 regulatory axis.

Results: Elevated intact FGF23 coincides with the earliest indicators of renal dysfunction (elevated NGAL), and precede changes in urinary phosphate wasting or changes in iron homeostasis. Histological abnormalities are apparent at postnatal day 14, but proteinuria is not apparent until day 24, with splenomegaly at day 28. Serum Epo was normal until disease was well established, at 1 month, but was preceded by transferrin loss in the urine (day 20).

Conclusions: Elevated FGF23 has been shown to negatively regulate erythropoiesis. We conclude that it is primary elevations in FGF23 that drive the subsequent perturbations of phosphate and iron homeostasis in this model, and not a primary Epo-insufficiency generated by the actions of Ebf1 within the renal stroma.

Funding: NIDDK Support

Fibroblast Growth Factor 23 Associates with Resistance to Erythropoietin-Stimulating Agents in Maintenance Hemodialysis Patients

Naoto Hamano,1 Hirotaka Komaba,1 Takahiko Wada,2 Takatoshi Kakuta,1 Masafumi Fukagawa,1 Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan;1The Inst of Medical Sciences, Tokai Univ, Isehara, Japan.

Background: A recent experimental study has shown that fibroblast growth factor 23 (FGF23) inhibits erythropoiesis through suppression of erythropoietin production and downregulation of its receptor. However, it is unknown whether high levels of FGF23 affect renal anemia in hemodialysis patients.

Methods: To assess the relationship between resistance to erythropoiesis stimulating agents (ESA) and FGF23 levels, we used baseline data from the Tokai Dialysis Cohort Study, a prospective observational study of 654 hemodialysis patients. Erythropoietin resistance index (ERI), serum intact FGF23, Fet-A, and CPP of this model.

Results: A total of 458 patients were receiving ESA at baseline and were included in the analysis. The median ERI was 6.9 IU/kg/wk/g/dl (IQR 3.9-11.4 IU/kg/wk/g/dl) and the median FGF23 was 1,955 pg/ml (IQR 572-5,263 pg/ml). Multivariate logistic regression analysis identified body mass index, serum albumin, transferrin saturation, and FGF23 (OR 1.65, 95%CI 1.01-2.71 per 10-fold increase in FGF23) as independent risk factors for ESA resistance.

Conclusions: Our findings suggest that elevated FGF23 contributes to ESA resistance in patients undergoing hemodialysis. Future research should focus on whether FGF23-lowering treatment improves control of renal anemia in end-stage renal disease.

Effect of Iron Deficient Diet on Fetuin A and FGF23 Regulation of Adriamycin-Induced CKD Model Mouse

Masanori Takaia,1 Kosei Hasegawa,1 Takayuki Miyai,2 Dept of Pediatrics, Matsuyama Red Cross Hospital, Matsuyama, Ehime, Japan;1Dept of Pediatrics, Okayama Univ Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Background: FGF23 is involved in the pathogenesis of CKD-MBD and cardiovascular disease. Deficiency of Fetuin A (Fet-A) is associated with increased arterial calcification and mortality in CKD. Fetuin-mineral complex, calciprotein particles (CPP), is increased in CKD and reflects extraosseous calcification stress. Previously, we produced a mouse model of renal anemia with FGF23 downregulation of its receptor. However, it is unknown whether high levels of FGF23 affect renal anemia in end-stage renal disease.

Methods: Upon making 6 groups (2% Fe and 2% Fe-CKD –fed a 2% Fe diet; 0.6% Fe and 0.02% Fe-CKD), we measured baseline data from the Tokai Dialysis Cohort Study, a prospective observational study of 654 hemodialysis patients. Erythropoietin resistance index (ERI), serum intact FGF23, Fet-A, and CPP of this model.

Results: A total of 458 patients were receiving ESA at baseline and were included in the analysis. The median ERI was 6.9 IU/kg/wk/g/dl (IQR 3.9-11.4 IU/kg/wk/g/dl) and the median FGF23 was 1,955 pg/ml (IQR 572-5,263 pg/ml). Multivariate logistic regression analysis identified body mass index, serum albumin, transferrin saturation, and FGF23 (OR 1.65, 95%CI 1.01-2.71 per 10-fold increase in FGF23) as independent risk factors for ESA resistance.

Conclusions: Our findings suggest that elevated FGF23 contributes to ESA resistance in patients undergoing hemodialysis. Future research should focus on whether FGF23-lowering treatment improves control of renal anemia in end-stage renal disease.

Klotho Modulates FGF23-Mediated NO Synthesis and Oxidative Stress in Human Coronary Artery Endothelial Cells

Maren Leithead-Nesler, Beatrice Richter, Jacqueline Haller, Dieter Haffner. Dept of Pediatric, Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany.

Background: Endothelial dysfunction (ED) characterized by an imbalance of NO bioavailability and ROS formation is an early hallmark of CKD, a state investigated for FGF23, membrane-bound and soluble Klotho, intracellular NO synthesis cascade, and ROS formation by p47, immunoblotting, and flow cytometry.

Methods: Membrane-bound Klotho is expressed in HCAEC, and FGF23 increases the expression of the Klotho shedding protease ADAM17, and consequently the secretion of soluble Klotho. FGF23 stimulates NO release via FGFKlotho-Akt-dependent activation of endothelial NO synthase (eNOS). Both FGFKlotho-dependent ROS formation via NADPH oxidase 2 (Nox2) and ROS degradation via superoxide dismutase 2 (SOD2) and catalase (CAT) are stimulated by FGF23. Pre-incubation with Klotho inhibitor blunt the FGF23-stimulated Akt-eNOS activation and NO synthesis, decreases ROS degradation by blocking SOD2 and CAT enzymes, whereas FGF23-stimulated ROS synthesis via Nox2 is unaffected, resulting in low NO bioavailability and increased oxidative stress.

Conclusions: Our data indicate that in the presence of Klotho, FGF23 induces NO release in HCAEC and its stimulating effects on ROS production are counterbalanced by increased ROS degradation. In states of Klotho deficiency, e.g. CKD, FGF23-mediated NO synthesis is blunted and ROS formation overrules ROS degradation. Thus, FGF23 excess may primarily promote oxidative stress and consequently endothelial dysfunction.

Solute Klotho and Mortality in Maintenance Hemodialysis Patients

Hisae Tanaka,1 Hirokata Komaba,1 Takao Sugiy1, Takahiko Wada,2 Takatoshi Kakuta,1 Masafumi Fukagawa,1 Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan;1The Inst of Medical Sciences, Tokai Univ, Isehara, Japan;2Medical Corporation Showakai, Tokyo, Japan.

Background: Klotho is a transmembrane protein that functions as a co-receptor for fibroblast growth factor 23 (FGF23). Klotho also exists as a soluble circulating protein, and recent experimental data demonstrated that soluble Klotho has multiple beneficial functions including renoprotection, prevention of vascular calcification, and inhibition of oxidative stress. However, it is unknown whether soluble Klotho levels are associated with risk of death in patients on hemodialysis.

Funding: Private Foundation Support

Parameter | Univariable analysis | Multivariable analysis
--- | --- | ---
| | std. b | p-value | std. b | p-value |
| Age | 0.09 | 0.02 | | |
| eGFR | -0.54 | <0.001 | -0.39 | <0.001 |
| Calcium | 0.04 | 0.33 | | |
| Phosphate | 0.39 | <0.001 | 0.23 | <0.001 |
| PTH | 0.19 | <0.001 | 0.12 | <0.001 |
| 25(OH) Vitamin D | 0.04 | 0.44 | | |
| Hemoglobin | -0.14 | 0.001 | | |
| Ferritin | -0.11 | 0.008 | 0.16 | <0.001 |
| Albumin | 0.02 | <0.001 | 0.22 | <0.001 |
| CRP | 0.23 | <0.001 | 0.13 | <0.001 |

TH-PO543

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Methods: We conducted a prospective cohort study of 654 maintenance hemodialysis patients (the Tokai Dialysis Cohort Study). The primary exposure variable was the baseline soluble Klotho level. The primary outcome was 3-year, all-cause mortality. Soluble Klotho levels and full-length FGF23 levels were measured using a sandwich ELISA kit (Immunological Laboratories, Co., Ltd, Gunma, Japan) and a chemiluminescence immunoassay (Kainos, Tokyo, Japan), respectively.

Results: At study enrollment, the mean (±SD) soluble Klotho level was 377± 231 pg/ml and the median (IQR) FGF23 level was 1.878 (571-4932) pg/ml. Higher levels of soluble Klotho correlated with longer dialysis duration, higher hemoglobin, higher creatinine, and lower total cholesterol; there was no correlation with serum calcium, phosphorus, parathyroid hormone, or FGF23. In univariate analysis, soluble Klotho levels were not significantly associated with risk of mortality. This result was unchanged after multivariable adjustment.

Conclusions: Soluble Klotho levels were not related to parameters of bone mineral metabolism and did not predict mortality in patients undergoing hemodialysis. Further research is required to determine whether soluble Klotho plays a role in bone disease and vascular calcification in end-stage renal disease.

Funding: Government Support - Non-U.S.

TH-PO546

Klotho and Inflammation in Early Stages of Chronic Kidney Disease

Fiewela Lukaszyk1, Mateusz Lukaszyk2, Ewa Koc-Zorawiska1, Jolanta Malyzko1,2
12nd Dept of Nephropathy and Hypertension with Dialysis Centre, Medical Univ of Bialystok, Bialystok, Poland; 2Dept of Allergy and Internal Medicine, Medical Univ of Bialystok, Bialystok, Poland.

Background: One of the major functions of Klotho is its role as an obligatory co-receptor for fibroblast growth factor 23 (FGF23). Hypothesis: The effect of Klotho FGF23 system is opposite to hypoxia-inducible factor 1α (HIF1α). The reduced expression of Klotho may contribute to a number of complications of chronic kidney disease. Similarity inflammation is also well-known risk factor of progression and complications of CKD. The aim of the study was to assess Klotho status in patients in early stages of chronic kidney disease with inflammation in correlation to inflammation parameters.

Methods: 89 patients with CKD stage 2-3A according to KDIGO were enrolled to the study and divided into two groups – with and without subclinical inflammation according to hsCRP measurements. Serum creatinine was obtained using standard laboratory methods in certified local central laboratory. Commercially available kits were used to measure FGF23, Klotho, hscRP, IL-6, and vitamin D. Analyses of the correlation of each parameter were performed using Pearson or Spearman correlation coefficients.

Results: Klotho concentration was significantly lower in patients with inflammation defined as elevated hsCRP (>10 mg/dl; p<0.01). Klotho was significantly correlated with vitamin D in all patients, however in patients with inflammation this correlation was stronger (r = 0.49, p<0.05). Similarly we observed significant correlation between Klotho and GDF-15, especially marked in patients with inflammation (r = -0.4, p<0.05). No statistically significant correlations between Klotho and FGF23 as well as inflammatory parameters such as hscRP and IL-6 have been observed. In multiple regression analysis vitamin D and GDF-15 were found to be predictors of Klotho.

Conclusions: Lower Klotho concentrations are connected with subclinical inflammation in patients with early stages of chronic kidney disease. As Klotho is linked to life expectancy, inflammation may contribute to shortened survival in CKD.

TH-PO547

The Metabolic Bone Disease Associated with the Hyp Mutation Is Independent of Osteoblastic HIF1α Expression

Julia M. Ham1,2
1Erica Clinkenbeard1, Pu Ni1, Matthew R. Allen2, Kenneth E. White1,2 1Dept of Medical and Molecular Genetics, Indiana Univ School of Medicine, Indianapolis, IN; 2Dept of Anatomy and Cell Biology, Indiana Univ School of Medicine, Indianapolis, IN.

Background: Fibroblast growth factor-23 (FGF23) is a hormone controlling key responses to systemic phosphate increases through its actions on the kidney. FGF23 also positively responds to iron deficiency anemia and hypoxia in rodents and humans and is responsible for late-onset ADHR. The disorder X-linked hypophosphatemia (XLH) is characterized by elevated FGF23 and an intrinsic bone mineralization defect. Further, the H yp mouse model of XLH has disturbed osteoblast to osteocyte differentiation with altered expression of FGF23. Since Hypoxia inducible factor-1α (HIF1α) has been implicated in FGF23 expression and function in bone cell differentiation, the goals of this study were to determine whether HIF1α activation under normal iron conditions could influence FGF23, and to test the role of HIF1α on the Hyp endocrine and skeletal disease in vivo.

Methods: Treating primary cultures of osteoblasts/osteocytes and UMR-106 cells with HIF1α activator, AG490. Generation of Hyp mice bred onto the HIF1α/Osteocalcin-Cre background.

Results: Treatment of primary bone cultures and UMR-106 cells with the AG490 resulted in HIF1α stabilization and increased FGF23 mRNA (50-100 fold; p<0.01-0.001). Since expression of HIF1α is elevated in the Hyp mouse, we sought to determine whether a bone-specific HIF1α deletion would correct FGF23 production and the Hyp disease phenotype. Although HIF1α effects on bone could be detected, the cross of Hyp-HIF1α-OCN had no effect on the metabolic bone disease associated with the Hyp mutation.

Conclusion: In summary, FGF23 can be driven by ectopic HIF1α activation under normal iron conditions in vitro, but factors independent of HIF1α activity after mature osteoblast formation are likely responsible for the elevated FGF23 in Hyp mice in vivo. Clinically, these findings suggest that although iron therapy holds promise for ADHR, patients with XLH would likely benefit from other treatment approaches.

Funding: Private Foundation Support

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Underline represents presenting author.

TH-PO548

KRKN23, a Fully Human Monoclonal Antibody to FGF23, Reverses Renal Phosphate Wasting and Improves Rickets in Children with X-Linked Hypophosphatemia

Anthony A. Portale1, Javier San Martin2, Thomas Carpenter1,3 1Pediatrics, Univ of California San Francisco, San Francisco, CA; 2Ultryagen Pharmaceutical, Inc., Novato, CA; 3Pediatrics, Yale Univ School of Medicine, New Haven, CT.

Background: In patients with X-linked hypophosphatemia (XLH), high circulating FGF23 impairs renal phosphate (Pi) reabsorption and 1,25(OH)2D3 production, resulting in hypophosphatemia, defective bone mineralization, and rickets. Conventional treatment with oral Pi and active vitamin D fails to restore Pi homeostasis and often leads to nephrocalcinosis and hyperparathyroidism.

Methods: In a phase 2 study, we administered KRKN23, which binds and inhibits the renal actions of FGF23, to children (ages 5-12 years, ≤ Tanner 2) with XLH, either biweekly (Q2W) or monthly (Q4W) by subcutaneous injection. KRKN23 doses were titrated to achieve age-appropriate serum Pi concentrations, which were measured biweekly.

Results: At enrollment, 35 of the first 36 participants had received conventional treatment for a mean of 6.6 years. After 40 weeks of KRKN23 treatment, renal TiP/GFR, serum Pi, and 1,25(OH)2D3 increased significantly, and alkaline phosphatase decreased. Increases in serum Pi were more stable and sustained with Q2W dosing. In this interim analysis, increases in 1,25(OH)2D3 did not impact serum or urinary calcium, PTH, or nephrocalcinosis. Radiographic findings of rickets improved substantially in most patients, with greater improvements in the subset with higher-severity rickets at baseline.

Funding: Pharmaceutical Company Support - Ultryagen Pharmaceutical, Inc.

TH-PO549

High Serum Levels of Fibroblast Growth Factor 23 Are Associated with Decreased Renal Blood Flow in Early Autosomal Dominant Polycystic Kidney Disease

Michel Chonchol1, Berenice Y. Gitomer2, Chonchol M.1,2 1Medicine/Nephrology, Univ of Colorado, Aurora, CO; 2Medicine/Nephrology, Northwestern Univ Feinberg School of Medicine, Chicago, IL.

Background: Previous studies have reported a 4-fold elevation in circulating fibroblast growth factor 23 (FGF23) levels in early autosomal dominant polycystic kidney disease (ADPKD) when compared to other etiologies of chronic kidney disease (CKD). FGF23 levels have been associated with impaired vasoreactivity in CKD. We tested the hypothesis that higher serum FGF23 is a risk factor for a decrease in renal blood flow (RBF) in early ADPKD.

Methods: Intact FGF23 (iFGF23) serum levels (Kainos) were measured in 343 hypertensive ADPKD patients who participated in the HALT-PKD trial study A. Participants were randomized to standard or low blood pressure control and to either lisinopril plus telmisartan or lisinopril plus placebo, with evaluation of RBF by abdominal magnetic resonance imaging at baseline, 24, 48, and 60 months. The study population was divided into tertiles of iFGF23. We used mixed effect models to examine the associations between tertiles of FGF23 with repeated measures of RBF during the course of the study.

Results: At baseline, participants mean age, CKD-EPI-eGFR and RBF were 37 ± 9 years, 88 ± 16 ml/min/1.73m2, 606 ± 205 ml/min/1.73m2, respectively. The median (IQR) iFGF23 was 40.5 (33-55) pg/ml. After adjustment for age, gender, race, randomization group, body mass index, systolic blood pressure, eGFR, urine albumin excretion, serum calcium, and phosphate, the highest iFGF23 tertile was associated with greater RBF decline (β: -42.76, 95% CI -2.38 to -83.14; p = 0.03) compared with the lowest iFGF23 tertile. Similarly, when evaluated as a continuous variable, higher levels of iFGF23 were associated with lower RBF (β: -35.88, 95% CI -2.23 to -69.53; p = 0.03) per natural log unit increase.

Conclusions: High serum iFGF23 levels are associated with a lower RBF over time in patients with early ADPKD. Further studies are required to determine the mechanisms underlying these relationships and to test whether interventions that reduce FGF23 levels might be renoprotective in early ADPKD.

Funding: IKDDK SE poster.
FGF23 Can Predict the Worsening of Cognitive Impairment in Dialysis Patients

TH-PO550

FGF23 is a hormone released from osteocytes in response to elevated serum phosphate levels, and it is associated with cardiovascular disease. The genetic background of the Col4a3 KO mice to elevated FGF23 levels requires further study.

Methods: We backcrossed 129X1/SvJ-Crl:Col4a3 KO with C57Bl6/J mice and generated Col4a3 KO and WT on a mixed background with either 25% C57Bl6/J (129) or 94% C57Bl6/J (B6) genomes. We compared overall survival and assessed renal function, FGF23 levels and cardiac phenotype in two mouse models of CKD: Col4a3 null (Alport syndrome) and adenine diet (chronic tubulointerstitial nephritis). Both mouse models have progressive renal dysfunction as evidenced by elevated BUN, creatinine, phosphate, and FGF23 serum levels. Our aim was to measure changes in expression of FGF23 in the hearts of Col4a3 null and adenine-fed mice and also determine if exercise would prevent these changes.

Results: Basal cardiac FGF23 expression was low in Col4a3 WT and control diet mice, with an average delta CT of 16.9 in relation to \( \beta \)-actin expression. Cardiac FGF23 expression was increased 3.2 fold in Col4a3 null mice (p<0.05; n=5) and increased 3.6 fold in adenine-fed mice (p<0.05; n=6) compared to control mice. Exercise did not improve kidney function in adenine-fed mice and FGF23 expression was elevated 3.2 fold (p<0.05; n=5).

Conclusions: FGF23 expression was increased in the hearts of CKD mice indicating that FGF23 may have paracrine effects on cardiac remodeling during CKD and could prove to be an important therapeutic target. This particular exercise regimen did not abate FGF23 expression and may be adverse for CKD disease.

Funding: Private Foundation Support

FGF23 Can Predict the Worsening of Cognitive Impairment in Dialysis Patients

TH-PO552

FGF23 can predict the worsening of cognitive impairment in patients with chronic kidney disease (CKD). FGF23 levels rise with the progression of chronic kidney disease (CKD) and are associated with cardiovascular disease and mortality. While bone release of FGF23 is known to increase during CKD, it has not been fully elucidated if the heart directly contributes to FGF23 expression and if it is increased during CKD. To test this hypothesis, we utilized two mouse models of CKD: Col4a3 null (Alport syndrome) and adenine diet (chronic tubulointerstitial nephritis). Both mouse models have progressive renal dysfunction as evidenced by elevated BUN, creatinine, phosphate, and FGF23 serum levels. Our aim was to measure changes in expression of FGF23 in the hearts of Col4a3 null and adenine-fed mice and also determine if exercise would prevent these changes.

Methods: We performed a prospectively study (baseline, T0 and after 1 year, T1) in chronic dialysis (HD and PD) patients. The primary outcome of interest was change in cognitive impairment. We evaluated data in CKD patients on dialysis and shows a prevalence on the rise. Especially cognitive performance was significantly associated with \( \text{cGFR} \) in all domains except language. Several studies showed the uremia-related factors for cognitive impairment in CKD-stage V but its development remain unclear. Recently FGF23 was associated with worse performance on a composite memory score. FGF-23 levels in hemodialysis patients may contribute to cognitive impairment.

The aim of our study was to determine if the FGF23 could predict the worsening of cognitive impairment.

Results: Baseline, we enrolled 133 pts, 58 HD and 75PD (mean age 64.09±11.65 yrs; 71% M, median dialysis time: 2.79 (1.38-6.03) years). The median cFGF-23 level baseline was 1493 (927-4035) RU/mL. The cognitive assessment of pts are shown in table 1. The linear regression model showed for all increase of 100 RU/ml of cFGF23 a decrease of 0.056 MoCA (ES) at the time of heart transplant. FGF23 levels were associated with worse performance on a composite memory score. FGF-23 levels in hemodialysis patients may contribute to cognitive impairment.

Conclusions: FGF-23 levels seem to be associated with worse performance on a composite memory score. FGF-23 levels in hemodialysis patients may contribute to cognitive impairment. Further studies are needed to confirm our data and to investigate the impact of different dialysis modalities on CI.

Funding: NIDDK Support

Correlation of Fibroblast Growth Factor Receptor and Fibroblast Growth Factor 23 Expression with Cardiac Structure and Function in Failing Human Hearts

TH-PO553

Introduction

FGF23 can predict the worsening of cognitive impairment in patients with chronic kidney disease (CKD). FGF23 levels rise with the progression of chronic kidney disease (CKD) and are associated with cardiovascular disease and mortality. While bone release of FGF23 is known to increase during CKD, it has not been fully elucidated if the heart directly contributes to FGF23 expression and if it is increased during CKD. To test this hypothesis, we utilized two mouse models of CKD: Col4a3 null (Alport syndrome) and adenine diet (chronic tubulointerstitial nephritis). Both mouse models have progressive renal dysfunction as evidenced by elevated BUN, creatinine, phosphate, and FGF23 serum levels. Our aim was to measure changes in expression of FGF23 in the hearts of Col4a3 null and adenine-fed mice and also determine if exercise would prevent these changes.

Methods: We performed a prospectively study (baseline, T0 and after 1 year, T1) in chronic dialysis (HD and PD) patients. The primary outcome of interest was change in cognitive impairment. We evaluated data in CKD patients on dialysis and shows a prevalence on the rise. Especially cognitive performance was significantly associated with \( \text{cGFR} \) in all domains except language. Several studies showed the uremia-related factors for cognitive impairment in CKD-stage V but its development remain unclear. Recently FGF23 was associated with worse performance on a composite memory score. FGF-23 levels in hemodialysis patients may contribute to cognitive impairment.

The aim of our study was to determine if the FGF23 could predict the worsening of cognitive impairment.

Results: Baseline, we enrolled 133 pts, 58 HD and 75PD (mean age 64.09±11.65 yrs; 71% M, median dialysis time: 2.79 (1.38-6.03) years). The median cFGF-23 level baseline was 1493 (927-4035) RU/mL. The cognitive assessment of pts are shown in table 1. The linear regression model showed for all increase of 100 RU/ml of cFGF23 a decrease of 0.056 MoCA (ES) at the time of heart transplant. FGF23 levels were associated with worse performance on a composite memory score. FGF-23 levels in hemodialysis patients may contribute to cognitive impairment.

Conclusions: FGF-23 levels seem to be associated with worse performance on a composite memory score. FGF-23 levels in hemodialysis patients may contribute to cognitive impairment. Further studies are needed to confirm our data and to investigate the impact of different dialysis modalities on CI.

Funding: NIDDK Support
TH-PO554

FGF23 Is Not Predictive of Functional Cardiovascular Reserve in Advanced CKD

Kathleen Lim,1 Stephen M. Ting,1 Dihua Xu,2 Sahir Kalim,1 David H. Ellisson,3 Ravi I. Thadhani,1 Daniel Zehnder,4 Thomas F. Hiemstra,3 1Div of Nephrology, Massachusetts General Hospital, Boston, MA; 2Dept of Medicine, Heart of England NHS Foundation Trust, United Kingdom; 3Div of Nephrology & Hypertension, Oregon Health and Science Univ, Portland, OR; 4Div of Metabolic & Vascular Health, Warwick Medical School, United Kingdom; 5School of Clinical Medicine, Univ of Cambridge, United Kingdom.

Background: Chronic kidney disease (CKD) patients exhibit impaired functional cardiovascular reserve with reduced peak exercise oxygen consumption (VO2max), a predictor of survival. In CKD, bone derived FGF23 is elevated and has been implicated in the development of cardiovascular disease. We sought to determine whether FGF23 is a predictor of VO2max in CKD.

Methods: In this cross-sectional study, we enrolled 171 CKD stage V patients and 88 controls with essential hypertension: age 46.7±14.3 vs 53.2±8.1 years (p<0.001), male 60.2% vs. 48.9%, MAP of 98±13.4 vs 104±2.9 mmHg (p<0.001). VO2max was determined by cardio-pulmonary exercise test (CPET) and left ventricular mass index (LVMI) by 2D echocardiogram.

Results: CKD patients had higher FGF23 levels (2845.4±452.4 pg/mL, IQR 1993.5-10947 vs 41.7±9.5 pg/mL, IQR 35-51.7, p<0.001), higher LVMI (110±36.5 g/m2 vs 87±16.9, p<0.001), and markedly reduced VO2max (19.8±12.1 vs 24.8±23.4 mL/min/kg, p<0.001). Univariate regression showed that lnFGF23 was not associated with VO2max (p=0.05), but was associated with LVMI (p<0.05) in CKD; lnFGF23 were neither associated with VO2max or LVMI in controls. In a multivariate regression model for CKD: lnFGF23 was not associated with LVMI and VO2max at age (p=0.001), HR (p=0.009) and LVMI (p=0.002). In control: lnFGF23 was also not associated with VO2max (p=0.07, p=0.4), but positively associated with HR (p=0.001) and LVMI (p=0.0001) but not with age (p=0.6).

Conclusions: As previously observed, this study describes an association between FGF23 and LVMI in both CKD and essential hypertension. However, FGF23 did not predict cardiovascular reserve in the context of hypertension alone or CKD and hypertension.

Funding: Private Foundation Support

TH-PO555

Fibroblast Growth Factor 23 Is Not Associated with Incident Acute Kidney Injury among HALT PKD Study B Participants

Anita Janeenovich,1,2 Zhiying Yu,1 Berenice Y. Gitomer,1 Myles S. Wolf,1 Michel Chonchol1,2 1Denver VA Medical Center; 2Univ of Colorado Denver; 3Northwestern Univers.

Background: Fibroblast growth factor 23 (FGF23) levels are elevated in acute kidney injury (AKI) independent of other bone mineral metabolism parameters. Furthermore, higher pre-operative FGF23 levels predict more severe AKI and greater need for renal replacement therapy among patients undergoing cardiopulmonary bypass surgery. To further evaluate the relationship between AKI and FGF23, we investigated the association of baseline serum FGF23 levels and AKI among patients with autosomal dominant polycystic kidney disease (ADPKD).

Methods: In this cross-sectional study, we enrolled 171 CKD stage V patients and 88 controls with essential hypertension: age 46.7±14.3 vs 53.2±8.1 years (p<0.001), male 60.2% vs. 48.9%, MAP of 98±13.4 vs 104±2.9 mmHg (p<0.001). VO2max was determined by cardio-pulmonary exercise test (CPET) and left ventricular mass index (LVMI) by 2D echocardiogram.

Results: CKD patients had higher FGF23 levels (2845.4±452.4 pg/mL, IQR 1993.5-10947 vs 41.7±9.5 pg/mL, IQR 35-51.7, p<0.001), higher LVMI (110±36.5 g/m2 vs 87±16.9, p<0.001), and markedly reduced VO2max (19.8±12.1 vs 24.8±23.4 mL/min/kg, p<0.001). Univariate regression showed that lnFGF23 was not associated with VO2max (p=0.05), but was associated with LVMI (p<0.05) in CKD; lnFGF23 were neither associated with VO2max or LVMI in controls. In a multivariate regression model for CKD: lnFGF23 was not associated with LVMI and VO2max at age (p=0.001), HR (p=0.009) and LVMI (p=0.002). In control: lnFGF23 was also not associated with VO2max (p=0.07, p=0.4), but positively associated with HR (p=0.001) and LVMI (p=0.0001) but not with age (p=0.6).

Conclusions: As previously observed, this study describes an association between FGF23 and LVMI in both CKD and essential hypertension. However, FGF23 did not predict cardiovascular reserve in the context of hypertension alone or CKD and hypertension.

Funding: Private Foundation Support

TH-PO556

Activin A and Sclerostin in Blood Increase before PTH and FGF-23 in CKD Stages 2 to 5

Florence Lima, Marie-Claude M. Fauerge, Hanna W. Mawad, Amr S. Mohamed, Hartmut H. Mallucci. 1Div of Nephrology, Bone & Mineral Metabolism, Univ of Kentucky, Lexington, KY.

Background: Renal osteodystrophy (ROD) develops in early stages of chronic kidney disease (CKD) and progresses during loss of kidney function. Serum levels of intact parathyroid hormone (iPTH) have been used as the primary indicator of bone abnormalities in ROD. There are other markers that may be useful for assessment of ROD in patients with various stages of CKD. This study evaluated changes in levels of iPTH, fibroblast

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TH-PO558

FGF23 Initially Plays a Important Role on Phosphate Homeostasis in Chronic Kidney Disease

Takaki Kimura,1 Kazuhiro Shizikazi,2 Makoto Kuro-o,2 Takashi Yasigawa.1 1Div of Renal Surgery and Transplantation, Dept of Urology, Jichi Medical Univ, Shimotuke-City, Tochigi, Japan; 2Div of Anti-Aging Medicine, Center for Molecular Medicine, Jichi Medical Univ, Shimotuke-City, Tochigi, Japan.

Background: It has been well known that phosphate homeostasis is regulated by the increased level of fractional excretion of phosphorus (FEP), which is the ratio of clearance of phosphorus and creatinine, excreted by both fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) as the phosphaturic hormones, so serum phosphate level is kept within the normal range until the end stage of chronic kidney disease (CKD). However, the precise mechanism and the induction point of such kind of compensatory mechanism for the phosphate homeostasis in CKD have not been recognized. We evaluated the phosphate homeostasis in the artificial CKD model, which is the patients undergone a nephrectomy (Nx) as the kidney donors.

Methods: Twenty-one kidney donors were included and the estimated glomerular filtration rate (eGFR) overall and stratified by sex. The mean age was 56.8 years, with 56% women and 25% black. At baseline, the serum fibroblast growth factor 23 (FGF23), parathyroid hormone (PTH), and phosphorus with follow-up through 2013, we first assessed the cross-sectional association of serum FGF23 with infection risk at around values corresponding to eGFR 45 ml/min/1.73m2; 29.2 per 1,000 person-years). Higher FGF23 and higher PTH, but not phosphorus, were associated with higher risk of hospitalization with infection (80.5 events/1,000 person-years) (Table 1). In the fully adjusted model, whereas no statistically significant association of FGF23 with risk of infection in CKD patients, the association of higher FGF23 with increased risk of infection in CKD patients, the association of higher FGF23 with increased risk of infection remained on high phosphate diet, or were fed regular chow for 6 months.

Conclusions: This is the first evidence indicating that the FGF23-mediated cardiac hypertrophy in vivo, elevated serum FGF23 levels in wild type mice by administration of a high phosphate diet, followed by 3 months of regular chow. Control animals remained on high phosphate diet, or were fed regular chow for 6 months. Results: FGF23 and anti-FGFR4. To study the reversibility of FGF23-mediated cardiac hypertrophy in vivo, we elevated serum FGF23 levels in wild type mice by administration of a high phosphate diet, followed by 3 months of regular chow. Control animals remained on high phosphate diet, or were fed regular chow for 6 months.

Conclusions: These findings indicate that cardiac hypertrophy caused by FGF23 elevation is reversible when FGF23 levels are normalized. Hence, we propose that FGF23-mediated cardiac hypertrophy in vivo is reversible when FGF23 levels are normalized. Hence, we propose that FGF23-mediated cardiac hypertrophy in vivo is reversible when FGF23 levels are normalized. Hence, we propose that FGF23-mediated cardiac hypertrophy in vivo is reversible when FGF23 levels are normalized. Hence, we propose that FGF23-mediated cardiac hypertrophy in vivo is reversible when FGF23 levels are normalized. Hence, we propose that FGF23-mediated cardiac hypertrophy in vivo is reversible when FGF23 levels are normalized. Hence, we propose that FGF23-mediated cardiac hypertrophy in vivo is reversible when FGF23 levels are normalized. Hence, we propose that FGF23-mediated cardiac hypertrophy in vivo is reversible when FGF23 levels are normalized.
TH-PO562

Intravenous Calcium Loading Increases Fibroblast Growth Factor 23 in Normal and Uremic Rats

Yasuto Shibika,1 Masahide Mizobuchi,1 Takashi Inoue,2 Toma Hamada,3 Hiroaki Ogata,4 Fumihiko Koiva,5 Takanori Shihata,6 1Div of Nephrology, Dept of Medicine, Showa Univ School of Medicine, Tokyo, Japan; 2Dept of Internal Medicine, Showa Univ Northern Yokohama Hospital, Kanagawa, Japan; 3Div of Nephrology, Dept of Medicine, Showa Univ Fujigaksa Hospital, Yokohama, Kanagawa, Japan.

Background: The mechanisms underlying the stimulation of FGF23 remain to be investigated. We studied the effect of intravenous calcium (Ca) loading on FGF23 levels in normal and 5/6 nephrectomized uremic rats.

Methods: Normal SD rats were fed a standard diet for 8 weeks and then divided into 2 groups: 1) with the standard diet (Normal-control), and 2) with intravenous calcium (20 μl/hr through an intravenous catheter). An infusion using a microinfusion pump (normal IV, volume=IV). Blood and urine were collected at day 1 and 7 and the kidneys were obtained at day 7 after the interventions. 5/6-nephrectomized uremic rats with the same protocol were also examined (Nx-control group and Nx-IV group).

Results: Serum creatinine and phosphorus levels were comparable throughout the period between Normal-control (Cre: 0.26±0.02 mg/dL, P: 6.1±0.2 mg/dL) and Normal-IV rats (Cre: 0.26±0.03 mg/dL, P: 6.0±0.2 mg/dL). Ionized Ca levels in blood and urinary Ca excretion at day 7 were significantly higher in Normal-control (iCa: 1.6±0.02 mmol/L, urinary Ca: 11.0±3.5 mg/day) than those in Normal-control (iCa: 1.3±0.10 mmol/L, urinary Ca: 0.7±0.1 mg/day, p<0.05 respectively). FGF23 levels at day 7 in Normal-IV (1928±485 pg/mL) were significantly higher than those in Normal-control (431±22 pg/mL, p<0.05). Noteworthy finding was that urinary phosphate excretion at day 7 in Normal-IV (2.7±1.95 mg/day) was significantly suppressed compared with Normal-control (19.5±1.2 mg/day) despite of ionized Ca levels in blood and urinary Ca excretion at day 7 being significantly higher in Normal-IV compared with Normal-control. Renal Klotho mRNA expression in Normal-IV was prominently lower than that in Normal-control. These changes in the parameters were augmented in uremic rats.

Conclusions: These results suggest that intravenous Ca loading increases FGF23 in normal and uremic rats, however renal phosphate excretion was abolished suggesting that the bioactivity of FGF23 was inhibited. Decrease in renal Klotho expression might have some roles in this pathological process.

TH-PO563

Effects of Ferric Citrate Administration in a Murine Model of CKD

Conor Francis,1 Samantha Neuburg,2 Lixin Qi,3 Xueyan Wang,4 Corey Dussold,5 Aline Martin,5 Yves M. Wolf,6 Valentin David,7 Div of Nephrology and Hypertension, Dept of Medicine, and Center for Translational Metabolism and Health, Inst for Public Health and Medicine, Northwestern Univ-Feinberg School of Medicine, Chicago, IL.

Background: Elevated levels of fibroblast growth factor 23 (FGF23) are strongly associated with cardiovascular disease, mortality and progression of chronic kidney disease (CKD). Hyperphosphatemia and iron deficiency are powerful stimuli of FGF23 production. This suggests that reducing dietary phosphate intake or absorption and increasing serum iron may lower FGF23 levels and improve clinical outcomes in CKD.

Methods: We investigated the effects of ferric citrate, which simultaneously corrects iron deficiency while also binding phosphate. We fed 4 week-old wild-type (WT) mice and Col4a3−/− mice (CKD), a mouse model of progressive CKD, a control diet or 5% ferric citrate-enriched diet (FC) for 6 weeks.

Results: At 10 weeks, CKD mice fed the control diet displayed a decline in renal function with a 7-fold increase in BUN and a 9-fold increase in urinary albumin compared to WT (6.5±1.2 mg/dL at week 52) and 195 patients did not respond. Differences in baseline characteristics and serum levels of CKD-MBD between these two subgroups were analyzed.

Conclusions: Age and baseline serum phosphorus levels appeared to be predictive of treatment responses to SOFOH or SEV. Greater reductions in serum phosphorus were associated with more pronounced decreases in serum iPTH and FGF23, although the impact of concomitant medications should also be considered.

TH-PO565

Effect of Non-Calcium Phosphate Binders on CKD-MBD Indices in Dialysis Patients: A Post Hoc Analysis of a Phase 3 Study

Markus Ketteler,1 Stuart M. Sprague,2 Anjay Rastogi,1 Bruce S. Spivonitis,2 Sylvain Larroque,3 Sebastian Walpen,4 Jürgen Flego,5 'Coburg Clinic and KJH-Dialysis Center, Germany; 'NorthShore Univ Health System, Chicago; 'Gr. T. Popa’ Univ of Medicine and Pharmacy, Romania; 'Univ of California; 'New York Hospital Queens; 'Vifor Pharma, Switzerland; 'RWTU Univ Hospital Aachen, Germany.

Background: Post hoc analysis of a 52-week Phase 3 study evaluated the impact of serum phosphate control on CKD-MBD indices among 682 patients treated with the iron-based binder sucroferric oxyhydroxide (SFOH) or sevelamer carbonate (SEV). Methods: 1059 patients were randomized 2:1 to SFOH (1.0–3.0 g/day, n=710) or SEV (2.4–14.4 g/day; n=349) for 12 weeks’ dose titration then 12 weeks’ maintenance. Eligible patients enrolled in a 26-week extension. Since SFOH and SEV had a comparable phosphorus-lowering effect during the 52-week study and a similar impact on CKD-MBD indices, treatment groups were pooled for this analysis.

Results: Table displays changes in CKD-MBD indices. Serum phosphate control was maintained throughout the study. Significant decreases in serum FGF-23 were observed over 52 weeks. Serum iPTH decreased after 24 weeks, but returned to near baseline levels by wk 52. Only minimal changes in serum calcium were observed over 1 year. Of the bone resorption markers, TRAP5b decreased significantly over 1 year, whereas CTX levels maintained controls and increased, returning to near baseline levels by wk 52. Serum levels of the bone formation markers BSAP and OST increased during the study.

Conclusions: Age and baseline serum phosphorus levels appeared to be predictive of treatment responses to SFOH or SEV. Greater reductions in serum phosphorus were associated with more pronounced decreases in serum iPTH and FGF23, although the impact of concomitant medications should also be considered.

Table: Baseline means and values in changes in phosphorus, iPTH and FGF23 in responders and non-responders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>Time point</th>
<th>Responders to SFOH (N=302)</th>
<th>Non-responders to SFOH (N=195)</th>
<th>P value responders vs non-responders</th>
</tr>
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</table>

TH-PO568

Characteristics of Responders and Non-Responders to Phosphate Binder Therapy: A Post Hoc Analysis of a Phase 3 Study

Bruce M. Sprague,1 Anjay Rastogi,1 Markus Ketteler,2 Stuart M. Sprague,2 Sylvain Larroque,3 Sebastian Walpen,4 Jürgen Flego,5 'Coburg Clinic and KJH-Dialysis Center, Germany; 'NorthShore Univ Health System, Chicago; 'Univ of California; 'Coburg Clinic and KJH-Dialysis Center, Germany; 'Gr. T. Popa’ Univ of Medicine and Pharmacy, Romania; 'Vifor Pharma, Switzerland; 'RWTU Univ Hospital Aachen, Germany.

Background: Post hoc analysis of a 52-week Phase 3 study to evaluate predictors of treatment response to the iron-based phosphate binder sucroferric oxyhydroxide (SFOH) or sevelamer carbonate (SEV) in dialysis patients.

Methods: Overall, 1059 patients were randomized to SFOH (1.0–3.0 g/day, n=710) or SEV (2.4–14.4 g/day; n=349) for 12 weeks’ dose titration then 12 weeks’ maintenance. Eligible patients enrolled in a 24-week extension study. Out of 497 patients who completed the 52-wk study, 302 responded to either SFOH or SEV (i.e. achieved serum phosphorus levels of ≤5.5 mg/dL at wk 52) and 195 patients did not respond. Differences in baseline characteristics and serum levels of CKD-MBD between these two subgroups were analyzed.

Results: Comparison of baseline characteristics showed that responders were older than non-responders (p=0.005). Baseline serum phosphorus levels were significantly lower in responders vs non-responders (p=0.001) (Table). Reductions in serum phosphorus levels during the study were greater in responders vs non-responders (p<0.001). Serum iPTH levels decreased in responders but increased in non-responders during the 52-wk study (p<0.001). FGF-23 decreased to a greater extent among responders vs non-responders after 24 and 52 wks (p=0.017).

Table: Baseline means and changes in phosphorus, iPTH and FGF23 in responders and non-responders

<table>
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</tr>
</thead>
</table>

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

Underline represents presenting author.
Conclusions: One year of treatment with SFOH or SEV was associated with significant reductions in serum FGF-23; this may be of clinical benefit in CKD patients. The observed trend toward increased levels of bone formation markers indicates a beneficial effect of phosphate-binder therapy for the activation of bone metabolism; however, the potential impact of concomitant medications needs further evaluation.

TH-PO566
Phosphocalcic Markers and Calcification Propensity for Assessment of Intersitial Fibrosis and Vascular Lesions in Kidney Allograft Recipients

Robert E. Ollivier,1 Tamara Isakova,2 Brad C. Astor,1 Haiman Barnhart,1 Lawrence J. Appel,1 Paul E. Dzw2,6 Myles S. Wolf;2 Julia J. Scialla.1 1Duke Univ; 2Northwestern Univ; 3Univ of Wisconsin Madison; 2Johns Hopkins Univ; 3Univ of Minnesota.

Background: Higher serum phosphorus (P) and P, regulatory hormones [fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH)] associate with higher risk of cardiovascular disease (CVD) including left ventricular hypertrophy, stroke, and heart failure (HF). While these outcomes are highly BP dependent, it is unknown if P, FGF-23, and PTH associate with adverse 24h ambulatory BP (ABP) profiles as a possible mechanism.

Methods: P, intact FGF-23, PTH, and ABP were measured at baseline in African Americans with CKD in the AASK Cohort Study. Participants were treated to contemporary BP goals with preference for an ACE inhibitor or ARB. We modeled the association of each mineral metabolite (MM) with mean 24h systolic BP (SBP) and diastolic BP (DBP), and with blunted nocturnal dipping (<10% drop in both SBP and DBP).

Results: In 396 participants with complete data, mean eGFR was 42.6 ± 19.4 mL/min/1.73m², mean P was 3.59 ± 0.77 mg/dL, median FGF-23 was 45.4 pg/mL (IQR 25.0-75.3 pg/mL), and median PTH was 41.9 pg/mL (IQR 27.5-67.5 pg/mL). Mean SBP and DBP were 136.5 ± 17.0 and 80.5 ± 10.5 mmHg respectively, and 79% had blunted nocturnal dipping. We saw no consistent association between any MM and mean SBP or DBP (p>0.05 for all). In unadjusted models, higher P associated with lower risk of blunted nocturnal dipping, but we saw no linear trend on full adjustment (p=0.08). CKD severity did not modify any relationships between MMs and ABP (p-interaction=0.05 for all).

Conclusions: With CKD and well-treated BP, higher MM levels do not associate with adverse ABP profiles in African Americans. Whether previously documented MM associations with CVD are independent of ABP or mitigated by aggressive BP control remains to be determined.

Funding: Other NIH Support - NIH T32 Research Training Grant in Nephrology, # 5-T32-DK773119

TH-PO568
Impact of Residual Kidney Function on the Association Between Parameters of Mineral Bone Disorder and Mortality in Hemodialysis Patients

Mehrotra,1 Zadeh,4 Mehrotra,1 Kalantar,2 Drawz,1本人,4 Scialla,1 1UC Irvine; 2Fudan Univ, Shanghai, China; 3Univ of Tenn.; 4Univ of Wash.

Background: The relationship between mineral and bone disorders (MBD) and survival has not yet been studied in hemodialysis patients according to their residual kidney function (RKF). We hypothesized that RKF modifies the association between MBD parameters and mortality.

Methods: The associations of serum phosphorus, uncorrected and albumin-corrected calcium, intact parathyroid hormone (PTH) and alkaline phosphatase (ALP) with all-cause mortality were examined across three strata of baseline residual renal urea clearance (CLurea) using Cox models with adjustment for clinical characteristics and laboratory parameters and mortality.

Results: There was an incremental mortality risk across higher serum phosphorus concentrations, which was pronounced among patients with higher CLurea (Pinteraction=0.001). Lower intact PTH were associated with higher mortality among patients with low CLurea (i.e., <15 mL/min/1.73m²; Pinteraction=0.02) while higher concentrations showed a trend toward higher mortality risk among patients with high CLurea (i.e., ≥3.0 mL/min/1.73m²; Pinteraction=0.002). CLurea did not modify the associations of uncorrected total calcium, corrected total calcium, and ALP with all-cause death (Pinteraction=0.8, 0.4, 0.14 respectively); higher concentrations of these markers were linearly associated with higher mortality risk across all CLurea strata.

Conclusions: RKF modified the association of serum phosphorus and intact PTH with mortality. RKF levels should be accounted for in better risk assessment of serum phosphorus and intact PTH. Additional studies are needed to better understand the mechanism behind these associations.

Funding: NIDDK Support

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TH-PO569

Vitamin D Supplementation Does Not Improve Gastric Bypass-Related Bone Resorption

Benjamin Canales, Shahab Bozorgmehr, Anne Schafer, Thomas Carpenter.

University of Florida, Gainesville, FL; Medicine, San Francisco Veterans Affairs Medical Center, San Francisco, CA; Medicine, Yale Univ, New Haven, CT.

Background: Roux-en-Y gastric bypass (RYGB)-associated bone resorption is believed to be driven by vitamin D deficiency (VDD) and secondary hyperparathyroidism. However, in humans, bone turnover markers (BTM) remain elevated despite adequate vitamin D supplementation (VDS) and PTH correction. We sought to determine additional drivers of bone resorption in a diet-induced obese (DIO) RYGB model.

Methods: Forty DIO female rats were randomized to sham or RYGB surgery. Post-operatively they were placed on 10% fat/1% calcium diet and assigned to RYGB VDD (n=10), RYGB VDS (n=10), sham pair-fed (n=10) or ad lib (n=10) groups. Caltrectic hormones, serum gut hormones, sex hormones, BLM, and urinary calcium/creatinine (UCC) were measured baseline and q4 weeks until week 12 euthanasia. Femurs were analyzed using micro-computed tomography (uCT) and 3 point bending test (BT).

Results: Compared to controls, RYGB animals had lower body weight, UCC, insulin, C-peptide, leptin, and progesterone levels along with higher GLP-1 and PYY hormones. RYGB VDS rats had higher 25-hydroxyvitamin D and lower parathyroid hormone levels than their VDD counterparts, reflecting vitamin D repletion. Despite VDS, both RYGB groups had elevated 1,25-dihydroxyvitamin, coupled increases in BTMs, more brittle bone by BT, and uCT skeletal findings of reduced trabecular bone volume and thickness (figure 1) and reduced cortical volume and thickness versus controls.

Conclusions: In our DIO model, RYGB-related bone resorption and calcium gut absorption occur independent of vitamin D status. Gut and sex hormones, particularly PYY and progesterone, may play a role in bone mass differences. Further mechanistic research to explore these differences may identify targets for RYGB bone loss prevention.

Funding: NIDDK Support

TH-PO570

MEMO1 Deletion in Mice Causes a Mineral Disorder Resembling Hypophosphatasia

Matthias B. Moor, Saresh Krishna Ramakrishnan, Barbara Haenzi, Willy Hofstetter, Olivier Bonny, Cambridge Centre for Brain Repair, Dept of Clinical Neuroscience, Univ of Cambridge, Cambridge, England, United Kingdom; Dept of Clinical Research, Univ of Bern, Bern, Switzerland; Service of Nephrology, Lausanne Univ Hospital, Lausanne, Switzerland.

Background: Hypophosphatasia is a bone mineralization disorder generally caused by mutations in the gene coding for tissue-nonspecific alkaline phosphatase (ALPL). Mediator of ErbB2-driven Cell Motility 1 (Mema) is a redox protein and an intracellular signaling modulator of growth factors. We previously showed that renal FGF23-induced signaling requires Mema.

Methods: Exon 2 of the Mema gene was deleted in Mema fl/fl mice using a tamoxifen-inducible Cre recombinase to obtain conditional knockout (eKO) mice. Littermates without Cre served as controls. Bones were studied by micro-computed tomography and histomorphometry. Serum, tissue and urinary chemistry were analyzed.

Results: Mena eKO mice developed empty distal femoral metaphysis with severely disturbed trabecular structure and mineral apposition. The mice displayed higher serum calcium levels, hypercalciuria, and increased urinary inorganic pyrophosphate excretion. Serum and bone tissue ALP activities were decreased in eKO, and intracellular redox state in Mena null bone tissue was altered. Native PGE and thiol conjugation studies revealed no differences in bone ALP protein between genotypes, but bone tissue from Mena eKO animals revealed a diminished ALP stability. Primary cultured osteoclasts and osteoblasts from Mena control and eKO animals were of comparable cellular function, but Mena null osteoblasts revealed an altered metabolic profile.

Conclusions: Mena deletion leads to a mineral disorder that may constitute a novel secondary form of hypophosphatasia associated with distinct metabolic changes in the bone.

Funding: Private Foundation Support

TH-PO571

Early Cessation of Nephrogenesis in Mouse Model of Prematurity

Jennifer R. Charlton, Valeria M. Pearl, Hwot M. Abate, Jennifer M. Laws, Maria Luisa S. Sequeira Lopez, Univ of Virginia.

Background: Premature neonates are at risk of developing chronic kidney disease (CKD). Human nephrogenesis is completed by 36 weeks gestation, whereas in rodents nephrogenesis continues until a postnatal age (PNA) of 4 days. Completion of nephrogenesis is dependent on self-renewing cells in the nephrogenic zone (NZ), but their fate following premature birth is unknown. Using a mouse model of prematurity which develops CKD as an adult, we hypothesize that NZ depletion is determined by PNA not postconceptional age.

Methods: CD-1 dams underwent C-section at post-conception age (PCA) 18 days. The term group delivered at PCA20. All pups were fostered. Pups were euthanatized in the first week of life or as adults. In the pups, NZ was measured on midstaligial kidney sections, apoptosis by TUNEL, and cells and proximal tubular (PT) fraction by lotus lectin. In the adults, glomerular area and PT fraction were measured.

Results: Both body (BW) and kidney weights (KW) were smaller in the premature group as compared in the term group on PNA 2 and 4 days (n=5/grp). The NZ of the premature mouse kidney persisted at PNA 4, but was depleted by PNA 5, truncating nephrogenesis by one day in prematurely born mice.

Funding: NIDDK Support

TH-PO572

Assessment of Total Kidney Volume at Birth as a Surrogate of Nephron Mass

Marissa J. Defreitas, Wacharee Seelarnvong, Chryso P. Katsouflis, Teresa C. Cano, Marta G. Galarza, Salih Y. Yasen, Gaston E. Zilleruelo, Carolyn L. Abitol. Pediatric Nephrology, Univ of Miami/Holtz Children's Hospital, Miami, FL; Neonatology, Univ of Miami/Holtz Children's Hospital, Miami, FL; OB/GYN, Univ of Miami/Holtz Children's Hospital, Miami, FL.

Background: An individual's "nephron endowment" has implications for lifelong renal health and is determined by the intrauterine environment and gestational age (GA). Our objective was to determine if neonatal total kidney volume (TKV) indexed to body surface area (BSA) would reveal an advantage of nephron mass across GA groups and to provide baseline normative data to be followed prospectively relative to patient function.

Methods: A cross-sectional cohort of 140 healthy newborns, 84 preterm (PT; ≤37 weeks GA) and 56 term (T; >37 weeks GA), was enrolled at birth for evaluation of kidney size and function. Infants with congenital anomalies, acute kidney injury by KDIGO modified criteria, ≤24 weeks GA, and ≤500 g were excluded. TKV was determined by renal ultrasound and reported in milliliters (ml) indexed to body size parameters. Kidney function was assessed by serum creatinine (Cr) and Cystatin C (CysC).

Results: TKV correlates closely with kidney function in the neonate. TKV/BSA (ml/ m²) is independent of GA. Average Scr ± SD for the entire cohort was 0.6 ± 0.2, while T-Scr was 0.5 ± 0.1 compared to PT-Scr of 0.7 ± 0.2 mg/dl (p<0.001). Similarly, CysC distinguished T from PT infants (1.3 ± 0.2 vs 1.5 ± 0.2 mg/L; p<0.001).

Conclusions: TKV/BSA offers an assessment of nephron mass that is independent of gestational age providing a simple and non-invasive measure of renal adaptation potentially across a lifespan.

Funding: Private Foundation Support

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

Underline represents presenting author.
TH-PO573
The Endocytic Role of OCRl and INPP5b in Mouse Proximal Tubulopathy
Kazunori Inoue,1 Xuefei Tian,2 Tong Wang,2 Shuta Ishibeh.1 1Internal Medicine, Yale Univ School of Medicine, New Haven, CT; 2Cellular and Molecular Physiology, Yale Univ School of Medicine.

Background: Human mutations in inositol polyphosphate 5-phosphatase, OCRl (Oculocutaneousrenal Syndrome of Lowe) has been demonstrated to cause proximal tubulopathy in Lowe Syndrome (LS) patients. In-vitro cell culture work suggests the role of OCRl in phagocytosis of clathrin-coated pits and endocytosis. Yet, the in vivo mechanisms on how the loss of function of OCRl results in Fancin’s Syndrome remains unclear.

Methods: Genetic ablation of Ocrl doesn’t recapitulate the human phenotype in mice models suggesting that an OCRl paralog, Inpp5b may compensate for the lack of OCRl. Therefore doxycycline (Dox) induced renal tubule specific Inpp5b knockout mice on an underlying OCRl KO background (OCRl−/−, Pax8Cre+, TetO-Cre Inpp5bLox/− (DKO)) were generated. To assess endocytosis in vivo, fluorescein tagged lactoglobulin, dextran, or horseradish peroxidase (HRP) was injected in control, OCRl KO, and DKO mice. Results: DKO mice exhibited robust low molecular weight proteinuria, phosphaturia (control 6.70 (Urinary phosphate/urine creatinine ratio)) vs DKO:16.30, 3 months after Dox induction), glucosuria, and acidemia which mimics what has been observed in LS patients. DKO mice displayed massive reduction in endocytic uptake of lactoglobulin, dextran, and HRP in the proximal tubules. To further elucidate how marked inhibition of endocytosis would impact NaPi2a function, we examined NaPi2a trafficking in-vivo. DKO mice showed a marked delay in NaPi2a internalization after PTH injection. DKO mice also displayed elevated plasma and urine PTH. Lastly, after 8 months following Dox induction, the mutant mice develop kidney failure and fibrosis.

Conclusions: We have generated a genetic mouse model of LS developing a proximal tubulopathy and have revealed that loss of Ocrl and Inpp5b function in vivo results in significant defects in clathrin mediated endocytosis suggesting that this fundamental process likely contributes to the kidney manifestations observed in LS.

TH-PO574
AT2R Deficiency Induces Podocyte Apoptosis and Epithelial Mesenchymal Transformation via Ectopic Hedgehog Interacting Protein Gene Expression Mediated by Hedgehog Ligand Upregulation
Liubin Liu,1 Xuefei Tian,2 Shuo Zhang,2 Shao-Ying Zhang,1 Chaohong Luo,1 Isabelle Chenier,1 Julie R. Ingelfinger,1 John S.D. Chan,1 Shao-Ling Zhang,1 CRCHUM, Univ of Montreal, Montreal, QC, Canada; 2Pediatr Nephrol Unit, Mass. Gen. Hosp., Boston, MA.

Background: Angiotensin type 2 receptor (AT2R) deficient mice (AT2RKO) exhibit a spectrum of congenital abnormalities of the kidney and urinary tract (CAKUT); however, the mechanisms by which these abnormalities occur are poorly understood. We aimed to study whether AT2R deficiency impairs glomerulogenesis via podocyte apoptosis and/or epithelial mesenchymal transformation (EMT) and also to elucidate the underlying mechanisms in vivo and in vitro.

Methods: Embryonic kidneys of nephrin-cyan fluorescent protein (CFP)-transgenic (Tg) (Nephrin-CFP-Tg) and Nephrin/AT2RKO mice were used to assess glomerulogenesis; kidneys from neonate to 3 weeks old of suckling pups —both wild-type (WT) and AT2RKO mice were used to evaluate mature podocyte morphology/function. Immortalized mouse podocytes (mPDCs) were employed for in vitro studies.

Results: AT2R deficiency resulted in diminished glomerulogenesis in E15 embryos, but no difference in actual nephron numbers in neonates. Pups lacking AT2R displayed features of renal dysplasia —e.g., lower glomerular tuft volume and podocyte number, and retarded podocyte maturation, as revealed by podocyte markers (Wilms tumor-1 (WT-1), p57, nephrin and synaptopodin). In vivo and in vitro studies, demonstrated that loss of AT2R was associated with significantly elevated oxidative stress and increased ectopic hedgehog interacting protein (Hhlig) gene expression in podocytes, which in turn, led to podocyte apoptosis. Concomitantly, the increased Hhlig expression enabled interaction with TGFβ1 RII/II, targeting TGFβ1-Smad2/3 cascades to trigger epithelial-mesenchymal transition (EMT) in podocytes.

Conclusions: Loss of AT2R is associated with podocyte apoptosis and EMT, and the underlying mechanism appears to be mediated, at least in part, via augmented Hhlig expression. Funding: Government Support - Non-U.S.

TH-PO575
Caspase-3 Mediates Inhibition of Ureteric Branching and Nephrogenesis by Maternal Nutrient Restriction in a Mice Model of Proximal Tubulopathy
Masayuki Inoue,1,2 Midori Awazu,1,3 Takanori Miyata,1,2 Hiroki Kamei,1,2 Shinzo Yamaguchi,1,2,3 Isabelle Chenier,1,4 John S.D. Chan,1,2,3 Shao-Ling Zhang,1,2 CRCHUM, Univ of Montreal, Montreal, QC, Canada; 1Dept of Pediatrics, Keio Univ School of Medicine, Tokyo, Japan; 2Dept of Pathology, Keio Univ School of Medicine, Tokyo, Japan; 3Center for Clinical and Translational Research, The Research Inst at Nationwide Children’s Hospital; 4Urology Div, Nationwide Children’s Hospital; 5Nephrology Section, Nationwide Children’s Hospital; 6Dept of Anatomy, Ohio State Univ.

Background: Maternal nutrient restriction (NR) not only reduces nephron number but may also affect tubules, interstitium, capillary density, and endothelial function. We reported that NR aggravates tubular necrosis and interstitial fibrosis after unilateral ureteral obstruction (UUO) without affecting peritubular capillary density (ASN 2015). Increased or decreased nitric oxide (NO) has been shown to alleviate or aggravate UUO-induced renal injury, respectively. We examined whether augmented UUO-induced renal injury in NR is due to decreased renal NO production and if so investigated the mechanism.

Methods: Six-week-old offspring from rats given food ad libitum (CON, n=7) and those subjected to 50% food restriction throughout pregnancy (NR, n=11) were subjected to left UUO. Urine weight, blood pressure (BP), blood urea nitrogen (BUN) were examined before and after UUO. Urine from the left kidney were collected at the time of sacrifice. Urine NO was measured by ELIZA. Kidneys were stained with HE and Masson trichrome for the quantification of collagen. Expression of eNOS was assessed by immunoblot.

Results: Before UUO, body weight was significantly lower (131±6 vs 163±8 g) and BP was significantly higher in NR than CON (104±3 vs 94±6 mmHg). After UUO, there was no difference in body weight between CON and NR (153±8 vs 177±5 g). Systolic BP was significantly higher in NR (118±5) but not in CON (105±7 mmHg). BUN also did not change in CON (20.5±0.7 to 23.1±2.8) but increased significantly in NR (16.8±1.1 to 20.7±1.4 mg/dl) after UUO. Tubular necrosis was more extensive and the collagen area ratio of the obstructed kidney was significantly greater in NR compared with that in CON (5.4±3 vs 2.6±0.3%). Urine NO of the obstructed kidneys was significantly decreased in NR compared with that in CON (57±4 vs 586±238 nmol/mg Cr). eNOS expression of the obstructed kidney was increased vs contralateral kidneys in both CON and NR, but the extent was less in NR.

Conclusions: Decreased renal NO production in NR may explain more severe UUO-induced renal injury. Funding: Government Support - Non-U.S.

TH-PO577
Uropilaks Play a Protective Role during Obstructive Nephropathy
Ashley R. Jackson,1 Christina B. Ching,2 Brian Becknell,3,4 Kirk M. McHugh,2,4 1Center for Clinical and Translational Research, The Research Inst at Nationwide Children’s Hospital; 2Urology Div, Nationwide Children’s Hospital; 3Nephrology Section, Nationwide Children’s Hospital; 4Dept of Anatomy, Ohio State Univ.

Background: Studies involving the mgb- mouse model of congenital obstructive nephropathy indicate an adaptive role for the renal urothelium during the development of progressive hydronephrosis. Specifically, uroplakin transcripts and protein expression were significantly increased, as well as the Kr14 progerin cell marker. Recently, the tetrascarpien uropilak, Upk1h, has been implicated in urinary plate formation and stabilization of renal urothelium. We hypothesize that urothelial remodeling and increased urothelial plate formation during obstructive nephropathy is a protective measure against the development and progression of hydronephrosis.

Methods: To test our hypothesis, we destabilized the urothelial plate through genetic ablation of Upk1h in mgb- mice and quantitated hydronephrosis using ultrasound. Biochemical and immunohistochemical stainings were used to characterize uropilak, Kr14, Kr5, and K67 expression patterns in renal tissue.

Results: In WT, NR significantly reduced fetal body weight (156±4 vs 167±5 mg) and ureteric tip number (15.9±1.6 vs 36.8±3.4 k/d) at embryonic day 13 (E13). Glomerular number counted at 7 weeks was decreased in NR by 20% (P<0.05). At E15, body weight of Casp3-/- was not different vs Casp3+/+(131±10 vs 139±18 mg, n=5-6), but ureteric tip number was significantly reduced.

Conclusions: NR significantly decreased ureteric branching of Casp3-/- without affecting body weight (124±10 vs 139±18). In contrast, NR had no effect on body weight or ureteric tip number of Casp3+/-. Under NR conditions, there was no difference in glomerular density between Casp3-/- and Casp3+/+ at E15 and E16.

Funding: Government Support - Non-U.S.
Results: Loss of Upk1b caused destabilization of the urothelial plaque in mgbh6 mice, including the loss of urothelial cell layer in the renal pelvis and ureter. Expression of Ker14 and Ker17 basal urothelial cells. Electron microscopy and a FICT–Dexter phenotype assay identified defective in the urine permeability barrier in the absence of Upk1b. Compound heterozygotes (mgbh6:Upk1b+/mgbh6) develop worse, bilateral hydrenephrosis at an earlier age than either mouse strain (mgbh6: unilateral, moderate; mgbh6: unilateral, bilateral; moderate), and often die prematurely suggesting the loss of the urothelial plaque leads to earlier and faster disease progression.

Conclusions: To our knowledge, we provide the first evidence that remodeling of the renal pelvis urothelial plaque functions to protect the kidney in the context of congenital obstruction in a mouse model. The clinical significance of this finding remains to be fully evaluated in children with similar defects, such as ureteropelvic junction obstruction.

Funding: NIDDK Support

TH-PO578

Conditional Ablation of Urothelial Cells for Identification of Context Specific Roles during Renal Disease

Ashley R. Jackson, 1 Christina B. Ching, 1,2 Birong Li, 3 Kirk M. McHugh, 4 Brian Becknell. 5 1 Center for Clinical and Translational Research, Nationwide Children’s Hospital Research Inst; 2Urology Div, Nationwide Children’s Hospital; 3Nephropathy Section, Nationwide Children’s Hospital; 4Dept of Anatomy, Ohio State Univ.

Background: Urothelium serves vitals roles in establishing a urine permeability barrier, in part through the elaboration of uroplakin (Upk) plaques. Upk1b deficiency leads to hydrenephrosis, urothelial dysplasia, and altered infectious susceptibility. To better understand the role of Upk+ cells in renal disease, we adapted a technique to ablate Upk+ cells in an inducible manner. Here we provide the first report of genetic ablation of Upk2+ urothelial cells in the renal pelvis and urethelium.

Methods: The Upk2−/−Cre mouse was used to drive Cre;LoxP dependent expression of a tdTomato reporter (A14) or a floxed HBEFG (Diphertheria Toxin Receptor; DTR) in a tamoxifen (TM)-dependent manner. Five daily doses of 75 mg/kg body weight TM were administered through the drinking water. Adult Upk2−/−Cre ROSA/tdTom +/−; ROSA26.R26R;ROSAiDTR iCre+;Ai14+ mice were used to drive Cre/LoxP dependent expression of tdTomato or DTR at 1 week of age. Adult Upk2−/−Cre ROSA/tdTom +/−; ROSA26.R26R;ROSAiDTR iCre +/− mice were Cre activated as above followed by a single IP dose of 0.25mg/kg or 0.5mg/kg body weight diphertheria toxin (DT). Mice were euthanized 24 hours after DT administration and cellular ablation was analyzed by routine histology and dual immunofluorescent labeling.

Results: Cre-recombinase specificity in Upk2+ cells was confirmed in Upk2−/−Cre;Ai14+ mice by anti-RFP detection. Multiple layers of bladder, ureter and renal pelvis urethelium were RFP+, whereas isolated RFP+ cells were identified in the renothelium. In Upk2−/−Cre;ROS26.R26R;ROSA26.R26R;ROSAiDTR iCre+;Ai14+ mice Organotypic cultures harvested at 1 week. Adult Upk2−/−Cre ROSA/tdTom +/−; ROSA26.R26R;ROSAiDTR iCre+;Ai14+ mice were used to drive Cre/LoxP dependent expression of tdTomato or DTR at 1 week of age. Adult Upk2−/−Cre;Ai14+ mice were CRE activated as above followed by a single IP dose of 0.25mg/kg or 0.5mg/kg body weight diphertheria toxin (DT). Mice were euthanized 24 hours after DT administration and cellular ablation was analyzed by routine histology and dual immunofluorescent labeling.

Conclusions: Temporally controlled, cell specific ablation of Upk+ cells can be achieved using the Upk2−/−Cre;Ai14+ mice. This technique will be utilized to determine the impact of urothelial destabilization on renal injury in the settings of pyelonephritis and obstructive nephropathy.

Funding: NIDDK Support

TH-PO579

Morphologic Basis for Urothelial Remodeling during Obstructive Nephropathy

Rachel Milner, 1 Ashley R. Jackson, 2 Kirk M. McHugh, 3,4 Christina B. Ching, 1,2 Brian Becknell. 5 1 Center for Clinical and Translational Research, Nationwide Children’s Hospital Research Inst; 2Urology Div, Nationwide Children’s Hospital; 3Depart of Anatomy, Ohio State Univ; 4Urology Div, Nationwide Children’s Hospital.

Background: Ureteropelvic junction obstruction (UPJO) is the most common cause of pediatric obstructive nephropathy. The urothelium establishes the urine permeability barrier and protects obstructed renal parenchyma. Here, we investigated the morphologic basis for pelvic urothelial remodeling during UPJO.

Methods: Resected tissues were obtained with informed consent from 15 patients undergoing pyeloplasty. Adult male FVB/N mice underwent unilateral ureteral obstruction or sham operation, followed by euthanasia at post-operative days 1, 3, 7, or 14. Sections from UPJO, proximal renal pelvis, and distal ureter were subject to histologic stains and immunofluorescence microscopy using uroplakin markers (C5; CK14; UPK3A) and proliferation antigens (Ki67; PCNA).

Results: In UPJO cases, urothelial thickening occurs in the proximal pelvis, with loss of structural integrity compared to distal ureter. Obstructed UPJ and renal pelvis exhibit absent or patchy UPK3A staining, whereas UPK3A is distributed uniformly at the apical surface of the urothelium in distal ureters. While urothelial remodeling may initially occur as a physiologic response to urine back-pressure, this may prove maladaptive and contribute directly to renal pathology in obstructive nephropathy. Further studies are warranted to test this hypothesis directly.

Funding: NIDDK Support
Methods: We performed experimental UTI by transurethral inoculation of uropathogenic Escherichia coli (UPEC) in IL-6 knockout versus wild-type mice, as well as mice treated with IL-6-neutralizing antibody or isotopic control. We determined the role of bacterial endothelial signaling in Stat3 Tyr705 phosphorylation through Tlr4 hypomorphic mice. We measured Stat3 activation based on Tyr705 phosphorylation in infected urinary tract and primary human urothelial cells by immunoblotting. We localized pStat3 Tyr705 in experimentally infected urothelium by immunofluorescence. We measured mRNA expression of Stat3 target genes including AMPs by quantitative RT-PCR.

Results: UPEC inoculation leads to brisk Stat3 Tyr705 phosphorylation in bladder and renal urothelium in a Tlr4-dependent manner. IL-6 neutralization or gene ablation significantly reduces urothelial pStat3 Tyr705 levels. Conversely, administration of recombinant IL-6 leads to Stat3 Tyr705 phosphorylation in murine and human urothelium. We globally identify transcriptional targets of IL-6/pStat3 Tyr705 signaling in UPEC infected urothelium and demonstrate that IL-6 knockout mice exhibit significantly impaired expression of the AMPs Reg3g and Reg3h following experimental UTI.

Conclusions: IL-6/pStat3 Tyr705 signaling drives a conserved transcriptional program of AMP expression in UPEC infected urothelium. Deficiencies in IL-6/pStat3 Tyr705 activation may explain infection predisposition in certain patients with UTI. Conversely, local pharmacologic activation of pStat3 Tyr705 through IL-6 may promote mucosal immunity in individuals with recurrent UTI.

Funding: NIDDK Support

TH-PO583

Urinary YKL-40 as a Candidate Biomarker for Febrile Urinary Tract Infection in Young Children Jin-Sook Sub, Byoung-Soo Cho, Department of Pediatrics, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea; Director of MIRAE-ING Kidney Center, MIRAE-ING Kidney Center.

Background: YKL-40 is regarded as a site-specific inflammatory marker. We sought to evaluate the association of YKL-40 with urinary tract infection (UTI) in febrile children.

Methods: We enrolled 44 children aged from 0 to 24 months with febrile UTI and 35 controls who were matched for age and sex, but had other causes of fever. An enzyme-linked immunosorbent assay was used to determine the level of YKL-40 in urine collected from each child.

Results: The ratio of urinary YKL-40/creatinine (Cr) was higher in the children with UTI than in the controls (P = 0.001). The area under a receiver-operator characteristic curve for detecting UTI was 0.88 for urinary YKL-40/Cr, 0.86 for pyuria, and 0.71 for positive nitrite on urinalysis. We applied a cutoff value of 125.23 pg/mg to urinary YKL-40/Cr for detecting UTI. Eight of nine children in the control group with pyuria and UTI had a urinary YKL-40/Cr levels lower than 125.23 pg/mg, and the one child in the UTI group without pyuria or positive nitrite had a urinary YKL-40/Cr level greater than 125.25 pg/mg.

Conclusions: Determining the levels of urinary YKL-40-Cr, may help identify true UTI in febrile young children, especially when they have pyuria, but not nitrite.

TH-PO584

Urine NGAL in Distinguishes Urinary Tract Infection from Colonization in Children on Clean Intermittent Catheterization Catherine Forster, Elizabeth C. Jackson, Stuart Goldstein, Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background: Children with neurogenic bladders who require clean intermittent catheterization (CIC) frequently have bacteriuria, although distinguishing between urinary tract infection (UTI) and colonization (UTC) in this population can be difficult. Urinary neutrophil gelatinase-associated lipocalin concentrations [uNGAL] are increased in UTCs. We hypothesize that [uNGAL] will be higher in UTC compared to UTC and negative cultures.

Methods: Urine samples were obtained from children requiring CIC who had a urine culture sent for clinical care. Urine cultures were grouped as no growth, UTC, or UTI based on the opinion of the managing clinician who did not know the [uNGAL]. Cultures with growth of mixed organisms or fungi, and from patients with concern for acute kidney injury were excluded. [uNGAL] was measured by ELISA, and [urine creatinine] by assay. Normally distributed continuous variables were compared by ANOVA and t-test; non-normally distributed continuous variables were compared by Mann-Whitney U. Categorical variables were compared by chi-square.

Results: 171 cultures from 157 patients were included (no growth = 80, UTC = 77, UTI = 4). Patients with no growth were younger than those with UTI (9.4±6.5 vs 14.7±6.7 years, P = 0.02). There were more females in the UTC group compared to no growth (64.9% vs 38.8%, P < 0.01). There was no difference in etiology of neurogenic bladder between groups. Median [uNGAL/Cr] was higher in the UTI group (746.1±205.7 vs 38.8%, P < 0.01). There was no difference in etiology of neurogenic bladder between UTI=14). Patients with no growth were younger than those with UTI (9.4±6.5 vs 14.7±6.7 years, P = 0.02).

Conclusions: Median [uNGAL/Cr] was higher in the UTI group (746.1±205.7 vs 38.8%, P < 0.01). There was no difference in etiology of neurogenic bladder between UTI.

Funding: Other NIH Support - NRSA T32 General Pediatrics Training Grant

TH-PO585

Usefulness of Plasma NGAL as a Marker to Predict Renal Parenchymal Involvement in Infants with Febrile UTI Eun Mi Yang, Dept of Pediatrics, Chonnam National Univ Hospital, Gwangju, K..

Background: Accurate detection of renal parenchymal involvement in febrile urinary tract infections (UTI) is important, especially in infants. The aim of this study was to evaluate the predictive accuracy of plasma neutrophil gelatinase-associated lipocalin (NGAL) for biomarker of renal parenchymal involvement in infants with acute febrile UTI.

Methods: A total of 61 infants, who were admitted with febrile urinary tract infection, were enrolled in this study. Enrolled patients were divided into the cortical defect group (n = 40) and non-cortical defect group (n = 21), according to the result of renal scan.

Results: The patients’ mean age was 4.4 ± 3.2 months. There were no significant differences between two groups in respect of age, gender, and fever duration. In cortical defect group, the white blood cell count and C-reactive protein levels were significantly higher than non-cortical defect group, respectively (11.7 ± 5.1 vs 21.0 ± 19.5 10^3/mm^3, P < 0.01; 2.2 ± 1.3 vs 5.5 ± 4.5 mg/dL, P = 0.001). Plasma NGAL also significantly increased in cortical defect group than non-cortical group (119 ± 135 vs. 677 ± 1951 ng/mL, P = 0.013). The most optimal cut-off value of plasma NGAL for predicting renal parenchymal involvement was defined as 230 ng/mL in the receiver operating characteristics curve analysis (sensitivity, 67.5%; specificity, 71.4%; AUC, 0.69; P = 0.006).

Conclusions: Plasma NGAL is significantly higher in cortical defect group. Although not a standalone test, plasma NGAL could be used for early detection renal parenchymal involvement in infants with acute febrile UTI.

TH-PO586

Use of Urine Sodium to Creatinine Ratio Multiplying by the Estimated Urine Creatinine for Prediction Urine Sodium in Pediatric Hypercalciuria Eun Yi Yang, Dept of Pediatrics, Chonnam National Univ Hospital, Gwangju, K..

Background: Elevated sodium excretion in urine resulting from excessive sodium intake can lead to hypercalciuria and contribute to the formation of urinary stones. The spot urine sodium to potassium ratio (Na/K) is a convenient method to estimate sodium excretion. The aim of this study was to evaluate the accuracy of predicting 24-hour urine sodium using spot urine sample in pediatric hypercalciuria.

Methods: This study included 58 children with hypercalciuria. The 24-hour urine creatinine level was estimated with the use of three existing equations: one equation for adult (Cockcroft-Gault formula) and two equations for children (Ghazali-Barratt and Hellerstein equation). The correlation was evaluated between spot urine samples, such as Na/K and urine creatinine by assay. Normally distributed continuous variables were compared by ANOVA and t-test; non-normally distributed variables were compared by Mann-Whitney U. Categorical variables were compared by chi-square.

Results: The patients’ mean age was 8.5 years, 30 patients presented hypernaturia (52%). There was a no significant correlation among Na/K, Na/Cr and 24-hour urinary sodium excretion. A moderate correlation was found between corrected Na/Cr by 24-hour creatinine excretion and 24-hour urine sodium (r = 0.387, P = 0.000). After estimating the 24-hour urine sodium levels by using the estimated urine creatinine, the correlation coefficients between the estimated and measured 24-hour urine sodium levels were 0.335, 0.372, and 0.351, respectively (All P < 0.05).

Conclusions: The calculated Na/Cr by 24-hour creatinine excretion improved the prediction of estimating 24-hour urine sodium. And spot Na/Cr multiplying by the estimated urine creatinine is not inferior to that of the corrected Na/Cr by measured 24-hour creatinine. The spot Na/Cr multiplying by the estimated urine creatinine can be used to predict 24-hour urine sodium in pediatric hypercalciuria.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
TH-PO587

Inflammatory Excess in Experimental Reflux Neprhopathy

Christina B. Ching,1 Birong Li,1 Ashley R. Jackson,1 Brian Becknell,1,2 Center for Clinical and Translationa, Research Inst at Nationwide Children’s Hospital; 1Urology Div, Nationwide Children’s Hospital; 1Nephrology Section, Nationwide Children’s Hospital.

Background: Children with vesicoureteral reflux can develop renal scars after pyelonephritis, and this reflux nephropathy is associated with hypertension, proteinuria, and renal insufficiency. Limited knowledge of histopathology, immune cell recruitment, and gene expression changes during pyelonephritis restricts the development of therapies to prevent acquired renal scarring. Here, we address this knowledge gap using inbred, immunocompetent mice with vesicoureteral reflux.

Methods: Female C3H/HeOuJ mice with 100% vesicoureteral reflux were transurethrally inoculated with uropathogenic Escherichia coli (UPEC) strain CF2073. Kidneys were analyzed by histopathology and flow cytometry. Pyelonephritis transcriptomes were evaluated by RNAseq and pathway analysis.

Results: Transurethral inoculation of UPEC leads to renal mucosal injury, tubulointerstitial nephritis, and cortical fibrosis. Fibrosis correlates most significantly with inflammation 7 and 28 days post infection. Flow cytometry identifies recruitment of neutrophils and inflammatory macrophages to infected kidneys, in proportion to renal bacterial burden. Transcriptome analysis reveals molecular signatures associated with renal ischemia-reperfusion injury, immune cell chemotaxis, and antimicrobial peptide production.

Conclusions: This murine model recapitulates the cardinal histopathologic features observed in humans with acquired renal scarring following pyelonephritis. The integration of histopathology, flow cytometry, and transcriptome data begins, for the first time, to define potential mechanisms of tissue injury during pyelonephritis in the context of an intact immune response. The relationship between inflammatory cell recruitment and fibrosis supports the hypothesis that acquired renal scarring arises as a consequence of excessive host inflammation and suggests that immunomodulatory therapies should be investigated to reduce renal scarring in patients with pyelonephritis.

Funding: NIDDK Support

TH-PO588

The Childhood Nephrotic Syndrome Observational Study: A Midwest Pediatric Nephrology Consortium Study

Michelle N. Rheaule,1 Lea Zhang,1 Halima S. Janjua,2 Donna J. Claes,3 Tarak Srivastava,4 Alejandro Quiroga,5 Jason Misurac,6 Takeshi Ninochi,7 Kazumoto Iijima,7 Oleh M. Akchurin,8 Larry A. Greenbaum,1 John D. Mahan,9 William E. Smoyer,10 1Univ of Minnesota Masonic Children’s Hospital; 2Cleveland Clinic; 3Cincinnati Children’s Hospital Medical Center; 4Children’s Mercy Hospital; 5Helen DeVos Children’s Hospital; 6Univ of Iowa; 7Kobe Univ Graduate School of Medicine; 8Weill Cornell; 9Emory Univ; 10Nationwide Children’s Hospital.

Background: Childhood nephrotic syndrome (NS) is one of the most common pediatric glomerular disorders. Modern, large-scale natural history studies are lacking. Methods: The Childhood NS Observational Study (CNOS) is a prospective, longitudinal study of children 1-18 yrs with incident NS. Children w/ secondary NS are excluded. Data are collected at presentation, 3 mo, and yearly. Two-sample t-tests were used for continuous values and Fisher’s exact tests for categorical values. Results: 126 children from 10 sites had 3-month data. Prior to diagnosis, children had an avg (range) of 1.1 (0-6) primary care visits and 0.8 (0-3) ER visits w/ NS symptoms. 62% Meth were hospitalized at dx. 84% of children were treated w/ a standard 12 week course. Steroid-sensitive (N=96; 76%) and steroid-resistant (N=30; 24%) NS were evaluated by RNAseq and pathway analysis. Kidneys were analyzed by histopathology and flow cytometry. Pyelonephritis transcriptomes were compared to those of CNOS registry.

Conclusions: Children w/ NS have high healthcare utilization around the time of dx. Children w/ steroid resistant NS are older and have lower eGFR at presentation. The CNOS registry will provide a framework for future observational and interventional studies in pediatric NS.

Funding: Private Foundation Support

TH-PO589

Race and Growth Velocity in Children with Nephrotic Syndrome: A Midwest Pediatric Nephrology Consortium Report

Oleh M. Akchurin,1 Jason Misurac,2 Hoda T. Hammad,1 Paul Christos,1 Tarak Srivastava,1 Alejandro Quiroga,1 John D. Mahan,1 William E. Smoyer,1 Larry A. Greenbaum,1 Michelle N. Rheaule,1 1Weill Cornell Medicine; 2Children’s Mercy Hospital; 3Helen DeVos Children’s Hospital; 4Univ of Iowa; 5Nationwide Children’s Hospital; 6Emory Univ; 7Univ of Minnesota.

Background: Delayed linear growth occurs in a subset of children with nephrotic syndrome (NS), but the cause is incompletely understood. An association between race and growth and has been reported in children with CKD, but it is unknown whether race affects growth in children with NS.

Methods: Growth velocity of children enrolled in the multicenter prospective Childhood Nephrotic Syndrome Observational Study was assessed as the difference between height z-scores at enrollment and 1 year follow-up. Children were enrolled at the time of initial diagnosis. Race and other variables were compared between children with growth velocity below vs. above the cohort median (S = "slow" growth group vs. F = "fast" growth group, respectively) using the two-sample t-test and chi-square test. The paired t-test was used to compare height z-scores between enrollment and 1 year follow-up.

Results: Growth data were available for 71 children (54% Caucasian, 26% Black, 11% Hispanic). Height z-score was 0.07±1.49 at enrollment and 0.11±1.17 at 1 year (p=0.90). Racial distribution was significantly different between the S vs. F groups (p=0.009): non-Hispanic Blacks were more prevalent in the S and Hispanics in the F groups; the prevalence of Caucasians was not different between the groups. Gender, birthweight, gestational age and type of health insurance were not different between the groups. There was a trend toward higher prevalence of steroid-responders in the F group (p=0.06).

Conclusions: Despite steroid exposure, height z-score did not change 1 year after diagnosis in this contemporary cohort of children with NS. However, growth rates were slower in Blacks and faster in Hispanics. Further analyses are ongoing to determine whether the effect of race on growth is mediated by steroid responsiveness and development of CKD.

Funding: Other NH1 Support - NIH/NCATS Grant #ULTR00457 awarded to the Clinical and Translational Science Center, Weill Cornell Medicine

TH-PO590

Vincristine Is Effective in Some Children with Challenging Nephrotic Syndrome

Vladimir Belostotsky, Steven Arora. Pediatrics, McMaster Children’s Hospital, Hamilton, ON, Canada.

Background: Vincristine was proven to be effective in some children with Nephrotic Syndrome (NS) who had Frequently Relapsing (FRNS), Steroid Dependent (SDNS) or Steroid Resistant (SRNS) disease. Clinical trials were suggested in late 1990s to early 2000s, but never happened due to development of other therapeutic agents including Calcineurin Inhibitors (CNIs) such as tacrolimus (Tac), ciclosporin (CsA); MMF and rituximab (Rit). Aim: To review Vincristine use in our institution in complex cases of nephrotic syndrome where treatments with Steroids (S), CNIs, MMF were unsuccessful in inducing remission (Remipients 1,3,4,5,6) or maintaining low frequency of relapses (patient 2)

Methods: Records of 6 children who received Vincristine for NS over last 5 years were reviewed.

Results: Vincristine was given at the dose of 1.5 mg/m² (max 2 mg) IV weekly for 4 doses. If successful in inducing remission then it was continued, otherwise it was stopped. Findings are summarized in table 1.

Funding: Private Foundation Support

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

Underline represents presenting author.

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COQ6 Mutations in Children with Steroid-Resistant Focal Segmental Glomerulosclerosis and Sensorineural Hearing Loss

Eunjin Park,1 Yo Han Ahn,2 Hee Gyung Kang,2,3 Young Seo Park,2 IL-Soo Ha,2 Hae Il Cheong.12

1Dept of Pediatrics, Seoul National Univ Children’s Hospital, Seoul, Republic of Korea; 2Dept of Pediatrics, Seoul National Univ Kangnam Sacred Heart Hospital, Seoul, Republic of Korea; 3Research Coordination Center for Rare Diseases, Seoul National Univ Hospital, Seoul, Republic of Korea; 4Dept of Pediatrics, Korea Univ Guro Hospital, Seoul, Republic of Korea; 5Dept of Pediatrics, Asan Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea.

Background: The phenotype combination of steroid-resistant focal segmental glomerulosclerosis (SR-FSGS) and sensorineural hearing loss (SNHL) has been mainly reported in patients with mitochondrial cytopathies, including primary coenzyme Q10 (CoQ10) deficiency.

Methods: In this study of ten children with SR-FSGS and SNHL, we identified six patients with CoQ10 deficiency caused by biallelic COQ6 mutations. We performed genotype and phenotype analyses of these six patients.

Results: The median age at the onset of nephrotic syndrome was 29 months (range 15–47 months). All patients progressed to end-stage renal disease within the median duration of 13 months (range 1–27 months) after onset. Kidney biopsies revealed FSGS with variable degrees of glomerular sclerosis, and abnormal mitochondrial proliferation in podocytes was a constant finding. None of the five patients who underwent kidney transplantation developed recurrence of FSGS.

Conclusions: Primary CoQ10 deficiency due to COQ6 mutations should be considered in children presenting with both SR-FSGS and SNHL. The condition is treatable when CoQ10 supplementation begins in the early stage; therefore, early diagnosis of COQ6 mutations is essential. We recommend early kidney biopsy because detection of abnormal mitochondrial proliferation in podocytes might provide a means to earlier diagnosis.

ADCK4-Associated Focal Segmental Glomerulosclerosis in Children

Young Seo Park,2 IL-Soo Ha,2 Hae Il Cheong.12

1Dept of Pediatrics, Seoul National Univ Children’s Hospital, Seoul, Republic of Korea; 2Research Coordination Center for Rare Diseases, Seoul National Univ Hospital, Seoul, Republic of Korea; 3Dept of Pediatrics, Asan Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea.

Background: ADCK4 is one of the novel genes causing autosomal-recessive steroid-resistant nephrotic syndrome (SRNS). ADCK4 interacts with components of the CoQ10 biosynthesis pathway. ADCK4 mutations usually manifest as isolated adolescent-onset focal segmental glomerulosclerosis (FSGS).

Methods: Here we tried to figure out the incidence of ADCK4 mutations in our Korean pediatric cohort of SRNS as well as phenotype analyses of the patients with ADCK4 mutations.

Results: The incidence of ADCK4-associated FSGS was 7.5% (4/53) of 5-year-old or older children with multidrug-resistant FSGS. Two additional patients were included for the phenotype analyses; one detected by family screening and the other with cyclosporine-responsive FSGS and medullary nephrocalcinosis. All six patients presented with incidentally found proteinuria. The median age at the onset was 110 months (range, 60–153 months), and five patients progressed to ESRD within a median duration of 46 months (range, 36–79 months) after the onset. Kidney biopsy revealed FSGS in all the patients (n=5), including a not otherwise-specified (NOS) variant in three patients and a collapsing variant in two patients. Abnormal mitochondrial proliferation was detected in podocytes as well as in renal tubular epithelial cells. Interestingly, all patients accompanied bilateral medullary nephrocalcinosis of various degrees. None of the patients had neutrophilic or other extrarenal manifestations.

Conclusions: ADCK4 mutations should be considered in older children presenting with SR-FSGS. An early diagnosis of ADCK4 mutations is essential because the condition is treatable when CoQ10 supplementation is started at the early stage. Abnormal mitochondrial proliferation in the kidney biopsy and accompanying medullary nephrocalcinosis may be useful diagnostic clues.

Injuries of Glomerular Capillaries and Basement Membrane May Be Involved in Renal Dysfunction in Thin Basement Membrane Disease

Yusuke Kaiimoto, Takefumi Kanemitsu, Michiko Aoki, Yusuke Okabayashi, Shinya Nagasaka, Dedong Kang, Akira Shimizu, Kiyotaka Nagahama.

Analytic Human Pathology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan.

Background: Thin basement membrane disease (TBMD) is diagnosed by diffuse reduction of the thickness of glomerular basement membrane (GBM) in electron microscopy (EM), and characterized clinically by benign familial hematuria. However, some cases progress to end-stage renal disease. In the present study, we performed the clinicopathological analyses of TBMD, especially focusing on glomerular capillary injuries, including morphological and qualitative alterations of GBM and glomerular capillaries, and correlated with clinical findings.

Methods: In our department, 27 renal biopsy cases of TBMD was identified in 1395 renal biopsy cases. We investigated clinicopathological characteristics using clinical records. We also examined pathological characteristics using light microscopy and EM, immunostaining for CD34, which can detect glomerular capillaries, immunostaining for α5 (IV) chains of type IV collagen, which is one of the main components of GBM, and low-vacuum scanning electron microscopy (LV-SEM), which allows detailed three-dimensional observation of GBM surface.

Results: In our cases, 26 cases (96.3%) had hematuria, 21 cases (77.8%) had proteinuria. In 6 cases, the eGFR declined in G3a to G4 in clinical CKD stage. In image analysis for CD34 immunostaining using a computer, narrowed glomerular capillaries significantly increased with accumulation of glomerular extracellular matrix (ECM) that may be associated with renal dysfunctions, compared with controls. In immunofluorescence, α5 (IV) expression was significantly reduced in the GBM with partial enhancement of α2 (IV).

In LV-SEM observations, thinning and flatterting of GBM was noted with multiple small holes and coarse manufactures in the surface of GBM.

Conclusions: In TBMD, narrowing glomerular capillaries with alterations of GBM developed with increased glomerular ECM, which may be associated with urinary abnormalities and renal dysfunctions. Injuries of glomerular capillaries and GBM may be developed in TBMD, and be associated with urinary abnormalities and renal dysfunction.
TH-PO595

Efficacy of Cyclosporine A for Severe Henoch-Schönlein Purpura Nephritis in Children

Takahisa Hirakata-i, Jiro Kino, Sohsko Yamanouchi, Chikushi Suruda, Shoji Tsuji, Kazunari Kaneko. 

Pediatrics, Kansai Medical Univ, Hirakata-shi, Osaka, Japan.

Background: Though the treatment for severe Henoch-Schönlein purpura nephritis (HSPN) is not established. While methylprednisolone and urokinase pulse therapy (MUPt) or intensive multiple-drug therapy including steroid (MDT) have been reported to be effective in some patients with HSPN of poor prognosis, others do not respond to these therapies. Recently, cyclosporin A (CsA) has been postulated to be effective for children with severe HSPN. Our aim was to assess the efficacy of CsA as the rescue therapy for steroid-resistant HSPN or the first line treatment for severe HSPN.

Methods: 9 children with severe HSPN (5 boys, median age 7.3: range 4-13 years) were enrolled. Severe HSPN was defined as both the histological severity of grade III-V and the clinical severity showing nephrotic range proteinuria. 4 patients allocated for the rescue therapy (G-I) received MUPt or MDT initially without success and were switched to CsA administration. Their median protein-to-creatinine (PC) ratios at the time of CsA initiation was 10.3 g/gCr. 5 patients allocated for the first line treatment (G-II) did not receive any steroid before the administration of CsA. Their median PC ratios at the time of CsA initiation was 16.1 g/gCr. CsA dosage ranged from 2.5 to 4 mg/kg per day. All patients in both groups received an angiotensin-converting enzyme inhibitor before CsA initiation. This study was approved by the ethical committee of Kansai Medical University.

Results: We excluded 1 patient in G-II from the study, as she developed hypertension after initiation of CsA. Except for this patient, other 8 patients responded well to CsA: proteinuria disappeared in all with the median period after CsA commencement of 4.7 months in G-I and 6.0 months in G-II. The total period of pharmacological treatment in G-II was shorter than that in G-I (10.6 vs 6.0 months, P=0.08).

Conclusions: CsA is effective to reduce the amount of proteinuria not only as the rescue therapy for steroid-resistant HSPN but also as the first line treatment for severe HSPN.

TH-PO596

Metabolic Syndrome and Associated Longitudinal Changes in Kidney Function in Children with CKD

Shwetal P. Lalan, Derek Ng, 2 Fernanda Kupferman, 3 Susan L. Furth, 1 Bradley Warady, 4 Mark Mitsnefes. 1 Brookdale Univ Hospital Center; 2 Johns Hopkins Bloomberg School of Public Health; 3 Cincinnati Children’s Hospital; 4 Children’s Mercy Hospital, The Children’s Hospital of Philadelphia.

Background: While individual CV risk factors are frequent in children with CKD, incidence of metabolic syndrome (MS) and its effect on CKD progression are not well known. The goal of this study was to describe prevalence of MS and associated longitudinal changes in renal function in children in the CKD study.

Methods: MS was defined as presence of obesity (BMI >90th percentile) and at least 2 of the 4 comorbidities: high triglycerides (TG) >200 mg/dl, low HDL cholesterol (<40mg/ dl), hypertension (HTSHBP/DHR >95th percentile, diagnosis or use of antiHT therapy) and hyperglycemia (>100mg/dl). Subjects were classified as never MS, incident MS, resolved MS and persistent MS with annual eGFR change. Wilcoxon rank sum tests compared the distributions of annual percent change in GFR by MS classification, overall and pairwise with never MS as the reference group.

Results: Of 706 children, 64 (9%) had MS at the baseline. The majority had high TG levels (83%) and HT (78%), hyperglycemia occurred in 31%, 71% of those with MS had 3 and 30% had 4 components of MS. Of those without MS at baseline, 43% had HT, 38% had high TG and 12% had hyperglycemia. Among those free of MS, 96% continued to be free (never MS) and 5% developed incident MS. Of the 64 with baseline MS, 42% did not have MS after 2 years (resolved MS) and 58% continued to have MS (persistent MS). Children with and without MS had similar eGFR at baseline. The decline in eGFR per year was faster in children with persistent MS, -11.4% compared to never MS, -5.1% (P=0.04).

Conclusions: Persistent MS was associated with accelerated eGFR decline, preventing or treating these comorbidities, particularly obesity, may slow the progression of CKD.

TH-PO597

The Excretory Activity of the Kidneys in Children Treated for Overweight or Obesity

Tomasz Jerzy Irzykiewicz, 1,2 Anita Kocieba-Laciak, 3 Izabela Maciejewska-Paszek. 1 Department of Health Promotion and Community Nursing, Faculty of Health Sciences, Medical University of Silesia, Katowice, Poland; 2Department of Nephrology/ENDO, MSiR Hospital, Katowice, Poland; 3Medical Univ of Silesia, Katowice, Poland.

Background: Children with excess weight usually exhibit elevated kidney perfusion resulting from glomerular hyperfiltration. Unfortunately, there are no noninvasive methods to precisely evaluate GFR in children. A useful method of GFR estimation in obese children is the calculation of eGFR according to the Bouvet formula. The aim of the study was to evaluate the influence of excess weight and successful weight reduction on the excretory activity of the kidneys in overweight or obese children.

Methods: Creatinine (Cr) and cystatin C (cyst) concentrations were determined and eGFR was calculated using the Bouvet formula in a group of 95 children (9-13y.), of whom 62 were overweight and 33 obese. The results were compared to the values, which could be found in the population of Polish children (PC) with BMI at the 50th percentile (BMI 17.5±0.8kg/m², Cr 0.6±0.2mg/dl, cyst 0.54±0.1mg/L). eGFR 53±1.4ml/min was obtained before and after a 6-month weight reduction period in 23 patients, who demonstrated BMI reduction of over 5% were also analyzed.

Results: Children with excess weight had higher eGFR and GFR compared to PC. Despite of the different BMI (30.4±25.3±2kg/m²), eGFR and GFR were only slightly higher in obese compared to overweight children (1.21±0.05 vs 1.14±0.4mg/L - ns and 100.7±29.7 vs 90.8±25 ml/min, P=0.08). In contrast to overweight, in obese children, after a 6-month weight reduction program, the decreases in cystatin C level (1.3±0.8 vs 0.8±0.4mg/L) and eGFR (107±46.5 vs 97.3±29.2 ml/min, P=0.01) were significant. Further calculations revealed that the decrease in cystatin C level (p=0.04) and eGFR (p=0.04) was only significant in male obese patients.

Conclusions: 1. Excess weight in children causes glomerular hyperfiltration. 2. Due to glomerular hyperfiltration, weight loss has a beneficial effect on the excretory activity of the kidneys, in obese children. 3. Following weight reduction, a significant decrease in cystatin C level and eGFR value occurs but only in obese boys.

TH-PO598

Identification and Staging of Blood Pressure Using the STOP Intervention in Pediatric Nephrology Ambulatory Care

Hailey Woollen, Donald J. Weaver, Charles P. McKay, Susan F. Massengill. Pediatric Nephrology, Levine Children’s Hospital, Charlotte, NC.

Background: Prior studies in pediatric patients with chronic kidney disease (CKD) have shown an association with declining kidney function and hypertension (HTN), yet the prevalence of blood pressure (BP) control in children with CKD has not been well described. Sequential BP control in children with CKD is not established. While methylprednisolone and urokinase pulse therapy (MUPT) or cyclosporine A (CsA) are effective in some patients with HSPN of poor prognosis, others do not respond to these therapies. Recently, cyclosporine A (CsA) has been postulated to be effective for children with severe Henoch-Schönlein purpura nephritis (HSPN) is not established. While methylprednisolone and urokinase pulse therapy (MUPt) or intensive multiple-drug therapy including steroid (MDT) have been reported to be effective in some patients with HSPN of poor prognosis, others do not respond to these therapies. Recently, cyclosporin A (CsA) has been postulated to be effective for children with severe HSPN. Our aim was to assess the efficacy of CsA as the rescue therapy for steroid-resistant HSPN or the first line treatment for severe HSPN.

Methods: 9 children with severe HSPN (5 boys, median age 7.3: range 4-13 years) were enrolled. Severe HSPN was defined as both the histological severity of grade III-V and the clinical severity showing nephrotic range proteinuria. 4 patients allocated for the rescue therapy (G-I) received MUPt or MDT initially without success and were switched to CsA administration. Their median protein-to-creatinine (PC) ratios at the time of CsA initiation was 10.3 g/gCr. 5 patients allocated for the first line treatment (G-II) did not receive any steroid before the administration of CsA. Their median PC ratios at the time of CsA initiation was 16.1 g/gCr. CsA dosage ranged from 2.5 to 4 mg/kg per day. All patients in both groups received an angiotensin-converting enzyme inhibitor before CsA initiation. This study was approved by the ethical committee of Kansai Medical University.

Results: We excluded 1 patient in G-II from the study, as she developed hypertension after initiation of CsA. Except for this patient, other 8 patients responded well to CsA: proteinuria disappeared in all with the median period after CsA commencement of 4.7 months in G-I and 6.0 months in G-II. The total period of pharmacological treatment in G-II was shorter than that in G-I (10.6 vs 6.0 months, P=0.08).

Conclusions: CsA is effective to reduce the amount of proteinuria not only as the rescue therapy for steroid-resistant HSPN but also as the first line treatment for severe HSPN.

TH-PO599

Ambulatory Blood Pressure Tracking in Pediatric Kidney Transplant Recipients

Gilad Hamdani, 1 Edward Nehus, 1 Coral D. Hanevold, 2 Judith C. Easley-VinSickle, 2 Scott E. Wenderfer, 1 David K. Hooper, 1 Bradley Warady, 4 Mark Mitsnefes. 1 Pediatric Nephrology and Hypertension, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Pediatric Nephrology, Seattle Children’s Hospital, Seattle, WA; 3Pediatric Nephrology, Children’s Mercy Hospital, Kansas City, MO; 4Pediatric Renal Section, Texas Children’s Hospital, Houston, TX.

Background: Hypertension (HTN) is common after kidney transplantation, and is associated with adverse outcomes. We aimed to assess blood pressure (BP) control by using ambulatory BP monitoring (ABPM) in pediatric and young adult kidney transplant recipients.

Methods: A retrospective chart review of all kidney transplant recipients in 4 pediatric centers with at least two ABPMs during the follow up post transplantation. Casual HTN was defined as systolic/diastolic BP ≥95th percentile. The final reading but only 13% had an intervention of additional evaluation or therapy change. The remaining 17% forms an at-risk group for practice improvement. The study is ongoing and will address the blood pressure control outcome in an expanding cohort of children with CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: One hundred and twenty four patients (median age 17y, 40% young adults, 69% male) were included in the study. Median time between first and last ABPM was 2 years. More patients were taking BP medications at last follow up (79% vs. 71%, p=0.001); 47% had normal first ABPM and 62% had normal last ABPM (p=0.01). At initial ABPM, 36% and 17% of patients were classified as having masked and sustained HTN, respectively, compared with 31% and 7% at last ABPM. The proportion of controlled HTN (normal BP on hypertensives) increased from 27% to 42%, whereas uncontrolled HTN decreased from 41% to 32% (table). Proportion of patients with masked HTN not on hypertensives decreased from 11% to 4%.

### TH-PO600

**Left Ventricular Hypertrophy in Pediatric Hypertension and Obesity:**  
**A Systematic Review of Echocardiographic Studies**  
Jwona Dziewa, Haseena Sahib, Katarina Supe-Markovina, Robert Woroniecki. Pediatrics and Pediatric Nephrology, Stony Brook Children's Hospital, Stony Brook, NY.

**Background:** Left ventricular hypertrophy (LVH) is an important end point of hypertension (HTN), and/or obesity-associated cardiovascular disease. However, there are multiple definitions of LVH in children, and it is unclear how those definitions affect LVH prevalence. Our objective was to perform a systematic review of literature to report LVH prevalence as determined by echocardiography (ECHO) in children with HTN and/or obesity, and to examine how various definitions affect LVH prevalence.

**Methods:** PubMed search was performed in accordance with the PRISMA statement. We used terms: left ventricular hypertrophy, LVH, LVMI, obesity, hypertension, echocardiogram, ECHO, cardiac hypertrophy, obesity, cardiomyopathy, and limited search to infants, children and adolescents. Full text published articles in English from 01/01/2000 to 05/31/2016 were included. Subjects with kidney transplantation or chronic dialysis were excluded. We examined effect of 4 definitions on LVH, based on left ventricular mass index (LVMI): (A) LVMI> 51 g/m², (B) LVMI >38.6 g/m² (Daniels et al.), (C) LVMi- the 95th-tile LMS reference (Foster et al.), and (D) LVMI>95th-tile for gender and chronological age (Khoury et al).

**Results:** Our search yielded 111 articles, and 13 studies that met inclusion/exclusion criteria were included in the final analysis. There were 1613 subjects, 13:9±1.9 years old, 56.1% males, with body mass index (BMI) 27.4±5.1, 44.9% were obese. 7/13 (53.8%) gender and chronological age (Khoury et al).

**Conclusions:** Using ABPM to monitor BP, we observed improvement in BP control in pediatric and young adult kidney transplant recipients during follow up.

### TH-PO601

**Left Ventricular Hypertrophy and Associated Factors in Children with Chronic Kidney Disease:**  
Results from the KoreanN Cohort Study for Outcomes in Patients with Pediatric Chronic Kidney Disease (KNOW-Ped CKD)  
Heeyeon Cho,1 Kyong Hee Han,2 Seong Heon Kim,4 Hee Sun Baek,3 Min Hyun Cho,2 Jae Il Shin,4 Joo Hong Lee,5 Young Seo Park,4 Hyun-Jin Choi,7 Hee Gying Kang,4 IL-Soo Ha,9 Hae Il Cheong.1 Pediatrics, Samsung Medical Center, Seoul, Korea; Pediatrics, Kyunggok National Univ Children's Hospital, Daegu, Korea; 1Pediatrics, Asan Medical Center, Seoul, Korea; 1Pediatrics, Pusan National University Hospital, Pusan, Korea; 1Pediatrics, Seoul National Univ Children's Hospital, Seoul, Korea; 1Pediatrics, Severance Hospital, Seoul, Korea; 1Pediatrics, Yeouido National Univ Hospital, Jeju, Korea.

**Background:** Children with chronic kidney disease (CKD) is known to be a high risk group of cardiovascular disease, and left-ventricular hypertrophy (LVH) is an early marker of cardiovascular disease. We assessed the prevalence and contributing factors of LVH in pediatric CKD patients.

**Methods:** We conducted a cross-sectional study using baseline data from the KoreaN cohort study. Outcome in patients With Pediatric Chronic Kidney Disease (KNOW-Ped CKD), a nationwide, prospective, and observational cohort study of pediatric CKD. Univariate and multiple logistic regression analysis were performed to evaluate the association of variables with LVH. LVH in children has been widely defined as a left ventricular mass index (LVMI)>95 percentile. However, LVMI increases with decreasing height in young children, and we used a novel method of expressing left ventricular mass relative to body size in children. The patients with left ventricular mass above the 95th percentile for height (z score>1.64) were classified as having LVH.

**Results:** Total 381 children with CKD were enrolled, and the mean age was 9.9±3.45 years. Thirty patients (9.1 %) were diagnosed with LVH. Univariate logistic regression revealed positive association between LVH and primary disease (glomerulonephritis), body mass index, and systolic hypertension. Primary disease of glomerulonephritis and systolic hypertension were independently associated with LVH in multivariate logistic regression (p=0.005, p<0.001).

**Conclusions:** The results of this study suggest that the history of glomerulonephritis and systolic hypertension might predispose to increased LVMI in pediatric patients with CKD.

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

### TH-PO602

**Carotid Intima Media Thickness in Children with Chronic Kidney Disease**  
Abdullahi Mudir,1,2 Zaiboonsana Holland,3 Caroline Dickens,5 Daynia Ballott,4 Cecil S. Levy.4 1Dept of Paediatrics and Child Health, Univ of the Witwatersrand and Charlotte Maxeke, Johannesburg Academic Hospital, Johannesburg, South Africa; 2Dept of Paediatrics, Bayero Univ, Kano, Nigeria; 3Dept of Radiology, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; 4Dept of Medicine, Univ of the Witwatersrand, Johannesburg, South Africa.

**Background:** Cardiovascular disease (CVD) is a common complication of chronic kidney disease (CKD). In children with CKD, CVD may manifest as early changes in arterial thickness and or stiffness. We aimed to determine the correlates of carotid intima media thickness (cIMT) in children with CKD.

**Methods:** Seventy-one children with CKD stage 1–5 had a physical examination, routine follow up blood tests and a Carotid Doppler ultrasound to determine the average cIMT.

**Results:** The mean age of the children was 11.1± 3.4, with 46/71 males and 25/71 females and a mean cIMT of 0.504mm ± 0.062. There were 43/71 pre-dialysis CKD patients and 28/71 on chronic dialysis. The mean cIMT and mean arterial pressure(MAP) were greater in patients on dialysis (0.530mm ± 0.067 and 92.0mmHg ± 2.67) when compared to CKD patients without dialysis (0.496±0.054 and 84.4±2.54), and there was a significant difference between the means (p=0.005 and 0.004).

**Conclusions:** There was a significant positive correlation of cIMT with MAP, blood urea, alkaline phosphatase and PTH levels (p<0.05). There was also a significant negative correlation of cIMT with haemoglobin levels (p<0.05). Duration on dialysis also showed a positive correlation with cIMT. After adjusting for the various correlates in a multivariate regression model, only MAP had a significant association with cIMT (p=0.023).

### TH-PO603

**Circulating Mid-Region Pro-Adrenomedullin is Associated with Abnormal Aortic Pulse Wave Velocity in Pediatric Chronic Kidney Disease**  
Isaac Liu,1 Qiao-Zhi Chee,1 Mya Than,1 Lingli Gong,2 Josephine Berboson Lunaria,2 Teng Hiang Heng,1 Chloe Chan,1 Yew Peng Perry Lau,1 Wee Song Yeo,1 Li Hang Ling,1 Mark Richards,2 Yiong Huck Chan,3 Kar Hui Ng,1 Hui Kim Yap,1 1Shaw-NKF-NUH Children’s Kidney Center, KTP- Univ Children’s Medical Inst, National Univ Health System, Singapore; 2Cardiovascular Research Inst, National Univ Health System Singapore; 3Biostatistics Unit, Yong Loo Lin School of Medicine, National Univ of Singapore, Singapore.

**Background:** Children with chronic kidney disease (CKD) are at risk of early arteriopathy and aortic pulse wave velocity (PWV) is a predictor of cardiovascular mortality. This study examined its association with circulating biomarkers such as mid-regio proadrenomedullin (MR-proADM).

**Results:** There were 107 patients (61 males, 46 females) aged 5–18 years. PWV was divided into normal (< 1400 cm/s) and abnormal (≥ 1400 cm/s) based on age and sex. The PWV was significantly higher in the abnormal group compared to the normal group (1308.9 ± 202.5 vs. 1101.0 ± 172.5 cm/s, p < 0.05). The median (IQR) PWV was higher in patients with MR-proADM levels of ≥ 100 pg/mL (1362.0 ± 307.5 cm/s) compared to those with MR-proADM levels of < 100 pg/mL (1160.0 ± 173.5 cm/s, p = 0.012). There was no significant difference in PWV between patients with normal and abnormal albuminuria (1289.0 ± 231.5 vs. 1254.0 ± 195.5 cm/s, p = 0.433). The median PWV was significantly higher in patients with eGFR < 60 mL/min/1.73 m² compared to those with eGFR ≥ 60 mL/min/1.73 m² (1398.0 ± 217.5 vs. 1135.0 ± 143.5 cm/s, p < 0.001).

**Conclusions:** PWV is an independent correlate of cIMT in both pre dialysis and dialysis CKD children.
Methods: Cross-sectional analysis of baseline parameters was carried out in a cohort of 67 (39 male) consecutive patients (mean age 14.2±6.3 years) and their CKD stage 2–5D (mean duration of disease 10.66±6.4 years). Aortic PWV was measured by B-mode ultrasound. MR-proADM, N-terminal pro-B-type natriuretic peptide (NT-proBNP), asymmetric dimethylarginine (ADMA), and high-sensitivity C-reactive protein were measured along with routine biochemical parameters including hemoglobin, uric acid, calcium, and phosphate. Univariate and multivariate logistic regression was performed to examine associations between abnormal PWV (>2 SD for height) and biomarkers with performance of ROC analysis.

Results: Thirteen (19.4%) patients had abnormally increased PWV. On univariate analysis, phosphorus (OR 3.17; 95%CI 1.01–9.88; p=0.048) and MR-proADM (OR 2.50; 95%CI 1.30–4.82; p=0.006) were significantly associated with abnormal PWV. On multivariate logistic regression, MR-proADM remained independently associated with abnormal PWV (OR: 4.37; 95%CI 1.18–16.19; p=0.027). MR-proADM discriminated normal from elevated PWV by ROC analysis (AUC=0.75; 95% CI 0.60-0.90; p=0.005). MR-proADM >1.44 mmol/L, had 85% sensitivity and 67% specificity for detection of elevated PWV.

Conclusions: MR-proADM is an independent identifier of abnormally increased aortic PWV. MR-proADM may be useful for predicting arteriopathy in children with CKD.

Funding: Government Support - Non-U.S.

TH-P0604

Improving Blood Pressure Control in a Pediatric Chronic Kidney Disease Population

Dona J. Claes, MasatoshI Ashiki, De S. Dahale, David K. Hooper. 1Div of Pediatric Nephrology, Cincinnati Children’s Hospital, Cincinnati, OH; 2James M Anderson Center of Healthcare Excellence, Cincinnati Children’s Hospital, Cincinnati, OH.

Background: Intensive blood pressure (BP) control can slow pediatric chronic kidney disease (CKD) progression, yet many have untreated or uncontrolled BP. We wished to understand how system-level interventions would improve systolic BP (SBP) control.

Methods: We developed an EMR CKD registry, pre-visit planning, and patient care tools that displayed the 3 previous clinic SBP and achievement of CKD care goals. The registry was queried monthly for the last clinic SBP%. Using cross-sectional analysis or statistical process control (SPC), we assessed 1) "perfect BP measurement" elements 2) anti-hypertensive therapy in pts with SBP > 75%, & 3) controlled clinic SBP to < 90%, and how each might improve adherence. System-level interventions led to improved SBP control to < 75% in a system-wide effort.

Results: 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) during 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) during 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) during 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) during 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) during 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) during 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) during 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) during 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) during 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) 3/2016, we observed improvement in SBP control to < 75% (56% to 72%; p=0.03); there was no significant increase in anti-hypertensive therapy in pts with SBP > 75%, & 3) controlled clinic SBP to < 90%, and how each might improve adherence. System-level interventions led to improved SBP control to < 75% in a system-wide effort.

Conclusions: System-level interventions led to improved SBP control to < 75% in a pediatric CKD population. Further interventions to optimize medication dosing, reduce cycles of hospitalization in those poorly controlled, and recognize & mitigate barriers to adherence are needed.

Funding: Government Support - Non-U.S.

TH-P0605

Genomic Imbalances in Children with Chronic Kidney Disease

Benita S. Lipska-Zielaskiewicz, Magdalena Koczkowka, Elke Wuehl, Craig S. Wong, Anette Melk, Uwe Querfeld, Franz S. Schaefer, 1Medical Univ of Gdańsk, Poland; 2Univ of Heidelberg, Germany; 3Univ of New Mexico; 4Hannover Medical School, Germany; 5Charite Berlin, Germany.

Background: Chromosomal microarrays are routinely utilized for genetic testing of pediatric patients with clinically suspected syndromic disease. The most frequent imbalances were 17q12 deletions encompassing the CHD1L locus (n=7) and rearrangements at 22q11.2 (n=5). Small, including single gene, rearrangements were reported for CHN1, EYA1, HNF1B, PDK1, TSC2, FMAM8A, BMP2 and TAF1PA2 loci.

Conclusions: The detection of a genomic imbalance allowed for reverse phenotyping in most cases, resulting in clinical interventions such as evaluation for extra-renal involvement and multidisciplinary care. Genomic disorders account for a small but significant portion of children with severe kidney disease. Early recognition has important implications for genetic counseling and clinical management.

Funding: NIDDK Support

TH-P0606

Office Blood Pressure Has Similar Associations with ESRD and Death as 24 Hour Ambulatory Blood Pressure in Hypertensive CKD

Elaine Ku, Charles E. McCulloch, Francis B. Gabbai, Joachim H. L., Chi-Yuan Hsu. 1UCSF; 2UCSD.

Background: Although ambulatory blood pressure monitoring (ABPM) is considered the best method of assessing blood pressure, few studies have performed comparisons of the ability of ABPM vs. office blood pressures (BPs) to discriminate risk of adverse outcomes in patients with CKD.

Methods: In the African American Study of Kidney Disease Cohort (AASK) study (N=527), we compared office vs. ABPM BPs in their prediction and discrimination of risk for two outcomes: i) concurrent left ventricular hypertrophy (N=285) by echocardiography and ii) subsequent ESRD or death (N=557). Unadjusted models were used to compare the association between these outcomes and i) one office systolic (SBP) or diastolic (DBP) reading vs. ii) mean 24 hour SBP or DBP ABPM readings taken concurrently. C-statistics were determined for all models, and net reclassification indices (NRI) determined in models where ABPM was added to office BPs.

Results: For all outcomes, c-statistics were similar for models with office vs. ABPM BPs, and differences in the c-statistics did not achieve statistical significance for either SBP or DBP (all p>0.05). There was no improvement in NRIs if ABPM BPs were added to office BPs (all p>0.05).

Funding: Government Support - Non-U.S.

TH-P0607

BMI and Height Trajectory with Declines in Kidney Function in Children with CKD

Elaine Ku1, Charles E. McCulloch, Joel D. Kopp,2 Mark Mitsnefes,3 Kirsten L. Johansen, 1UCSF; 2Harbor-UCLA; 3Univ of Cincinnati.

Background: Protein-energy wasting and short stature are associated with poorer prognosis for children with CKD. However, few studies have rigorously described the relationship between CKD progression and longitudinal weight or height changes. We examined weight (assessed by changes in body mass index [BMI]) and height trajectory with declines in renal function over time in children in the Chronic Kidney Disease in Children (CKiD) cohort study.

Methods: We included 836 participants with CKD for longitudinal analysis. Weight, height, and serum creatinine C were measured annually. All BMI and height values were converted into age and sex standardized z-scores using Center for Disease Control normative standards. We used segmented, mixed effects regression for modeling the repeated measures of BMI z-score and linear mixed models for modeling height z-scores as a function of estimated GFR (using the 2012 Schwartz equation).

Results: Mean BMI z-score was 0.46, and mean height z-score was -0.55 at baseline. During mean follow-up of 3.1 years, BMI z-score was stable until eGFR of approximately 30 mL/min/1.73 m^2. When eGFR dropped below 30 mL/min/1.73 m^2, a 0.35 (95% CI 0.2, 0.4) decline in BMI z-score was noted with each 10 mL/min/1.73 m^2 decline in eGFR. The associations between eGFR and BMI z-score trajectory before and after an eGFR of 30 mL/min/1.73 m^2 were statistically significantly different (p<0.001). In contrast, for height, there was a continuous and linear 0.01 decrease in height z-score with every 10 mL/min/1.73 m^2 decline in eGFR.

Funding: Government Support - Non-U.S.
Disparities in Transplant Access Partially Mediate Higher Risk of Mortality in Black versus White Children with ESRD

Barbara Ku, Charles E. McCulloch, Barbara A. Grimes, Kirsten L. Johansen. UCSF.

Background: Although black race is associated with worse health outcomes in the general population, observational studies have reported that black adults receiving dialysis have paradoxically better survival than their white counterparts. Whether this racial "survival paradox" exists in children with ESRD is unclear. Our objective was to compare the mortality risk among black versus white children treated with renal replacement therapy.

Methods: Retrospective analysis of mortality risk in black (N=8,782) or white (N=3,108) children who developed ESRD between 1995-2011 and were followed through 2012 in the national ESRD registry (US Renal Data System) using Cox models.

Results: During median follow-up of 7.1 years, 8,791 transplants and 1,579 deaths occurred. Risk of death was 1.58 times higher in black vs. white children (95% CI 1.42-1.76). The higher risk of death in black (vs. white) children did not differ significantly by age category, body mass index, initial treatment modality, cause of ESRD, or calendar period (all p>0.05 for interaction), but did differ by sex (p=0.003) and insurance status (p=0.04) such that the disparity was more pronounced among girls and children without insurance.

Overall cohort (N=11,890) Hazard ratio (95% CI) P-value

Unadjusted model 1.86 (1.68-2.05) <0.001

Adjusted model* 1.58 (1.42-1.76) <0.001

Adjusted model with transplant as time dependent covariate* 1.21 (1.08-1.34) 0.001

*Adjusted for co-variates listed in Figure

The higher risk of death in black (vs. white) children did not differ significantly by age category, body mass index, initial treatment modality, cause of ESRD, or calendar period (all p>0.05 for interaction), but did differ by sex (p=0.003) and insurance status (p=0.04) such that the disparity was more pronounced among girls and children without insurance.

Conclusions: In children with CKD, steeper declines in BMI mostly occur when eGFR is ≤30 mL/min/1.73 m², whereas height exhibited a continuous and linear decline with advancing CKD. Further research is needed to determine whether earlier interventions to prevent weight loss and improve height accrual with advancing stages of CKD will improve outcomes.

Funding: Other NIH Support - NHLBI

TH-PO608

Systemic Anticoagulation with Enoxaparin in Children with End Stage Renal Disease Receiving Hemodialysis or Peritoneal Dialysis


Background: Due to predictable pharmacokinetics (PK) and anticoagulation response, enoxaparin is the preferred anticoagulant in children. However, enoxaparin is renally cleared and bioaccumulation over time leading to over-anticoagulation and increased bleeding risk is a concern in End Stage Renal Disease (ESRD). The effect of Hemodialysis (HD) & Peritoneal Dialysis (PD) on enoxaparin PK is not clearly understood and there are no reports on the safety and efficacy of enoxaparin in pediatric dialysis patients. We report our center’s experience with a recently implemented protocol for enoxaparin anticoagulation in children with ESRD receiving HD or PD.

Methods: Enoxaparin was initiated at an age- and weight-based dose administered at half the standard frequency (once daily) after HD or PD. Peak and trough anti-Factor Xa levels were monitored closely and dose and/or frequency were adjusted to achieve target peak anti-FXa levels and maintain trough anti-FXa ≥2.0 U/mL. We retrospectively reviewed the records of patients on dialysis who received enoxaparin for treatment or prevention of thromboembolism according to this protocol.

Results: 9 patients (3 males, median age 4 years) with ESRD on HD(5) or PD(4) received 10 enoxaparin courses (5 therapeutic, 5 prophylactic) per our protocol. 5 patients had at least 2 thrombophilic risk factors, with factor VIII elevation being the most common risk factor (63%). At the time of this study, the median duration of anticoagulation was 4.5 months (1-32) with 5 patients still receiving enoxaparin. Bioaccumulation was observed in 3 patients receiving daily therapeutic enoxaparin (2 PD, 1 HD) which resolved after adjusting the dose frequency to every other day. There were no anticoagulation failures or bleeding complications.

Conclusions: Enoxaparin is a feasible option for systemic anticoagulation in children on HD or PD but requires close laboratory monitoring to ensure safe and optimal anticoagulation. Larger studies are needed to clarify safety and efficacy of our protocol.

Funding: Government Support - Non-U.S.

TH-PO610

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Funding: Government Support - Non-U.S.

TH-PO611

Assessment of the Long-Term Safety and Efficacy of Multiple Doses of C.E.R.A. (Continuous Erythropoietin Receptor Activator – Methoxy Polyethylene Glycol-Epoetin β) for Maintenance Treatment of Anemia in Pediatric Patients with Chronic Kidney Disease (CKD) on Hemodialysis (HD) (N119707, NCT00171366)

Michel Fischbach, Elke Wuchl, Sylvie C. Meyer Reigner, Zoe Morgan, Franz S. Schaefer. 1Univ Hospital Strasbourg, CHU HautePierre, Strasbourg, France; 2Heidelberg Univ Hospital, Heidelberg, Germany; 3F. Hoffman-La Roche Ltd, Basel, Switzerland.

Background: The objective of this study was to document the long-term safety and efficacy of C.E.R.A. administration in pediatric patients with anemia associated with CKD.

Methods: This open-label multicenter study included a 2-week screening period, 16-week dose-titration period, and 4-week evaluation period. Stable patients (hemoglobin
Additional studies are needed to better understand the reasons for these differences.

**Conclusions:** C.E.R.A. was efficacious in maintaining stable Hb levels in pediatric patients on HD with stable anemia of CKD when switched from maintenance treatment with epoetin alfa/beta or darbepoetin. Safety was consistent with the known safety profile for C.E.R.A. in adults.

**Funding:** Pharmaceutical Company Support - F Hoffman-La Roche Ltd

**TH-PO612**

**Racial/Ethnic Disparities in Use of Peritoneal Dialysis and Transfer to In-Center Hemodialysis among Pediatric Patients**

Melissa Sooho,1 Elani Streja,1 Matthew B. Rivara,2 Scott V. Adams,3 Connie Rhee,4 Keith C. Norris,3 Kamyar Kalantar-Zadeh,5 Rajnish Mehrotra.3 1UC Irvine; 2Univ of Wash; 3UCLA.

**Background:** Racial/ethnic disparities exist in adult end-stage renal disease (ESRD) patients, showing that minorities are less likely to utilize peritoneal dialysis (PD) and African-Americans are more likely to transfer off of PD, compared to whites. PD is increasingly used for treating ESRD; however, racial/ethnic differences in utilization and outcomes among pediatric PD patients remain understudied.

**Methods:** We used logistic regression to examine the odds of PD use according to race/ethnicity among 14,109 pediatric (age<20 years) patients who initiated dialysis between 2000-2013 and treated for at least 60 days during follow-up, according to USRDS records. Among 6,551 pediatric PD patients, we used competing risk regression to examine the association of race/ethnicity with mortality, transplantation and transfer to in-center hemodialysis. Models were stratified by age at ESRD incidence and adjusted for cause of ESRD, demographics and socioeconomic factors.

**Results:** Among pediatric patients, African-Americans<20 years old and Hispanic whites ≤18 years old were less likely to use PD, compared to whites. The cohort treated with PD was comprised of 48% whites, 25% African-Americans and 27% Hispanic whites. We did not observe significant racial/ethnic survival differences while using PD. However, African-Americans and Hispanic whites had a lower risk of receiving a kidney transplant while on PD compared to whites. Finally across strata of age, African-American patients ≥5 years old had a higher risk of transferring to in-center hemodialysis(ref/whites).

**Conclusions:** Racial/ethnic and age disparities are present in the utilization of PD as well as transplantation and transfer to in-center hemodialysis among pediatric PD patients. Additional studies are needed to better understand the reasons for these differences.

**Funding:** NIDDK Support

**TH-PO613**

**Peritoneal Expression of Antimicrobial Ribonucleases in Pediatric Patients Undergoing Chronic Peritoneal Dialysis**

Neha Dhingra,1 Rose M. Ayoub, Brian Becknell.2 1Nephrology Section, Nationwide Children’s Hospital; 2Center for Clinical and Translational Research, Nationwide Children’s Hospital.

**Background:** Peritoneal dialysis (PD) is the most common dialysis modality for children with End Stage Renal Disease (ESRD). PD catheter-related infections cause significant morbidity and mortality in children. Antimicrobial peptides serve critical roles in epithelial defense throughout the body, but their roles in the peritoneum are mostly unexplored. The Ribonuclease (RNase) A superfamily encodes multiple AMPs with potential microbicidal activity against pathogens implicated in peritonitis. We hypothesize that antimicrobial RNases are present in the peritoneum of children undergoing PD.

**Methods:** With institutional review board approval, we recruited 7 patients from our dialysis unit aged 3-21 years on chronic continuous cycling PD (CCPD). Up to 200 ml of PD effluent was collected from each patient, prior to starting nightly PD. Viable cells were isolated by centrifugation, and subject to protein extraction. Antimicrobial RNases and the Ribonuclease Inhibitor (RNH1) were detected by immunoblotting. RNase activity was measured by RNA hydrolysis. Since these patients underwent omentectomy at the time of PD catheter placement, we localized RNases in omentum by immunostaining.

**Results:** RNase activity was detectable in PD effulents, which expressed RNase3, RNase6, and RNase7 proteins by immunoblotting. When effluents were subject to centrifugation, the RNase3, RNase6, and RNH1 proteins were detected in the leukocyte-rich cellular sediment. Within omentum, RNase3 and RNase6 localized to neutrophils and mononuclear leukocytes, whereas RNase7 localized to mesothelium.

**Conclusions:** Leukocytes and mesothelial cells collaborate to release antimicrobial RNases into the peritoneal fluid in the absence of peritonitis. This process is likely under tight regulation by RNH1, to prevent RNase cytotoxicity. These findings have important ramifications for our understanding of mechanisms governing sterility within the peritoneal space. Strategies aimed at enhancing antimicrobial RNase levels and activity may reduce the incidence and severity of infectious peritonitis in ESRD patients.

**Funding:** 1Akrnon Nephrology Associates, Akron, OH; 2Internal Medicine, Akron General Medical Center, Akron, OH; 3Northeast Ohio Medical Univ, Rootstown, OH; 4Akrnon Nephrology Associates, Parma, OH; 5Kidney and Urology Inst, Medanta, India; 6Children’s Hospital of Michigan.

**TH-PO614**

**Hemodialysis in Neonates and Infants: A Systematic Review**

Prashanthi Vijayaghavan,1 Mohit Gupta; Rupesh Raina;2 Vinod Krishnapa;3 1Akrnon Nephrology Associates, Akron, OH; 2Internal Medicine, Akron General Medical Center, Akron, OH; 3Northeast Ohio Medical Univ, Rootstown, OH; 4Akrnon Nephrology Associates, Parma, OH; 5Kidney and Urology Inst, Medanta, India; 6Children’s Hospital of Michigan.

**Background:** Hemodialysis (HD) in neonates and infants is difficult to implement and maintain due to a lack of machines adapted to neonatal blood flow volumes. Subsequent issues include hemodynamic instability and difficult vascular access. Hence, peritoneal dialysis is preferred in neonates and infants. The purpose of this study was to systematically review HD and discuss innovations in HD for neonates and infants.

**Methods:** PubMed was searched for “hemodialysis,” along with the Medical Subject Heading term, “infant”. 1,310 potential matches were returned, of which 9 studies met inclusion and exclusion criteria. Pooled descriptive statistics were calculated, weighted according to the number of subjects in each study. Data regarding patient characteristics, hemodialysis innovations, parameters, and patient outcomes was recorded.

**Results:** The total number of subjects across the nine selected studies was 104, with a mean age of 3.1 months (range: 2 days to 12 months). Among all subjects there was a 62% survival rate. Indications for HD included inborn errors of metabolism, acute kidney injury, and renal dysplasias. The most common complications were cather dysfunction, hypotension, and anemia.

**Conclusions:** Indications for hemodialysis included acute renal failure, primary intrinsic renovascular disorders, inborn errors of metabolism, and intoxications. Hemodialysis techniques used for neonates and infants included blood priming of extracorporeal circuits, minimizing extracorporeal circuit volumes and use of smaller catheters. This paper concludes with a discussion of techniques that are best suited for neonates and infants.

**Funding:** F Hoffman-La Roche Ltd

**TH-PO615**

**Pediatric Intradialytic Hypotension: A Systematic Review**

Prashanthi Vijayaghavan,1 Mohit Gupta; Vinod Krishnapa;3 Gaurav Kapur;2 Siddharth Sethi;4 Rupesh Raina;3 1Internal Medicine, Akron General Medical Center, Akron, OH; 2Akrnon Nephrology Associates, Akron, OH; 3Children’s Hospital of Michigan, Detroit, MI; 4Medanta, Medicyte Hospital, India.

**Background:** Intradialytic hypotension (IDH) is commonly encountered in pediatric patients that receive hemodialysis (HD) sessions lasting 4 hours. The purpose of this study was to systematically review publications discussing IDH in pediatric patients and preventive measures taken in the particular patient population.

**Methods:** PubMed/MEDLINE was searched for the terms “hemodialysis” and “hypotension”, with the word “peritoneal” excluded. The Medical Subject Heading (MeSH) terms included hypotension, infant, child, or adolescent, again with the word “peritoneal” excluded. 183 potential matches were returned, of which 11 met inclusion and exclusion criteria.

**Results:** The total number of subjects across the ten selected studies was 148 with ages ranging from 2 days – 18 years old, patient weight ranged from 3.2 kg to 61.4 kg. Non-invasive blood monitoring (NIVM) was implemented with HD in 65% of patients. Ultrafiltration (UF) strategies were not uniform across all studies. UF either remained constant throughout the study duration or UF profiles were implemented based on changes observed in dry weight. Similar to UF, sodium levels were not synonymous across studies and either remained constant or sodium ramping in linear and/or stepwise fashion was observed. Although not reported in all studies, percent frequency of hypotensive events ranged from 19.6% - 75%, with lower percentages observed in patients who received NIVM during HD.

**Conclusions:** Indications for hemodialysis included acute renal failure, primary intrinsic renovascular disorders, inborn errors of metabolism, and intoxications. Hemodialysis techniques used for neonates and infants included blood priming of extracorporeal circuits, minimizing extracorporeal circuit volumes and use of smaller catheters. This paper concludes with a discussion of techniques that are best suited for neonates and infants.

**Funding:** F Hoffman-La Roche Ltd

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

Underline represents presenting author.

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Conclusions: Among studies reviewed, use of NIVM was helpful in achieving appropriate dry weight as well as predicting and preventing intradialytic hypotension. Although such findings appear significant, studies reviewed had small patient populations and relatively short study durations. Hence, future studies involving larger study populations and NIVM utilization with the goal of reducing episodes of intradialytic hypotension will be necessary in determining the effectiveness of this approach in HD therapy in pediatric patients.

TH-P0616
Interinstitutional Cooperation Program in Pediatric Kidney Transplantation and the Impact on Transplant Count

Maria Goretti M.G. Penido, Marcelo S. Tavares, Carolina Moura Diniz Ferreira Leite, Mariana G. Penido de Paula, Felipe B.P. De Caux. Pediatric Nephrology Unit, Santa Casa de Belo Horizonte, Belo Horizonte, MG, Brazil.

Background: Kidney transplantation is the preferred treatment for the end stage of chronic renal disease in children and adolescents. The aim of this study was to evaluate an interinstitutional cooperation program between an experienced pediatric transplantation center and a developing center in other state, 600 km apart, and the count of kidney transplantation surgeries performed during the 3-year duration of the cooperation.

Methods: The cooperation consisted of short periods of fellowship (max 1 month) of pediatric nephrology residents, nurse and 2 physicians (one ped-nephrologist and 1 surgeon), along a 3-year period, as well as weekly teleconferences for case discussions once a week. The yearly count of pediatric kidney transplants (p-KT) in the developing center was compared to the national mean as well to the state's mean.

Results: Since 2011, thirty pediatric patients were transplanted, 1 in 2011, 1 in 2012, 8 in 2013, 8 in 2014 and 12 in 2015. The interinstitutional program was held between 2012 and 2014. In comparison to the national count of p-KT, the developing center was responsible for 0.34% (2011), 0.26% (2012), 2.59% (2013), 2.29% (2014) and 3.79% (2015) of all p-KT. The analysis of the p-KT performed within the state showed that the developing center had a progressive participation on this procedure: 5% (2011), 3.2% (2012), 3.47% (2013), 36.3% (2014) and 46.15% (2015). However, there was a fall on the total count of p-KT during the period until 2014, but rose in 2015: 20 (2011), 31 (2012), 23 (2013), 22 (2014) and 26 (2015).

Conclusions: The results reflect a successful case of interinstitutional cooperation program that was valid for the development of a p-KT center, with progressive results. Investments in educational campaigns, targeting specifically the medical community as well the general public may allow an even higher increase of p-KT counts in the coming years. The model may be valid for localities with same goal of increasing the number of kidney transplantations.

TH-P0617
Latin America Pediatric Urolithiasis Register: Preliminary Report

Maria Goretti M.G. Penido, Michelle M. Lopez, Nilzete Liberato Bresolin, Laura Alconcher, Mary Velasco, Stella M. Dieguez, Ana Paula Spizitirri, Jose Maria Ojeda, Judith Exantus, Morgana De Moro, Marcela Thiemi Korogi, Maria A. Colina. Latin America Pediatric Urolithiasis Register - Multicentric Study.

Background: Considering the socioeconomic and geographic variables, the objective of this study was to outline an epidemiological profile of primary pediatric urolithiasis in Latin America.

Methods: This is an observational, descriptive and retrospective study of pediatric patients with confirmed urolithiasis from Pediatric Nephrology Centers of Latin American from December of 1995 to December of 2015. Data were collected from medical records and placed at a database created online. The study was approved by each institutional review board.

Results: Of the 512 patients (58%M) all had normal serum creatinine, electrolytes and minerals. Urolithiasis was diagnosed by ultrasound in 80% of cases and by computerized tomography in 20%. Median age at diagnosis was 8,0 years (4,9-11,0). Morphologic or gross hematuria (36%), as well as flank or abdominal pain (58%) were the most common clinical presentations. Family history of kidney stones was positive in half of the cases (51%). The most common metabolic urinary abnormalities were idiopathic hypercalciuria (63%) and idiopathic hypoxaturia (52%), alone or in combination with other abnormalities. 22% of the patients had urine flow less than 1.0 ml/kg/hour, 30% had hyperuricosuria and 11% had idiopathic absorptive hypoxaturia. Twenty-five patients had cystinuria (5%) and in 20% no metabolic abnormalities were found. The majority of kidney stones were unilateral (76%) and most of the patients had from 1 to 4 stones (80%).

Conclusions: Despite some differences between the populations, the leading causes of primary pediatric urolithiasis in Latin America were idiopathic hypercalciuria, followed by idiopathic hypoxaturia and “oliguria”. The male-female ratio was almost equal, with a slight predominance of males. The diagnosis was done by ultrasound in the majority of the cases and hematuria associated to abdominal or flank pain was the most common clinical presentation. The finding of near similarity between the populations studied calls for combined efforts in addressing these challenging matters.

TH-P0618
Incidence and Clinical Impact of Cytomegalovirus in Pediatric Kidney Transplantation: Ten Years of Experience in a Single Center

Lilianna Rubio, Pediatric Nephrology, Hospital Univ San Vicente Fundacion, Medellin, Antioquia, Colombia.

Background: Cytomegalovirus is opportunistic agent after transplantation, pediatric recipients are more likely to be CMV seronegative 62.7%. This study evaluated incidence CMV infection/disease and risk factors after transplantation and usefulness of prophylaxis with valganciclovir.

Methods: 56 pts. 1 to 15 yrs underwent transplantation, during 10 yrs. Pre transplantation test was done for CMV status using enzyme-linked assay for IgG antibod. D+/R-; D+/R- received prophylaxis, IV ganciclovir (5mg/Kg/BID) was given for 55% of the pts for two weeks, mean dose was 175.2 mg/day during 9.8 days followed by valganciclovir once a day at 100 % of pts. The dose was (mg)= 7 x surface area (m2) x creatinine clearance (mL/min per 1,73 m2). The mean daily dose of valganciclovir was 501mg/day for 125 days.

Results: CMV Serostatus: R+/D-=4,R+/D+=42,R-/D-=10. Seven pts (12.5%) had CMV viremia, one patient had detectable CMV viremia before prophylaxis began, remaining 6 were positive after prophylaxis ended. The development of viremia was 54 days, the number of transplant with viremia positive was 5 in 100 days and 1 after 200 days. CMV disease occurred in 10,7% all received 100 days prophylaxis. The univariate analysis shows that the highest risk group of CMV viremia was D+/-R- with 40 % of cases and that D+/-R+ increases 9.5 times the risk of CMV infection. (p= 0.01).

Younger age of recipient was associated with higher incidence of infection, 7 yrs vs 10.5 yrs in the CMV-negative infection.

Conclusions: Kidney transplants recipients at highest risk for CMV viremia are those without preexistent CMV specific immunity. The main strategy against CMV in pediatric renal transplantation is universal prophylaxis with valganciclovir. Extending prophylaxis to 6 months in high-risk kidney transplantation is a recommendation that appears to provide a significant benefit.

Funding: Private Foundation Support
Group Differences (Md, IQR).

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<th>Gly170Arg</th>
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<td>Data</td>
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<td>On Vit B12 Rx (%)</td>
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<tr>
<td>Vit B12 Dose (mg/day)</td>
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<td>UrOx (nmol/L/1.73m²)</td>
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<td>Ur Calcium (mg/kg/d)</td>
<td>1.17 (0.6,2.5)</td>
<td>1.02 (0.7,1.6)</td>
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<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>84.2 (7,104)</td>
<td>66.0 (5,93)</td>
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Conclusions: PH1 Gly170Arg patients on Vit B12 had lower UrOx and downregulated inflammatory and fibrotic factors, ET1 and IL17E but upregulated MIF and MMP9. No differences in oxidative stress and calcification inhibition or calcification promotion markers were seen between the groups. Vit B12 therapy for Gly170Arg m’or’ may not offer significant suppression of extracellular matrix breakdown, macrophage accumulation and fibrosis despite lowering UrOx. B12 compliance monitoring with targeted UrA proteins should be considered.

Funding: NIDDK Support

TH-PO620

Genetic Determinants of Uremic Toxins in Hispanic Children: The Viva La Familia Study

V. Saroja Vorugunti,1 Geetha Chittoor,2 Katie A. Meyer,3 Karin Haack,2 Sandra L. Laston,2 Nitesh R. Mehta,1 Shelley A. Cole,2 Anthony Gean Comuzzi,2 Nancy F. Butte,4 1Univ of North Carolina at Chapel Hill,2Texas Biomedical Research Insitute,3Univ of Texas Rio Grande Valley,4Baylor College of Medicine.

Background: Uremic toxins are organic compounds, which in excess concentrations negatively impact biological functions. Uremic toxins have been linked to oxidative stress, endothelial dysfunction, increased risk for chronic kidney disease and acute kidney injury, and cardiovascular events and mortality. Adult studies showing environmental and genetic factors affecting uremic toxins cannot be extrapolated to children. Thus, our aim was to identify genetic determinants of 11 serum uremic toxins (low molecular weight molecules: creatinine, creatine, xanthine, hypoxanthine, asymmetric dimethylarginine, adenylyl, uridine, and protein-bound molecules: p-cresol sulfate, indole acetate, kynurenic, kynurenate) in 868 Hispanic children.

Methods: Uremic toxins were measured by untargeted metabolomics profiling. A genome-wide association analysis was conducted using a weighted genotype approach accounting for kinships.

Results: All uremic toxins were significantly heritable (h² = 0.2-0.9, p < 0.005).

Conclusions: In summary, we demonstrate significant genetic influence on uremic toxins in Hispanic children.

Funding: NIDDK Support

TH-PO621

A CE-MS Pipeline for Long Term Comparable Assessment of the Urinary Metabolome

Panagiotis Moulopoulos,1,2 Valérie Brunchart,1 Benjamin Brouillé,1 Franck Boizard,1 Julie Klein,1 Stepanne Decramer,1 Jean-Loup Bascands,3 Joost Schanstra,4 Benedicte Buffin-Meyer,1 1INSERM U1048/I2MC, Toulouse, France; 2HybridStat Predictive Analytics, Athens, Greece; 3CHU Toulouse, Hôpital des Enfants, Toulouse, France.

Background: ‘Urinary omics’ strategies are promising tools of high relevance in the clinical setting as they have already led to the design of multimarker protein-based models for the diagnosis of complex diseases. Compared to proteins, metabolites are in the closest biological proximity to the phenotype and can thereby provide functional signatures of biological samples. Advances in two-dimensional liquid chromatography coupled to mass spectrometry (2D-LC-MS) have been made in recent years. The EASY-nLC platform allows to acquire comprehensive metabolite fingerprints in urine samples.

Methods: Most metabolomics studies use NMR spectroscopy and LC-MS. In contrast, capillary electrophoresis coupled to mass spectrometry (CE-MS) has been rarely used for metabolite analysis due to issues related to stable coupling of CE to MS instrument and limited loading capacity of CE columns. Here, we report an optimized CE-MS setup and data analysis pipeline that allows comparing the metabolite content in urine samples. We implemented a data normalization and annotation procedure using endogenous stable urinary metabolites was developed based on the combined metabolome of 75 different urine samples from healthy and disease individuals. Using this normalization method, the CE-MS platform displayed high performance in terms of long-term stability as it allowed comparison of the same sample analyzed nearly 130 times over a range of 4 years. Next we evaluated the clinical utility of the CE-MS platform for the discovery of putatively novel metabolites as obstructive nephropathy in infants. We compared the urine metabolome of 34 newborns with ureteropelvic junction (UPJ) obstruction and 15 healthy newborns. This led to the identification of 32 differentially excreted metabolites. Combination of the 32 compounds in a SVM classifier predicted with 88% sensitivity and 86% specificity (AUC 0.90) UPJ obstruction in a separate validation cohort of 24 individuals.

Conclusions: This proof-of-concept study demonstrates the feasibility to use CE-MS as a tool for identification of clinically relevant urinary metabolites.

Funding: NIDDK Support

TH-PO622

Newly-Identified Symptoms of Left Renal Vein Entrapment Syndrome Mimicking Orthostatic Disturbance

Tomoki Miyawaza, Keisuke Sugimoto, Kohei Miyazaki, Hidehiko Yanagida, Mitsuhiro Okada, Tsukasa Takeamura. Pediatrics, Kindai Univ Faculty of Medicine, Osaka, Japan.

Background: In addition to the urinary abnormalities, symptoms of left renal vein entrapment between the aorta and superior mesenteric artery (left renal vein entrapment syndrome, LRVES) may include abdominal and flank pain as well as chronic fatigue. We investigated various LRVES symptoms in this study.

Methods: In 53 pediatric LRVES patients treated at our department, 22 had a score of 5 points or higher on orthostasis. Initial evaluation of LRVES by abdominal ultrasonography showed a stenotic-to-pretreatment renal diameter ratio of 0.2 or less. Definitive diagnosis was made by computed tomography and magnetic resonance angiography. Cortisol, catecholamine (CA), and brain natriuretic peptide (BNP) were also measured.

Results: The frequency of LRVES was 2.5 times higher in girls than in boys. Low or very low body mass indexes were seen in both sexes. The most common finding was urine abnormalities, followed by dizziness and malaise. In 6 patients, orthostasis precluded school attendance. 10 patients had orthostasis scores above 12. Patients unable to attend school had either low levels of plasma or urinary cortisol. Middosterone significantly decreased orthostasis scores. None of the patients required treatment with flavocortisol. Plasma CA, renin, and BNP levels were all normal.

Conclusions: Locally excessive venous pressure may cause reversible adrenal dysfunction with transitory Addisonian symptoms. Children with cryptogenic malaise or severe orthostasis should be evaluated for LRVES.

TH-PO623

The Relationship of Kidney Disease Knowledge with Self-Management and Healthcare Transition Readiness

M. Ferris,1 Meaghan Nazareth,1 Julie A. Wright Nunes,1 Karina Avascular,1 Alex Philips,2 Sarah Elizabeth Cohen,2 Jane Ferris,3 Karin Klein,1 Miranda A.J. van Tilburg,1 Stephen R. Hooper,1 Keisha L. Gibson,1 Dorey A. Glenn,1 Keia Sanderson,1 Eniko Rak,1 1UNC Chapel Hill, Chapel Hill, NC, 2University of Michigan, Ann Arbor, MI.

Background: Successful transition from pediatric to adult-focused services requires knowledge and effective self-management of the chronic kidney disease (CKD).

Methods: English speaking adolescents and young adults (AYA) who attended the UNC Kidney Center clinic in 2015 completed the Kidney Knowledge Survey (KKS) and the TRANSITION Scale. Regression was used to explore this relationship while controlling for percentage of life with the disease, sex, race, and insurance.

Results: 155 AYA aged 10-20 years old completed the surveys (mean age 15.7 ± 2.34). Participants were 50.3% females, 36.8% white, 34.2% African American, 53.5% in CKD stages 3 and 5. 87% of participants had been diagnosed with CKD stages 1 to 5. The model as a whole predicted healthcare transition readiness (β=−0.654, p<0.000). This relationship was significantly related to kidney disease knowledge (β=0.340, p=0.000) and percentage of life with the disease (β=0.216, p=0.013). Race, sex, and insurance were not significant. Correlations of the 10 TRANSITION Scale domains with the KKS Score were performed, and Type of illness (r=0.366, p<0.000), Race (r=0.250, p<0.000), Issues of Reproduction (r=-0.276, p=0.001) demonstrated significant, positive correlations.

Conclusions: Participants who had a great understanding of kidney disease knowledge were prepared to transition to adult care. Increased kidney disease knowledge may also relate to increased knowledge in specific domains of transition readiness, although this relationship must be further explored. In turn, percentage of life with the disease was negatively related to transition readiness. Increase in percent of life with the disease is associated with a decrease in transition readiness.

Funding: Private Foundation Support

TH-PO624

All You Need Is Love: A Low Literacy Curriculum for CKD Education and Self-Management

Meaghan Nazareth,1 Jordan Richards, Jessica Cuttance, Karina Jalvarkar, Alex Phillips, Sarah Elizabeth Cohen, Eniko Rak, Miranda A.J. van Tilburg, Stephen R. Hooper, Brian H. Pitts, Maria E. Ferris. 1UNC Chapel Hill, Chapel Hill, NC.

Background: To successfully manage chronic kidney disease (CKD), patients need to be able to understand their condition. The efficacy of a low-literacy curriculum developed with interdisciplinary input needs to be assessed.

Methods: The ALL YOU NEED IS LOVE Curriculum provides CKD education, self-management tips, and mindfulness in 6 weeks. A graded intervention was deployed in two groups of adolescents and young adults (AYA). One group received CKD education and self-management and the second group received the same information enhanced with mindfulness activities. Mindfulness provides training in self-acceptance and coping, buffering stress resulting from having a chronic health condition as it integrates openness and present-moment awareness. English speaking AYAs (aged 12-29) with CKD stages 3 to 5 were randomized to receive the curriculum or standard care. A validated self-report questionnaire was completed to assess CKD knowledge and self-management skills.

Results: The ALL YOU NEED IS LOVE Curriculum provided CKD education, self-management tips, and mindfulness in 6 weeks. A graded intervention was deployed in two groups of adolescents and young adults (AYA). One group received CKD education and self-management and the second group received the same information enhanced with mindfulness activities. Mindfulness provides training in self-acceptance and coping, buffering stress resulting from having a chronic health condition as it integrates openness and present-moment awareness. English speaking AYAs (aged 12-29) with CKD stages

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

236A
1-5 at pediatric and adult clinics of the UNC Kidney Center, received a booklet and a DVD player. The outcome was change in the STARs Questionnaire (Ferris 2015), a self-management and transition readiness tool with a best score of 90. Paired t-tests were used to determine significance of changes in transition readiness.

Results: 20 AYA in pediatric and adult clinics have completed the study. Among the pediatric patients, 24% have an ADHD or ADD diagnosis, and 40% have an Individualized Education Plan or 504 plan at school. Mean STARs Questionnaire scores significantly improved, with a greater increase in those with the additional mindfulness intervention (Table 1).

Conclusions: Initial results suggest that this low-literacy curriculum is having a positive impact on knowledge and self-management of CKD among AYAs with this condition. Further exploration is ongoing.

<table>
<thead>
<tr>
<th>mean</th>
<th>median</th>
<th>std. dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.02</td>
<td>11.92</td>
<td>3.01</td>
</tr>
<tr>
<td>9.86</td>
<td>10.86</td>
<td>2.93</td>
</tr>
<tr>
<td>7.89</td>
<td>8.89</td>
<td>2.86</td>
</tr>
</tbody>
</table>

Table 1: Mean STARs Questionnaire scores for 504 participants.

Funding: Private Foundation Support

TH-PO625
Parent-Child Kidney Disease Knowledge Concordance
Jordan Richards, 1 Meaghan Nazareth, 1 Julie A. Wright Nunes, 1 Karina Jawalkar, 1 Alex Phillips, 1 Sarah Elizabeth Cohen, 1 Jessica Cuttance, 1 Miranda A.I. van Tilburg, 1 Eniko Rak, 1 Stephen R. Hooper, 2 Maggwa Dwayne Shaun Ndugga, 1 Maria E. Ferris. 1
UNC Chapel Hill, Chapel Hill, NC; 2Univ of Michigan, Ann Arbor, MI.

Background: Parents must help manage their children’s chronic kidney disease (CKD). It is not how much disease-specific knowledge parents have and how concordant it is to their children’s knowledge. It is also not clear how this knowledge relates to health care transition readiness.

Methods: English speaking adolescents and young adults (AYA) at the UNC Kidney Center and their parents completed an abridged form of the Kidney Knowledge Survey (KiKS) (max score 100%) as well as the TR-ANSITION Scale (best score is 10). AYA and their parents reported demographic information including AYA age, age at diagnosis, race, and insurance status. Linear regression was used to examine the relationship between the parent kidney knowledge score and youth transition scale score total while controlling for percentage of life with the disease, sex, insurance, and race. Pearson’s correlation was used to examine parent-AYA KiKS and TR-ANSITION Scale concordance.

Results: 41 parent-AYA dyads completed the surveys. AYA’s characteristics included females (68.3%); mean age 15.05 ± 1.89 (range 12-19); mean age at diagnosis 7.71 ± 6.26; private insurance (49%) and Caucasians (49%). The majority of parent participants were mothers (92.7%). The mean parent KiKS score was 70.2% ± 12.9% (range 40 – 100%). The mean AYA KiKS score was 60.7% ± 15.6% (range from 13.3 – 86.7%). Mean parental TR-ANSITION Scale score was 8.1 ± 0.9, and mean AYA TR-ANSITION Scale score was 6.6 ± 1.5. The model was not significant. Correlation between parent and AYA transition scales was significant (r=0.413, p=0.008), while correlation between parent and youth kidney knowledge was not significant.

Conclusions: Parents have lower than expected disease knowledge and transition preparation. Parents with more disease-specific knowledge are likely better prepared for their child’s transition readiness.

Funding: Private Foundation Support

TH-PO626
The Prognostic Value of the Furosemide Stress Test in Predicting Delayed Graft Function Following Deceased Donor Kidney Transplantation
Blaithin A. McMahon, 1 Edward S. Kraus, 1 Tessa Kimberly Novick, 2 Steven Menez, 2 Sami Alsafar, 1 Nilaj Desai, 1 Lakhmir S. Chawla, 1 Jay L. Koyner, 2 Johns Hopkins Univ School of Medicine, Johns Hopkins Univ, Baltimore, MD; 2Dept of Medicine, Univ of Chicago, Chicago, IL; 3Dept of Medicine, The George Washington Univ, San Diego, CA.

Background: The Furosemide Stress Test (FST) is a novel dynamic assessment of tubular function that has been shown in preliminary studies to predict patients who will progress to advanced stage Acute Kidney Injury, including those who receive dialysis. The aim of this study is to investigate if the urinary response to a single intravenous dose of furosemide predicts delayed graft function (DGF) in patients undergoing deceased donor kidney transplant (DDKT).

Methods: This is a single center retrospective cohort analysis of 300 patients undergoing kidney transplantation (KT) at Johns Hopkins Hospital from January 2012 to October 2016. All patients undergoing KT received a single 100mg dose of intravenous furosemide monitoring UO at 2 and 6 h post furosemide administration. We utilized the 2 and 6 hour post FST urine output along with multiple logistical regression analysis and area under the receiver operator curves (AUC) to determine DGF (defined as receipt of RRT within 7 days of transplantation).

Results: In multivariate analysis, the FST predicted the need for dialysis after adjusting for donor age, donor race, recipient weight, cold ischemic time, pre-transplantation baseline urinary flow rates (classified as oliguria versus non oliguria) and donor serum creatinine. The AUC for prediction of DGF based on a UO of <150mLs at 2 hours and 6 hours was 0.84 and 0.86, respectively. The median length of hospital stay among FST responders (<600mLs at 6 hours) was 8 days compared to 12 days in non FST responders (<600mLs at 6 hours). There was no significant difference in the prevalence of hypoponatremia and hypokalemia (within 24 hours), as well as graft loss and death in those patients who were FST responders compared to those who were not (median follow up 1.69 years).

Conclusions: The FST is a predictor of DGF post DDKT and has the potential to identify patients requiring RRT early after KT.

Funding: NIDDK Support

TH-PO627
A Sensitive Urinary Furosemide HPLC Assay to Complement the Furosemide Stress Test
Jaspreet Kaur, Medicine, Jonathan Street, 1 Erik H. Kozlowski, 1 Lakhmir S. Chawla, 2 Peter S. T. Yuen, 1 Robert A. Starr, 1 NIDDK, Bethesda, MD; 2JA, Washington, DC.

Background: The furosemide stress test has been reported as a functional biomarker with good performance in predicting adverse outcomes after AKI. Furosemide binds and inhibits NKCC2, causing a diuresis that can be easily measured. To reach the NKCC2 on the apical surface of the thick ascending limb furosemide must be actively secreted by the proximal tubule. We hypothesized that the excretion of furosemide may provide additional information beyond the urine volume. To investigate this we developed a sensitive assay for urinary furosemide.

Methods: We used a reverse phase HPLC separation with detection by absorbance at 335 nm to sensitively detect furosemide. A 5 µL sample of urine is mixed with 100 µL albumin, then centrifuged to pellet precipitated proteins, and the supernatant dried. The HPLC assay utilizes a 50 mm PRP-C18 column with a 10 min isocratic elution using 70% 20 mM potassium phosphate pH 4.5 / 30% acetonitrile as the mobile phase. The dried samples are reconstituted in mobile phase prior to injection.

Results: The furosemide assay was linear from 0.5 to 500 ng/µL with R2 = 0.999. The protocol had a coefficient of variation of 6%. Furosemide standard was spiked into urine and samples stored for 0, 4 and 24 hours at room temperature. There was no degradation with storage over this period (100% recovery). Furosemide was also stable over multiple freeze-thaw cycles with no change observed between 1 and 4 cycles. The assay was robust in the presence of albumin with no change in stability or variability.

Conclusions: Furosemide assay is sensitive, reproducible, and robust. Furosemide is stable in urine over both prolonged storage and multiple freeze-thaw cycles. The protocol is able to accurately measure furosemide concentration in 5 microliters of urine over ranges expected in both human and rodent studies.

Funding: NIDDK Support

TH-PO628

Background: In recent years several approaches for identifying patients at risk of AKI were used; among them 2 have been of increasing interest: the furosemide stress test (FST) and the renal angina index (RAI). We recently used Perazella et al. urinary sediment scores (USS) to predict subsequent development of AKI. All these approaches is aimed to identify patients at risk for subsequent AKI. We assessed the performance of these 3 different approaches to identify patients at risk of AKI in an ongoing cohort of adult critically ill patients.

Methods: We analyzed data from 30 hospitalized patients admitted to a Medical ICU. We measured serum creatinine (sCr) every 24 h for 7 consecutive days following ICU admission, and urine volume was assessed hourly each 24 h. At admission (day 0), we applied the FST at day 0 (as describe by Chawla et al. Crit Care 2013; 17(5):R207). We assessed the performance of these 3 tests to predict the subsequent development of AKI using KDIGO sCr and urinary volume criteria.

Results: Of note, we consider a cut-off point of <600 cc of urine at 2 h for AKI. Furosemide assay is sensitive, reproducible, and robust. Furosemide is stable in urine over both prolonged storage and multiple freeze-thaw cycles. The protocol is able to accurately measure furosemide concentration in 5 microliters of urine over ranges expected in both human and rodent studies.

Funding: Private Foundation Support

TH-PO629
Performance of the different tests and scores

<table>
<thead>
<tr>
<th>Performance of the different tests</th>
<th>Furosemide stress test</th>
<th>Renal angina index</th>
<th>Urinary sediment score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>75</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>96</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>100</td>
<td>100</td>
<td>67</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>96</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ROC-AUC (p-value)</td>
<td>0.990 (0.002)</td>
<td>1.00 (0.002)</td>
<td>0.981 (0.002)</td>
</tr>
</tbody>
</table>

Of note, we consider a cut-off point of <600 cc of urine at 2 h for FST since none of the patients who developed AKI had <200 cc of urine as the original cut-off proposed value.

Conclusions: The RAI, FST and USS have robust predictive capacity to identify critically ill patients at high risk of developing AKI before a rise in sCr occurs. These preliminary data of our ongoing study warrants future studies to validate these findings.
TH-PO629

Subclinical Acute Kidney Injury Is an Early Stage of Acute Kidney Injury
Rolando Clauere-Del Granado, 1 Vania Cecilia Prudencio Ribera, 1 Ravindra L. Mehta, 2 Medicine, Hospital Obrero 92 - CNS, Cochabamba, Bolivia; 2Medicine, Univ of California San Diego, CA.

Background: A recent ADQI consensus on AKI biomarkers has suggested that novel biomarkers (NGAL, KIM-1, and 1GFBP-7) can identify kidney damage prior serum creatinine (sCr) elevations. Combining damage and functional markers can thus permit recognition of an early stage of AKI termed subclinical AKI (S-AKI). We tested the hypothesis that a panel of damage biomarkers could detect S-AKI and would predict the subsequent development of clinical AKI (C-AKI).

Methods: We included 50 consecutive patients admitted to a Medical ICU. Daily sCr, urine albumin (uAlb) and urine β2-Microglobulin (uβ2-M) levels were measured each 24 h for 7 consecutive days; we evaluated urine sediment (USS) and assigned a score using Perazella et al. criteria. We define S-AKI if any of the following criteria was reached in the absence of sCr elevations: new onset of uAlb ≥15 mg/L, or uβ2-M ≥3.2 mg/L, or USS ≥2. C-AKI was defined by KDIGO sCr criteria. We analyzed the predictive value of each of these biomarkers for the subsequent development of C-AKI as well to predict survival.

Results: Of the 50 patients, 11(22%) did not develop AKI while 39(78%) developed S-AKI. Of the 39 patients with S-AKI, 26(67%) progressed to C-AKI while 13(33%) did not. The predictive value of uAlb, uβ2-M and USS at 24 and 48 h are show in table 1.

<table>
<thead>
<tr>
<th>Predictive value of the different biomarkers</th>
<th>ROC-AUC (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Albumin (≥15 mg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>0.753 (0.612-0.894)</td>
<td>0.02</td>
</tr>
<tr>
<td>48 h</td>
<td>0.707 (0.555-0.859)</td>
<td>0.01</td>
</tr>
<tr>
<td>Urinary Microglobulin (≥2.5 mg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>0.770 (0.624-0.916)</td>
<td>0.01</td>
</tr>
<tr>
<td>48 h</td>
<td>0.703 (0.545-0.861)</td>
<td>0.14</td>
</tr>
<tr>
<td>Urinary Sediment Score (≥ 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>0.818 (0.638-0.998)</td>
<td>0.001</td>
</tr>
<tr>
<td>48 h</td>
<td>0.773 (0.580-0.965)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

28-day mortality did not differ between patients with S-AKI who didn’t developed C-AKI and patients with S-AKI who developed C-AKI.

Conclusions: Our data shows high incidence of S-AKI that progressed to C-AKI. These findings support the ADQI recommendations to consider S-AKI based on positive damage biomarkers alone as an early phase of AKI. Identification of S-AKI would potentially allow earlier intervention with preventive and treatment strategies to reverse kidney injury and improve recovery.

TH-PO630

Clinically Relevant Furosemide Stress Test Is Predictive for AKI Progression in ICU Patients with Elevated Plasma NGAL Level
Ryo Matsura, 1 Yohei Komura, 1 Yoshihisa Miyamoto, 1 Teruhiko Yoshida, 1 Kohei Yoshimoto, 2 Rei Ishikii, 1 Kengo Mayumi, 1 Tetsushi Yamashita, 1 Yoshifumi Hamaaki, 3 Masaoi Nangaku, 1 Eisie Noiri, 1 Kent Doi, 2 1Dept of Nephrology and Endocrinology, The Univ of Tokyo Hospital, Tokyo, Japan; 2Dept of Emergency and Critical Care Medicine, The Univ of Tokyo Hospital, Tokyo, Japan; 3Dept of Dialysis and Apheresis, The Univ of Tokyo Hospital, Tokyo, Japan.

Background: Furosemide stress test (FST), which evaluates urine output after furosemide administration, has been suggested for predicting progression of severe AKI. Although the standardized dose (1 mg/kg) is required in FST, different doses are used to see urine output responsive to furosemide in the clinical. In addition, biomarker information would potentially allow earlier intervention with preventive and treatment strategies to reverse kidney injury and improve recovery.

Methods: We evaluated retrospectively plasma NGAL and furosemide response (FR), defined as urine output measured for 2 hours after injection, for stratifying the risk of AKI progression in our ICU. Furosemide dose was determined by clinical judgement based on the severity of illness including renal and cardiac function.

Results: 95 ICU patients were analyzed in this study. 18 patients developed AKI stage 3 within one week (19%). ROC analysis showed the AUC and cutoff values as follows: plasma NGAL 0.80 [0.67-0.88], 142 mg/nL and FR 0.87 [0.73-0.94], 3.9 mg/L furosemide. Only one patient with lower NGAL level (<142 ng/L) progressed to AKI stage 3. FR provides the AUC of 0.84 [0.67-0.94] for prediction of the development to AKI stage 3 even in the patients with higher NGAL (>142 ng/L). With the cutoff value of 3.9 mg/L/ furosemide dose (ng), 13 NGAL-high patients with FR negative developed AKI stage 3 (86.7%), while four FR positive patients developed to AKI stage 3 (11%) with the odds ratio of 52 (8.5-319.5) (p<0.01).

Conclusions: Although different doses of furosemide were administered, FR showed good performances for predicting AKI progression even in high plasma NGAL patients. This suggests combination of FR and biomarkers can stratify the risk in AKI progression in the clinical settings.

TH-PO631

Monitoring and Diagnosing Acute Kidney Injury Using Biochip Array Technology
Candace M. Adamo, 1 Amar Sethi, 1 Ebbihlin M. Mccoe, 2 Marie Mcgevery, 2 Ciaran Richardson, 2 Peter Fitzgerald, 3 John Lamont, 3 Timothy H. Carlson, 1 Pacific Biomarkers, Seattle, WA; 3Randox Teoranta, Dungloe, Co. Donegal, Ireland; 3Randox Laboratories, Crumlin, Co. Antrim, United Kingdom.

Background: The risk of acute kidney injury (AKI) is currently assessed by serum creatinine and clinical representation using the KDIGO classification. Recent efforts have identified several novel biomarkers that are more specific and sensitive in the monitoring and diagnosis of AKI.

Methods: The collective response in 20 subjects of five urinary biomarkers (KIM-1, cystatin C, NGAL, osteopontin (OPN) and clusterin) were measured by ELISA and by a newly developed multiplexed biochip array (Randox Evidence Investigator).

Results: Correlation coefficients (r²) between the two methods were above ≥0.98 for all biomarkers except for clusterin (r²=0.80), with a slope between 0.86 – 1.43, indicating excellent agreement. Preliminary comparison of sensitivity (NGAL=0.78 ng/mL; KIM-1=15.61 pg/mL) and dynamic range (data not shown) between the two methods showed equal or better performance. Multiplexing suggests improved AKI detection as subject 3 with normal eGFR had 3 of 5 biomarkers elevated, indicating renal injury; subject 1 with CKD and eGFR <60 mL/min had biomarker elevations in 4 of 5 tested. The biomarker profiles for the remaining subjects at risk for AKI differed, indicating reduced renal function may be better captured by several biomarkers, as each biomarker reflects different mechanisms that lead to the same injury outcomes (representative data shown below).

TH-PO632

Evaluating Renal Injury and Function in Marathon Runners Using Injury and Repair Biomarkers
Sherry Mansour, 1 Gagan Verma, 1 Rachel W. Pata, 2 Thomas Martin, 2 Chirag R. Parikh, 2 1PATR, Yale Univ; 2Quinnipiac Univ.

Background: There is growing interest in the effects of strenuous activity on renal function, in light of the recent kidney disease epidemic among Mesoamerican sugarcane workers. Marathon running serves as a model of extreme activity and heat stress. This prospective study evaluated renal function of runners during the 2015 Hartford Marathon using conventional and novel renal biomarkers.

Methods: We enrolled 22 runners and collected samples 24 hours pre-marathon (Day 0), immediately after marathon (Day 1) and 24 hours post-marathon (Day 2). Six injury biomarkers: IL-6, IL-8, IL-18, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin and tumor necrosis factor alpha, and two repair biomarkers: YKL-40 and monocye chemoattractant protein-1 (MCP-1) were measured. Serum creatinine, creatine phosphokinase (CPK), urine microalbumin and urine microscopy were also evaluated. We assessed changes in biomarker levels, AKI (stage 1 or higher by AKIN criteria) and urine microscopy score ≥ 2 (strong predictor of ATN).

Results: The mean age of runners was 44 years old and 41% were males. 27% used NSAIDs pre-race. Serum creatinine was elevated on Day 1 versus Day 0 (1.33 mg/dL vs 0.85 mg/dL, p<0.01). Urine microalbumin was elevated on Day 1 versus Day 0 (0.46 mg/dL vs 0.57 mg/dL, p<0.01). On Day 2 creatinine and microalbumin levels started decreasing. 82% of runners developed AKI and 73% had a positive microscopy score. Serum CPK increased from Day 0 to Day 1 and continued to rise on Day 2 (110.32 U/L vs 299.86 U/L vs 769.19 U/L respectively, p<0.01). Urine biomarkers of injury were significantly elevated on Day 1 versus Day 0 and all biomarkers except IL-8 and TNF-α remained significantly elevated on Day 2 versus Day 0. Repair biomarkers were significantly elevated on Day 1 versus Day 0 but only MCP-1 remained significantly elevated on Day 2 versus Day 0.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Marathon runners developed AKI and urines sediments predictive of ATN. A novel urinary injury and repair biomarkers further indicated structural damage. Furthermore, changes in renal function of runners may elucidate mechanisms of nephropathy in Mesoamerican sugarcane workers. Our results should be validated in larger cohorts.

Funding: Other NIH Support - T-32 grant

TH-PO633

Back to Basics: Is Urinary Sediment Earlier Marker Than Urinary NGAL or KIM-1 for Diagnosis of AKI after Open Heart Surgery? Salah S. Naga, Nephrology, Alexandria Faculty of Medicine, Alexandria, Egypt.

Background: AKI is common after open heart surgery (CPB). Several biomarkers have been used including urinary NGAL and KIM-1 for the early diagnosis of AKI. This study was carried out to evaluate the role of urinary sediment scoring (USS) in comparison to NGAL and KIM-1 in the early detection of AKI after CPB.

Methods: This prospective cohort study was carried out on 45 adult patients of both sexes with a Cleveland score (CCS) (0-5) and scheduled for CPB surgery in Alexandria Main University Hospital. The renal function of the patients was assessed before and every day after surgery. Freshly voided urines were taken from every patient and centrifuged for microscopic examination of the urine sediments and for measurement of NGAL and KIM-1 before, 2, 6, 12 and 24 hours after CPB.

Results: Eleven patients developed AKI. Patients with AKI had a higher CPB and cross clamp times (90+/−16.2 in comparison to 60.9+/−8.1 minutes in the non-AKI patients). Serum creatinine started to be significantly higher in the AKI group from the second postoperative day with a mean value of 1.56+/−0.28 mg/dl compared to a mean value of 0.85+/−0.14 mg/dl in the non AKI group. Urine sediment score (USS) 1 and 2 were higher in the AKI group 2 hours after CPB in the first 12 hours of the day with area under the curve (AUC) average of (0.865). Urinary NGAL significantly increased in the AKI group 2 and 6 hours after CPB with corresponding AUC of (0.710 a 0.700). Urinary KIM-1 was higher in the AKI group 12 and 24 after CPB with AUC of 0.725 and 0.703, respectively. Combination of USS, NGAL and KIM-1 gives an AUC of 0.906 in predicting AKI. Multivariable binary logistic regression analysis revealed that the most powerful independent predictors of AKI were USS 24 hours (RR 4.752) and urinary NGAL 6 hours (RR 1.020) after CPB.

Conclusions: Urinary microscopic examination to detect urinary sediments, which is often neglected, was found to have a higher sensitivity and specificity for early detection of AKI in comparison to the novel biomarkers NGAL and KIM-1. They can also be used in combination to improve their performance.

TH-PO634

Urinary Biomarkers at the Time of AKI Diagnosis as Predictors of Progression of AKI among Patients with Acute Cardiorenal Syndrome Xiaoqing Yang, Fan Fan Hou. Renal Div, Nanfang Hospital, Southern Medical Univ, Guangzhou, China.

Background: A major challenge in early treatment of acute cardiorenal syndrome (CRS) is the lack of predictor for progression of AKI. Weaim to investigate the utility of urinary angiotensinogen and other renal injury biomarkers in predicting AKI progression in CRS.

Methods: In this prospective, multicenter study, we screened 732 adults who admitted for acute decompensated heart failure from September 2011 to December 2014, and evaluated whether renal injury biomarkers measured at time of AKI diagnosis can predict worsening of AKI. In 213 patients who developed KDIGO stage 1 or 2 or AKI, six renal injury biomarkers, including urinary angiotensinogen (uAGT), urinary and plasma neutrophil gelatinase-associated lipocalin (NGAL), urinary IL-18 (uIL-18), urinary kidney injury molecule-1 (uKIM-1), and urinary albumin to creatinine ratio (UACR), were measured at time of AKI diagnosis. The primary outcome was AKI progression defined by worsening of AKI stage (50 patients). The secondary outcome was AKI progression with subsequent death (18 patients).

Results: After multivariable adjustment, the highest tertile of three urinary biomarkers remained associated with AKI progression compared with the lowest tertile: uAGT (OR, 10.8; 95%CI, 3.4-34.7), uNGAL (OR, 4.7; 95%CI, 1.7-13.4) and uIL-18 (OR, 3.6; 95%CI, 1.4-9.5). Urinary ATG was the best predictor for both primary and secondary outcomes with AUC of 0.78 and 0.85. These three biomarkers improved risk classification compared with the clinical model alone, with uAGT performing the best (category-free net reclassification improvement 17.7% and 17.5%; P=0.001). The secondary outcome with urinary ATG (AUC 0.76; 95%CI, 0.6-1.06) and uKIM-1 (95%CI, 0.50-1.36; P=0.001). Excellent performance of uAGT was further confirmed with bootstrap internal validation. 

Conclusions: Urinary ATG, uNGAL and uIL-18 measured at time of AKI diagnosis improved risk stratification and identified CRS patients at highest risk of adverse outcomes.

TH-PO635

Urinary [TIMP-2]·[IGFBP7] for Risk Prediction of Acute Kidney Injury in Diabetic Injured and Heart Failure Mortiz Schanz, Jing Shi, Christoph Wasser, Mark Dominik Alsheer, Martin Kimmel.1 1 General Internal Medicine and Nephrology, Robert-Bosch Hospital, Stuttgart, Germany; 2 Walkers Bioscience, Carlsbad, CA.

Background: Acute decompensated heart failure (ADHF) is a common reason for hospitalization and the risk of acute kidney injury (AKI) is high. Early detection of patients at risk for cardiorenal syndrome is important. We tested urinary [TIMP-2]·[IGFBP7], a new FDA-cleared test to assess AKI risk, in a cohort of hospitalized ADHF patients.

Methods: 400 patients were enrolled in the ED at Robert-Bosch-Hospital, Stuttgart, Germany. Timpanolipid associated protein (TIMP-2) and Insulinlike growth factor binding protein-7 (IGFBP7) were measured at enrollment, after 6 hours, and the following mornings over up to 7 days. We examined the predictive ability of urinary [TIMP-2]·[IGFBP7] for development of AKI stage 2 or 3 within 24 hours of sample collection in patients with ADHF. Operating characteristics were determined for the previously validated [TIMP-2]·[IGFBP7] cutoffs of 0.3 and 2.0. [TIMP-2]·[IGFBP7] results are reported in units of (ng/mL)/1000.

Results: Eleven (27.5%) of the 40 ADHF patients met the AKI stage 2-3 endpoint within 7 days. [TIMP-2]·[IGFBP7] discriminated for risk of AKI stage 2-3 with an AUC (95% confidence interval) of 0.84 (0.72-0.95) for initial presentation (within 24 hours) and 0.77 (0.65-0.88) for samples collected within 7 days.

At the 0.3 cutoff for [TIMP-2]·[IGFBP7], the sensitivity was 86% and the specificity was 71% for prediction of AKI stage 2-3 and at the 2.0 cutoff, the sensitivity was 43% and the specificity was 95% for samples collected within 24 hours of enrollment. Kaplan-Meier curves showed a trend (p=0.09) for decreased survival over one year in patients who reached AKI stage 2 or 3 within 7 days compared with those who did not.

Conclusions: In conclusion, urinary [TIMP-2]·[IGFBP7] predicts moderate-to-severe AKI in patients with ADHF.

Funding: Pharmaceutical Company Support - Astute Medical, San Diego, USA, Private Foundation Support

TH-PO36

Urinary [TIMP-2]·[IGFBP7] in Platin-Induced Renal Injury Moritz Schanz, Martin Kimmel, Mark Dominik Alsheer. General Internal Medicine and Nephrology, Robert-Bosch Hospital, Stuttgart, Germany.

Background: Platin-based chemotherapy is a potent antineoplastic agent, but cisplatin nephrotoxicity is a limiting side effect. Identifying those patients who are at risk for developing platin-induced renal injury is an important issue. We tested urinary [TIMP-2]·[IGFBP7], a new FDA-cleared test to assess AKI risk, in a cohort of patients with malignant disease receiving platin-based chemotherapy (PBC).

Methods: 58 patients were enrolled in this study. N=32 patients had available both, urinary [TIMP-2]·[IGFBP7] prior to PBC application and subsequent serum creatinine values for detecting AKI within 72 hours. Urinary [TIMP-2]·[IGFBP7] was collected on the same day prior to PBC application and the earliest available specimen after chemotherapy administration. We examined the predictive ability of [TIMP-2]·[IGFBP7] for development of KDIGO stage 1-3 within 72 hours after administration of chemotherapy in 32 patients with malignant disease. Operating characteristics were determined for the previously validated [TIMP-2]·[IGFBP7] cutoff of 0.3. [TIMP-2]·[IGFBP7] results are reported in units of (ng/mL)/1000.

Results: Four (12.5%) patients developed AKI stage 1-3 within 72 hours. Primary disease was in n=25 (40.6%) lymphoma and in n=19 (40.6%) solid tumors. Eight patients (25.0%) received carboplatin, n=24 (75.0%) cisplatin. [TIMP-2]·[IGFBP7] discriminated for risk of AKI stage 1-3 with an AUC (95% CI) of 0.86 (0.73-0.98). At the 0.3 cutoff for [TIMP-2]·[IGFBP7], the sensitivity was 75% and the specificity was 82% for prediction of AKI stage 1-3.

Comparing urinary [TIMP-2]·[IGFBP7] values prior to and after PBC application, a significant decrease of urinary [TIMP-2]·[IGFBP7] was remarkable (p=0.026). Despite due to prehydration, specimens gathered prior to chemotherapy seem to be more eligible for risk prediction of AKI.

Conclusions: [TIMP-2]·[IGFBP7] prior to PBC identifies patients who are at risk for developing platin-induced acute kidney injury. Because of a significant decrease of urinary [TIMP-2]·[IGFBP7] after PBC application (p=0.026), presumably due to prehydration, specimens gathered prior to chemotherapy seem to be more eligible for risk prediction of AKI.

Funding: Pharmaceutical Company Support - Astute Medical, San Diego, USA, Private Foundation Support
TH-PO637
Cost-effectiveness of Nephrocheck® for Acute Kidney Injury in Critical Care
Andrew J.P. Lewington, Alison F. Smith, David M. Meads, Michelle Hutchinson, Elizabeth D. Mitchell, Judy M. Wright, David Allan Cairns, Michael P. Messenger, Rebecca L. Kit, Claire Louise Corps, Patrick Hamilton, Aleksandra Sobota, Peter S. Hall.

Background: Cost utility analysis has been conducted to evaluate Nephrocheck® for AKI. However, this analysis was performed in the UK, and the costs of such testing have not been measured in the United States (US) or other countries. The objective of this study was to evaluate the cost effectiveness of Nephrocheck® in the US. Methods: We estimated the cost of testing from patients’ admission to ICU until discharge from hospital. The primary clinical outcome variables were renal replacement therapy (RRT), renal recovery and in-hospital mortality. Results: We prospectively enrolled 253 patients with AKI. AKI was diagnosed using the AKIN criteria. The threshold for testing was $20,000 and $50,000. The AKI was scored as mild-moderate, severe, or life-threatening, respectively. The combined outcome was defined by either death or the need for renal replacement therapy. The primary outcome was the incremental cost of Nephrocheck® testing per QALY gained, per QALY gained. We estimated the cost of testing, and the probability of the primary outcome was estimated using the Akaike Information Criteria for model selection. Results: The Nephrocheck® produced an average of 0.06 (95% CI: -0.21 to 0.37) extra QALYs at an additional cost of £20,000 [$28700] and £50,000 [$71800]. The results were sensitive to parameters such as willingness-to-pay, and the probability of the primary outcome was 65-68% and 68-69% at willingness-to-pay per QALY of £20,000 and £50,000, respectively. However, plasma creatinine and urine biomarkers did not show statistically significant difference and could not predict recovery and the death in this study. Conclusions: This prospective observational study could suggest that Urinary TIMP2 might be served as a strong predictor for the need for the renal replacement therapy early in the course of AKI.

Funding: Government Support - Non-U.S.

TH-PO638
Comparison of Nephrocheck(R) and Neutrophil Gelatinase-Associated Lipocalin for Risk Prediction in Combat Casualties
Jan J. Stewart, Jonathan Sosnow, Kevin Chung, Javier Tercero, Elisabeth H. Babcock.

Background: The Nephrocheck®, which measures the product of tissue inhibitor of metalloproteases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7), has been shown to predict the subsequent development of AKI. We have previously shown that other novel urinary biomarkers for AKI, such as neutrophil gelatinase-associated lipocalin (NGAL), are associated with poor outcomes in a homogenous population of combat casualties from the war in Afghanistan. We hypothesized that the Nephrocheck® would also predict poor outcomes in this patient population.

Methods: We conducted a prospective, observational study in a combat support hospital in Afghanistan. Patients that were US military members that suffered traumatic injury and were admitted to the intensive care unit (ICU) were included for analysis. Urine was collected at the time of admission to the ICU, frozen and shipped back to the US for later analysis. The combined outcome was defined by either death or the need for renal replacement therapy.

Results: Eighty seven patients were included in our study. Of these, 12 either died or required renal replacement therapy. Median admission product of TIMP-2 and IGFBP7 was higher in patients that subsequently developed the outcome (0.35, IQR 0.07-0.98) compared to those that did not (0.11, IQR 0.06-0.26), but this difference was not statistically significant (p=0.1). The area under the curve (AUC) for predicting the combined outcome was 0.65 and did not reach statistically significant (p=0.19). This stands in contrast to our prior prior work examining urinary NGAL, which demonstrated an AUC of 0.82 (p=0.001).

Conclusions: In a group of young, critically injured military members, Nephrocheck® did not predict the combined outcome or death for patients requiring renal replacement therapy. While the Nephrocheck® has shown great promise for diagnosing AKI early, our work suggests that other urinary biomarkers, such as NGAL, may be superior at predicting other outcomes.

Funding: Other U.S. Government Support

TH-PO639
Urinary Biomarker TIMP2 Predicts Adverse Outcomes in Patients with Acute Kidney Injury
Sung Yoon Lim, Jihyung Young, Young Ja Na, Myung-Gyu Kim, Sang-Kyung Je, Won-Yong Cho. Korea Univ Anam Hospital, Korea.

Background: Several recent studies have shown that insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteases-2 (TIMP-2) is a promising biomarker for the early detection of acute kidney injury (AKI), but the role of IGFBP7 and TIMP2 in predicting adverse clinical outcomes has not been well addressed. The purpose of this study was to evaluate the usefulness of urine IGFBP7 and TIMP2 as outcome predictor in patients with AKI.

Methods: This was a prospective cohort study enrolling established AKI patients. Urinary biomarkers, including IGFBP7, TIMP2 and NGAL were determined on admission and change from hospital. The primary clinical outcome variables were renal replacement therapy (RRT), renal recovery and in-hospital mortality.

Results: We prospectively enrolled 253 patients with AKI. Initial plasma creatinine concentrations and urinary biomarkers at AKI diagnosis were significantly higher in the RRT group. Logistic regression model for creatinine and urine testing) from a UK NHS prospective.

Methods: All patients (AKI KDIGO stage1) were assumed to be tested on ICU admission. True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) cohorts were created using results from a systematic review and meta-analysis (sensitivity 0.91; specificity 0.49). A probabilistic lifetime Markov model was constructed and used daily cycles (day 0-90) to capture ICU KDIGO AKI stages, and annual cycles thereafter to capture long-term Chronic Kidney Disease (CKD) and mortality. TPs were assumed to have reduced risks (RR=0.78) of AKI progression due to early intervention; no harm was assumed for FP/FN results. In the absence of a published price for Nephrocheck®, a range of values were tested.

Results: Nephrocheck®: produced an average of 0.06 (95% CI: -0.21 to 0.37) extra QALYs at an additional cost of £15 (±22) to £154 (±143) to £200 ($28700) per QALY. Incremental Cost-Effectiveness Ratios (ICERs) ranged from £2,420 ($3477) to £5,225 ($7507) per QALY. The test had a 65-68% and 57% thresholds of £20,000 [$28700] and £50,000 [$71800]. Results were sensitive to parameters including the AKI incidence and impact of early treatment.

Conclusions: Nephrocheck® can be considered sufficient justification for further research. The cost-effectiveness of Nephrocheck® compared to other market competitors should now be evaluated.

Funding: Government Support - Non-U.S.
either first or peak uNGAL values (AUCs 0.88, 0.795, and 0.724, respectively). There were 235 in-hospital adverse events in 144 subjects. The first PCr was a better predictor of this composite outcome than either first or peak uNGAL (0.687, 0.648, and 0.604, respectively).

Conclusions: Urine NGAL was not superior to plasma creatinine for the prediction of AKI or adverse in-hospital outcomes in patients hospitalized with AHF. The use of uNGAL to diagnose AKI in AHF cannot be recommended at this time.

Funding: Pharmaceutical Company Support - Abbott Labs; Alere

TH-P0642
No Evidence of Chloride Nephrotoxicity Using Urinary Excretion of NGAL as Biomarker between 155 mmolar Chloride Infusion with 98 mmolar Chloride in Patients Undergoing Primary Uncremented Hip Replacement Andreas Nygaard Jorgensen,1 Jesper N. Bech,1 Erling B. Pedersen,1 Soren Bowling,1 Niels Efter Ekeløf.2 1Dept of Medical Research, Univ Clinic in Nephropathy and Hypertension, Holstebro, Denmark; 2Dept of Anesthesiology, Holstebro Hospital, Holstebro, Denmark; 3Dept of Orthopedic Surgery, Holstebro Hospital, Holstebro, Denmark.

Background: The use of fluids containing high amounts of chloride (Cl) reduced the need for renal replacement-therapy. Animal studies showed that CI reduced renal blood flow. Thus, Cl might cause acute ischemic kidney injury. The purpose of the study was to measure whether chloride induced kidney damage in a clinical study using urinary excretion rate of neutrophil gelatinase associated lipocalin (u-NGAL) as biomarker for nephrotoxicity.

Methods: In a randomized, double-blinded, placebo-controlled study of patients undergoing primary uncremented hip replacement, thirty eight were randomized to receive either isotonic saline (155 mmolar chloride) or plasma-lyte (98 mmolar chloride) 15ml/kg during the first hour and 5ml/kg the following two hours after start of surgery. Urine was collected in four periods: Period 1: 24 hours before surgery, Period 2: 4 hours from the start of surgery, Period 3: from period 2 to 7.30 the next day and Period 4: 24 hours 10-12 days later. In addition, spot urine samples were collected before surgery and before discharge. Blood was collected before surgery and at the end of period 2 and period 3. We measured urinary u-NGAL and plasma concentrations of chloride (p-Cl) and creatinine (p-Crea).

Results: U-NGAL (median values) was the same in the saline group and the plasma-lyte group in all four periods. Period 1: 15.92 (plasma-lyte)/15.60 (saline) ng/ml (p=0.54); Period 2: 22.51/9.88 ng/ml (p=0.68); Period 3: 10.95/6.44 ng/ml (p=0.05); Period 4: 4.08/2.04 ng/ml (p=0.05). In the saline group p-Cl (mean value) 110.5 mmol/l was significantly higher than in the plasma-lyte group 107.9 mmol/l (p = 0.004). P-Crea was significantly higher than in the plasma-lyte group 107.9 mmol/l (p = 0.004).

Conclusions: No evidence of nephrotoxicity was detected between infusions of high and low concentrations of chloride in a clinical trial using urinary excretion of NGAL as marker of kidney damage.

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

TH-P0643
Neutrophil Gelatinase-Associated Lipocalin (NGAL) Correlates to AKI Stage in ICU Patients Ladan Golestanian,1 A. Osama Gaber,2 Sahir Kalim,3 Peter A. McCullough,4 Michael J. Germain.3 1Medicine, Albert Einstein College of Medicine, Bronx, NY; 2Medicine, Houston Methodist Hospital, Houston, TX; 3Medicine, Massachusetts General Hospital, Boston, MA; 4Medicine, Baystate Medical Center, Springfield, MA.

Background: Acute kidney injury (AKI) is a commonly encountered complication in ICU patients and associated with poor outcomes. The diagnosis is based on serum creatinine (sCr) elevations compared to a poorly defined baseline. NGAL is a marker of AKI that has been shown to increase early in urine and plasma of different patient populations with AKI. We evaluated the ability of NGAL to detect AKI in a heterogeneous ICU cohort.

Methods: Four sites participated in this study and recruited a total of 245 ICU patients. Blood and urine samples were taken daily and stored. Concentrations were determined with the NGAL Test (BioPorto) in batched samples by a central laboratory. Three clinicians adjudicated each patient case according to KDIGO guidelines and also determined the AKI stage once present. The clinical reviewers were blinded to the NGAL results.

Results: There was a statistically significant relationship between NGAL level and stage of AKI. For the subjects classified as not having AKI, median plasma NGAL was 97 ng/mL and urine NGAL was 53 ng/mg in urine. The median plasma NGAL levels for AKI stage 1: 170 ng/mL and 53 ng/mg in urine; AKI stage 2: plasma 274 mg/mL and urine 300 ng/mL in urine; AKI stage 3: plasma 838 mg/mL and urine 629 mg/mL in urine.

Conclusions: NGAL is progressively increased in a graded fashion with ascending stages of AKI. These data suggest NGAL is a useful, objective tool, not only to identify patients with AKI but to also gauge the severity of their AKI.

TH-P0644
Impacts of Serial Plasma Neutrophil Gelatinase-Associated Lipocalin Measurement as Biomarker for Diagnosis and Prognosis in Acute Kidney Injury Patients of Emergency Room Hyun Ho Ryu,2 Hyun Lee Kim.1 1Emergency Medicine, Chonnam National Univ Hospital, Gwangju, Republic of Korea; 2Internal Medicine, Chon Univ Hospital, Gwangju, Republic of Korea.

Background: Acute kidney injury (AKI) is a common and serious condition, the diagnosis of which currently depend on functional markers such as serum creatinine measurement. Neutrophil gelatinase-associated lipocalin (NGAL) appears to be a promising novel biomarker for the early diagnosis of AKI patients and a wide range in its predictive value has been reported. The aim of this study was to evaluate the predictive value of serum NGAL and serial measurement in patients with established AKI in emergency room.

Methods: Serum NGAL was measured in 701 patient at admission and 24hr later. Patients were divided four groups: group 1 includes patients with normal renal function, group 2 includes patients with AKIN stage 1, group 3 includes patients with AKIN stage 2, group 4 includes patients with AKIN stage 3. Serum NGAL was measured by ELISA at admission. We studied possible relationship between serum NGAL, estimated glomerular filtration rate (eGFR), and mortality in patient with AKI.

Results: Serum NGAL levels were significantly higher in AKI patient than in healthy control (452.19 ± 471.57 ng/mL vs. 183.12 ± 259.46 ng/mL, p < 0.001). The serum NGAL level showed a significant inverse correlation with GFR (r=0.164, p<0.018). The discriminatory ability of NGAL for AKI also increased with increasing AKIN stage. (AKIN1 56.0 (52.0-548.0), AKIN2 159.0 (77.5-425.5), AKIN3 503.5 (88.0-1300.0), p < 0.001).

Conclusions: From this results, we concluded that serum NGAL is a reliable marker of renal function in AKI patient. Serial NGAL measurement has impacts for diagnosis and prognosis, but monitoring protocols are needed for early detection and management of AKI patients.

TH-P0645
Urinary Angiogenin Reflects the Magnitude of Kidney Injury at the Infra-Histological Level Nicolas Pallet,1,2 Quentin Tavernier,2 Alexandre Karras,1 Eric Thervet,1 Dany Anglicheau,3 'Hôpital Évrylo Georges Pompidou; 1'Inst National de la Santé et la Recherche Médicale, 2'Hôpital Necker.

Background: The ribonuclease angiogenin is secreted by renal epithelial cells upon activation of the IRE1a-sXBP1 axis. It is a pro-inflammatory cytokine that modulates cell death, survival, and differentiation and primes non-stressed renal epithelial cells to activate the Integrated Stress Response pathway (PERK/IRE2/ATF4), thereby promoting cell preconditioning. In a cohort of 242 kidney transplant recipients with an acute allograft dysfunction, higher urinary angiogenin levels at the time of the biopsy were associated with a worse renal function and higher proteinuria, but did not correlate with histological injury and determined the biochemical characteristics of urinary angiogenin, as well as its diagnostic and prognostic values.

Results: In a cohort of 242 kidney transplant recipients with an acute allograft dysfunction, higher urinary angiogenin levels at the time of the biopsy were associated with a worse renal function and higher proteinuria, but did not correlate with histological lesions, as defined in the Banff classification. The risk of graft failure of kidney transplant recipients with urinary angiogenin amounts in the highest 50% was 3.59 times as high (95% confidence interval, 1.12-15.94) as that in the lowest 50%. We demonstrate that in the early post transplantation period, angiogenin is produced in large amounts in response to ischemia/reperfusion injury and acts as a paracrine mediator produced by renal epithelial cells under ER stress and primes non-stressed renal epithelial cells to activate the Integrated Stress Response pathway (PERK/IRE2/ATF4), thereby promoting cell preconditioning. After 3 months, angiogenin is produced following the activation of sXBP1, as a consequence of smoldering immune infiltration (angiogenin levels are associated with interstitial inflammation scores, and sXBP1 is expressed by immune cells, including dendritic cells and B cells) and of non-immune insults associated with the activation of the IRE1a-sXBP1 axis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: The prognostic value of urinary angiogenin is related to the magnitude of renal injury, and angiogenin is not instrumental in the process of kidney allograft damage. Urinary angiogenin is a non-invasive indicator of the extent of tissue damage independent of the histological lesions, and a risk predictor of kidney allograft failure.

TH-PO646

The Role of Urine NGAL for Early Detection of Colistin-Induced AKI: A Randomized Controlled Trial

Saduee Peerapornratana,
Nattachai Srisawat.
Div of Nephrology, Dept of Medicine, Chulalongkorn Univ, Bangkok, Thailand.

Background: Colistin-induced acute kidney injury (AKI) are common cause of hospital acquired AKI. Neutrophil gelatinase-associated lipocalin (NGAL) is a promising biomarker for early detection of AKI which have been validated in various settings except in this specific setting. The aim of this study was to validate the role of serial urinary NGAL measurement in improvement the detection of colistin-induced AKI.

Methods: We conducted a randomized controlled trial at King Chulalongkorn Memorial Hospital, Bangkok, Thailand during June 2015 and January 2016. Adult patients treated by colistin were randomized into two groups, using urinary NGAL or serum creatinine for AKI monitoring on day 1, 2, 3, 5, 7, 14 and 28. We also notified the primary physician when urinary NGAL >400 mcg/L in NGAL monitoring group or when achieving KDIGO stage 1 criteria in creatinine monitoring group. The primary outcomes was median time to AKI detection after colistin initiation.

Results: Thirty one patients were enrolled into the study. The mean age of patients were comparable in both group. Baseline glomerular filtration rate were 121.5±34.1 and 73.7±52.7 ml/min/1.73 m² in NGAL and creatinine monitoring group, respectively (P = 0.02). The overall incidence of colistin-induced AKI within 28 days was 70.9%. The median times to AKI detection were 1 and 5 days in NGAL monitoring and creatinine monitoring group, respectively (P = 0.001). There were no significant difference in renal replacement therapy and 28-day mortality.

Conclusions: Urinary NGAL monitoring could detect colistin-induced AKI more earlier than routine serum creatinine monitoring. The further study in larger population is still warrant.

Funding: Government Support - Non-U.S.

TH-PO647

Serum Neutrophil Gelatinase-Associated Lipocalin Levels Predict Acute Kidney Injury in Visceral Leishmaniasis

Gudyllon C. Meneses,1
Elizabeth F. Daher,1 Geraldo B. Silva Junior,2 Gabriela F. Bezerra,1 Alexandre B. Liborio,1 Alice M. C. Martins.1,2
1Federal Univesity of Ceara; 2Univesity of Fortaleza, Brazil.

Background: Acute Kidney Injury (AKI) can be found in a significant proportion of patients with Visceral Leishmaniasis (VL). The aim of this study is to investigate the role of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in the diagnosis of AKI in VL patients before specific treatment.

Methods: This is a prospective study with 41 patients with confirmed diagnosis of VL. This study was conducted in the Sáo Jose hospital, a reference hospital of infectious disease in the state of Ceará, Brazil. At admission and before specific treatment for VL, blood and urine samples were collected. A control group was included with 13 healthy people. AKI was defined according to the KDIGO criteria. NGAL was measured in blood (sNGAL) and urine (uNGAL) through sandwich ELISA assay (R&D systems Inc). Urine biomarkers were expressed as ratios to urinary creatinine concentration (mg/g-Cr).

Results: Patients' average age was 45±19 years and 88% were male. In comparison with healthy controls, VL patients presented higher sNGAL and uNGAL levels than controls (sNGAL: 153±61 vs. 83±23ng/ml, p<0.001; uNGAL: 12±5.9 vs. 7.9±6.9ng/ml, p=0.03). Compared to healthy controls, patients with AKI had a maximum increase in serum creatinine corresponding to stage 1-2 AKI. Urine CuZn SOD concentration was able to predict the combined outcome of stage 3 AKI, RRT, and mortality with an area under the ROC curve of 0.75 (95% C.I. = 0.59-0.91, p = 0.017).

Conclusions: This study demonstrates the potential for CuZn SOD to serve as a novel prognostic biomarker for AKI.

Funding: NIDDK Support

TH-PO649

Plasma Uric Acid and Development of Acute Kidney Injury in the Critically Ill

Aman Srivastava, David E. Leaf, Venkata S. Babbisetty, Sushrut S. Waikar. Renal Div, Brigham & Women’s Hospital, Boston, MA.

Background: Elevations in plasma uric acid (PUA) may lead to acute kidney injury (AKI) through multiple mechanisms: tubular injury, mitochondrial dysfunction, endothelial dysfunction, oxidative stress, and intra-renal inflammation. The association between PUA levels and incident AKI in critically ill patients has not been rigorously evaluated.

Methods: Urine samples were obtained from 37 patients who developed stage 1 AKI within 48 hours of cardiothoracic surgery. Urine samples were diluted at 1:20 with phosphate-buffered saline (PBS), and urinary CuZn SOD was quantified by ELISA. Data were analyzed and a receiver operating characteristic curve (ROC) was constructed using Graphpad Prism 7.0.

Results: We found a significant increase in CuZn SOD concentration in the urine of patients that developed Stage 3 AKI, required renal replacement therapy (RRT), or died within 30 days when compared to patients who had a maximum increase in serum creatinine corresponding to stage 1-2 AKI. Urine CuZn SOD concentration was able to predict the combined outcome of stage 3 AKI, RRT, and mortality with an area under the ROC curve of 0.75 (95% C.I. = 0.59-0.91, p = 0.017).

Conclusions: Higher PUA levels have higher levels and lower eGFR at enrollment than those who did not develop AKI (Table):

<table>
<thead>
<tr>
<th>Incident AKI</th>
<th>No Incident AKI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUA, mg/dl</td>
<td>5.6±2.3</td>
<td>4.2±1.7</td>
</tr>
<tr>
<td>Age, years</td>
<td>62.7±12.2</td>
<td>62.0±15.3</td>
</tr>
<tr>
<td>Female</td>
<td>40.6%</td>
<td>36.5%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>87.5%</td>
<td>91.8%</td>
</tr>
<tr>
<td>eGFR, ml/min/m²</td>
<td>75.1±23.5</td>
<td>92.4±18.7</td>
</tr>
<tr>
<td>APACHE II</td>
<td>14 [11-17]</td>
<td>14 [10-17]</td>
</tr>
</tbody>
</table>

*Data presented are Mean ± SD or Median [Interquartile range]

After adjusting for age, sex, race, eGFR, and APACHE II score, PUA levels remained significantly associated with incident AKI (odds ratio 1.29, 95% confidence interval 1.02 to 1.64) and severe AKI (odds ratio 1.39, 95% confidence interval 1.01 to 1.90), but not the composite end point of RRT/mortality.

Conclusions: Higher PUA levels are associated with an increased risk for the development AKI in critically ill patients admitted to the ICU, independent of confounding factors including enrollment eGFR and severity of disease. These results are consistent with a pathogenic role for uric acid in the development of AKI.

Funding: NIDDK Support
TH-PO650
Platelet Aggregability as a Predictor of Acute Kidney Injury and Cardiovascular Events in Vascular Surgeries
Mauricio Teixeira,1 Daniela Calderaro,1 Etienne Macedo,1,2 \textit{USP}; 3\textit{INCOR}; 4\textit{UCSD}.

\textbf{Background:} Platelet aggregation is one theory that can explain the AKI process after the reperfusion is obtained in the ischemic model. In the population with arterial illness, this process may play a role in acute ischemic events like AKI and Cardiovascular Events (CvEv). Evaluation of platelet aggregability is used to study perioperative cardiovascular risk. The purpose of this study is to evaluate if the platelet aggregation could be a marker to predict AKI and CvEv in patients submitted to vascular surgeries.

\textbf{Methods:} Analysis of a prospective cohort of patients submitted to a major vascular surgery from whom the platelet aggregation test was performed. The extent of aggregation assesses the amount of platelet aggregates after the exposure to some agonists. The arachidonoid acid (AA) is the most important agonist in the present study because every patient was under chronic use of aspirin. This medicine inhibits platelet aggregation by blocking cyclooxygenase. This is a validated tool for the measure of aspirin response.

\textbf{Results:} A total of 185 patients were analyzed. The main vasculopathy was in the aorta, 36.2%. We had 70 (37.3%) patients with AKI and 42 (22.7%) CvEv. There was a significant association between higher platelet response to AA and AKI. The mean of resistance in the no AKI group was 5.062 (n=115) and in the AKI group was 6.92, p = 0.037. We could demonstrate that the response to AA increases with the severity of AKI: 5.88 in the KDIGO 1 group (n = 43), 10.5 in KDIGO 2 group (n = 9) and 7.82 in the KDIGO 3 group (n = 161), p = 0.022. There was also association between platelet aggregation and CvEv: 5.3, 3.0 in the no CvEv and 7.4 in the CvEv group, p = 0.04. We also had an association between AKI and CvEv: 57% of the CvEv were in the AKI group, p = 0.003.

\textbf{Conclusions:} Platelet aggregation may play a critical role in the pathophysiology of AKI and of CvEv. This can be one of the common pathways that predisposes some patients to develop ischemic events. In our cohort we showed that there was an association between platelet aggregation and AKI and also an association between AKI and CvEv.

TH-PO651
Urine Klotho Is a Potential Marker of AKI Recovery in the Intensive Care Unit

\textbf{Background:} AKI carries increased risk for subsequent CKD. Klotho deficiency has been observed in AKI and low Klotho post-AKI is associated with progression to CKD in rodents. We aim to characterize post-AKI urine Klotho trajectories in ICU patients with and without 7-day AKI recovery.

\textbf{Methods:} We conducted a prospective study of 54 AKI patients and 52 controls without AKI in the ICU setting. We excluded patients with baseline eGFR<60 or kidney transplant. Urine Klotho was measured by immunoprecipitation-immunoblot. Nonparametric tests were used for comparison.

\textbf{Results:} Mean (SD) age was 57 (16) years, 57% were men and 70% white. Patients with AKI had higher critical illness scores than controls without AKI. Most AKI cases (76%) were attributed to ATN and/or sepsis. A total of 24 (44%) patients died and 18 (33%) required RRT in the AKI group. Urine Klotho adjusted by urine creatinine (uKlotho/Cr) was significantly lower in AKI cases than in controls, median 7 [IQR 5–10] vs 28 [11–59] ng/ml/mg, p<0.001. Furthermore, uKlotho/Cr significantly increased with time in patients that exhibited AKI recovery (n=8, Δ±266%, p=0.02) but not in those that did not (n=16, Δ±31%, p=0.10), between-group p=0.03, median follow-up 6 (3-7) days.

\textbf{Urine Klotho/Cr by AKI recovery status}

\textbf{Conclusions:} Urine Klotho is significantly lower in patients with AKI when compared to ICU controls without AKI. Urine Klotho significantly recovered only in patients that exhibited 7-day AKI recovery. Urine Klotho may be a prognostic marker of AKI recovery in ICU.

\textbf{Funding:} Other NIH Support - P30 DK079328-06; 1UL1 TR001105

TH-PO652
Proteomic Approaches to Identify Differentially Expressed Proteins in Cardiovascular Surgery Associated Acute Kidney Injury
Ravi C. Dwivedi,1 Mario Navarrete,1 Nora Choi,1,2 Vic Spicer,1 Peyman Ezzati,1 Claudio Rigatto,2 Rakesh C. Arora,2 Oleg Krokhin,1 Julie Ho,2,3 John A. Wilkins,2 1\textit{Monash Centre for Proteomics & Systems Biology, Health Sciences Centre, Univ of Manitoba; 2Dept of Internal Medicine, Section of Nephrology, Univ of Manitoba; 3Dept of Immunology, Univ of Manitoba; 4Cardiac Sciences Program, St. Boniface Hospital, Winnipeg}.

\textbf{Background:} Acute kidney injury (AKI) after cardiopulmonary bypass (CPB) is an important cause of morbidity and mortality. Mass-spectrometry (MS)-based proteomics may allow us to improve our understanding of ischemia-reperfusion injury (IRI) and identify ‘at-risk’ individuals. The goal was to perform an in-depth proteomic analysis of patients undergoing CPB.

\textbf{Methods:} A nested case-control cohort (5 AKI & 5 non-AKI) from a prospective cohort of 306 adult CPB patients was evaluated at: baseline, start CPB, 1hr CPB, arrival to ICU, POD day 1 and 3-5. Pooled urines were processed using modified Filter Assisted Sample Preparation, separated and analyzed by 2D-LC-MS/MS for protein identification and to generate an ion library. A label-free approach was applied for protein quantitation. Protein identification accuracy was increased by analyzing the same samples with SWATH-MS (Sequential Window Acquisition of All Theoretical Fragment ion spectra Mass-Spectrometry). Protein relative abundance was compared in AKI vs non-AKI using both 2D-LC-MS/MS and SWATH.

\textbf{Results:} Using a high-content MS approach we confidently identified 2,061 proteins (≥2 peptides, log(e)<-3) across all time-points. For more complete comparison we used SWATH-MS to provide quantitative data on 826 proteins, which demonstrated some overlap with the 2D-LC-MS/MS data. Differential analysis detected 10 decreased and 11 increased proteins in AKI vs non-AKI patients, based on normalized Z-scores >1 across all time-points. Urinary MMPI was validated as decreased in AKI versus non-AKI pooled urines using ELISA.

\textbf{Conclusions:} This study provides high quality protein quantitation in AKI vs non-AKI patients throughout IRI. The differential proteomic changes identified may provide insight into the pathophysiology of IRI and potential novel biomarker identification.

\textbf{Funding:} Government Support - Non-U.S.

TH-PO653
Low Regulatory T Cell Abundance before Cardiac Surgery Is Associated with Increased Risk of AKI: A Pilot Study
Gilbert R. Kinsey,1 Jennie Z. Ma,1 John Kern,2 Mark D. Okusa,1 Charles H. Brooks,3 Sandra Burks,4 Ashley Caddick,4 Adrienne Lynne Stimson,1 Victoria L. Yu,2 Brian K. Stevens,1 1Div of Nephrology and Center for Immunity, Inflammation and Regenerative Medicine, Univ of Virginia; 2Public Health Sciences, Univ of Virginia; 3Surgery, Univ of Virginia.

\textbf{Background:} Patients who undergo cardiac surgery (CS) are at high risk of developing post-surgical acute kidney injury (AKI). The pathogenesis of AKI involves inflammation, nephrotoxins and ischemia-reperfusion injury (IRI). Preclinical studies have demonstrated regulatory T cells (Tregs) protect the kidney from inflammation and dysfunction induced by IRI and nephrotoxins. We hypothesized that patients with low circulating Treg numbers at time of surgery from whom the platelet aggregation test was performed. The extent of aggregation assesses the amount of platelet aggregates after the exposure to some agonists. The arachidonoid acid (AA) is the most important agonist in the present study because every patient was under chronic use of aspirin. This medicine inhibits platelet aggregation by blocking cyclooxygenase. This is a validated tool for the measure of aspirin response.

\textbf{Results:} Mean (SD) age was 57 (16) years, 57% were men and 70% white. Patients with AKI had higher critical illness scores than controls without AKI. Most AKI cases (76%) were attributed to ATN and/or sepsis. A total of 24 (44%) patients died and 18 (33%) required RRT in the AKI group. Urine Klotho adjusted by urine creatinine (uKlotho/Cr) was significantly lower in AKI cases than in controls, median 7 [IQR 5–10] vs 28 [11–59] ng/ml/mg, p<0.001. Furthermore, uKlotho/Cr significantly increased with time in patients that exhibited AKI recovery (n=8, Δ±266%, p=0.02) but not in those that did not (n=16, Δ±31%, p=0.10), between-group p=0.03, median follow-up 6 (3-7) days.

\textbf{Urine Klotho/Cr by AKI recovery status}

\textbf{Conclusions:} Urine Klotho is significantly lower in patients with AKI when compared to ICU controls without AKI. Urine Klotho significantly recovered only in patients that exhibited 7-day AKI recovery. Urine Klotho may be a prognostic marker of AKI recovery in ICU.

\textbf{Funding:} Other NIH Support - P30 DK079328-06; 1UL1 TR001105

\textbf{Key:} TH - Thursday; FR – Friday; SA - Saturday; OR – Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Urinary Excretion of Active Serine Hydrolases in Cardiac-Surgery-Associated Acute Kidney Injury Mario Navarrete,1 Julie Ho,1,2 Ravi C. Dwivedi,1 Nora Choi,1,2 Peyman Ezzati,1 Oleg Krokhn,1 Vic Spicer,1 Rakesh C. Arora,1 Claudio Rigato,3 John A. Wilkins.1 1Manitoba Centre for Proteomics & Systems Biology, Health Science Centre, Univ of Manitoba, Winnipeg, MB, Canada; 2Internal Medicine, Section of Nephrology, Univ of Manitoba, Winnipeg, MB, Canada; 3Immunology, Univ of Manitoba, Winnipeg, MB, Canada; 4Cardiac Science Program, St. Boniface Hospital, Winnipeg, MB, Canada.

Background: Changes in enzyme activity are physiologically relevant and may be independent of enzyme quantity. Activity-based protein profiling (ABPP) is a proteomic approach to assess the functional status of enzymes. ABPP may offer insight into ischemia-reperfusion injury (IRI) and identify novel acute kidney injury (AKI) markers following cardiac surgery-cardiopulmonary bypass (CPB).

Methods: A nested case-control cohort (8 AKI & 8 non-AKI patients) from a prospective cohort of 306 adult cardiac surgery patients was evaluated at: baseline, start CPB, 1hr CPB, arrival to ICU, POD 1 and 3-5. ABPP was visualized by SDS-PAGE and protein by Coomassie. Serine hydrolase composition was determined by MS/MS. Active serine hydrolases were affinity purified and identified on MS/MS.

Results: Serine hydrolase activity remained stable throughout IRI in non-AKI. AKI urines demonstrated early differential intraoperative serine hydrolase activity that was independent of protein quantity.

Conclusions: We demonstrated novel serine hydrolase activity and confirmed differential enzyme activity in AKI vs. non-AKI patients. These findings have implications in understanding the serine hydrolase response to IRI and may be a potential early intraoperative marker of AKI.

Funding: Government Support - Non-U.S.

Figure 1. Serine hydrolase ABPP demonstrates early enzyme activity, independent of protein concentration, that differ between AKI versus non-AKI patients

AKI urines had 53 serine hydrolases on compositional analysis, whereas 31 were identified in their active state. Quantitative assays confirm differential enzyme activity between AKI and non-AKI.

Conclusions: We demonstrated novel serine hydrolase activity and confirmed differential enzyme activity in AKI vs. non-AKI patients. These findings have implications in understanding the serine hydrolase response to IRI and may be a potential early intraoperative marker of AKI.

Funding: Government Support - Non-U.S.

Latent Class Analysis Identifies AKI Sub-Phenotypes with Differing Biomarker Profiles of Endothelial Dysfunction and Relation to Risk of Death and Need for Renal Replacement Therapy Pavan K. Bhatruj,1 Cassianne Robinson-Cohen,2 Jonathan Himmelfarb,3 Mark M. Wurfel.1 1Pulmonary and Critical Care, Univ of Washington, Seattle, WA; 2Kidney Research Inst, Univ of Washington, Seattle, WA; 3Kidney Research Inst, Univ of Washington, Seattle, WA.

Background: The heterogeneity of acute kidney injury (AKI) may limit identification of patients at highest risk of poor outcomes. Latent class analysis (LCA) is a statistical modeling technique to identify unobserved sub-groups using observed clinical and biologic parameters. We hypothesized that LCA would identify AKI sub-phenotypes with differing biomarker profiles and associations with outcomes.

Methods: We applied LCA to 806 ICU subjects with AKI (change in serum creatinine of 0.3 mg/dl, >72 hours of ICU admit) from a cohort of patients with systemic inflammatory response syndrome. Subjects were equally split into discovery and validation sets. In the discovery group the LCA included 25 biological and clinical variables measured on day 1.

Results: During the first 72 hours of ICU admission, 816 (65%)subjects developed AKI. Of these 480 (59%) had a resolving sub-phenotype and 336 (41%) had a non-resolving sub-phenotype. The hospital mortality rate of subjects with no AKI was 4%, resolving sub-phenotype was 10% and a non-resolving sub-phenotype was 23%. Plasma sFAS, sTNFR-1 and sVCAM-1 concentrations were identically associated with a non-resolving sub-phenotype compared to resolving after adjustment for age, body mass index, diabetes and apache III scores (p < .001). Notably, after adjustment for endothelial dysfunction (sVCAM-1), a doubling of sFAS and sTNFR-1 remained strongly associated with a non-resolving sub-phenotype (RR 1.25 (95% CI 1.11, 1.42, p<0.001) and RR 1.20 (95% CI 1.09, 1.33, p<0.001), respectively.

Conclusions: This work suggests research identifying modifiable targets in the sFAS and sTNFR-1 pathways may allow the prevention and treatment of a severe sub-phenotype of AKI.

Funding: Other NIH Support - R01-HL-089807 from the National Institutes of Health and the Heart Lung and Blood Institute


Background: Limited evidence suggests serum cystatin C (cysC) peaks earlier than serum creatinine (sCr) during the course of acute kidney injury (AKI). Earlier identification of AKI recovery could support less intensive resource utilization and earlier hospital discharge. We conducted an observational pilot study to determine the relative time course of sCr and cysC change in hospitalized patients with AKI in a tertiary medical center.

Methods: Hospitalized patients with AKI at our institution between May 2015 and May 2016 who had serial sCr and cysC levels measured during their hospitalizations were identified. AKI was defined based on the Acute Kidney Injury Network criteria. Demographic data, baseline creatinine, cause of AKI, and other significant comorbidities were collected by medical record review.

Results: Overall, 63 patients were identified. Mean age was 58.7 ± 13.9 years, 62% were men, 95% were white, and median BMI was 27.8 kg/m². Baseline median sCr was 0.05 (IQR 0.8-1.3), 13% had a kidney transplant and 37% had received corticosteroids. Co-morbidities included malignancy (38%), diabetes (33%), thyroid disorder (16%) and heart failure (19%). The majority of cases were AKI stage III (61%) with 22 patients (35%) requiring dialysis. The cause of AKI was ATN in 71% of patients. CystC peaked before sCr in 68% of patients (6% 3 days, 16% 2 days, 46% 1 day sooner), on the same day in 24%, and in 5 patients (8%) sCr peaked after CysC. Overall cysC peaked a mean of 0.92 days prior to sCr (95% CI 0.65-1.18, p<0.001). Exploratory analyses did not reveal effect of patient co-morbidities on the timing of peak cysC compared to sCr. Lower baseline eGFR predicted earlier recovery by cysC (P=0.035). Overall cysC performed equally well or better than sCr in 92% of patients in this study for monitoring recovery from AKI.
Conclusions: This study suggests cysC peaks earlier than sCr in the majority of hospitalized AKI patients. These findings have significant clinical implications for managing AKI with the potential for shortening hospital stay and reducing costs. A large prospective study is warranted to confirm these findings.

TH-PO668
Temporal Profiling Refines the Prognostic Value of Acute Kidney Injury Urinary Biomarkers
Margaret Rachel Ninemire1, Shina Menon2, Erin K. Stenson3, Stuart Goldstein4, Rajit K. Basu5, Margaret Stenson6, Stuart Goldstein7, Rajit K. Basu8,9,10

Background: Acute kidney injury (AKI) is common in critically ill children with sepsis, and persistent AKI (pAKI) is associated with poor clinical outcomes. Novel urinary biomarkers used for AKI prediction have been studied in many populations. However, these studies generally only compare individual biomarkers measured at a single time point. Analysis of biomarker measurement trends over time to predict pAKI is not well described.

Methods: We conducted a single center, prospective study of children admitted to the intensive care unit (ICU) with multiple urinary biomarker levels (neutrophil gelatinase associated lipocalin (uNGAL) and kidney injury molecule-1 (uKIM-1)) in the first 36 hours to test the hypothesis that predictive performance of pAKI by changes in biomarkers was superior versus changes in serum creatinine (sCr). Stage 2-3 KDIGO sCr criteria 72 hours after admission defined pAKI.

Results: 173 pts (51% male, median age 6.7 yrs), including 42 with sepsis (24%) and 31 with pAKI (18%) were studied. Combination of a persistent elevation in uNGAL (>150 on days 1 and 2) and an increasing uKIM-1 (rising value from day 1 to 2) increased the likelihood of pAKI nearly 2-fold compared to doubling of sCr from baseline. When stratified by sepsis, the positive likelihood of pAKI predicted by the biomarker changes in combination remained statistically significant versus the changes in sCr.

Conclusions: Temporal urinary biomarker changes over time may provide added insight for AKI prediction compared to single measurements and refine AKI stratification compared to current clinical standards. Further studies are needed to validate these findings.

TH-PO669
Biomarkers at Discontinuation of Renal Replacement Therapy Predict 90-Day Clinical Outcomes in Critically Ill Patients with Acute Kidney Injury
Tingting Yang1, Baishu Su2, Dept of Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China.

Background: There is no consensus on the specific indications of weaning renal replacement therapy (RRT) in acute kidney injury (AKI). This study aimed to explore the prognostic value of several biomarkers at discontinuation of RRT for 90-day outcomes and find potential indicators for discontinuation of RRT.

Methods: We prospectively enrolled 102 patients with AKI who require RRT from the intensive care unit (ICU) with multiple urinary biomarker levels (neutrophil gelatinase associated lipocalin (uNGAL) and kidney injury molecule-1 (uKIM-1)) in the first 36 hours. We compared the changes in biomarkers for prognosis with the changes in serum creatinine and urine output. Multivariate logistic regression and ROC analysis were performed to assess the predictive value of each biomarker for prognosis.

Results: Patients who survived had lower levels of all serum and urinary biomarkers. Serum opn was an independent predictor of 90d mortality (OR, 1.029; 95% CI, 1.013-1.047; p=0.001). Lower sCr and sL-6 were associated with greater odds of 90d survival (area under the ROC curve (AUC), 0.812 and 0.751). Lower sCysC was associated with greater odds of 90d renal recovery (AUC, 0.743). The AUC reached best when combining biomarkers with conventional indicators at discontinuation of RRT (0.881 for predicting survival and 0.923 for predicting renal recovery).

Conclusions: Serum and urinary biomarkers at discontinuation of RRT can be predictive for 90d survival and renal recovery in critically ill AKI patients. Serum opn, IL6 and CysC are promising indicators for discontinuation of RRT.

Funding: Government Support - Non-U.S.

TH-PO660
Urinary Retinol-Binding Protein as a Risk Factor of Poor Prognosis in Acute-on-Chronic Renal injury
Yanhong Yuan1, Shaowei Mou2, Dept of Nephrology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong Univ, Shanghai, China.

Background: We recently determined that pediatric AKI after cardiac surgery (CS) is not associated with an increased risk of CKD at 5 years of follow-up. We evaluated if at 5 years after CS, there was evidence of subclinical kidney injury, measured by renal injury biomarkers, in patients with vs. without AKI.

Methods: The Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) long-term study is a 3 center prospective cohort study of children 1 month to 5 years old after cardiac surgery. Patients were followed till 5 years and urinary retinol-binding protein (uRBP) and uNAG were measured at monthly intervals and at a median of 5 years. Multivariate analysis was performed to test the hypothesis that urinary biomarkers could be used as a non-invasive prognostic marker in acute-on-chronic renal injury patients.

Results: 108 adult patients with pre-existing chronic kidney disease presenting with acute-on-chronic renal injury were included. Urinary retinol-binding protein, N-Acetyl-b-D-Glucosaminidase and albumin was quantified.

Conclusions: Urinary retinol-binding protein was an independent risk factor for outcome of acute-on-chronic renal injury patients by multivariate logistic regression analysis.
18 years old who underwent cardiopulmonary bypass for CS and survived hospitalization. At 5 years post-CABG, we measured urine interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-1 (MCP-1), and YKL-40 to evaluate for subclinical chronic renal injury. Biomarker levels were compared between patients with AKI (≥25% or ≥3.0 mg/dl serum creatinine rise) vs. without. At baseline, 36 (8.6%) patients were admitted to the ICU following surgery and 15 (3.5%) were discharged to the floor. Out of 364 patients admitted to the ICU following hospitalization: 4 (1.1%) died after discharge; 110 (32%) participated in the 5-year follow-up (median 5.4 years follow-up). Mean age at follow-up was 8.7 years; 52% were male. 49/110 (45%) had AKI. At 5 years, there was no significant difference in any of the biomarker concentrations between AKI groups (see Table). 

Conclusions: Post-operative pediatric AKI is not associated with elevation of kidney injury biomarkers 5 years after CS. This may either represent a lack of chronic renal injury after pediatric AKI, that longer follow-up is needed to determine long-term AKI renal damage, or that our studied biomarkers are inadequate for evaluating subclinical chronic renal injury.

<table>
<thead>
<tr>
<th>TH-PO662</th>
<th>Proteinuria Is an Independent Predictor for Acute Kidney Injury following Coronary Artery Bypass Grafting</th>
<th>Kevin Hageman</th>
<th>Bruce Sortor</th>
<th>Michael Zopf</th>
<th>Kent Noiri</th>
<th>( T. )</th>
<th>( H. )</th>
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<tr>
<td>Methods:</td>
<td>A retrospective cohort study was conducted on patients undergoing first-time CABG between 2004-2014 with a preoperative urine study. Patients with age &lt;18, eGFR &lt;30, history of RRT and combined cardiac surgery were excluded. A total of 255 patients were included. AKI diagnosis was based on SCr &gt;48 hours after CABG, and was defined by AKIN criteria. Logistic regression was used to analyze the associations between proteinuria and AKI, AKI requiring RRT, and in-hospital mortality. The association models were further adjusted for baseline variables (age, race, gender, HTN, DM, CVA/TIA, CHF, anemia, CVA/TIA, PVD, smoking) known to correlate with AKI.</td>
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<td>Results:</td>
<td>The incidence of AKI in patients with preoperative proteinuria is higher than that without proteinuria [39.9% vs 18.9%, OR 2.85, 95% CI (1.95-4.20), ( p = 0.001 )]. Compared with no proteinuria, mild proteinuria increased the risk of AKI 12.13 times [95% CI (1.95, 24.20)], moderate proteinuria 3.58 times [95% CI (1.70, 7.49)] and severe proteinuria was associated with a 5.97 fold higher risk of AKI [95% CI (3.09, 11.75)]. After adjusting for covariates, proteinuria was still strongly associated with higher AKI incidence (OR 2.44, 95% CI (1.15-5.17)). The incidence of AKI requiring RRT was higher in patients with proteinuria compared to patients without proteinuria, however, the difference is not statistically significant due to rare cases of AKI requiring RRT (2.8% vs 2.5%). The incidence of preoperative proteinuria was strongly associated with post-CABG AKI before and after adjustment of covariates. The incidence of AKI increased along with the severity of proteinuria.</td>
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<td>Funding:</td>
<td>Private Foundation Support</td>
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TH-PO663

Prognosis Prediction by Biomarkers on Dialysis-Containing Severe Acute Kidney Injury: Tetsushi Yamashita | Eisie Noiri | Kengo Matsuura | Ryo Matsuura | Masaomi Nangaku, Kent Doi | The Univ of Tokyo, Tokyo, Japan. |

Background: Many biomarkers have been developed mainly for early detection of AKI. Another challenge is prediction of mortality and renal recovery. It is clinically important to predict these outcomes of severe AKI patients requiring renal replacement therapy. This study was conducted to evaluate the performance of biomarkers measured at CRRT initiation for severe AKI.

Methods: This study enrolled 98 AKI patients who needed CRRT in the adult mixed ICU of the University of Tokyo Hospital from October 2013 to March 2015 by consecutive sampling. Blood biomarkers of NGAL, NT-proBNP, Cystatin C, and HMGB-1 and urine biomarkers of L-FABP, NAG, α1- microglobulin and TIMP-2 were measured at CRRT initiation. We evaluated whether these biomarkers could predict mortality and renal recovery by receiver operating characteristic (ROC) analysis. We also evaluated whether the addition of biomarkers to a clinical model, which consisted of age and SOFA score, is helpful to predict mortality and renal recovery using category-free net reclassification improvement (cNRI) and integrated discrimination improvement (IDI).

Results: In-hospital mortality was 46% in this cohort and only urine L-FABP was significantly higher in the non-survivors than the survivors. ROC analysis showed the AUC-ROC of 0.64 [0.52-0.75]. The cNRI demonstrated addition of L-FABP to the clinical model improved mortality prediction. Thirty-nine patients (40%) showed renal recovery, whereas none of them was defined as being free from dialysis on discharge with a less than 50% decrease in eGFR. Only plasma NGAL was significantly lower in these patients than the others. The AUC-ROC of plasma NGAL for renal recovery prediction was 0.71 [0.60 - 0.81]. The cNRI and IDH demonstrated addition of NGAL to the clinical model showed significant improvement of renal recovery prediction.

Conclusions: Urine L-FABP and plasma NGAL measured at CRRT initiation could predict mortality and renal recovery, respectively. Even in the most severe AKI, which requires RRT, L-FABP and NGAL have potential to predict hard outcomes.

Funding: Government Support - Non-U.S.

TH-PO664

Urinary Heparin-25 Is Elevated after Cardiac Surgery in Non-AKI versus AKI Patients: Nora Chou | Claudio Rigatto | Brett M. Hiebert | Ang Gao | Simon Christie | Michael Zappitelli | Rakesh C. Arora | Julie Ho | \( T. \) | \( H. \) | \( T. \) | \( H. \) | \( T. \) | \( H. \) |

Background: Acute kidney injury (AKI) following cardiac surgery results in increased morbidity and mortality. Using proteomic techniques, we previously identified urine hepcidin-25 as a predictor for AKI avoidance. The goal of this study was to independently validate urine hepcidin-25 as an early AKI marker in a prospective observational cohort of cardiothoracic surgery patients (CPB).

Methods: Serial urines were collected at baseline, start CPB, 1hr CPB, arrival to ICU, post-operative day (POD) 1 and 3-5. Urine hepcidin-25 was evaluated with ELISA in a nested, time-controlled cohort of non-AKI, non-CAbG across 6 time points and at POD1 in the full cohort (n=306). AKI was defined using KDIGO (creatinine >50% or 26.5μmol/L/48hrs). Stepwise logistic regression was performed using significant urinary predictors of AKI.

Results: Peak hepcidin-25 levels were confirmed at POD1 in AKI and non-AKI patients. Univariate predictors of AKI were hepcidin-25, age, baseline eGFR & creatinine, diabetes (DM), congestive heart failure and THAKAR & EuroSCORE II. Urine hepcidin-25 was an independent predictor for AKI avoidance on multivariate analysis. The combined model with eGFR, DM and hepcidin-25 had an AUC 0.815.

Table 1. Urine hepcidin-25 is an independent predictor for avoidance of AKI after cardiac surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
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<tr>
<td>eGFR (mL/min/1.72 m²)</td>
<td>0.96</td>
<td>0.95 - 0.98</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.09</td>
<td>1.47 - 6.45</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Average Heparin-25 Concentration (mg/L)</td>
<td>0.87</td>
<td>0.55 - 0.95</td>
<td>0.02</td>
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</tbody>
</table>

Funding: NIDDK Support

TH-PO665


Background: Acute kidney injury (AKI) has been associated with cardiovascular disease (CVD) in observational studies. However, it remains unclear whether kidney injury is causally linked to CVD or whether the observed association between AKI and CVD is simply reflective of changes in renal perfusion due to underlying cardiac and hemodynamic dysfunction.

Methods: In a prospective multicenter study, we examined 968 adults who underwent cardiac surgery in the TRIBE-AKI cohort. On postoperative days 1-3, we measured the validate urine biomarkers of cardiac injury (II-18, NGAL, KIM-1, L-FABP, and TIMP-2) and measured at CRRT initiation. In addition, we measured the following plasma biomarkers of cardiac injury: NT-proBNP, hs-CtTn, C-tTn, and H-FABP. AKI was defined as a ≥50% or ≥0.3 mg/dl increase in serum creatinine, within 7 days of surgery. CVD and death were ascertained using administrative linkages with national datasets during a median follow-up of 3.8 (3.1-4.6) years.

Results: During follow-up, 136 (14.1%) patients experienced CV events and 83 (8.6%) patients died. We found that the magnitude and duration of postoperative creatinine-based AKI were strongly associated with CVD and mortality (Figure). However, peak postoperative elevations in urinary kidney injury biomarkers were not significantly associated with risk for future CV events and mortality (Figure). Instead, elevations in four cardiac injury biomarkers, independent of kidney injury, strongly associated with future CV events and mortality (Figure).

Conclusions: These results suggest that creatinine-based AKI may be a surrogate for an inability of the kidneys of some patients to compensate to cardiovascular stress or injury, rather than an independent pathway for adverse cardiovascular outcomes.

Funding: Other NIH Support - CIHR
Serum and urinary hepcidin, but not Free iron as Protective and Inverse Biomarkers of CI-AKI in Patients Undergoing Percutaneous Coronary Interventions-PCI

Jacek S, Małyszko,1 Hanna Gajewska,2 Ewa Koc-Zorawska,1 Jolanta Małyszko,2 Sławomir Dobrzycki,1 11st Dept Nephrol, Medical Univ, Bialystok, Poland; 2Dept Invasive Cardiology, Medical Univ, Bialystok.

Background: Contrast-induced acute kidney injury (CI-AKI) is a common and potentially serious complication of percutaneous coronary interventions-PCI. Hepcidin, a peptide hormone that regulates iron homeostasis, is supposed to be crucial in cell regeneration. We tested the hypothesis whether serum hepcidin could represent an early protective biomarker of CI-AKI in 80 patients with normal serum creatinine undergoing PCI. We also assessed serum and urinary NGAL, cystatin C in these patients as well as LPI (labile plasma iron) and eLPI (NTBI-non transferrin bound iron).

Methods: Serum and urinary hepcidin as well as NGAL, cystatin C, were evaluated before and after, and 4, 8, 24 and 48 hours after PCI using commercially available kits. LPI and eLPI were assessed by Aferrix, Israel. Serum creatinine was assessed before, after 2, 4, 8, 24 and 48 hours after PCI.

Results: We found a significant rise in serum hepcidin as early as after 4 hours when compared to the baseline values. It was also significantly higher 8 and 24 hours after PCI. Serum NGAL increased after 2, 4 and 8 hours, and in urinary NGAL after 4,8 and 24 hours after PCI. We found a significant rise in serum NGAL after 2, 4 and 8 hours, and in urinary NGAL and IL-18 after 4, 8 and 24 hours after PCI. Serum cystatin C significantly increased 8 hours, reaching peak 24 hours after PCI and then decreased after 48 hours. In all the patients both LPI and eLPI. When contrast nephropathy was defined as an increase in serum creatinine by >25% of the baseline level 48 hours after PCI, the prevalence of CI-AKI was 4/26. Urine hepcidin were significantly lower 8 and 24 hours after PCI in patients with CI-AKI, while serum and urine NGAL were significantly higher in patients with CI-AKI. Hepcidin correlated negatively with NGAL (r=−0.42, p=0.05).

Conclusions: Our findings suggest that serum hepcidin might be an early predictive biomarker of ruling out CI-AKI after PCI, thereby contributing to early patient risk stratification. Free iron does not appear to be involved in CI-AKI.

TH-PO669

Microparticles and Kidney Injury in Stroke

Begoña Campos, Charuhas V. Thakar, Anthony C. Leonard. 1IM Div of Kidney CARE, Univ of Cincinnati, Cincinnati, OH.

Background: Acute kidney injury (AKI) affects 1-3 in 3 hospitalizations, and is more common in setting of other vital organ injury. Recent evidence demonstrates that in response to stress or injury cells release phenotypically distinct micro particles (MP's), which can be both markers or mediators of disease. The objective of this study was to evaluate type and quantity of MP’s in setting of kidney injury (KI) and stroke.

Methods: In a prospectively collected biological repository of 38 eligible stroke subjects (14 ischemic and 24 hemorrhagic) and 37 controls. Demographic, comorbid and laboratory variables were collected at the time of admission. Injury (KI) was defined as either admission creatinine > 1.2 mg/dl or development of AKI. Comparisons were made across Group I (Stroke) (IA = no KI; IB = KI) and Group II (no Stroke) (IA = no KI; IB = KI). Flow Cytometric analysis measured MP's in plasma for CD146 (endothelial cells), CD10 and CD13 (monocytes) and RPTP markers. Flowcytometry evaluated MP’s, and levels were expressed as 107 and compared by Wilcoxon test (two-sided p-values).

Results: For Group I and II, CD146 MP’s were 48.8 vs 39.3 (p = 0.0026); where as CD 10 MP’s were 8.4 vs 15.4 (p = 0.001); and CD13 MP’s were 19.4 vs 20.6 (p = 0.21) For Group II, RPTP MP’s were higher in IBs; CD10 levels were 22.5 vs 14.0 (p = 0.048), and CD 13 were 23.4 vs 19.9 (p = 0.023). Within Group I, RPTP MP’s and endothelial MP’s were not different by KI status. When KI status was compared across Groups I and II (IB vs IB), CD13 levels were 50.6 vs 39.6 (p = 0.002); CD10 were 8.9 vs 22.5 (p = 0.0027); CD 13 were 19.3 vs 23.4 (p = 0.013).

Conclusions: We confirm that endothelial MP’s are increased in Stroke. In non Stroke patients, RPTP MP’s are higher associated with KI; however this difference is not significant in Stroke subjects. Interestingly, when KI status was compared across Stroke vs Control, RPTP MP’s were significantly decreased in Stroke patients. This suggests an interplay between up-regulation of endothelial MP’s and down regulation of RPTP MP’s in the setting of dual organ injury. This is one of the first study to detect RPTP MP’s in plasma of patients with vital organ dysfunction.

Funding: Clinical Revenue Support.
TH-PO670
Extracellular Histones in Relation to Organ Dysfunction and Inflammation during Kidney-Lung Crosstalk. Xin Wang, Yasser M.Z. Gendoo, Changchun Cao. Dept of Nephrology, Nanjing First Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Mortality rates due to kidney-lung crosstalk have remained high despite advances in the management of AKI and ARDS. The inflammatory mediators believed to be responsible for this are yet unidentified. Extracellular histones are known to exacerbate inflammation and tissue injury. Here we investigate whether there is a clinical correlation between blood histone concentrations, kidney function, and lung function during AKI and ARDS.

Methods: In a prospective cohort, blood samples were collected from 54 patients upon admission to our hospital who were diagnosed with AKI, ARDS, community acquired pneumonia, or a combination of these. Serum histone concentrations were measured by ELISA and plotted against PaO2/FiO2, eGFR, neutrophils, and CRP. Pearson correlation test was performed and p < 0.05 was considered significant.

Results: The scatter-graphs show histone concentrations against the four parameters. In the overall sample population, histone concentrations were significantly correlated with PaO2/FiO2 (P=0.0017, R2=0.1652); change of eGFR from baseline (P=0.0001, R=0.3017); neutrophil counts (P=0.0174, R2=0.1021) and CRP (P=0.0004, R2=0.2207). However, when patients were divided according to diagnosis, there was no significant correlation between these same parameters.

Conclusions: When viewed in light of the adverse effects of extracellular histones, the correlations reported in this study strongly suggest that extracellular histones may be potential mediators of kidney-lung crosstalk. Additional research is necessary to reveal the mechanisms of their involvement and whether they participate in or are merely a consequence of a injury. Further endeavours to understand the pathophysiology of crosstalk will likely lead to improved treatment strategies and outcomes.

Funding: Government Support - Non-U.S.

TH-PO671

Background: Prediction for postoperative AKI can be helpful to identify high risk patients and elicit early intervention. In this study, we incorporated several pre- and intraoperative factors to build a prediction model for postoperative AKI using various machine learning methods.

Methods: We included adult (age ≥ 18 years) patients who received noncardiac major (duration>1 hour) surgery in Seoul National University Hospital from 2004 to 2013. Patients with baseline creatinine (Cr) over 4 mg/dl or maintenance renal replacement therapy (RRT) were excluded. AKI was diagnosed according to both KDIGO and AKIN criteria based on Cr measurements and initiation of RRT within 14 days after surgery. Variables used include age, sex, department, BMI, BP, comorbidities, medication, ASA class, anesthesia type, Cr measurements and initiation of RRT within 14 days after surgery. AKI was diagnosed according to both KDIGO and AKIN criteria based on Cr measurements and initiation of RRT within 14 days after surgery.

Results: Among a total of 58,919 cases, 4,092 (6.95%) and 3,347 (5.68%) AKI were identified by KDIGO and AKIN, respectively. Prediction accuracy using preoperative (A), intraoperative (B), pre- and intraoperative variables (C) were demonstrated in Figure 1.

Conclusions: AKI prediction using pre- and intraoperative variables by machine learning algorithms showed fairly acceptable sensitivity and specificity. Further efforts are needed until clinical implication of machine learning algorithms.

TH-PO672
More Accurate AKI Diagnosis by Incorporating Urinary Biomarkers with No Reference Serum Creatinine Value. Rei Ishihaki,1 Maki Sumida,1 Yoshifumi Hamasaki,1 Massomio Nagakura,1 Eisai Noiri,1 Kent Dos1.2 (Nephrology and Endocrinology, Univ Hospital, Univ of Tokyo, Tokyo, Japan; 1Emergency and Critical Care Medicine, Univ Hospital, Univ of Tokyo, Tokyo, Japan.

Background: The KDIGO guideline defines AKI based on relative changes in serum creatinine from baseline values, which is sometimes unavailable. This study was aimed to evaluate whether urinary biomarkers is useful to reduce misclassification rates of AKI compared with employing estimated serum creatinine value calculated by MDRD formula assuming a GFR of 75 ml/min/1.73m2 (e-sCr).

Methods: We conducted a prospective observational study that included adult ICU patients with known baseline serum creatinine values. Misclassification rate of AKI was calculated when using e-sCr instead of available baseline values. A predictive model incorporating urinary biomarkers (NGAL and L-FABP) using decision tree analysis was developed for reducing AKI misclassification.

Results: Of 135 patients, 44 patients (32.6%) had developed AKI at ICU admission. When using e-sCr, 28 patients were misclassified as AKI (false positive rate 30.8%) and 4 patients were misclassified as non-AKI (false negative rate 9.1%). The total number of misclassification was 32 in all the enrolled patients (23.7%). Levels of urinary NGAL were significantly higher in the true AKI patients compared with the patients who were misclassified as AKI (839.8 vs 161.6 mg/ml; p=0.0047), however urinary L-FABP level showed no significant difference. Urinary NGAL alone showed a similar misclassification rate (22.9%) with the Youden-index cut-off value of 430 ng/ml. Decision tree analysis incorporating absolute serum creatinine values and urinary NGAL at ICU admission revealed that the misclassification rate was decreased to 17.7%. The area under the curve (AUC) for this developed decision tree analysis model was 0.87 (95%CI, 0.80-0.92), whereas the model using e-sCr alone showed a significantly lower AUC value (0.80 [0.73-0.86]; p=0.0002).

Conclusions: Even when no baseline serum creatinine value is available, urinary NGAL in addition to the absolute serum creatinine value at ICU admission can show more accurate AKI diagnosis compared with back calculation of baseline serum creatinine by MDRD formula.

TH-PO673
Severe Acute Kidney Injury in Hospitalized Patients Can Be Predicted from the Emergency Department: A Feasibility Study. Holly R. Hanson, Michael Adam Carlisle, Rachel S. Bensman, Terri Byczkowski, Stuart Goldstein, Rajit K. Basu. Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Early recognition of patients at risk of acute kidney injury (AKI) may expedite supportive and preventive care. We previously derived and validated an AKI risk stratification methodology, renal angina, for prediction of severe AKI in patients during 48 hours after admission to the intensive care unit (ICU). Use of renal angina applies context to patients, optimizing the predictive performance of biomarkers for subsequent AKI. AKI risk stratification in the emergency department (ED) has not been well described.

Methods: We conducted a prospective, single-center observational study in a tertiary pediatric ED to derive and validate a modified “acute” RAi (aRAI) for the prediction of severe AKI (5CR KDIGO Stage 2 or 3) at 48-72 after hospitalization. The aRAI was determined at the time of disposition from the ED.

Results:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Risk Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED Concern for Sepsis or Shock</td>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>History of Transplant and/or active Oncologic Disease</td>
<td>High</td>
<td>3</td>
</tr>
<tr>
<td>&gt;40 mL/kg intravenous fluid and/or ED Intubation</td>
<td>Very High</td>
<td>5</td>
</tr>
</tbody>
</table>

Injury Score

<table>
<thead>
<tr>
<th>Change from Baseline Creatinine</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5x</td>
<td>1</td>
</tr>
<tr>
<td>≥ 1.5x to &lt;2x</td>
<td>2</td>
</tr>
<tr>
<td>≥ 2x to &lt;3x</td>
<td>4</td>
</tr>
<tr>
<td>≥3x</td>
<td>8</td>
</tr>
</tbody>
</table>

aRAI = Risk Strata Score x Injury Score

n=6 fulfills renal angina

Results: 118 children were enrolled (48% male, mean age 7.8 ± 6.4 years). 11% were RAi positive for renal angina in the ED, 16% were admitted to the ICU, and 66% remained hospitalized after 48 hours (ICU or ward). The rates of severe AKI at 48 and 72 hours were 8.0% and 7.7%. The aRAI demonstrated a positive predictive value of 0.29 (0.05, 0.70) and negative predictive value of 0.97 (0.82, 0.99) with an AUC of 0.76 (0.43, 1.00) for severe AKI.

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

Underline represents presenting author.
Conclusions: Our pilot study demonstrates a sensitive screening tool for stratification of patients by risk for AKI from presentation in the ED, the earliest time possible for intervention. Biomarker incorporation into the aRAI model is anticipated to augment the post-test probability of AKI and creates a model useful for testing of strategies targeted at mitigating further renal insult.

Funding: Private Foundation Support

TH-PO674

Background: Impairment of renal function in acute kidney injury (AKI) is routinely evaluated by measurement of urea(NUN) and creatinine (Cr) which are markers largely of tubular reabsorption and glomerular filtration. Tubular secretory function in AKI has much less often been assessed.

Methods: Plasma levels for the normally secreted solutes indoxyl sulfate (IS) and phenylacetylglutamine (PAG) were measured along with levels of UN and Cr in 6 AKI and 25 maintenance hemodialysis (HD) subjects. Solute clearances were also measured in the AKI subjects and 9 normal (NL) subjects.

Results: (mean±stdev; *p<0.05 AKI vs NL; **p<0.05 AKI vs HD):

<table>
<thead>
<tr>
<th>Fractional clearance (kUN/kCr)</th>
<th>Plasma levels (mg/dl)</th>
<th>Concentration ratio HD/AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td>NL</td>
<td>AKI</td>
</tr>
<tr>
<td>IS 2.7 ± 0.5</td>
<td>0.4 ± 0.1</td>
<td>0.19 ± 0.08</td>
</tr>
<tr>
<td>PAG 2.9 ± 0.7</td>
<td>2.7 ± 0.5</td>
<td>0.22 ± 0.17</td>
</tr>
<tr>
<td>UN 0.3 ± 0.1</td>
<td>0.5 ± 0.1*</td>
<td>0.81 ± 0.14</td>
</tr>
<tr>
<td>GFR 2.3 ± 0.5</td>
<td>10.8 ± 3.3</td>
<td>4.8**</td>
</tr>
</tbody>
</table>

Clearances relative to the Cr clearance (fractional clearance; kUN/kCr) were well preserved for the secreted solutes in AKI. In contrast, the fractional clearance of UN was significantly reduced. As a result, the UN level in AKI was elevated to a similar degree as in HD. In contrast, the levels for the secreted solutes were significantly higher in HD than AKI subjects because hemodialysis does not replicate secretory function.

Conclusions: Secretory function is well preserved in AKI. Further studies of secreted solutes may enhance our ability to assess renal function in AKI and to determine the timing of dialysis initiation.

Funding: NIDDK Support, VA Support

TH-PO675
Predictive Value of Cystatin C-Based eGFR for Successful Weaning from Continuous Renal Replacement Therapy: A Prospective Observational Study Chang Seong Kim,1 Taey Ryom Oh,2 Ha Yoon Kim,1 Yong Un Kang,1 Eun Hui Bae,3 Seong Kwon Ma,1 Jong Un Lee,1 Soo Wan Kim.1 1Dept of Internal Medicine, Chonnam National Univ Hospital, Gwangju, Republic of Korea; 2Dept of Physiology, Chonnam National Univ Medical School, Gwangju, Republic of Korea.

Background: Continuous renal replacement therapy (CRRT) is the mainstay of treatment for critically ill patients with acute kidney injury. The aim of our study is to identify whether biomarkers or factors of renal function can predict successful weaning from CRRT.

Methods: We conducted a prospective observational study of 110 patients who had received CRRT and were weaned from it after renal recovery. Successful weaning from CRRT was defined as elimination of the requirement for RRT for at least 14 days after cessation of CRRT, whereas redialysis within 14 days was defined as restart-RRT. Serum levels of cystatin C (CysC), neutrophil gelatinase-associated lipocalin (NGAL), and conventional biomarkers of renal function were checked at the time of cessation of CRRT.

Results: Of the 110 patients we evaluated, 89 patients (80.9%) were successfully weaned from CRRT while 21 (19.1%) patients were not. Setting of CRRT and simplified acute physiology score III did not differ significantly between both groups. Serum CysC levels were lower and urine output was higher in the success group compared with the restart-RRT group at the time of cessation of CRRT (CysC: 1.70 ± 0.68 mg/L vs. 2.47 ± 0.93 mg/L, P < 0.001; urine output: 2.03 ± 2.10 mL/h/kg vs. 1.02 ± 0.93 mL/kg, P = 0.016). Multivariable logistic regression showed that CysC-based estimated glomerular filtration rate (eGFR) was an independent predictor for successful weaning from CRRT (OR 1.25; 95% CI, 1.04-1.51; P = 0.016) while NGAL and urine output were not associated with successful weaning from CRRT. The area under the receiver operating characteristic curve of CysC-based eGFR, which predicts successful weaning from CRRT, was 0.75 (95% CI, 0.63-0.86); sensitivity and specificity were 65.2% and 76.2%, respectively, at a cutoff of 32.9 mg/mL/1.73 m².

Conclusions: Cystatin C-based eGFR at the time of cessation of CRRT is a good predictor of successful weaning from CRRT in critically ill patients with acute kidney injury.

Funding: NIDDK Support

TH-PO676

Background: Pregnancy Related Acute Kidney Injury (PRAKI) may comprise up to 25% of the referrals to dialysis centers in developing countries and is associated with substantial maternal and fetal mortality.

Methods: We conducted a prospective cross sectional observational study to evaluate the etiological factors and final outcome of AKI with special reference to pregnancy related acute kidney injury. AKI was diagnosed as per AKIN (Acute Kidney Injury Network) criteria.

Results: In this prospective study between February 2012 to February 2016, total of 624 patients were studied among them 460 were admitted with medical causes (73.7%), 124 with obstetrical causes (19.8%) and 40 (6.4%) with surgical causes. The mean age among patients was 21±4 (17-36) years and duration of hospital stay was 9.4±1.7 days. Etiological factors include puerperal sepsis in 65(52.4%), pregnancy induced hypertension in 30(21.4%), 129(67%) patients had postpartum hemorrhage, 7(5.64%) antepartum hemorrhage, postpartum hemolytic uremic syndrome in 3 patients (2.41%) and miscellaneous causes was seen(7.6%). Renal biopsy was performed if a patient was oliguric or dialysis dependent at the end of 3 weeks. Biopsy was done on 22 patients and 6 of them had patchy cortical necrosis, 11 patients showed acute tubular necrosis, two with features of acute interstitial nephritis and three patients had thrombotic microangiopathy. Out of 124 patients101(81.45%) patients recovered from acute kidney injury, 4(3.22%) patient remained on dialysis and 2(1.61%) patient had partial recovery from renal failure. Seven patients died with mortality rate of 13.70%. Out of these 9 patients died within 48 hours of admission. Sepsis, multiorgan dysfunction, coagulation abnormalities and retained products of conception were factors associated with mortality.

Conclusions: Pregnancy related acute kidney injury was comprising about 19.8% of the patients. Puerperal sepsis is the most frequent etiological factor and accounts for a majority of maternal mortality.

TH-PO677
Pregnancy Outcomes following Clinical Recovery from Acute Kidney Injury in Young Women Jessica Sheehan Tangren,1 Camille Elise Powe,1 Elizabeth D. Ankers,1 Jessica Ecker,2 Kate Bramham,2 Michelle A. Hadunewich,2 S. Ananth Karumanchi,3 Ravi I. Thadhani.1,1 1Massachusetts General Hospital, Boston, MA; 2King’s College London, London, United Kingdom; 3Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 3Beth Israel Deaconess Medical Center, Boston, MA.

Background: Acute kidney injury (AKI) is a risk factor for future morbidity and mortality but the effect of clinically recovered AKI on future pregnancy outcomes is unknown. Our objective was to assess if a previous episode of AKI with subsequent recovery of renal function is associated with adverse pregnancy outcomes, including preeclampsia.

Methods: We conducted a retrospective cohort study of women who delivered infants between 1998 to 2008 at the Massachusetts General Hospital. Pregnancy outcomes in women with recovered AKI (r-AKI) without a history of chronic kidney disease (n=105) were compared to outcomes in women without kidney disease (n=24,640). AKI was defined as a rise in serum creatinine to 1.5 fold above baseline with subsequent clinical recovery (eGFR > 90) prior to conception.

Results: Pre-pregnancy serum creatinine measurements in women with r-AKI were 0.70±0.20 mg/dl vs 0.69±0.10 mg/dl in controls. Women with r-AKI had an increased rate of preeclampsia (23% vs 4%, p<0.001). Infants of women with r-AKI were born earlier (37.6±3.6 vs 39.2±2.2 weeks, p<0.001), with increased rates of small for gestational age births (15% vs 8%, p<0.03). After multivariate adjustment including age, race, parity, obesity, hypertension and diabetes, r-AKI remained associated with increased odds of adverse maternal-fetal outcomes.

Conclusions: An episode of AKI, despite return to normal renal function prior to pregnancy, is associated with adverse pregnancy outcomes. This describes a new group of women at high risk for preeclampsia and preterm delivery. This finding may help explain disparate rates of preeclampsia across the globe.

Funding: NIDDK Support
Rehospitalization after an Acute Kidney Injury Hospitalization

**Background:** Hospital acquired acute kidney injury (AKI) is common and is a risk factor for all-cause mortality and chronic kidney disease. The epidemiology and outcomes of patients with outpatient AKI are poorly characterized, particularly those whose creatinine returns to baseline.

**Methods:** Patients with at least two primary care visits within the Fairview Health Service’s electronic health record were included in this retrospective study. During an 18 month exposure period beginning with the second primary care visit, patients were categorized into five groups (no creatinine measurement, no AKI, AKI with recovery, AKI without recovery, and AKI without a repeat creatinine). AKI was defined by a 50% increase in creatinine compared to the average of the last three outpatient creatinine values between 30 and 365 days prior. Recovery was defined by any subsequent creatinine less than or equal to 110% of baseline creatinine. Mortality, obtained by Minnesota death certificate records, and a creatinine value >3 mg/dL at last follow-up were co-primary outcomes. Results: There were 1.77 million patients in the electronic health record and 464,474 that visited primary care at least twice. Of these, 55.3% had no creatinine measured, 43.2% had no AKI, 0.4% had AKI without recovery, 0.8% had AKI with recovery, and 0.3% had AKI without a repeat creatinine. Patients with AKI were more likely to have a final creatinine >3 mg/dL and were more likely to die during follow-up.

Conclusions: Outpatient AKI is associated with a significantly increased risk of development of chronic kidney disease and mortality regardless of whether creatinine returns to baseline.

**Hospital Readmissions after an Acute Kidney Injury Hospitalization**

**Background:** The risk of hospital readmission in acute kidney injury (AKI) survivors is poorly understood. We sought to estimate the rate of hospital use and identify the factors most strongly associated with the risk of hospitalization in patients with AKI.

**Methods:** We conducted a retrospective cohort study of adults admitted to the ICU with a diagnosis of severe sepsis or septic shock. Subjects were classified into 6 subgroups (2x3 matrix) according to pre-admission eGFR and AKI status during ICU stay: MDRD-eGFR <60 (CKD) vs ≥60 (no-CKD) and KDIGO serum creatinine (SCr)-criteria (no-AKI, AKI stage 1, AKI stage 2), respectively. Outcomes were 90-day mortality and a composite of AKI (incident AKI eGFR <60 and ≥25% reduction from baseline; progressive CKD eGFR <15 or ≥25% reduction from baseline), dialysis and death. Results: Of 6290 patients included in the study, 3642 (58%) suffered from AKI and 741 (12%) required acute RRT. The 90-day mortality rate was 26%. Among survivors, we identified 1249 patients who suffered from AKI, were RRT-free, and had available follow-up data. CKD occurred in 319 of the 1249 patients: 54% of those with incomplete (severe) recovery, 29% of those with incomplete (mild) recovery and 13% of those with complete recovery; median follow-up 2.5 years. 90-day AKI recovery status was an independent predictor of CKD: adjusted HR 4.7, 95% CI 3.5–6.3 for incomplete (severe) vs. complete recovery, 2.3, 1.7–3.1 for incomplete (mild) vs complete recovery and 2.1, 1.6–2.8 for incomplete (severe) vs incomplete (mild) recovery. Other predictors of post-AKI CKD were older age, black race, anemia, and higher admission SOFA score.

Conclusions: Incomplete AKI recovery within 90 days following hospital discharge is a strong and independent predictor of CKD in sepsis survivors. The timely evaluation of AKI recovery may serve to risk-stratify sepsis survivors and implement more vigilant surveillance for CKD in this susceptible population.

**Impact of CKD on Adverse Outcomes in Critically Ill Septic Patients with and without AKI**

**Background:** AKI is a common condition in the ICU associated with substantial morbidity and mortality, including CKD post-AKI. Similarly, CKD increases the risk of AKI, severe infections and death. The coexistence of CKD and AKI is frequently encountered in critically ill septic patients, but how their interplay affects clinical outcomes is not well elucidated.

**Methods:** Single-center, retrospective cohort study of adults admitted to the ICU with a diagnosis of severe sepsis or septic shock. Subjects were classified into 6 subgroups (2x3 matrix) according to pre-admission eGFR and AKI status during ICU stay: MDRD-eGFR <60 (CKD) vs ≥60 (no-CKD) and KDIGO serum creatinine (SCr)-criteria (no-AKI, AKI stage 1, AKI stage 2), respectively. Outcomes were 90-day mortality and a composite of CKD (incident CKD eGFR <60 and ≥25% reduction from baseline; progressive CKD eGFR <15 or ≥25% reduction from baseline), dialysis and death.

**Results:** Of 2632 patients were included and classified as no-CKD/ no-AKI (22.7%); no-CKD/AKI1 (13.8%); no-CKD/AKI2 (17.5%); no-CKD/no-AKI (20.4%); CKD/AKI1 (13.8%) or CKD/AKI2 (11.8%). Overall 90-day mortality rate was 26.7% and CKD/dialysis/death occurred in 19.1% over a median follow-up of 18 months. Multivariable Cox regression models adjusted for multiple demographic and clinical covariates.

**Conclusions:** Stage 1 AKI on CKD was not independently associated with an increased risk of adverse outcomes in critically ill septic patients. However, AKI stage ≥2 on CKD was associated with a 2-fold increase in the risk of adverse outcomes in critically ill septic patients. However, AKI stage ≥2 on CKD was associated with a 2-fold increase in the risk of adverse outcomes in critically ill septic patients.
homeostasis, in injury, they become activated and differentiate into myofibroblasts depositing pathogenic extracellular matrix, a hallmark of fibrosis. Previous work had highlighted the role of innate immune signaling in kidney injury and MyD88 knockout mice were protected. Surprisingly, neither macrophage- nor epithelial cell-specific deletion of MyD88 contributed to this protective phenotype. Here we show that pericyte-specific ablation of MyD88 significantly attenuates tissue injury and fibrosis.

Further mechanistic studies show that in culture, pericytes respond to the TLR ligands and endogenous injured kidney DAMPs by secreting pro-inflammatory cytokines and chemokines in a TLR-4/MyD88- and IRAK4-dependent manner. Injury DAMPs are sufficient to prime and activate NLRP3 inflammasome leading to secretion of IL-1b. Additionally, pericytes respond to IL-1β in a MyD88- and IRAK4-dependent manner and provide an autocrine loop amplifying inflammation. Unexpectedly, TLR2/4, MyD88 and IRAK4 also control TGFβ- or injury DAMPs-induced pericyte migration and myofibroblast differentiation. This mechanism is conserved, and human pericytes also activate inflammatory and fibrotic responses that require MYD88 and IRAK4.

Inhibition of IRAK4, a downstream kinase in TLR/MyD88 signaling, by a novel potent, highly selective small molecule BIBF-IRAK4 is highly protective in ischemia reperfusion injury and significantly reducing.

**TH-PO683**

**Prediction of Death and Renal Replacement Therapy in Hospitalised Patients with Acute Kidney Injury**

Vishal Nangalia,1 Alistair Connell,1 Simon T. Brown,1 Anne B. Dawney,1 Zadin Puthucheary,2 David Barber,1 Chris Laing,1 Geraint Rees,1 Hugh E. Montgomery,1 1UCLH, London, United Kingdom; 2UCLH NHS Trust, London, United Kingdom.

**Background:** Acute kidney injury (AKI) is reported to be common and associated with poor outcome. There is a need for renal replacement therapy (D-RRT). In 2015 The English National Health Service (NHSE) mandated that all hospitals implement an Kidney Disease: Improving Global Outcomes (KDIGO)-based algorithm (NHISE-algorithm) to detect and stage (for severity/risk) AKI. In the largest AKI study ever, we characterised AKI prevalence and progression, explored weaknesses in the NHISE-algorithm, and determined whether machine learning (ML) methodologies might better determine risk.

**Methods:** Demographics, blood results, diagnoses, and procedure codes from 14 NHISE Hospital Trusts (2005–2015) were collated. Admissions were grouped by comorbidities/ NHISE-algorithm-trigger-and-route, and D-RRT rates related to first (AKI1+) and maximum (AKI1-3+) AKI stage. A ‘gradient-boosting-machine’ ML model used data up to AKI1+ to predict D-RRT using positive predictive value thresholds 1:2 (ML50), 1:3 (ML33) and 1:4 (ML25).

**Results:** Of >1 million admissions, 170,596 (8.7%) developed AKI. Stage advanced 1 to 2 to 3 (25.3%) with similar AKI stage (subpopulation 1). We assessed whether the association between AKI stage and D-RRT was stronger in the history of chronic kidney disease (CHD) or not. We observed that the history of CHD was associated with an increased risk of D-RRT in all AKI stages.

**Conclusions:** AKI is prevalent and associated with increased morbidity and mortality. AKI stage poorly predicts individual risk, and machine learning models perform better. Funding: Government Support - Non-U.K.

**TH-PO684**

**Recognition and Management of Acute Kidney Injury in Children Around the World:** The ISN 0 by 25 AKI Global Snapshot Project

Etienne Macedonia,1 Rocco,2 Michael V. Rocco,2 Laing,5 Zudin Puthucheary,2 David Barber,1 Chris Laing,1 Geraint Rees,1 Hugh E. Montgomery,1 1UCLH, London, United Kingdom; 2UCLH NHS Trust, London, United Kingdom; 3UCLA, California, USA; 4Inst for Clinical Evaluative Sciences, London, ON, Canada; 5Nephrology, Vanderbilt University, Nashville, TN, USA.

**Background:** In low and middle-income countries, there is a lack of reliable data on the epidemiology of childhood acute kidney injury (AKI). The recently completed Global Snapshot, a study carried out by the International Society of Nephrology “0 by 25” AKI initiative, was an observational, cross-sectional analysis designed to evaluate AKI prevalence and outcomes around the world.

**Methods:** A web based survey tool was used to prospectively obtain data from individual clinicians about pts who had AKI based on KDIGO criteria. Countries were grouped into three categories based on gross national income per capita (GNI): High income with GNI > US$12,476, low and middle income with GNI < US$4035, and upper middle income with GNI between levels 1 & 3.

**Results:** Of the 3664 adults AKI pts included in the analysis 305 (1091) were from North and East Asia, followed by Latin America and Caribbean (516, 14%) and Africa (507, 14%). Almost all centers from North and East Asia were located in cities with more than 1.5 million people and were from HIC and UMIC. African and Caribbean centers were more often located at smaller cities. While most pts in North and East Asia developed AKI in the hospital setting (63%), about half the pts from Latin America and Caribbean (284, 55%) and the majority from Africa (430, 85%) developed AKI in the community. The creatinine level at both diagnosis and discharge, the severity of AKI at diagnosis and the need for renal replacement therapy varied by region.

**Conclusions:** There is wide variability in the incidence and severity of AKI by geographic region. Funding: Private Foundation Support

**TH-PO686**

**Characteristics and Outcomes of Adults Discharged Home from the Emergency Department with Acute Kidney Injury**

Ronald A. Cedillo,1 A. R. Nash,2 Samuel A. Silver,3 Matthew T. James,4 Michael J. Schull,5 Edward D. Siew,6 Michael Edwin Matheny,7 Andrew A. House,7 Neil S. Klar,8 Amit X. Garg,1,2,4 *Nephrology, London Health Sciences Centre, London, ON, Canada; 2Epidemiology and Biostatistics, Western University, London, ON, Canada; 3Nephrology, St. Michael’s Hospital, Toronto, ON, Canada; 4Inst for Clinical Evaluative Sciences, London, ON, Canada; 5Nephrology, Vanderbilt School of Medicine, Nashville, TN, USA; 6Veteran Affairs, Vanderbilt Univ Medical Center, Nashville, TN.*

**Background:** Adults discharged home from an emergency department (ED) with acute kidney injury (AKI) are not well described and may have poor outcomes.

**Methods:** We conducted a population-based retrospective cohort study in Ontario, Canada from 2003 to 2012 of 6,346 adults discharged from the ED with AKI. We used serum creatinine-based KDIGO criteria to define AKI. We assessed the 30-day all-cause mortality and receipt of acute dialysis after ED discharge. To compare outcomes, we used propensity score methods to match 4,379 of these adults to 4,379 adults hospitalized with similar AKI stage (subpopulation 1). We assessed whether the association between

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

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ED discharge versus hospitalization and mortality was modified by AKI stage. We also matched and enrolled 1,188 of these adults to 6,188 discharge home from the ED without AKI (subpopulation 2). Results: The mean age was 69 years, 4.6% had stage 2 AKI, and 0.7% had stage 3 AKI. Within 30 days of ED discharge, 2.3% (stage 2 AKI: 5.3%, stage 3 AKI: 15.9%) died, and 0.3% received acute dialysis. In subpopulation 1, an ED discharge versus hospitalization was associated with lower mortality (3.0% vs. 11.9%, RR: 0.25, 95% CI: 0.21-0.30). The difference in mortality was attenuated in adults with stage 3 AKI (15.9% vs. 15.9%, RR: 1.00, 95% CI: 0.38-2.64). In subpopulation 2, an ED discharge with AKI versus without AKI was associated with higher mortality (2.4% vs. 1.4%, RR: 1.75, 95% CI: 1.20-2.40).

Conclusions: Adults discharged from the ED stage 2 and 3 AKI are at risk of poor 30-day outcomes. A better understanding of AKI care among this population is warranted.

TH-PO678

Acute Kidney Injury Related to Renal Colic: A Neglected Condition?
Gabriela Acosta, Carolina Gelber, Andres Urrestarazu, Ricardo Silvariño, Alejandro Ferreiro, Oscar A. Noboa. Centro de Nefrología, Hospital de Clínicas, Facultad de Medicina, Univ de la República, Montevideo, Uruguay.

Background: kidney stone formation is highly prevalent with rates of up to 14.8%. Acute kidney injury during episodes of renal colic are frequently overlooked. The aim of this study is to determine the frequency of acute kidney injury (AKI) during acute episodes of renal colic (RC) of kidney stone etiology at the Emergency Department (ED) and its contributing factors.

Methods: This was a prospective, observational, single-center study. All patients assisted at the ED with a diagnosis of RC of renal stone etiology were prospective included. Clinical and laboratory data were collected. All patients were evaluated with transvaginal echography at admission. AKI was defined according to AKIN criteria. Informed consent was collected and the Hospital Ethics Committee approved the study protocol. Exclusion criteria: patients with lumbar-abdominal pain of etiologies other than kidney stones. Cases with incomplete data at admission or evolution were also excluded.

Results: Data were obtained from 34 patients, 25 (73.5%) male. Median age was 38.5 years (age range between 18-80). Previous history of RC was present in 21/34 (61.8%). Hematuria in urinalysis was present in 19/34 (55.8%). AKI was diagnosed in 31/34 (91 %) patients. In 10/11 (91%) stage 1 was stage 1. Mean creatinine at recovery was 0.87 ± 0.28 mg/dL vs creatinine at diagnosis 1.18 ± 0.43 (p=0.05). The mean estimated glomerular filtration rate decrease was 42 ± 24, 44 ± 1 min, and 1 case was stage 3 AKI. The average time to complete glomerular filtration recovery was 15 days. Significant association was observed between the use of nonsteroidal antiinflammatory (NSAIDs) drugs and development of AKI during the episode. AKI was associated to unilateral obstructive stones in 10/11 patients. None required renal replacement therapy.

Conclusions: AKI was frequent among those patients who consulted for RC in the ED (32.3%). NSAIDs consumption was significantly related with AKI development. Kidney stone obstruction was unilateral except for one patient that presented bilateral involvement.

TH-PO668

Long-Term Outcomes and Associated Risk Factors of Post-Hospitalization Dialysis-Dependent AKI (PHD-AKI)
Ayak Singh Rathore, Jennie Z. Ma, Warren Perhach, Emad M. Abdel-Rahman. 1Nephrology, Univ of Virginia, Charlottesville, VA; 2Public Health Sciences, Univ of Virginia, Charlottesville, VA.

Background: CMS has reversed its clarification allowing AKI patients to be dialyzed at the ED. Adults discharged from the ED with stage 2 and 3 AKI are at risk of poor long-term outcomes. Meticulous follow up of PHD-AKI is significant. Recovery, though minimal, is still possible in patients who remained dialysis dependent 90 days PHD. Baseline renal function and hemodynamic changes during hospitalization are predictors of long-term outcomes. Metuculous follow up of PHD-AKI patients in the outpatient dialysis facility is crucial.

TH-PO689

Preoperative Echocardiography Predicts Acute Kidney Injury and Long-Term Mortality in Coronary Artery Bypass Grafting
Seong Seok Han,1 Dong Ki Kim,1 Jeong Ok Kim,2 1Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; 2Internal Medicine, Seoul National Univ Bundang Hospital, Gyeonggi-do, Korea.

Background: Acute kidney injury (AKI) is a common complication in patients undergoing coronary artery bypass grafting (CABG), which is associated with significant morbidity and mortality. This study identified echocardiographic predictors of AKI and determined whether these predictors were related to long-term mortality in CABG.

Methods: This retrospective cohort study used 1,300 patients who underwent echocardiography before CABG at two tertiary referral centers. The best echocardiographic predictor of AKI was determined using multivariate and stepwise selection methods. Subsequently, patients were followed for 72 ± 28.8 months (maximum 11 years) for tracing all-cause mortality. Based on these information, we measured the adjusted odds ratio (OR) and hazard ratio (HR) for AKI and all-cause mortality, respectively, according to the chosen echocardiographic parameter.

Results: E/e’ was the best predictor of AKI among echocardiographic parameters (figure 1). The high E/e’ group (>15) exhibited a higher OR for AKI [2.2 (1.51–3.27)] than the low E/e’ group (≤8). The high E/e’ group required a longer hospital stay [16 days (12–23 days)] than the low E/e’ group [14 days (11–17 days)]. There were 272 deaths (20%) during the following period. The high E/e’ group exhibited a higher HR for mortality [1.9 (1.34–2.76)] than the low E/e’ group, and this difference remained significant, regardless of the occurrence of AKI and the size of the ejection fraction volume.

Conclusions: E/e’ in preoperative echocardiography is the best predictor of AKI and long-term mortality in patients undergoing CABG.

TH-PO690

Preoperative C-Reactive Protein Predicts Acute Kidney Injury and Long-Term Mortality after Coronary Artery Bypass Grafting
Seong Seok Han,1 Dong Ki Kim,1 Jeong Ok Kim,2 Ho Jun Chin,3 Ki Young Na,2 1Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; 2Internal Medicine, Seoul National Univ Bundang Hospital, Gyeonggi-do, Korea.

Background: Precise prediction of post-surgical acute kidney injury (AKI) is an important concern in patients with coronary artery bypass grafting (CABG) regarding high morbidity and mortality of AKI. The present study addressed whether preoperative C-reactive protein (CRP) is predictive of AKI and long-term mortality in CABG.

Methods: This retrospective cohort study included 1,700 patients whose high-sensitivity CRPs were measured before CABG at two tertiary referral centers from 2004 to 2010. The odds ratios (ORs) and hazard ratios (HRs) for AKI and all-cause mortality were estimated according to the tertiles of CRP levels after adjustment of multiple covariates. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to determine whether the addition of CRP to risk model for AKI improves prediction.

Results: The prevalence of AKI was higher in the 3rd tertile group (42.4%) than in the 1st tertile group (25.7%). The corresponding OR of AKI and P values were 1.90 (1.44–2.52) and <0.001, respectively. Compared with the reference risk model, the addition of CRP improved the predictability with 0.107 of NRI (P=0.037) and 0.005 of IDI (P=0.007). During the median duration of 89 months (maximum 12 years), 491 deaths (28.9%) were observed. The 3rd tertile group exhibited a higher HR for mortality [1.64 (1.29–2.08)] than the 1st tertile group. This predictability for mortality remained consistent irrespective of the presence of sepsis or AKI.

Conclusions: Preoperative CRP may be needed to predict post-surgical AKI and mortality in patients undergoing CABG.

TH-PO691

Cardiovascular Mortality after Major Surgery in Elderly
Negijn Pourafshar, Tercan Orrazgat-Balsam, Anis Davoudi, Parisa Rashidi, Mark S. Segal, Azra Bihorac. Univ of Florida, Gainesville, FL.

Background: In the developed world, the increase in life expectancy with the resultant increase in the age of the population has led to a rise in incidents related to cardiovascular disease. Among all the diseases in elderly, acute kidney injury (AKI) appears to have among the highest incidences and is a major risk factor for end stage renal disease (ESRD). The aim of this study is to determine the long-term cardiovascular-specific mortality in elderly patients with AKI or chronic kidney disease (CKD) after major surgery.

Methods: In a single-center cohort of 16,655 elderly (≥65 years-old) surgical patients undergoing major inpatient surgery, long-term cardiovascular-specific mortality was modeled using a multivariable subdistributional hazards model while treating any other cause of death as a competing risk. Preoperative ESRD and CKD and postoperative AKI were the main independent predictors and each model was adjusted for preoperative demographic and clinical variables.

Results: Prior to the admission, 3% and 12% of the cohort had preexisting ESRD and CKD with requiring renal replacement therapy, respectively. During hospitalization, 47% developed AKI. Among the 7768 deaths reported, the main causes of death were cardiovascular disease (32%) and cancer (31%). Adjusted cardiovascular mortality estimates for patients with no kidney disease, AKI without CKD, CKD without AKI, AKI with CKD, and CKD with AKI were 12.2%, 19.4%, 18.4%, 29.7%, and 45.8%, respectively. Adjusted hazard ratios (95% CIs) for cardiovascular mortality were significantly elevated among
patients with AKI without CKD (1.69 95% CI 1.52-1.87), CKD without AKI (1.59 95% CI 1.25-2.03), and with CKD (2.53 95% CI 2.47-3.24) and eESRD (5.21 95% CI 4.32-6.27), compared to patients with no kidney disease.

Conclusions: Perioperative AKI is common in elderly patients undergoing major surgery and is associated with a high risk for future cardiovascular-specific mortality. These findings emphasize the importance of preoperative and postoperative risk stratification for kidney disease and the application of strategies to prevent perioperative AKI.

TH-PO692

Development of Hypertension after Acute Kidney Injury in the Pediatric Intensive Care Unit


Background: Acute kidney injury (AKI) in the pediatric intensive care unit (PICU) is common and associated with poor hospital outcomes. Long-term renal effects of PICU-AKI like microalbuminuria (MA) and hypertension (HTN), are not well understood. We will determine the prevalence of MA and HTN in children admitted to the PICU 5-10 years ago.

Methods: Design & population: Ongoing longitudinal follow-up study of children (<18 years old) admitted to the Montreal Children’s Hospital PICU between 2005-2010. Patients in the neonatal ICU or with pre-PICU renal disease excluded. Study visit: Occur 5-10 years after PICU admission. We collect medical histories, anthropometric measures, 3 office BP measures, first morning urine for MA determination and 24-hour ambulatory BP monitoring (ABPM) for HTN determination. Exposure: KDIGO serum creatinine (SCr) AKI staging. Outcomes: MA defined by KDIGO (albumin/creatinine>30 mg/g). HTN defined by the 2014 American Heart Association guidelines (figure 1). Analysis: The prevalence of HTN and MA was calculated. ABPM HTN phenotypes were detailed. Univariate AKI vs. non-AKI comparisons were made using χ² tests.

Results: Study visits have been performed on 101 patients (male 51%, mean ±SD=11.0±4.8 years), 32/75 (42.7%) had past PICU-AKI (n=26 no SCr in PICU). 93 patients attempted the 24-hour ABPM, and 89 (96%) were successful. Of these, 11 (12.4%) had prehypertension, 4 (4.5%) had HTN (10 masked HTN, 1 ambulatory HTN), 1 (1.1%) patients attempted the 24-hour ABPM, and 89 (96%) were successful. Of these, 11 (12.4%) had prehypertension, 4 (4.5%) had HTN (10 masked HTN, 1 ambulatory HTN), 1 (1.1%) had masked HTN (10 masked HTN, 1 ambulatory HTN), 4 (4.5%) had prehypertension, 4 (4.5%) had HTN (10 masked HTN, 1 ambulatory HTN), 1 (1.1%) had white coat HTN, and 34/68 (50%) had non-BP dipping. 5/9% (17%) of AKI patients had masked HTN. Of 9/10 (90%) patients with urine samples analyzed (AKI: 3% vs. no AKI: 11.6%, p<0.02). Conclusions: HTN and non-BP dipping prevalence are high in children with past PICU admission. Future work must elucidate the risk factors for HTN to provide an evidence base for post-PICU follow-up guidelines.

TH-PO693

Acute Kidney Injury Is Associated with Long-Term Renal Outcomes Using Administrative Data in Children


Background: Acute kidney injury (AKI) in the pediatric intensive care unit (PICU) is common and associated with poor hospital outcomes. Long-term renal effects of PICU-AKI like microalbuminuria (MA) and hypertension (HTN), are not well understood. We will determine the prevalence of MA and HTN in children admitted to the PICU 5-10 years ago.

Methods: Design & population: Ongoing longitudinal follow-up study of children (<18 years old) admitted to the Montreal Children’s Hospital PICU between 2005-2010. Patients in the neonatal ICU or with pre-PICU renal disease excluded. Study visit: Occur 5-10 years after PICU admission. We collect medical histories, anthropometric measures, 3 office BP measures, first morning urine for MA determination and 24-hour ambulatory BP monitoring (ABPM) for HTN determination. Exposure: KDIGO serum creatinine (SCr) AKI staging. Outcomes: MA defined by KDIGO (albumin/creatinine>30 mg/g). HTN defined by the 2014 American Heart Association guidelines (figure 1). Analysis: The prevalence of HTN and MA was calculated. ABPM HTN phenotypes were detailed. Univariate AKI vs. non-AKI comparisons were made using χ² tests.

Results: Study visits have been performed on 101 patients (male 51%, mean ±SD=11.0±4.8 years), 32/75 (42.7%) had past PICU-AKI (n=26 no SCr in PICU). 93 patients attempted the 24-hour ABPM, and 89 (96%) were successful. Of these, 11 (12.4%) had HTN (10 masked HTN, 1 ambulatory HTN), 4 (4.5%) had prehypertension, 1 (1.1%) had white coat HTN, and 34/68 (50%) had non-BP dipping. 5/9% (17%) of AKI patients had masked HTN. Of 9/10 (90%) patients with urine samples analyzed (AKI: 3% vs. no AKI: 11.6%, p<0.02). Conclusions: HTN and non-BP dipping prevalence are high in children with past PICU admission. Future work must elucidate the risk factors for HTN to provide an evidence base for post-PICU follow-up guidelines.

TH-PO694

Evaluation of Height-Dependent and Height-Independent Methods of Estimating Baseline Serum Creatinine in Critically Ill Children


Background: Baseline serum creatinine (bSCr) is required for diagnosing acute kidney injury (AKI). In children, measured bSCr is often missing. The alternative, estimating bSCr with height-based glomerular filtration rate (GFR) equations, is not always feasible. We will evaluate the accuracy of back-calculating bSCr (estimated bSCr) from height-dependent and height-independent GFR equations.

Methods: Retrospective intensive care unit (ICU) cohort (two Montreal pediatric ICUs, 2003-2005 [n=2499]), excluded: no health care number, baseline renal disease). Patients with a measured bSCr, height, and ICU Scr (n=538) included. Height-dependent GFR: CKiD equation and age-based GFR norms. Height-independent method: Hoste et al equation and age-based GFR norms. Analysed bias, accuracy, and precision of estimated bSCr methods relative to measured bSCr. Calculated agreement of AKI ascertainment using measured and estimated bSCr. Performed multivariate analyses to assess the impact of estimated bSCr on AKI-outcome associations.

Results: Figure 1 shows results. Both methods slightly underestimated bSCr, had good accuracy (0-30% of estimated bSCr ≤ 10% measured bSCr), but poor precision (wide 95% limits of agreement). Agreement of AKI defined by estimated vs. measured bSCr was ~80% (n<0.5). AKI was associated with longer ICU stay and mechanical ventilation, but not ICU mortality (after adjustment), by measured and estimated bSCr methods.

Figure 1: Performance of estimated bSCr methods compared to measured bSCr (n=538).

Figure 2: Estimated bSCr methods showed good accuracy (~90% of estimated bSCr ≤ 10% measured bSCr), but poor precision (wide 95% limits of agreement). Agreement of AKI defined by estimated vs. measured bSCr was ~80% (n<0.5). AKI was associated with longer ICU stay and mechanical ventilation, but not ICU mortality (after adjustment), by measured and estimated bSCr methods.

Conclusions: The height-dependent and height-independent formulas perform similarly for bSCr estimation. When bSCr and height are missing, AKI can be defined using estimated bSCr by a height-independent method.
TH-PO695
Neonatal Acute Kidney Injury: A Survey of Neonatologists and Nephrologists’ Perceptions to Diagnosis and Follow-Up Jennifer R. Charlton,1 Cherry Mannem,2 Ronnie Guillent,1 Katja M. Gist,3 Tina Hanna,4 Ahmad I. El Samra,3 David T. Selewski,2 David J. Askren,7 Alison Kent.2 1Univ of Virginia; 2Univ of British Columbia and BC Children’s Hospital; 3Univ of Rochester; 4Univ of Cincinnati; 5Franciscan St. Elizabeth Health; 6Canberra and Australian National Univ; 7Univ of Michigan; 8Univ of Alabama at Birmingham; 9Children’s Hospital Colorado.

Background: Neonatal acute kidney injury (nAKI) is associated with increased morbidity and mortality. However, it is unclear if neonatologists and nephrologists diagnose, treat and follow up nAKI in similar ways. The aim of this study was to assess the knowledge and management of nAKI by surveying neonatologists and pediatric nephrologists.

Methods: An electronic survey containing both general questions and case-based scenarios was developed and distributed to neonatologists and pediatric nephrologists in Australia, New Zealand, Canada, USA and India on behalf of the Neonatal Kidney Collaborative (NKC).

Results: Of the 375 completed surveys 244 were returned by neonatologists (65%) and 131 by nephrologists (35%). The majority of neonatologists (60%) were unaware of the categorical definitions of nAKI. Nephrologists were more likely to recognize stage 1 AKI (80%, Neo: 60%). In the case-based scenarios, nephrologists were more likely to believe that neonates with stage 1 and 2 AKI were at risk of later chronic kidney disease (CKD). The majority of respondents (neonatologists: 92%; nephrologists: 86%) reported that neonates with stage 1 AKI were at risk of later chronic kidney disease (CKD). The majority of respondents (neonatologists: 92%; nephrologists: 86%) reported renal assessments were not included in their program’s growth and development follow-up.

Conclusions: Pediatric nephrologists who participated in this case-based survey were more aware than neonatologists to recognize nAKI and consider it risk for the development of CKD. There is minimal renal follow-up of neonates of CKD, an area for quality improvement projects.

TH-PO696
Pediatric Acute Kidney Injury after Cardiac Surgery - Incidence and Outcomes Garima Aggarwal. Nephrology, Amrita Inst of Medical Sciences, Kochi, Kerala, India.

Background: The aim of this study is to know the incidence of Acute Kidney Injury (AKI) in the immediate postoperative period following pediatric cardiac surgeries. To study the effect of AKI on adverse outcomes – death, mechanical ventilation and length of hospital stay, length of stay in pediatric Intensive Care Unit (PICU) and to identify the perioperative risk factors associated with AKI.

Methods: Children undergoing heart surgery in a tertiary hospital in Kerala were studied. After receiving institutional research ethics board approval, 180 consecutive children, age<18 years who underwent any type of cardiac surgery and admitted to the PICU were prospectively studied till length of hospital stay. Patients with diagnosed underlying kidney disease were excluded. Preoperative, intraoperative and postoperative possible risk factors for AKI and their relationship with adverse patient outcomes were assessed. To test the statistical significance of the association of AKI versus non AKI with different categorical variables chi squared test was applied and 21 variables were identified. Multivariate stepwise backward conditional logistic regression analysis was applied to identify significantly contributing variables with respect to presence or absence of post operative AKI.

Results: The prevalence of Acute Kidney Injury (AKI) was 32.8% in our study population. Fifty nine (developed AKI according to the rPRIFLE criteria, with 12 (20.3%), two (3.4%), and forty five (76.3%) patients classified in the R, I, and F groups, respectively. Neonatal age group, weight ≤ 5 kg, pre operative AKI, intra operative mean arterial pressure on Cardio Pulmonary Bypass (CPB) ≤40mmHg, use of albumin during CPB, isotope requirement for more than 48 hours in the post operative period and post operative albumin use were all associated with high incidence of AKI on multivariable analysis (p<0.05). Patients with AKI had longer duration of mechanical ventilation and longer duration of hospital stay (p=0.05).

Conclusions: AKI is common in the postoperative period in children following cardiac surgery and is associated with adverse clinical outcomes.

TH-PO697
AKI Outcomes in Young Adults Emily Lauren Joyce,1 Dana Y. Fuhrman,1,2 Priyanka Priyanka,1 John A. Kellum,2,3 1Dept of Pediatrics, Div of Nephrology, Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, PA; 2Crtical Care Medicine, CRISMA Center, Univ of Pittsburgh School of Medicine, UPMC, Pittsburgh, PA.

Background: Acute kidney injury (AKI) is associated with adverse outcomes including increased healthcare costs, morbidity and mortality. Outcomes of AKI in critically ill young adults have not been well described, and this is a unique population given that mortality is less confounded by chronic disease. The goal of this project was to assess outcomes in critically ill young adults who developed AKI.

Methods: Data was obtained from the HiDenIC database which contains > 45,000 critically ill patient records from UPMC. The cohort was divided into four age strata: young (<18 years), young adults (18-25 y), young adults (26-35 y) and young adults (36-45 y). The incidence of AKI was 39.8%, and is associated with poor outcomes including prolonged hospital and ICU length of stay, and 10.4% one-year mortality. One third of the mortality occurred after hospital discharge. See table 1 for outcomes of patients with AKI stratified by age. AKI, APACHE 3 score, multiple comorbidities and vasopressor use are strong predictors of ICU, hospital, 90-day and 1-year mortality in young adults.

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

TH-PO0699

Maria Isabel Acosta-Ochoa, Alicia Mendiluce.
Nephrology, Hospital Clinico Univ, Valladolid, Spain.

Background: AKI is a global public health problem, which increases mortality and bears long term consequences. We can find several definitions of renal recovery (complete cRR), partial RR (pRR) and no RR (nRR). Our aim was to compare currently used criteria by means of rates of RR, and to describe the differences between them.

Methods: Retrospective study of hospitalized patients with diagnosis of AKI, we excluded patients who died during the index hospitalization. We tested four RR criteria: ADQI 2004: cRR discharge Scr <1.5x baCr, pRR >1.5x and nRR HD persistence; Garzotto, et al. 2011: cRR discharge Scr <1.2x baCr, pRR 1.2-1.49x and nRR >1.5x or HD persistence; Rimes et al. 2012: cRR return to baEGFR, nRR any alteration of EGFR; Panu et al. 2013: nRR, doubling baCr, and plotted the results.

Results: 342 patients were included, mean age 71±14, 64% males, 40% diabetes, 85% hypertension, and 53% CKD, mean Charlson Index 4±2.4, KDIGO Stage 1 (29%), 2 (13%), 3 (38%), need for HD 13%, persistence in HD 3%. We found rates of RR: ADQI cRR 65%, pRR 32%, nRR 3% (persistence in HD); Garzotto: cRR 42%, pRR23%, nRR 32% <.3% HD persistence; Rimes: cRR 19%, nRR 81%; Panu: nRR 13%. Comparison of RR rates in figure 1.

Conclusions: We found a wide variability in renal recovery rates depending on the used author’s criteria. Renal recovery after AKI lacks of standard definition and absence of unified criteria (complete, partial, and no recovery, Cr based, eGFR based, HD dependence or not, and including vs. excluding in-hospital mortality). A consensus definition would contribute to the unification of study designs, results interpretation, refining the quest for risk and protective factors, and as public health tool in order for planning nephrology consultation needs and hemodialysis resources.

Acute Kidney Injury Followed by Complete Recovery Is Associated with Higher Infection Risk

TH-PO700

Anna Jeanette Jovanovich,1,2 Zhiying You,2 Kyle Hiyoranju,3 Benjamin Griffin,4 John R. Holmen, Sarah Faibbel,5 Michel Choncho1. 1Denver VA Medical Center; 2Univ of Colorado Denver; 3Intermountain Healthcare.

Background: Acute kidney injury (AKI) affects myriad organ systems including the immune system. Immune cells are altered in animal and human AKI. Sepsis may develop after AKI among hospitalized patients, and those with AKI requiring dialysis have a higher risk of sepsis after discharge compared to controls. We aim to determine the risk of infection in the year following a non-infectious hospital admission complicated by AKI with complete recovery in a well-matched cohort of cases and controls.

Methods: We identified 886 AKI cases (AKI Network definition) with complete kidney function recovery at the time of discharge, defined as serum creatinine <1.10 times the pre-admit baseline value, during a non-infectious hospital admission between January 1, 1999 and December 31, 2009 from an integrated health care delivery system. We matched 886 controls (no AKI during index admission) based on a propensity score including: age, sex, race, prior inpatient visits, coronary artery disease, congestive heart failure, chronic pulmonary disease, hypertension, diabetes, and admission day. The primary outcome was incidence infection, defined by ICD-9 codes, during the 12 months following discharge.

Results: Baseline characteristics among the cases and controls were similar: age 62±16 years, 45% female, 94% white, serum creatinine 0.9±2 mg/dL. During the 12 months after discharge, 342 cases and controls developed infection. Post-discharge infection was more common among cases compared to controls. In the periods between 30, 60, 90, and 365 days after discharge, infection developed in 90, 53, 44, and 133 cases compared to 29, 27, 21, and 65 controls, respectively. These events correspond to greater than 2-fold higher odds of infection among cases compared to matched controls (odds ratio 2.6 [95% CI, 1.3 – 3.3]; p<0.0001).

Conclusions: Among patients from an integrated health care delivery system, non-infectious AKI followed by complete recovery was associated with an increased risk of infection in the year after discharge. These data support long-term immune dysfunction after AKI.

Funding: VA Support

Risk Factors for Hospital Readmission and New-Onset CKD and Prevalence of Nephrology Follow-Up Care following AKI

TH-PO701

Grace M. Choong,1 Mark D. Faber;2 Denise White Perkins,3 Lois Lambertro. 1Wayne State Univ School of Medicine, Detroit, MI; 2Henry Ford Hospital, Detroit, MI; 3Henry Ford Health System, Detroit, MI.

Background: Many studies report the incidence and hospital-associated mortality of acute kidney injury (AKI) but less is known about follow-up care and longer term outcomes in this population. PURPOSE: to identify risk factors for hospital readmission and new-onset CKD, and to characterize follow up care, in hospitalized patients with AKI.

Methods: Retrospective, univariate analysis of individuals with AKI as defined by ICD-9-codes, hospitalized at 1 of 4 HFHS hospitals in 2012-2014. To enhance completeness of follow-up only patients enrolled in Health Alliance Plan of Michigan (HAP) for 6 months before and after AKI were followed. HAP is a managed care plan and subsidiary of HFHS. Individuals were 18-90 years old and excluded if they died during the index event. Subjects were followed for subsequent admissions and other aspects of care for 6 months after discharge.

Results: The study population (n=4002) had a mean age of 72.6, was predominantly male (52.5%) and non-African American (NAA) (57%). 17.7% of patients were readmitted within 30 days. Age, gender and race did not predict readmission. Readmission risk was increased by concurrent diabetes (DM), congestive heart failure (CHF), cancer, liver disease or preexisting CKD, whereas sepsis, COPD and peripheral vascular disease did not. 32.8% of individuals had CKD prior to the AKI event, while 20.6% developed CKD after the AKI. Being AA or <65 years old predicted new-onset CKD, as did having DM or CHF. Diagnoses of sepsis or hypertension were associated with a decreased risk of CKD. Despite having had AKI, only 10.6% of patients saw a nephrologist within 6 months of discharge.

Conclusions: Substantial opportunity exists to improve post discharge care of patients following hospitalization with AKI. Better understanding of risk profiles for readmission may help reduce the high and costly readmission rate. More importantly, deficient nephrology care following AKI discharge may place patients at risk for poor outcomes by denying patients the benefits of comprehensive multidisciplinary nephrology outpatient care.

Decrease in Serum Creatinine after ICU Admission Is Associated with Increased Mortality

TH-PO702

Hye Ran Kang, Sinac Lee, Jin Seok Jeon, Hyunjin Noh, Dong-Cheol Han, Soon HYO Kwon. Div of Nephrology, Soochunhyang Univ Hospital, Seoul, Republic of Korea.

Background: The elevation of serum creatinine (SCr), acute kidney injury (AKI), is associated with an increase of mortality in critically ill patients. However, it is uncertain whether decrease of SCr in intensive care unit (ICU) has an effect on outcome.

Methods: In a retrospective study, we enrolled 486 patients who admitted to an urban tertiary ICU from Jan 2014 to Dec 2014. The effect of change in SCr after ICU admission on 90 days mortality was analyzed. Patients were classified into 3 groups based on change in SCr after ICU admission: unchanged Cr group (△Cr<0.3 mg/dL within the prior 7 days), decreased Cr group (△Cr ≥ 0.3 mg/dL within the prior 7 days) and increased Cr group meeting the KDIGO AKI definition.

Results: SCr decreased in 123 (25.3%) patients after ICU admission. AKI developed in 125 (24.8%) patients. The overall 90-day mortality rate was 29.0%. In a Kaplan-Meyer analysis, the mortality in the AKI group was higher than that of other groups (p<0.001). Patients with decrement in SCr showed the higher mortality rate compared to those with unchanged SCr (p<0.001).
TH-PO703

Evaluation of Absolute Serum Creatinine Changes in Characterizing Stages for Cirrhosis-AKI and Its Association with Long-Term Outcomes

Fangfang Zhou,1 Qun Luo,1 Lina Han,1 Huadong Yan,1 Zemin Wang,1 Yunmei Li,1,2 1Dept of Nephrology, Ningbo NO.2 Hospital, Ningbo, Zhejiang, China; 2Dept of Infectious Diseases, Ningbo NO.2 Hospital, Ningbo, Zhejiang, China.

Background: Acute kidney injury (AKI) in cirrhotic patients is associated with worse outcomes. To date, there is no uniformity as to the classification for cirrhosis-AKI. We aimed to evaluate absolute serum creatinine (sCr) changes (\textit{Delta-sCr}) for characterizing stages of AKI, and its impacts on long-term outcomes in cirrhotic patients, compared with the KDIGO criteria.

Methods: We conducted a retrospective analysis of 333 hospitalized cirrhotic patients from January 2013 through December 2014. We defined AKI stages using: 1) KDIGO criteria, and 2) the Delta-sCr, defined by the difference between the baseline and the peak sCr value during hospitalization. The Delta-sCr cut-points were defined as: Stage 0, sCr change <0.3 mg/dl; Stage I, 0.3-0.7 mg/dl; Stage II, 0.7-1.2 mg/dl and Stage III, \geq 1.2 mg/dl. We compared the risk of death or readmission(OR=1.008; p=0.006) analysis and Cox hazard analysis both showed that Delta-sCr was significantly associated with readmission(OR=1.009; p=0.000). ROC analysis demonstrated that the Delta-sCr staging for AKI was more accurate than KDIGO staging in predicting 1-year mortality (AUC=0.825 vs 0.803; p=0.23). Though it did not achieve statistical significance, the values of specificity and positive likely ratio were both higher when classifying AKI stage III. And the Delta-sCr staging also modestly improved reclassification (C-index increased from 0.6699 to 0.6803; NRI= 22.9%, p=0.04).

Conclusions: The Delta-sCr is associated with the 1-year readmission and mortality. And the Delta-sCr staging may optimize the discrimination of risk prediction, especially when classifying AKI stage III.

Funding: Government Support - Non-U.S.

TH-PO704

Acute Kidney Injury and Its Prognosis in Patients with Decompensated Cirrhosis

Gullipalli Prasad,1 Prabhakar Doddii,1 Mitta Ravi Kumar,1 Raja Ramachandran.2 1Nephrology, Andhra Medical College; 2Nephrology, PGIMER.

Background: Acute kidney injury (AKI) occurs frequently in patients with cirrhosis. However, studies are limited on the impact of AKI on the mortality of patients with decompensated cirrhosis.

Methods: The present prospective observational study included subjects \geq 18 years of age with cirrhosis and AKI. Patients were recruited from January 2015 to December 2015 and were followed for 1 year. Cases with Cholemic Nephropathy, on renal replacement therapy at the time of admission, pregnant and lactating mothers, liver transplant candidates and those with diabetes mellitus were excluded. Outcome was mortality at end of the study. Acute kidney injury network criteria were used to diagnose AKI. Hepato-renal syndrome (HRS) was diagnosed based on the 2007 Aschtes Club Criteria. MELD score was used to predict severity of cirrhosis.

Results: Total 207 patients were admitted with cirrhosis and 56 patients (27%) had AKI. Mean age (yrs) was 52.20± 8.31. Mean serum creatinine (mg/dl) at admission and 48 hrs was 1.84±0.96 and 3.67±1.29. Mean MELD score was 30.60±6.47. Of the 56, patients with pre-renal azotomia (PRA) were 25 (44.64%), 15(26.78%) had acute tubular necrosis (ATN), patients with HRS were 13(23.21%) and 3 patients had other etiology. Mean age with cirrhosis and AKI. Patients were recruited from January 2015 to December 2015. Biopsies were processed and subjected to light microscopy and immunofluorescence. Bile casts were identified by light microscopy and confirmed using Fouchet’s stain. We studied and divided the all biopsies into two groups Group 1 with acute tubular necrosis (ATN) and Group 2 with Cholemic Nephropathy (CN) Results:of the 127 renal biopsies analyzed, 70 (55.1%) & 57(44.8%) were in group 1 and group 2 respectively. All baseline characteristics were similar except age, with patients in group 1 being older. On multivariate analysis the predictors was total bilirubin with OR=1.10, 95%CI (1.059-1.152, p=0.001) cut off value was 11.5 with sensitivity and specificity as 75 and 77 respectively. Conclusions: A high clinical index of suspicion of Cholemic nephropathy should be kept in all patients who have high serum bilirubin and it was found to be a significant predictor of cholemic nephropathy on multivariate analysis.

TH-PO707

Acute Kidney Injury and Long-Term Mortality after Orthotopic Liver Transplantation

Bernardo V. Reichert,1 Ramiaiane Aparecida Bridi,1 Nuzui Erika Mfnida,1 Camila Eleuterio Rodrigues,1 Igor Lepski Calii,1 Luiz M. Malbouisson,1 Luiz D. Albuquerque,2 Lucia Andrade,2 Victor F. Seabra,2,4 1Nephrology; 2Hepatology; 3Intensive Care Unit, Uniove Sao Paulo School of Medicine; 4Albert Einstein Hospital.

Background: There is limited data on the association of Acute Kidney Injury (AKI) and long-term mortality after liver transplantation.

Methods: We examined the association of AKI and perioperative characteristics with long-term mortality in cases of orthotopic liver transplantation using cox proportional hazards analyses.

Results: 139 participants were enrolled for this analysis. Mean age was 55 years, 67% were men, and mean MELD-Na score was 19.6. The participants were followed for mean of 391 days [interquartile range (IQR) 97 to 610 days]. The overall mortality was 33%. The figure shows the Kaplan Meier curve of probability of survival and KDIGO stages:

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Underline represents presenting author.

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In unadjusted analysis, KDIGO stage 3 AKI was associated with a 6.67-fold higher risk for mortality (P <0.001; 95% confidence interval, 2.36 to 18.82) and a 6.15-fold higher risk for mortality after adjustment for other covariates (P <0.01; 95% confidence interval, 1.83 to 20.74).

Conclusions: KDIGO stage 3 is associated with long-term mortality after liver transplantation. Larger studies are needed to confirm these findings. This study was supported by FAPESP.

Funding: Government Support - Non-U.S.

TH-PO708

Association of Perioperative Characteristics and Acute Kidney Injury with In-Hospital Mortality after Orthotopic Liver Transplantation

Bernardo V. Reichert,1 Ramaine Aparecida Bredi,1 Nuzzi Érica Minda,1 Camila Eleuterio Rodrigues,1 Igor Lepski Cali,2 Luiz M. Malboisson,3 Luiz D. Albuquerque,2 Lucia Andrade,1 Victor F. Seabra,1,4 *Nephrology; 1Intensive Care Unit, Univ Sao Paulo School of Medicine, Brazil; 2Albert Einstein Hospital.

Background: There is limited data on the association of Acute Kidney Injury (AKI) and other perioperative characteristics with mortality in patients undergoing liver transplantation.

Methods: We examined the association of AKI and perioperative characteristics with in-hospital mortality in cases of orthotopic liver transplantation using logistic regression analyses.

Results: 139 participants were enrolled for this analysis. Mean age was 55 years, 67% were men, and mean MELD-Na score was 19.6. The overall mortality was 22%, the incidence of AKI was 78%, and 49% required renal replacement therapy. In univariate analysis, KDIGO stage 3 AKI was associated with higher risk of in-hospital mortality when compared with subjects without AKI (odds ratio [OR], 10.50; 95% confidence interval [CI], 2.74–42.51). Perioperative variables (aortic cross-clamping time, warm ischemia time, and fulminant hepatitis) and intra-operative (number of packed red blood cells and frozen plasma transfusions and prolonged anesthesia time) variables were also associated with in-hospital mortality. In multivariate analysis, the association of KDIGO stage 3 AKI and higher in-hospital mortality persisted after adjustment for other variables (OR, 13.65; 95% CI, 2.16 to 279.86). In the final model, the presence of fulminant hepatitis (OR, 2.22) and duration of anesthesia (OR, 1.32; per hour increase) also were associated with higher in-hospital mortality.

Conclusions: AKI predicts in-hospital mortality after liver transplantation. Larger studies are needed to confirm these findings. Supported by FAPESP.

Funding: Government Support - Non-U.S.

TH-PO709

Prediction of Mortality or the Need for Continued Renal Replacement Therapy following Acute Kidney Injury Requiring Dialysis V. Shane Pankratz, Christos Argyropoulos, Orrin Myers, Mark L. Unruh. Univ of New Mexico, Albuquerque, NM.

Background: Managing the care of patients with acute kidney injury (AKI) remains inadequately defined. The availability of tools that simultaneously assess the probability of both mortality and continued need for renal replacement therapy (RRT) may enhance the decision-making process for clinicians caring for such severely ill patients.

Methods: Using data from the VA/NHLBI Acute Renal Failure Trial Network, we developed a regression model that simultaneously evaluated the risk of death or continued RRT at multiple time points (28 days, 60 days, and 1 year post randomization) using the KDIGO creatinine criteria. AKI duration was defined using the number of days from the start of AKI until discharge.

Results: 139 participants were enrolled for this analysis. Mean age was 55 years, 67% were men, and mean MELD-Na score was 19.6. The overall mortality was 22%, the incidence of AKI was 78%, and 49% required renal replacement therapy. In univariate analysis, KDIGO stage 3 AKI was associated with higher risk of in-hospital mortality when compared with subjects without AKI (odds ratio [OR], 10.50; 95% confidence interval [CI], 2.74–42.51). Perioperative variables (aortic cross-clamping time, warm ischemia time, and fulminant hepatitis) and intra-operative (number of packed red blood cells and frozen plasma transfusions and prolonged anesthesia time) variables were also associated with in-hospital mortality. In multivariate analysis, the association of KDIGO stage 3 AKI and higher in-hospital mortality persisted after adjustment for other variables (OR, 13.65; 95% CI, 2.16 to 279.86). In the final model, the presence of fulminant hepatitis (OR, 2.22) and duration of anesthesia (OR, 1.32; per hour increase) also were associated with higher in-hospital mortality.

Conclusions: AKI predicts in-hospital mortality after liver transplantation. Larger studies are needed to confirm these findings. Supported by FAPESP.

Funding: Government Support - Non-U.S.

TH-PO711

Nutritional Factors Associated to Survival in Acute Kidney Injury Patients in a Tertiary Health Care Hospital Rosalba Sotelo-Anaya,1 Jonathan Chavez,2 Fabiola Martin del Campo,1 Monica Consuelo Jimenez Cornejo,2 Gabriela Jazmin Abundis Mora,2 Guillermo Garcia-Garcia,2 *Dirección de Posgrados, Univ del Valle de Atemajac, Guadalajara, Jalisco, Mexico; 1Dept of Nefrología, Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Jalisco, Mexico.

Background: Malnutrition in hospitalized patients is associated with poor clinical outcomes. There is little evidence that KDIGO guidelines on nutritional management in AKI patients and outcomes in the hospital setting. We evaluated the impact of nutritional factors on survival on hospitalized patients.

Methods: 87 AKI patients admitted to the Hospital Civil de Guadalajara Fray Antonio Alcalde were included. Each patient had a clinical and biochemical evaluation; nutritional status was assessed by SGA, anthropometric data and 24-hour dietary recall.

Results:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors n=55</th>
<th>Non-survivors n=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>51±16</td>
<td>56±18</td>
</tr>
<tr>
<td>Male (%)</td>
<td>37(67)</td>
<td>25(78)</td>
</tr>
<tr>
<td>Surgical cases, (%)</td>
<td>20(36)</td>
<td>9(28)</td>
</tr>
<tr>
<td>AKI KDIGO stage, (%)*</td>
<td>13(24)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>23(42)</td>
<td>21(66)</td>
</tr>
<tr>
<td>3</td>
<td>13(23)</td>
<td>21(66)</td>
</tr>
<tr>
<td>Dialysis, (%)*</td>
<td>10(18)</td>
<td>6(19)</td>
</tr>
<tr>
<td>Mechanical ventilation, (%)*</td>
<td>50(90)</td>
<td>24(77)</td>
</tr>
<tr>
<td>Non-oliguric, (%)*</td>
<td>6(10)</td>
<td>14(45)</td>
</tr>
<tr>
<td>Fasting, (%)</td>
<td>3(7)</td>
<td>13(41)</td>
</tr>
<tr>
<td>Oral intake, (%)*</td>
<td>9(16)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Enteral nutrition, (%)</td>
<td>3(5)</td>
<td>4(12)</td>
</tr>
<tr>
<td>Parenteral nutrition, (%)</td>
<td>12(23)</td>
<td>15(47)</td>
</tr>
<tr>
<td>Energy intake (kcal/kg)</td>
<td>0.48±0.38</td>
<td>0.56±0.45</td>
</tr>
<tr>
<td>Protein intake (g/kg)</td>
<td>26±6.3</td>
<td>25±7.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25(46)</td>
<td>32(47)</td>
</tr>
</tbody>
</table>

*p <0.05

Age [OR 1.032 (95% CI 1.001-1.06) p=0.049], AKI KDIGO 3 [OR 3.04 (95% CI 3.17-6.77) p=0.006] and fasting [OR 7.04 (95% CI 2.12-23.29) p=0.001] increased the risk of death.

Conclusions: We confirmed that fasting was associated with increased hospital mortality in patients with AKI. Additionally a high proportion of malnutrition and poor nutrient intake was found.

TH-PO712

Effects of Acute Kidney Injury Duration on Outcomes in Critically Ill Patients Christine K. Federan,1 Theis S. Itenov,2 Kala M. Mehta,3 Raymond K. Hsu,1 Morten Bestle,4 Kathleen D. Liu.1 1UCSF; 2Anesthesiology, Nordsjølands Hospital, Denmark.

Background: Acute kidney injury (AKI) is a common and serious illness. Duration of AKI has been recognized as an important risk factor for adverse long-term outcomes, but less is known about the impact of AKI duration on mortality and other organ functions in critically ill patients.

Methods: We analyzed data from the NHLBI ARDS Network’s “Statins for Acutely Injured Lungs from Sepsis” (SAILS), a multicenter trial of ICU patients with sepsis-associated ARDS. Patients who developed AKI over the first 5 days of enrollment were identified using the KDIGO creatinine criteria. AKI duration was defined using the number of days from the start of AKI until discharge.

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

Underlines represent presenting author.
of consecutive days at which the KDIGO creatinine criteria were fulfilled, and categorized into four groups: transient (duration 1-2days), medium (3-7days), persistent (7+days), or death during AKI. Mann-Whitney test and Chi-square test were used to evaluate differences between the groups.

**Results:** Among the 249 SAILS participants who developed AKI during the first 5 days of enrollment, 77 had transient AKI, 47 had medium-duration AKI, 87 had persistent AKI, and 38 patients died while still suffering from AKI. There were no significant differences between the transient and medium-duration AKI groups in 30-day mortality, cardiovascular failure free days or ventilator free days. Patients with persistent AKI had significantly lower lengths of cardiovascular failure free days and ventilator free days.

The rank sum of factors suggested that abnormal BMI, lower preoperative hemoglobin, erythrocytes transfusion, duration of mechanical ventilation, presence of hypertension (11 out of 193 cases), CKD (9 out of 66 cases), low level of albumin (3.3 g/dL vs. 3.6 g/dL), hemoglobin (11.3 g/dL vs. 12.4 g/dL) and total CO2 (24.27 mmol/L vs. 26.53 mmol/L) content were related to AKI significantly. In subgroup analysis with CKD group, AKI was developed in 8 out of 63 cases. Low albumin (3.3 g/dL vs. 3.6 g/dL) and hemoglobin (10.59 g/dL vs. 11.7 g/dL) were related risk factor in CKD patients. Use of crystalloid fluid only or combined with colloid fluid did not have any significant means. Among perioperative crystalloid fluid, 2 AKI case in 5 unbalanced fluid (40%) and 6 AKI cases in 58 balanced fluid (10%) were developed.

**Conclusions:** In critically ill patients with sepsis-associated ARDS and AKI, patients with transient AKI did not have better outcomes compared to those with AKI lasting up to 7 days. Persistent AKI lasting >7 days was associated with worse outcomes, emphasizing the importance of developing interventions that shorten the length of renal injury to improve patient outcomes.

**Funding:** Other NIH Support - NHLBI

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**Results:** The incidence of kidney injury according to our definition was higher in cases as compared to controls (42.5% vs. 25.5%; OR 2.25 95% CI (1.18 - 4.27) p < 0.01). Risk factors for CKI on unadjusted analysis included baseline CKD, HTN, ACE inhibitor use and systemic vancomycin use. The most important baseline risk factors after multivariable adjustment that contributed to the predicted risk score included CKD (OR 2.37; 95% CI 1.17-4.82), and was compounded by spacer implantation (OR 2.25; 95% CI 1.18-4.27).

**Conclusions:** Kidney injury including AKI in the post-operative period as well as late kidney injury during the course of spacer implantation is significantly associated with two stage arthroplasty with ALS for PJH. The proposed risk prediction model can be used to better identify the patients at higher risk of nephrotoxic complications of the procedure.

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**Results:** Overall, AKI was developed in 13 among 351 cases (3.7%). Among the examined variables, presence of hypertension (11 out of 193 cases), CKD (9 out of 66 cases), low level of albumin (3.3 g/dL vs. 3.6 g/dL), hemoglobin (11.3 g/dL vs. 12.4 g/dL) and total CO2 (24.27 mmol/L vs. 26.53 mmol/L) content were related to AKI significantly. In subgroup analysis with CKD group, AKI was developed in 8 out of 63 cases. Low albumin (3.3 g/dL vs. 3.6 g/dL) and hemoglobin (10.59 g/dL vs. 11.7 g/dL) were related risk factor in CKD patients. Use of crystalloid fluid only or combined with colloid fluid did not have any significant means. Among perioperative crystalloid fluid, 2 AKI case in 5 unbalanced fluid (40%) and 6 AKI cases in 58 balanced fluid (10%) were developed.

**Conclusions:** We should monitor the renal function closely after orthopedic surgery in order to prevent AKI. In addition, use of balanced fluid is helpful to prevent AKI in CKD patients if there are no electrolyte abnormalities.

**Funding:** This study was a perspective cohort study. We used National Health Insurance database in Taiwan from 2000 to 2014 to collect 13,889 patients with acute renal injure requiring dialysis is unknown.

**Results:** There were 6,262 beta-blocker users and 7,636 beta-blocker nonusers identified; of whom 2,200 and 3,045 died in 5 years, respectively. The 5 years mortality in beta-blocker users and nonusers were 124.1 and 146.3 case per 1,000 person-years, respectively. In Cox’s proportional hazard model, after adjusting for age, gender, nephrologist care, myocardial infarction, stroke, diabetes mellitus (DM), chronic obstructive pulmonary disease, cancer, anti-hypertensive drugs used, oral antidiabetic drugs used, insulin, DM duration, statin, chronic kidney (CKD) stage, sepsis, heart failure, cardiovascular surgery, pesticide or metal poisoning, the hospital setting (treated as a cluster unit), and development of long-term dialysis (time dependent-variable), the mortality risk in beta-blocker users was 0.88 (95% confidence interval: 0.83 and 0.93, p value < 0.001). In addition, beta-blocked all-cause mortality, the beta-blocker-users also had lower mortality risk in cardiovascular, DM and congestive renal disease mortality. In subgroup analysis, the results in most subgroups were similar to the main results except those younger than 40, cancer patients, those stage 5 CKD and those who developed sepsis induced AKI.

**Conclusions:** We conclude that for the hypertensive patients who develop AKI requiring dialysis beta-blockers may be a preferred choice to prevent premature mortality.

**Funding:** Government Support - Non-U.S.
Acute Kidney Injury after Cardiac Arrest Is Associated with Neurological Outcome and Mortality, an Observational Follow-Up of 10 Years

Background: Acute kidney injury (AKI) is associated with early and long-term patient morbidity and mortality. In ICU patients, AKI is associated with a decrease in survival. AKI is considered a surrogate marker for illness severity and a consequence of the underlying disease. In evaluating the prevalence of AKI in cardiac arrest patients in association to their neurological outcome (according to the Cerebral Performance Categories score – CPC), their disease severity (APACHE Score) and hypoxia level (NSE) after administering therapeutic target temperature management at 33°C for 24 hours.

Methods: Observational single center study between 2006 und 2013 in a cardiac arrest center in Berlin, Germany. All out and in hospital cardiac arrest (OHCA / IHCA) patients were included. AKI was defined by the KDIGO guidelines. Main outcome was the assessment of good (CPC Scale 1-2) vs poor (CPC Scale 3-5) neurological outcome and its association with disease severity by APACHE Score, NSE levels as marker of hypoxia and AKI vs non-AKI as an independent risk factor. Long term monitoring of up to 120 months assessing mortality was performed.

Results: A total of 497 patients after cardiac arrest were evaluated. Their CPC Scale obtained at discharge from ICU. 242 patients had good neurological outcome (CPC 1-2) vs 255 with a poor neurological outcome (CPC 3-5). The CPC 1-2 group had a NSE-level at day 3 of 21.0 ± 9.5 vs poor (CPC Scale 3-5) neurological outcome and its association with disease severity by APACHE Score, NSE levels as marker of hypoxia and AKI vs non-AKI as an independent risk factor. Long term monitoring of up to 120 months assessing mortality was performed.

Conclusions: AKI is a prevalent issue in critically ill patients such as survivors of cardiac arrest with long-term follow-up issues. In addition to surviving cardiac arrest, the neurological long-term outcome remains a crucial subject. AKI is associated with mortality but also with poor neurological outcome after surviving cardiac arrest. New strategies may be needed to address this issue.

Acute Kidney Injury in Asphyxiated Neonates Treated with Therapeutic Hypothermia

Background: Mult-organ failure increases morbidity and mortality rates in severely asphyxiated neonates. Acute kidney injury (AKI) is one of the most severe complications in these patients, which can affect their short-term survival. In this study, we investigated the incidence and the outcomes of AKI in asphyxiated neonates treated with therapeutic hypothermia.

Methods: We retrospectively reviewed 105 cases of neonates who experienced perinatal asphyxia and treated with therapeutic hypothermia in a single neonatal intensive care unit (NICU) between June 2000 and June 2015. We used the proposed neonatal AKI definitions asphyxia and treated with therapeutic hypothermia in a single neonatal intensive care unit (NICU) between June 2000 and June 2015. We used the proposed neonatal AKI definitions to classify and to establish the stage of AKI. We investigated the incidence of AKI, dialysis, mortality, and prolonged renal insufficiency.

Results: AKI occurred in 33 of 105 severely asphyxiated neonates (31.4%), and oliguric AKI was present in 27.6% of patients. Four patients (12.1%) received continuous dialysis. Overall mortality rate was 4.8%, and it was much higher in those with AKI than in those without AKI (15.2% vs 0%). The mortality rate was 50% in neonates requiring dialysis. The mortality rate was 26.3% in neonates with oliguric AKI compared to 0% in those without oliguric AKI. Percent fluid overload was higher in the group of neonates who died than in those alive (15.4 ± 8.1% vs 7.5 ± 5.1%; p < 0.05). The peak value of serum creatinine in neonates with oliguric AKI was present in 57.6% of patients. Four patients (12.1%) received continuous dialysis.

Conclusions: The incidence of AKI in asphyxiated neonates treated with therapeutic hypothermia was lower than previously reported. The mortality rate of neonates with AKI remains high, especially in those requiring dialysis. Oliguric AKI and higher fluid overload are associated with increased mortality rates.

Impact of Therapeutic Hypothermia on Kidney Function Post Cardiac Arrest

Background: Mortality in cardiac arrest patients remain high with limited consensus on management following return of spontaneous circulation (ROSC). Therapeutic hypothermia post cardiac arrest leads to better neurological outcomes however its effect on kidney function is uncertain. To better assess this, we trended serum creatinine, to determine acute kidney injury (AKI) following initiation of therapeutic hypothermia at our hospital.

Methods: We conducted a retrospective case-control analysis of patients who achieved ROSC following cardiac arrest. Patients were divided into two cohorts i.e. hypothermia and normothermia. AKI was diagnosed as per AKIN criteria. Patients who had coma prior to arrest & were on dialysis were excluded. Eligible patients’ serum creatinine and urine output was assessed at different stages post cardiac arrest. Baseline variables in both cohorts were adjusted and multivariate adjusted at each timepoint.

Results: A total of 96 patients (hypothermia n= 53, normothermia n= 43) were studied. Baseline mean serum creatinine levels in both cohorts were similar. At 24 hours after ROSC, mean serum creatinine in normothermia cohort was greater than in hypothermia cohort however was not statistically significant (2.13 ± 1.97 vs 3.11 ± 1.46; p value = 0.15). Net difference of mean serum creatinine from baseline was increased more in normothermia cohort (+0.29 mg/dL, p value = 0.002), median length of stay (LOS) in normothermia group was also longer than in hypothermia group (20 ± 7 days, p value < 0.001). Both results were statistically significant. Mortality in hypothermia group was 2.5 times higher than in normothermia group (80.4% vs. 33.3%, p value < 0.001).

Conclusions: Therapeutic hypothermia may have a renoprotective role in cardiac arrest patients and this may predict reduced hospital stay. Absence of AKI however may not predict improved mortality outcomes in post cardiac arrest patients treated by Hypothermia protocol.

Acute Kidney Injury (AKI) is a prevalent issue in critically ill patients such as survivors of cardiac arrest with long-term follow-up issues. In addition to surviving cardiac arrest, the neurological long-term outcome remains a crucial subject. AKI is associated with mortality but also with poor neurological outcome after surviving cardiac arrest. New strategies may be needed to address this issue.

Acute Kidney Injury is associated with early and long-term patient morbidity and mortality. In ICU patients, AKI is associated with a decrease in survival. AKI is considered a surrogate marker for illness severity and a consequence of the underlying disease. In evaluating the prevalence of AKI in cardiac arrest patients in association to their neurological outcome (according to the Cerebral Performance Categories score – CPC), their disease severity (APACHE Score) and hypoxia level (NSE) after administering therapeutic target temperature management at 33°C for 24 hours.

Results: A total of 497 patients after cardiac arrest were evaluated. Their CPC Scale obtained at discharge from ICU. 242 patients had good neurological outcome (CPC 1-2) vs 255 with a poor neurological outcome (CPC 3-5). The CPC 1-2 group had a NSE-level at day 3 of 21.0 ± 9.5 vs poor (CPC Scale 3-5) neurological outcome and its association with disease severity by APACHE Score, NSE levels as marker of hypoxia and AKI vs non-AKI as an independent risk factor. Long term monitoring of up to 120 months assessing mortality was performed.

Conclusions: AKI is a prevalent issue in critically ill patients such as survivors of cardiac arrest with long-term follow-up issues. In addition to surviving cardiac arrest, the neurological long-term outcome remains a crucial subject. AKI is associated with mortality but also with poor neurological outcome after surviving cardiac arrest. New strategies may be needed to address this issue.

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TH-PO722

The KDIGO Criteria Are Superior Predictors of Mortality after Non-Carotid Major Surgery Compared to AKIN Criteria
Seokwoo Joo, Dong Ki Kim, Kwon Wook Joo, Youn Sun Kim, Hajeong Lee. Internal Medicine, Seoul National Univ of College of Medicine, Seoul, Korea.

Background: Postoperative acute kidney injury (AKI) is a serious adverse event which leads to higher mortality. Although several studies have been published on the subject, heterogeneous definitions of AKI in each study makes it difficult to synthesize study results. We aimed to compare the performance of the KDIGO criteria with the AKIN criteria for improving Global Outcomes criteria (KDIGO) and Acute Kidney Injury Network criteria (AKIN) in predicting patient outcomes after non-carotid surgery.

Methods: We included adult patients who received non-cardiac major surgery (duration >1 hour) in Seoul National University Hospital from 2004 to 2013. AKI was diagnosed according to both KDIGO and AKIN criteria based on Cr measurements and initiation of RRT within 14 days after surgery. Positive predictive value (PPV) and negative predictive value (NPV) for in-hospital, 30-day, and 90-day mortality were compared using generalized standard statistics. Discrimination ability was evaluated by c-statistics.

Results: Among a total of 58,919 cases, 4,092 (6.95%) and 3,347 (5.68%) were identified to be AKI by KDIGO and AKIN, respectively. KDIGO showed significantly lower PPV and higher NPV for in-hospital, 30-day, and 90-day mortality than AKIN.

<table>
<thead>
<tr>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDIGO</td>
<td>AKIN</td>
</tr>
<tr>
<td>In-hospital (%)</td>
<td>6.1</td>
</tr>
<tr>
<td>90-day (%)</td>
<td>6.0</td>
</tr>
<tr>
<td>1-year (%)</td>
<td>6.1</td>
</tr>
</tbody>
</table>

The differences between C-statistics of KDIGO and AKIN were statistically significant in all 3 clinical outcomes, namely in-hospital (0.82 vs. 0.80; p=0.002), 90-day (0.80 vs. 0.77; p<0.001) and 1-year (0.66 vs. 0.64; p<0.001) mortality.

Conclusions: KDIGO may be more useful for discriminating postoperative mortality than AKIN demonstrated by higher C-statistics. Also, considering prevalence of postoperative AKI and clinical relevance, superiority in sensitivity and discrimination power obtained by KDIGO compared to AKIN can outweigh inferiority in specificity. Implementing KDIGO criteria for defining postoperative AKI in non-cardiac surgery could prevent confusion in classification and help interpreting future studies in this field.

TH-PO723

Risk of ESRD Higher with Lower Adherence of DASH Diet in African Americans with Moderate CKD
Tanushree Saran, Tony Barany, Bengt Lindholm, Abdul Olof Heimburger, Peter Steninkiewicz. 1Nephrology, Hospital Espírito Santo, Vitória, Brazil; 2JHU; 3CDC; 4UM.

Background: Dietary modifications play an important role in management of patients with CKD and ESRD. Few studies have examined the association of adherence to a DASH-type diet with risk of CKD progression among adults with moderate CKD from different racial and ethnic backgrounds.

Methods: Among a cohort of 293 non-Hispanic black (NHBS) and 664 non-Hispanic white (NHWs) adults with moderate CKD (eGFR 30-59 mL/min) and with hypertension enrolled in HANES III (1988-1994), we used 24-hour dietary recall data to determine adherence score to a DASH-type diet. Adherence was defined as score ≥24.5 out of a possible score of 9. Development of ESRD was ascertained over follow-up via linkage with USRDS.

Results: The AUCs showed that pre-HD BMI, serum creatinine and urea nitrogen levels were more accurate than post-HD values for predicting mortality in HD patients.

Conclusions: Pre-HD values of nutritional factors, except serum albumin levels, were more accurate than post-HD values for predicting mortality in HD patients.

TH-PO724

Comparison of Accuracy between Pre- and Post-HD Values of Nutritional Factors for Prediction of Mortality in Hemodialysis Patients
Yoshiko Kanno,1 Eiichiro Kanda,2 1Tokyo Medical Univ, Japan; 2Tokyo Kyosai Hospital.

Background: To assess the nutritional status of patients receiving hemodialysis (HD), regularly measured pre-HD laboratory data are often used. However it has been included the problem whether the most diluted value would be appropriate to evaluate. We compared the pre-and post HD laboratory data to investigate their value to predict mortality.

Methods: 104289 maintenance hemodialysis (HD) patients (males 61.2%) were enrolled as subjects in this analysis as part of a prospective cohort study of the Japanese Society for Dialysis Therapy. The outcome events were one- and five-year mortalities. Their laboratory data included pre- and post-HD values of nutritional factors such as body mass index (BMI), and serum albumin, creatinine, and urea nitrogen levels. We compared the accuracy between pre- and post-HD values for the prediction of one- or five-year mortality using receiver operating characteristic (ROC) curves by the bootstrap resampling method.

Results: Mean age/standard deviation was 65.47±12.18 years, vintage, 8.62±7.05 years. The number of patients who died in one year was 6868 (6.6%); that in five years, 33188 (31.8%). The highest area under the ROC curve (AUCs) for the prediction of one-year mortality was HD serum albumin level [0.733 (95% CI 0.720, 0.746)]; and that of five-year mortality, pre-HD serum creatinine level [0.702 (95% CI 0.699, 0.706)].

Conclusions: Pre-HD BMI, serum creatinine and urea nitrogen levels which are more accurate than post-HD values (each p<0.0001). Although no statistical difference was observed among the AUCs of pre- and post-HD values of serum albumin levels for predicting one-year mortality (p=0.142), the post-HD serum albumin level was more accurate than the pre-HD level for predicting five-year mortality (p=0.0001). Stratification analysis based on gender, age, and diabetes mellitus as a cause of end-stage renal disease showed similar trends, that is, pre-HD BMI, and serum creatinine and urine nitrogen levels were more accurate than post-HD values.

TH-PO725

Inflammatory Status Markedly Affects Ability of Serum Albumin to Predict Outcome in Chronic Kidney Disease
Eliane a. Fagundes,1 Jia Sun,2 Abdul Rashid Tony Qureshi,2 Sunna Snaedal,2 Peter F. Barany,2 Bengt Lindholm,1 Peter Steninkiewicz. 1Nephrology, Hospital Espírito Santo, Vitória, Brazil; 2JHU; 3CDC; 4UM.

Background: Chronic kidney disease (CKD) is partly linked to its association with systemic inflammation, but it is not clear to what extent its predictive strength depends on concomitant systemic inflammation. Here we addressed this question in pts with CKD stage 3-5.

Methods: Serum albumin (S-Alb), inflammatory status (high sensitivity C-reactive protein, CRP), cardiovascular disease (CVD) and nutritional status were assessed at baseline in 854 pts comprising: 97 pts with CKD stages 3-4 (median S-Alb 37g/L, median CRP 2.7 mg/L), 523 pts with CKD stage 5 (median S-Alb 33g/L, median CRP 4.8 mg/L), 178 prevalent HD (median S-Alb 34g/L, median CRP 6.8 mg/L), and 56 prevalent PD pts (median S-Alb 31g/L, median CRP 4.4 mg/L). Pts were divided into four groups according to median levels of CRP and S-Alb in each cohort: Group 1 (n=298) - High S-Alb/Low CRP; Group 2 (n=211) - High S-Alb/High CRP, Group 3 (n=218) - Low S-Alb/Low CRP; Group 4 (n=218) - Low S-Alb/High CRP. Survival over 60 months was analyzed.

Results: In Cox analysis, Group 4 (Low S-Alb/High CRP) had increased mortality risk (adjusted HR (95%CI): 1.8 (1.26 - 2.61); p<0.01), whereas the augmented risks for Groups 2 and 3 in univariate analyses were lost after adjustments for age, sex, CVD, diabetes, smoking, handgrip strength, CKD stage and renal replacement therapy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Mortality risk is increased in CKD pts with low S-Alb and high CRP but not in pts with low S-Alb and low CRP or high CRP and high S-Alb, suggesting that inflammatory status should be taken into account when using S-Alb to predict outcomes in CKD patients.

**Funding:** Pharmaceutical Company Support - Baxter Healthcare, Government Support - Non-U.S.

**TH-PO726**

**Net Endogenous Acid Production, an Index of Dietary Acid Load, Is Associated with the Progression of CKD**

Koji Toda, Michihiro Hosojiya, Shoji Kuwahara, Ryohrei Kascda, Tomomichi Iida, Sawako Goto, Naohito Tanabe, Yoshiko Suzuki, Ichiro Narita, Akihiko Saito. Div of Clinical Nephrology and Rheumatology, Niigata Univ, Niigata, Japan; Dept of Clinical Nutrition Science, Niigata Univ, Niigata, Japan; Dept of Applied Molecular Medicine, Niigata Univ, Niigata, Japan; Health and Nutrition, Univ of Niigata Prefecture, Niigata, Japan; Health Administration Center, Niigata Univ, Niigata, Japan.

**Background:** Recent studies have suggested that metabolic acidosis mediates the progression of CKD. Dietary acid load, a potential cause of metabolic acidosis, might be associated with CKD progression, although few studies have analyzed this. Here, we investigated the association of dietary acid load with CKD progression by evaluating the net endogenous acid production (NEAP), an index of the dietary acid load, and reviewing clinical records of CKD patients.

**Methods:** Subjects of this study were 96 outpatients with CKD (61 patients with diabetes; average eGFR, 53.0±18.1 mL/min/1.73 m²) at Niigata University Hospital. We estimated their intake of foods and nutrients from the results of a self-administered dietary history questionnaire (DHIQ) completed in 2011. We estimated NEAP using the following formula: NEAP (mEq/d)=5.45 (protein [g/d])/(potassium [mEq/d]-10.2) (Sicilla, JJ et al. Clin J Am Soc Nephrol 2011). Progression of CKD was assessed by comparing eGFR between 2008 and 2014.

**Results:** Average NEAP was 50.0±18.1 (mEq/d). Urinary pH was significantly lower in patients with higher NEAP (p<0.01) and in those with lower NEAP (p<0.05). Higher NEAP was significantly associated with intake of more meat and less vegetables, fruit, and potassium. Protein intake was not significantly associated with NEAP. Reduction of NEAP from 2008 to 2014 was significantly greater in patients with higher NEAP than in those with lower NEAP (8.9 vs. -2.5 mL/min/1.73 m², p<0.03).

**Conclusions:** Higher NEAP could be a risk factor for CKD progression. Further studies are warranted to evaluate the protective effects of dietary acid control on CKD progression.

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

**TH-PO727**

**Muscle Strength Interaction with Insulin-Like Growth Factor-1 (IGF-1) Influences Survival in Chronic Kidney Disease (CKD)**

Chen Zhiminn, Erik Nilsson, Jia Sun, Bengt Lindholm, Olef Heimburger, Peter F. Barany, Peter Stenvinkel, Abdul Rashid Tony Qureshi, Kidney Disease Center, 1st Affiliated Hospital College of Medicine, Zhejiang Univ, Hangzhou, China; Renal Medicine and Baxter Novum, CLINTEC, Karolinska Inst, Stockholm, Sweden.

**Background:** CKD patients (pts) display resistance to IGF-1. Hand-grip muscle strength (HGS) is a reliable and easy-to-perform nutritional parameter. Both low IGF-1 and low HGS predict mortality. We hypothesized that concomitant presence of both conditions increases mortality risk in CKD.

**Methods:** IGF-1, HGS and other nutritional and inflammatory markers were measured in 724 pts (median age 58 years, 62% males) with different stages of CKD. Pts were stratified into 4 groups according to median levels of HGS and IGF-1 and all-cause mortality over 60 months was analyzed.

**Results:** Pts with low IGF-1 (<median) and low HGS (<median) were older and had elevated levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and tumor necrosis factor (TNF) and worse survival in Kaplan-Meier analysis, see Fig 1. Multivariable logistic regression analysis adjusted for age, gender, diabetes, cardiovascular disease (CVD), HGS, subjective global assessment (SGA), albumin, smoking and hsCRP, revealed that both predictors of lower IGF-1 and age, diabetes and low HGS. In receiver-operating characteristics curve (ROC) analysis, lower IGF-1 associated with higher mortality only in low HGS group. In Cox proportional hazards analysis, across the four HGS-IGF-1 categories, the group with low IGF-1 and low HGS had highest mortality after adjustments for age, gender, diabetes, CVD, SGA, smoking, hsCRP and albumin.

**Conclusions:** Among HD patients, hyperuricemia may be a marker of better nutritional status, and were paradoxically related to lower all-cause mortality risk in contrast to those in the general population. Future studies are needed to investigate the mechanism behind this association.

**Funding:** NIDDK Support

**TH-PO728**

**Serum Uric Acid Level and Mortality in Hemodialysis Patients**

Christina Park, Yoshitsugu Obi, Elani Streja, Melissa Soohoo, Kamyar Kalantar-Zadeh, UC Irvine.

**Background:** Elevated uric acid concentrations are associated with cardiovascular events and mortality in the general population. However, there are scarce data regarding the mortality risk associated with hyperuricemia in the hemodialysis (HD) population.

**Methods:** We retrospectively examined a subcohort of 4,298 HD patients whose first serum uric acid measurements were obtained during treatment in a large dialysis organization from 2007-2011. Patients were grouped into 5 uric acid categories. Using Cox proportional hazards model, we explored the association between serum uric acid levels and time to all-cause death from first uric acid measurement with adjustments for case-mix variables (demographics, comorbidities, and spKt/V) and laboratory markers of malnutrition and inflammation (MICS).

**Results:** Mean age was 63±15 years and 39% were women. Mean uric acid level was 6.6±1.8 mg/dL. There was a trend toward lower mortality risk across higher uric acid levels irrespective of the adjustment models (P trend <0.001). The highest category (≥8.0 mg/dL) showed non-significant lower mortality risk while the lowest category (<5.0 mg/dL) was significantly associated with higher mortality compared to the middle category (6.0-7.0 mg/dL). Both-adjusted HRs were 1.12 (95% CI, 1.01-1.23) and 0.89 (95% CI, 0.72-1.13), respectively. These findings were consistent across subgroups of age, gender, race, diabetes, albumin, and body mass index (P for interaction <0.1). However, mortality risk associated with low uric acid levels (<5.0 mg/dL) were significant among patients with low nPCR (<0.9 g/kg/day) but not among those with high nPCR (≥0.9 g/kg/day) (P trend <0.001).

**Conclusions:** serum uric acid is associated with adverse clinical outcomes including mortality in ESRD. In-center extended duration nocturnal hemodialysis (INHD) has been credited with a variety of clinical benefits but the impact of INHD on metabolic profiles remains unclear.

**Funding:** NIDDK Support

**TH-PO729**

**The Effect of Extended Duration Nocturnal Hemodialysis on the Human Metabolome**

Sahir Kalim, Ron Wald, Dihua Xu, Anders H. Berg, Eugene P. Rhee, Jeffrey Perl, Massachusetts General Hospital, Boston, MA; St. Michael’s Hospital, Toronto, ON; Beth Israel Deaconess Medical Center, Boston, MA.

**Background:** Human metabolite profiling has been increasingly used to describe the small molecule disparity that arises in ESRD and several specific “uremic solutes” have been associated with adverse clinical outcomes including mortality in ESRD. In-center extended duration nocturnal hemodialysis (INHD) has been credited with a variety of clinical benefits but the impact of INHD on metabolic profiles remains unclear.

**Methods:** We conducted a prospective, multi-center parallel arm observational study of 53 prevalent conventional HD patients (CHD, 4 session/3x/week) of whom 33 converted to INHD (7-8 h/session, 3 x/week) while 20 remained on CHD (controls). In both groups, we applied liquid chromatography-mass spectrometry based metabolite profiling at baseline and at 1-year. We examined longitudinal changes in metabolites among those who remained on CHD as compared to those who converted to INHD using Wilcoxon tests with significance thresholds adjusted for multiple comparisons using a false discovery rate correction (FDR).

**Results:** Among 164 polar metabolites examined, none significantly differed from baseline to study end in the control group. 27 metabolites differed in the INHD group, the majority of which actually increased with INHD including several among the three branched chain amino acids; all FDR adjusted P<0.05 suggesting the observed changes were not a direct effect of additional solute clearance. By contrast, several...
established uremic solutes including p-cresol sulfate, indoxyl sulfate, trimethylamine N-oxide, and symmetric- and asymmetric-dimethylarginine did not change with extended dialysis treatment (all adjusted P > 0.05).

**Conclusions:** INHD significantly alters metabolic profile, however this may be a secondary effect of other metabolic and nutritional changes and not directly related to increased solute clearance. No change in several uremic solutes measured by our platform was observed.

**Funding:** NIDDK Support

### TH-P0730

**Fibroblast Growth Factor 21, a Novel Hormone, Is Associated with Lipid Metabolism and Renal Function in Nondialyzed Chronic Kidney Disease Patients**

Joao Victor Salgado, Maria Dalboni, Aluizio B. Carvalho, Maria Eugenia F. Canziani. *Discipline of Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil.*

**Background:** Fibroblast growth factor 21 (FGF-21), a member of the endocrine FGF subfamily, is secreted mainly by the liver with critical role in glucose and lipid homeostasis. High FGF-21 levels are associated with metabolic disorders and predict kidney disease progression in patients with type 2 diabetes. However, it is still unclear what factors are truly affecting FGF-21 levels in CKD patients.

**Methods:** This study is post hoc analysis which included ninety five CKD patients stage 2-5 (age ≥ 18 and <70 yrs). Serum concentrations of total FGF-21 were quantified by enzyme-linked immunosorbent assay.

**Results:** Circulating FGF-21 did not change significantly with regards to age, gender and diabetes mellitus, but was different between CKD stages (2-5) (p=0.023) with highest values detectable in stage 5. Serum FGF-21 values correlated negatively with glomerular filtration rate based on the CKD-EPI equation (r=-0.28, p=0.007) and positively with serum creatinine (r=0.29; p=0.006), proteinuria (r=-0.21; p=0.046), fasting glucose (r=-0.21; p=0.047), triglycerides (r=-0.36; p=0.001) and alkaline phosphate levels (r=-0.25; p=0.018).

Multiple linear regression analysis revealed that triglycerides (β coefficient 0.395; p=0.001), GFR (β coefficient -0.309; p=0.001) and alkaline phosphate (β coefficient 0.215; p=0.016) remained independently associated with circulating FGF-21 levels after adjustment for age, gender, BMI, and diabetes mellitus.

**Conclusions:** Circulating FGF-21 levels increase with CKD progression and appear to be associated with lipid rather than glucose metabolism.

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

### TH-P0731

**Total Energy Expenditure as Estimated by Activity Trackers and Its Relationship to Hemodialysis Adequacy**

Chantal Williams,1 Maggie Han,1 Anna Meyring-Westen,1 Xiaoling Ye,1 Marcee Bonner,1 Candace Young,1 Daniel Marsh,1 Peter Potkanov.1,2 *Research, Renal Research Inst, New York, NY; 1Nephrology, Icahn School of Medicine, New York, NY; 2Research, Renal Associates Baton Rouge, Baton Rouge, LA.*

**Background:** While Kt/Vurea and urea reduction ratio (URR) are widely used indicators of hemodialysis (HD) adequacy, their conceptual flaws have been recognized. This method of evaluating adequacy may put those with low body mass index (BMI) at risk of under- dialysis. Metabolic rate, not Vurea, has an impact on toxin generation. Consequently, it is proposed that total energy expenditure (TEE) and metabolic rate may be more appropriate factors in determining HD dose adequacy (Singer, AJKD 2000). To do this, TEE needs to be measured routinely. Using activity trackers, clinically acceptable TEE can now be obtained (Murakami et al. JAM 2016). The aim of this study is to determine if a correlation between TEE and Kt/V exists.

**Methods:** Chronic HD patients wore the Fitbit® Flex™, a commercially available activity tracker, for 5 weeks. TEE, expressed in average daily calories burned, was obtained. Equilibrated Kr/ Vurea was taken from monthly HD lab reports. Using linear regression, the activity tracker, for 5 weeks. TEE, expressed in average daily calories burned, was obtained.

**Results:** The relationship between TEE and eKt/V was assessed. Confounding factors, e.g. gender and BMI, were adjusted for.

**Results:** 44 patients, with an average age of 53.8 ± 11.3 years, BMI of 28.3 ± 7.7 kg/m², 50% male and 75% Black were enrolled. Mean TEE was 2221 ± 457 kcal. eKt/Vurea & TEE were not correlated in unadjusted (R² 0.0149) nor adjusted (R² 0.0153) analysis.

**Conclusions:** TEE is not related to eKt/Vurea and not reflected in the current assessment of HD adequacy. This may be a flaw as TEE is a proxy of determining metabolic toxin production compared to Vurea (Sridharan, Hemodialysis Int’l 2013). It is important to consider TEE when determining HD adequacy. Studies should further explore the relationship of TEE with generation of toxins. Eventually, TEE may be considered for HD dose prescription.

### TH-P0732

**Protein Intake Is Inversely Associated with Renal Function in Class III and IV CKD Patients: The PROGREDIR Study**

Alisson Diego Machado,1 Fernanda Silva Nogueira dos Anjos,1 Maria Alice Muniz Domingos,1 Maria del Carmen B. Molina,1 Dirce Marchioni,1 Paulo Lotufo,1 Isabelba M. Benseror,1 Silvia M. Titim,1 *Nephrology, Div. of Nephrology, Instituto de Nefrologia, Sao Paulo Univ; Sao Paulo, Brazil; 2Nephrology, Federal Univ of Espirito Santo, Vitoria, Espirito Santo, Brazil; 3Nephrology, Dept. of Public Health, Sao Paulo Univ, Sao Paulo, Brazil; 4Epidemiological and Clinical Research Center, Univ Hospital, Sao Paulo Univ, Sao Paulo, Brazil.*

**Background:** Benefits of protein restriction in CKD are still controversial. In addition, phosphorus intake could be a major confounding variable in that relation.

**Methods:** We evaluated the association between protein intake and baseline renal function in 412 class III and IV CKD patients (Progredir Study). A validated food frequency questionnaire was applied and nutrient intake was estimated using USDA Database, with adjustment for energy. Models on the association between protein intake (g/kg) and renal function were built, adjusting for cardiovascular risk factors and phosphorus intake deattenuated of protein intake with those >0.8g/kg/d after matching for age, sex and BMI.

**Results:** Tertiles of protein intake were associated to female sex, HDL, and inversely related to waist circumference (WC), BMI, hemoglobin, HOMA, alcohol, and eGFR. In linear regression, protein intake was related to log eGFR [B = -0.20 (0.32 -0.07), p=0.002], BMI, WC and DBP. After adjustments for age, sex, hypertension, diabetes, dyslipidemia, alcohol, calcic and phosphorus intake, protein intake remained significantly associated with eGFR [B=-0.16 (0.30 -0.02), p=0.03]. Only 44 (9.7%) participants reported an intake of protein <0.8 g/kg/d, the KDOQI guideline. When we compared participants reporting >0.8 g/kg/d with those reporting ≥8.6g/kg/d after matching for age, sex and BMI, those >8.6g/kg/d presented a lower eGFR [B=-4.42 (1.81 -2.7), p=0.003], even after adjustments [B=-3.93 (1.87 -1.03), p=0.04].

**Conclusions:** In this cross-sectional study, higher protein intake was significantly associated with a lower eGFR, independently of phosphorus intake and other confounding variables.

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

### TH-P0733

**The Relative Contribution of Lean and Fat Body Mass on Response to Erythropoiesis Stimulating Agents in Hemodialysis Patients**

Lucia Del Vecchio,1 Valeria Aicardi,1 Selena Longhi,1 Vincenzo La Milia,1 Giuseppe Pontoriero.1 *Nephrology and Dialysis, A Manzoni Hospital ASSIST Lecco, Lecco, Italy; 1Nephrology and Dialysis, Clinica INDISA, Santiago del Chile, Chile.*

**Background:** High-dose ESA are associated with malnutrition and inflammation; little is known about ESA response according to lean and fat body composition.

**Methods:** 90 prevalent hemodialysis patients (MF: 53.37, mean age 68.8± 14.01 years) on ESA therapy underwent nutritional assessment by Body Composition Monitoring. Hyporesponsiveness to ESA defined as ERI<14.8, (<75% percentile). Considering that LTI and FTTI values vary according to age and gender, we analyzed the data according to Lean Tissue Index (LTI) and Fat Tissue Index (FTI) percentiles relative to an age- and sex-matched healthy population.

**Results:** Twenty (22%) and 19 (21%) patients had LTI and FTTI values below the 10th percentile, respectively.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ERI ≤ 14.8</th>
<th>ERI &gt; 14.8</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>27.26 ± 4.45</td>
<td>25.78 ± 3.08</td>
<td>NS</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.65 ± 0.51</td>
<td>3.13 ± 0.59</td>
<td>0.002</td>
</tr>
<tr>
<td>Muscular brachial area (cm²)</td>
<td>55.97 ± 12.30</td>
<td>48.84 ± 15.74</td>
<td>0.078</td>
</tr>
<tr>
<td>Fat brachial area (cm²)</td>
<td>20.40 ± 13.98</td>
<td>18.34 ± 13.41</td>
<td>NS</td>
</tr>
<tr>
<td>LTI (kg/m²)</td>
<td>13.16 ± 2.99</td>
<td>13.10 ± 2.45</td>
<td>NS</td>
</tr>
<tr>
<td>FTTI (kg/m²)</td>
<td>13.15 ± 4.53</td>
<td>11.14 ± 3.59</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 1 shows main data for ERI category. Ferritin levels and TSAT were not significantly different. FTTI values were inversely related to lnERI (r²= 0.203, beta -0.30, p<0.005). Patients with FTTI values below the 10th percentile had higher ERI compared to the 10th-90th and > 90th percentile (19.23 18.05, 11.6 ± 9.84 and 7.44 ± 7.69, respectively; p=0.025).

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

| Underline represents presenting author. |
TH-PO735

Muscle Mass Assessment by Computed Tomography at Lumbar Vertebra: Agreement with Surrogate Methods in Chronic Kidney Disease Patients

Juliana Giglio,1 Maria A. Kamimura,2 Antonio C. Cordeiro,2 André Valente Bichels,2 Nivaldo Pinho,3 Nilian Souza,4 Carla Maria Avesani,4 1Rio de Janeiro State Univ, Brazil; 2Federal Univ of Sao Paulo, Brazil; 3Dante Pazzanese Inst of Cardiology, Brazil; 4National Inst of Cancer, Brazil.

Background: The assessment of muscle mass by computed tomography (CT) has been suggested as the preferred method for analyzing skeletal muscle mass (SMM). We wish to evaluate the agreement of SMM assessed by CT at L3 with surrogates of muscle mass in chronic kidney disease (CKD) patients.

Methods: This is an ongoing study including 30 nondialyzed CKD patients (age: 59 ± 9 years; 56% men; glomerular filtration rate: 12 (9 - 28) mL/min/1.73 m²; median and interquartile range). SMM was evaluated by CT at the third lumbar vertebra for analysis of total muscle cross-sectional area (cm²), through the following muscles quantification: rectus abdominus, abdominal (lateral and oblique), psoas, and paraspinal quadratus lumborum, erector spinae) using Slice-O-Matic software (v.4.3; Tomovision, Canada). Lean body mass by bioelectrical impedance (LBM-BIA) and anthropometry (skinfold thicknesses) (LBM-ANT), SMM calculated from Janssen and Baumgartner equation and midarm muscle circumference (MAMC) were selected as surrogates of muscle mass. Low muscle mass was defined as the lower P50 according to gender for each method.

Results: The kappa coefficients and sensitivity between SMM assessed by CT and surrogates (table 1) showed that the highest kappa coefficients for low muscle mass was observed for MAMC, followed by SMM-Baumgartner and LBM-ANT. The univariate association with SMM assessed by CT on the other hand were stronger for SMM-Baumgartner and LBM-ANT.

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

Underline represents presenting author.

263A
Results: Glucose intolerance was diagnosed in 50% of subjects, and obesity was found in 40%. Patients with hyperlipidemia and 20% of patients with correct glucose levels. The subjects with an android body type were more susceptible to glucose intolerance compared to those with the gynoid body type (p=0.004). Increased glucose blood levels were significantly correlated to cyclosporin A and tacrolimus levels (p=0.05). Furthermore, the patients with an android body type had lower eGFR compared with people with the correct body weight (p=0.004).

Conclusions: One of the basic directions for management of kidney transplant patients with glucose intolerance accompanied by abdominal obesity is reduction of their body weight combined with a physical activity adapted to patients' current physical fitness. Treatment with calcineurin inhibitors (IC), particularly tacrolimus, may be a predictor for diabetes in transplant patients; therefore they should be regularly monitored.

Funding: Private Foundation Support

TH-PO740

Obesity Paradox in Hemodialysis: Could Omega 3 Be the Link?
Ana Rita Mateus Martins,1 Inês Filipa Moreira,1 Ana Sofia Ferreira,1 Iolanda Nunes Godinho,1 Teresa Adragão,2 Andre L. Weigert,2 1Davita Obidos, Davita Portugal, Portugal; 2Nephrology Dept, Hospital Santa Cruz, Lisbon, Portugal.

Background: In advanced chronic kidney disease (CKD), obesity is paradoxically linked with greater survival. The potential mechanisms underlying the “obesity paradox” in CKD are still not well known. Omega3 intake has been linked to many beneficial impacts in cardiovascular (CV) health, affecting lipid profile, insulin resistance, platelet aggregation. Therefore, we postulate that patients (pts) who consume large amounts of fish may have more favorable CV status.

Methods: Observational study in 155 prevalent Portuguese HD pts. We obtained baseline demographic data, blood biochemistry, comorbidities and daily diet. In order to evaluate omega 3 incorporation in red blood cell (RBC) membranes, we used frozen RBC for FAME (fatty acid methyl esters) and obtained the percentage of eicosapentaenoic (EPA) and docosahexaenoic (DHA) in the FAME.

Results: In our cohort 79 were male, mean age was 67 years, 39% had diabetes (DM) and average time on HD was 73 months. Body index mass (BMI) was 26.4±6.4 kg/m². The follow up period time was 21 months and there were 71 CV events and 52 hospitalizations. BIM was associated with RBC omega3 incorporation (Pearson; p=0.045). Higher BIM was associated with a lower number of CV events (Pearson; p=0.038) and with lower hospitalization time (Pearson: p=0.04). In a multivariate analysis (linear regression), a higher EPA/DHA RBC incorporation was associated with a higher BMI and albumin, in a model adjusted to time on dialysis and age (Exp(B) 0.088; p=0.05; IC 95% 0.502 to 0.177). Larger hospitalization time was correlated with lower EPA/DHA RBC incorporation (linear regression: Exp(B)-5.7; p=0.023; IC 95% -10.52 to -0.91), in a model adjusted to DM and age. In a binary regression, CV event were associated with EPA/DHA RBC incorporation (Exp(B) -1.56; p<0.05; IC 95% -2.36 to 0.98), in a model adjusted to age, time on HD and DM.

Conclusions: There appears to be a consistent association between obesity and an higher omega3 incorporation with better clinical outcomes in our cohort of HD pts. This fact may suggest a possible explanation for the reverse obesity epidemiology in advanced CKD.

Funding: Private Foundation Support

TH-PO737

Fetuin-A and Calcinoprotein Particles Profiles in Patients on Peritoneal Dialysis
Thulita Moura Santos Braga, Erica Adelina Guimarães, Rodrigo Souza Adao, Wagner Dominguez, Fabiana Graciolli, Hugo Abensur, Rosilene M. Elia, Rosa M.A. Moyses. Nephrology, Faculty of Medicine, Univ of São Paulo, São Paulo, Brazil.

Background: Fetuin-A is an inhibitor of mineralization that complexes with mineral apatite precursors generating high molecular weight fetuin-A-containing calcinoproteins particles (CPP), which are associated with aortic stiffness and all-cause mortality. CKD patients usually have low fetuin-A and high CPP, although data in peritoneal dialysis (PD) patients are scarce.

Methods: Dialysate and serum fetuin-A levels were measured in 13 patients on PD. CPP were obtained from the supernatant after high-speed centrifugation samples in both serum and dialysate. The patients were submitted to peritoneal equilibrium test (PET) and nutritional status evaluation by bioimpedance analysis.

Results: Patients aged 43 ± 15 years (69.2% women), were on PD for a median time of 23 (4-70) months. Ninety-two patients (69.2%) were well nourished/mild nutritional risk and 8 (61.5%) patients were classified as high/high average (HEA) transporters. Fetuin-A was 352 ± 61g/L and CPP was 29.8 ± 11.8µg/mL. The serum CPP was higher in H/HA than in low/low average transporters (34.1 ± 10.7% vs. 13.5 ± 1.9%, p=0.034) and correlated with dialysis vintage (r=0.579, p=0.030). The dialysate loss of fetuin-A correlated with the loss of albumin (r=0.967, p=0.0001), glucose absorption (r=0.626, p=0.022), muscle mass (r=0.620, p=0.042), cell mass (r=0.627, p=0.039), bone mass (r=0.791, p=0.004), and the percentage of fat body (r=0.624, p=0.040).

Conclusions: The CPP appears to be higher in patients longer on PD, especially in those with H/HA transporters characteristic. Muscle reserves and nutrition status may influence this exchange.

Funding: Government Support - Non-U.S.

TH-PO738

Fibroblast Growth Factor21 Is Increased in CKD Patients and React with Protein Restriction

Background: Fibroblast growth factor21 (FGF21) is known to play a role in glucose and lipid metabolism. Recent report showed that FGF21 expression is increased in response to starvation and ketogenic diets. However, detailed mechanism and significance of FGF21 has not been elucidated in CKD. CKD patients are taking a protein-restricted diet to starvation and ketogenic diets. However, detailed mechanism and significance of FGF21 has not been elucidated in CKD. CKD patients are taking a protein-restricted diet as the treatment. This study was designed to investigate the regulation of FGF21 of CKD patients with low-protein diet and elucidate relation FGF21 and nutritional parameters.

Methods: We made a continuously survey of CKD patient characteristics and outcomes in Kochi prefecture (Western area of Japan) for 24 months. Patients of CKD (total N=442) were enrolled. Serum sample was collected and measured FGF21 by using an ELISA kits. In addition, serum creatinine, hemoglobin, albumin, calcium, phosphate, NTproBNP and CPP were obtained of the supernatant after high-speed centrifugation samples in both serum and dialysate. The patients were submitted to peritoneal equilibrium test (PET) and nutritional status evaluation by bioimpedance analysis.

Results: Fetuin-A and CPP were measured in 13 patients on PD. Fetuin-A was 352 ± 61g/L and CPP was 29.8 ± 11.8µg/mL. The serum CPP was higher in H/HA than in low/low average transporters (34.1 ± 10.7% vs. 13.5 ± 1.9%, p=0.034) and correlated with dialysis vintage (r=0.579, p=0.030). The dialysate loss of fetuin-A correlated with the loss of albumin (r=0.967, p=0.0001), glucose absorption (r=0.626, p=0.022), muscle mass (r=0.620, p=0.042), cell mass (r=0.627, p=0.039), bone mass (r=0.791, p=0.004), and the percentage of fat body (r=0.624, p=0.040).

Conclusions: The CPP appears to be higher in patients longer on PD, especially in those with H/HA transporters characteristic. Muscle reserves and nutrition status may influence this exchange.

Funding: Government Support - Non-U.S.
TH-PO742

Restriction of Protein Intake in Non-Dialysis Chronic Kidney Disease Patients May Be Not Beneficial when a Renal Dietitian Is Not Available

Pablo Molina,1 Sandra Beltrán,1 Jose Roldan Ibarra,2 Marco Montomoli,1 Belen Vizzaino,1 Veronica Escudero,2 Cristina Castro,1 Jonay Pantoyo Perez,1 Ana Avila,1 Julia Kanter,1 Luis M. Pallardo,1 Jose L. Gorriz.1 Nephrology, Dr Peset Univ Hospital, Spain;2 Dietetic Unit, Alcar Teria, Spain.

Background: Due to safety concerns, CKD patients who are on a low-protein diet (LPD: 0.60-0.80 g/kg/d), should be carefully monitored. However, few patients receive dietary counseling before dialysis, and whether LPD without dietitian counseling is beneficial or risky remains unknown. We tested the hypothesis that LPD when an onsite renal dietitian is not available is independently associated with poor outcomes in CKD population.

Methods: The relation between dietary protein intake (DPI) and its change during the first 6 months, and mortality and kidney progression were examined in a 3-year cohort of 493 clinically stable patients with CKD stages 4-5 with a baseline DPI≥0.60 g/kg/d, using multivariate Cox models. General advice was given regarding reducing DPI, but a dietician did not routinely assess the patients. DPI was estimated by using 24-h urine nitrogen according to Maroni’s formula.

Results: At baseline, the mean DPI was 0.89±0.20 g/kg/d. After a median follow-up of 31 months, there were 72 deaths and 151 required dialysis. The best survival was associated with DPI<1.0 g/kg/d, whereas DPI between 0.6 to 0.8 g/kg/d was associated with greater mortality. A decrease in DPI during the first 6 months was associated with greater death risks in the subsequent 30 months, whereas an increase in DPI tended to correlate with better survival. DPI did not predict renal progression.

Conclusions: LPD or decrease in DPI over time was associated with increased risk for death in ND-CKD patients in which counseling with a renal dietitian was not available, with no benefits on kidney progression. These results reinforce the need for predialysis dietitian care, especially when LPD is prescribed.

Funding: Private Foundation Support

TH-PO744

Psoas Muscle Area Predicts Mortality among Incident Peritoneal Dialysis Patients

Yu Honda, Nanae Matsuo, Yukio Maruyama, Emi Kimoto, Yasuyuki Nakada, Masatsugu Nakao, Yudo Tanno, Ichiro Ohkido, Keitaro Yokoyama, Takashi Yokoo. Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.

Background: Cardiovascular disease (CVD) is common among chronic kidney disease (CKD) patients. Malnutrition, inflammation and atherosclerosis (MIA) syndrome was reported as one of the mechanisms of a high prevalence of CVD in this population. Since it was also associated with mortality, to assess the risk of MIA syndrome is an important issue in CKD patients. Body composition, especially estimated muscle mass, has been recognized as a useful nutritional marker. Total psoas muscle area (PMA) measured by computed tomography (CT) scan is one of the methods to estimate muscle mass. Although its usefulness already has been reported among non-renal patients, studies conducted in dialysis patients are limited. The aim of this study was to evaluate whether PMA at the start of peritoneal dialysis (PD) was associated with clinical parameters and mortality.

Methods: This study included 36 male patients (59±11 years, diabetes 36%) who initiated PD between 2007 and 2008. We evaluated the associations between PMA at the third lumbar vertebra (L3) level measured by CT scan and clinical parameters. We divided the patients into two groups based on the median PMA at the L3 level and compared each cumulative survival rates using Kaplan-Meier method.

Results: The mean PMA at the L3 level was 18.41 cm². PMA at the L3 level was inversely correlated with serum albumin (rho=-0.352, P<0.05) and positively with body weight (rho=0.514, P<0.01) and body mass index (rho=0.454, P<0.05). 6-year cumulative survival rates were significantly lower in the low PMA group than in the high PMA group (P<0.05).

Conclusions: PMA at the L3 level was related to mortality. We suggest that PMA assessed on CT is the useful parameter of body composition among incident PD patients.

TH-PO743

α Keto analogues of Amino Acids in Patients with Chronic Kidney Disease: Experience of a Nutritional Care Center

Rocio Urbina, Silvia Moran, Julia Nava, Verónica Figueroa, Rafael Montufar. Centro de Atención Nutricional, Fresniius Kabi México, Ciudad de México, Distrito Federal, Mexico.

Background: A low protein diet (LPD) supplemented with alpha keto analogues of amino acids (AKAAA) has a metabolic stabilizing effect, which prolongs the pre-dialysis stage and improves the quality of life.

Methods: The effects of LPD supplemented with AKAAA (sLPD) were assessed the body composition and renal function stage in patients in the stages 3, 4 and 5 of chronic kidney disease. This was a retrospective, longitudinal study at the Fresniius Kabi México’s Nutritional Care Center (NCC); records were reviewed with AKAAA treatment periods >6 months (1 tablet per 5 to 7 kg). LPD (0.5 to 0.6 g/kg of ideal body weight). The variables measured were; anthropology, body composition, dynamometry, blood pressure, laboratory test and creatinine clearance at 30,60 and 180 days. The information was captured and evaluated by personnel unrelated to the NCC, the software SPSS version 20 was used in the statistics evaluation.

Results: 210 cases were included; the mean age was 63.5 years, 119 male patients and 91 female patients. A cut-off was performed after 6 months of sLPD treatment, the results were 39 patients in stage 3, 105 patients in stage 4 and 66 patients in stage 5; body weight, fat mass and fat-free mass decreased significantly; an increase in muscle strength was observed; serum albumin and total protein did not change. Blood pressure showed no difference; urea, creatinine and creatinine clearance, show a decrease levels showed significant decreases (p<0.0001); measures of uric acid and Ca/P declined during the study. LPD: Supplemented with nutritional therapy AKAAA, allowed address metabolic abnormalities of uric acid, calcium, phosphorus, glucose, cholesterol and triglycerides. No alterations were observed in nutritional status according to anthropometric and biochemical parameters. It is proposed that this procedure may be a link in the model of comprehensive care of patients with CKD.

Funding: Pharmaceutical Company Support - Fresniius Kabi

TH-PO745

Serum Albumin Concentration, Estimated Glomerular Filtration Rate, and Survival among 1999-2010 NHANES Participants

Amanda R. Tortorici1 Elani Streja,1 Melissa Sooho,1 Daniel L. Gillen,1 Connie Rhee,1 Keith C. Norris,2 Kamyar Kalantar-Zadeh.1,1 UC Irvine; 2 UCLA.

Background: As a potential strong predictor of longevity in the general population and in those with chronic kidney disease, we sought to examine whether higher serum albumin (Alb) levels are associated with greater survival in the nationally representative NHANES cohort.

Methods: We identified 31,274 participants from the 1999-2010 continuous NHANES survey who had available Alb measurements and laboratory values for calculation of eGFR, as well as survival data. Follow up time began the date after Alb measurement until December 31, 2011. We analyzed the association of Alb (<4.2, 4.2-<4.4 and ≥4.4 g/dL) with mortality across strata of eGFR (<60, 60-<90, and ≥90 mL/min/1.73m²) using Cox proportional hazards models adjusted for age, sex, race, and education.

Results: The mean±SD age of the cohort was 48±20 years, among whom 52% were female, 20% were African-American, 22% were Mexican-American, and 7% were other Hispanic American. Across all eGFR strata, participants with Alb levels >4.2 g/dL (n=11,384 people) had higher mortality rates compared to the reference group (Alb 4.2-<4.4 g/dL, n=10,793 people). In contrast, participants with Alb levels <4.2 g/dL, and eGFR 60-<90 mL/min/1.73m² (n=1,911) experienced lower rates. See figure for adjusted hazard ratios.

Funding: Pharmaceutical Company Support - Fresniius Kabi
Conclusions: Among 1999-2010 continuous NHANES participants, lower Alb levels were associated with 40% to 80% greater mortality risk irrespective of the eGFR values.

Funding: NIDDK Support

TH-PO746

Association of Pre-ESRD Uric Acid with Post-ESRD Mortality: A Transition of Care in CKD Study

vanessa a. ravel,1 connie rhee,1 elani streja,1 yoshitsugu obi,1 jason chou,1 melissa soohtoo,1 daniel l. gillen,1 csaba p. kovesdy,1 kamyar kalantar-zadeh.1 1uc irvine; 2univ of tenn.

Background: Although uric acid is commonly elevated in chronic kidney disease (CKD) patients, it has only recently been postulated as a possible risk factor contributing to the progression of CKD. To date, most studies have focused on linking pre-ESRD uric acid to adverse pre-ESRD outcomes. We sought to examine the association between pre-ESRD serum uric acid and post-ESRD mortality among US veterans.

Methods: From a cohort of US veterans who transitioned to dialysis between 10/2007-09/2011, we identified 6,086 patients with a pre-dialysis uric acid measurement in the 6 months before transitioning to ESRD. We examined pre-ESRD uric acid as a predictor of all-cause mortality within the first 3 months post-transition using Cox proportional hazards models with adjustment for case-mix covariates, BMI at prior to initiation and additional adjustments for laboratory values and eGFR (both 6-month averaged and last available before dialysis initiation).

Results: The mean age of the cohort was 67±11 years old and included 2% females, 71% diabetics, and 34% African Americans. The 6-month prelude uric acid average was 7.1 mg/dL, of which 64% were <7 mg/dL, 18% were 7-8 mg/dL and 18% were >8 mg/dL. Overall, 9.3% of patients died during the first 3 months on dialysis. The 50th percentile (IQR) of uric acid from 6 months before transitioning to ESRD was 6.07 ± 2.03 mg/dL. At baseline, median (IQR) of uric acid with CLurea was 0.94 (0.77, 1.14) g/kg/day. In the fully adjusted model, baseline nPCR< 0.7 g/kg/day was significantly associated with higher mortality, and nPCR > 1.1 g/kg/day was significantly associated with better survival compared to the reference (0.8-0.9 g/kg/day). Finally, a decrease in nPCR < 0.1 g/kg/day was associated with higher mortality whereas an increase in nPCR< 0.5 g/kg/day was associated with better survival.

Conclusions: Among incident HD patients, patients with low nPCR accounting for CLurea, and those who decreased in nPCR over the first 6 months of HD had a higher risk of death. Additional studies are needed to investigate the differences in mortality risk prediction for nPCR with and without factoring CLurea.

Funding: NIDDK Support

TH-PO747

Associations of Dietary Protein Intake with Mortality in Incident Hemodialysis Patients: Using Normalized Protein Catabolic Rate Accounting for Residual Kidney Function

rieko eriguchi, yoshitsugu obi, elani streja, connie rhee, melissa soohtoo, kamyar kalantar-zadeh. UC Irvine.

Background: There are inconsistent reports on the association of normalized protein catabolic rate (nPCR), an index of dietary protein intake, with mortality among hemodialysis patients. This discrepancy may be partly due to not accounting for residual renal urea clearance (CLurea) among hemodialysis patients when evaluating nPCR.

Methods: Among 36,713 incident hemodialysis (HD) patients in a large dialysis organization from 1/2007 to 12/2011, we examined baseline and change in nPCR during the first 6 months of dialysis accounting for residual kidney function. Cox proportional hazard models with adjustment for case-mix covariates and markers of the malnutrition-inflammation cachexia syndrome (MICS) were used to examine associations of these nPCR markers with mortality.

Results: Patients were 62±15 years old, 37% female, 28% African-American, and 47% diabetics. At baseline, median (IQR) of nPCR with CLurea was 0.94 (0.77, 1.14) g/kg/day. In the fully adjusted model, baseline nPCR< 0.7 g/kg/day was significantly associated with higher mortality, and nPCR > 1.1 g/kg/day was significantly associated with better survival compared to the reference (0.8-0.9 g/kg/day). Finally, a decrease in nPCR < 0.1 g/kg/day was associated with higher mortality whereas an increase in nPCR< 0.5 g/kg/day was associated with better survival.

Conclusions: Among incident HD patients, patients with low nPCR accounting for CLurea, and those who decreased in nPCR over the first 6 months of HD had a higher risk of death. Additional studies are needed to investigate the differences in mortality risk prediction for nPCR with and without factoring CLurea.

Funding: NIDDK Support

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

266A
Table: Selection of Known Metabolites Associated with Dietary Protein Intake in the MDRD Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pathway</th>
<th>β-coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>eGFR (mL/min/1.73m²)</td>
<td>-0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>eGFR (mL/min/1.73m²)</td>
<td>-0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>eGFR (mL/min/1.73m²)</td>
<td>0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>eGFR (mL/min/1.73m²)</td>
<td>0.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Conclusions: Among CKD patients, an untargeted metabolomic platform identified multiple pathways and metabolites affected by randomized groups of dietary protein consumption. Further research is necessary to characterize unknown compounds and evaluate the ability of these metabolites to predict CKD progression.

Funding: NIDDK Support

TH-PO749
Dietary Modifications for Adults with Chronic Kidney Disease: Meta-Analysis of Randomized Trials
Sugtonia Palmer, Katrina L. Campbell, 2 Jonathan C. Craig, 3 David W. Johnson, 4 Marinella Ruoso, 4 Allison Tong, 3 Giovanni F.M. Strippoli, 1,4 1 Univesity of Otgo Chutchison; 2 Univesity of Queensland; 3 Univesity of Sydney; 4 Diavem; 5 Univesity of Bari.

Background: Dietary changes are routinely recommended in patients with CKD on the basis of randomized evidence in the general population and non-randomized studies in CKD that suggest healthy eating patterns may prevent cardiovascular events (CVEs) and mortality. Patients with CKD have prioritized dietary interventions as an important treatment uncertainty. This systematic review aimed to assess the benefits of dietary modification in patients with CKD.

Methods: Meta-analysis of randomized clinical trials (RCTs) of any dietary modification adults in CKD was conducted. Electronic databases were searched in January 2016 without language restriction. Evidence quality was assessed using GRADE.

Results: The meta-analysis included 10 RCTs (874 patients) of dietary counseling, Mediterranean diet, low-carbohydrate, polyphenol-enriched diet, or increased fruit and vegetable intake for 12 months on average. Evidence quality was very low. Dietary counseling significantly lowered diastolic blood pressure (-8.6 mmHg, CI -13.3 to -3.9) but not systolic blood pressure (-6.73, CI -16.9 to 3.44). A Mediterranean diet lowered serum LDL cholesterol levels by 1.00 mmol/l (CI -3.26 to 1.26) and increased serum albumin levels by 0.60 g/l (CI 0.31-1.09). Increased fruit and vegetable intake lowered systolic blood pressure by 7.10 mmHg (CI -9.60 to -4.60), while effects on diastolic blood pressure were not available. A carbohydrate-restricted diet with higher olive oil intake and lower red meat content reduced risk of serum creatinine doubling (RR 0.53, CI 0.33-0.86).

Quality of life outcomes were sparse. Dietary modification had uncertain effects on ESKD, CKD mortality, and mortality.

Conclusions: Dietary interventions in adults with CKD have potentially beneficial effects on chronic disease risk factors including serum cholesterol, blood pressure, and serum albumin levels, but have uncertain effects on patient-level outcomes such as CVEs, ESKD, mortality, and quality of life.

TH-PO750
Reproducibility of a Test-Battery for Physical Performance and Protein-Energy Wasting in Hemodialysis Patients
Manouk Dam, 1 Peter Jm Weijis, 2 Caroline Douma, 2 Krista C. van Jaarsveld, 3,4,5 1 Nutrition and Dietetics, VU University Medical Center, Amsterdam, Netherlands; 2 Nephrology, Spaarne Gasthuis, Hoofddorp, Netherlands; 3 Nephrology, VU University Medical Center, Amsterdam, Netherlands.

Background: The assessment of physical performance (PP) and protein-energy wasting (PEW) is hampered by large variability and controversy between researchers about which test to use. Combining different tests is advocated, but variation in test outcomes has not been studied. We studied reproducibility of a test-battery for PP and PEW in HD pts.

Methods: Two measurements with 1-2 month interval, without interventions in between, were performed by one investigator in 33 HD pts (2-4xs/wk, 3-5 hr). PP was measured by the short physical performance battery (SPPB: gait speed, chair rises, balance), 6-min walk test, handgrip strength and 7-day physical activity monitor (PAM). PEW was measured by the visual analogue scale for appetite (V AS), subjective global assessment (SGA), mid-upper arm muscle circumference (MUAMC), fat free and fat mass measured by bio-electrical impedance. Reproducibility was assessed by paired t-tests and intraclass correlation coefficients (ICC).

Results: No differences were found between the 1st and 2nd measurement, apart from a slight increase in the SPPB.

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

TH-PO751
Prediction of LBM Using One Day Urinary Creatinine Excretion and Creatinine Clearance Rate in Non-Dialysis CKD Patients
Tomohito Matsunaga, Kidney Center, Eijinkai Hospital, Osaki, Miyagi, Japan.

Background: The assessment of lean body mass (LBM) is quite important to monitor the nutrition status of CKD patients. And it is well known that one day urinary creatinine excretion (UCE) reflects LBM (muscle mass) strongly. The purpose of this study is to predict LBM using one day urinary creatinine excretion and creatinine clearance rate in non-dialysis CKD patients.

Methods: UCE were measured by one day urinary collection in 35 non-dialysis CKD3-5 patients (27 males, 8 females; mean age 68.4±7.7 years; 12 DM patients). Ccr was calculated by UCE and Serum Creatinine, not collected body surface area. LBM was measured using BIA (inbody 3.6).

Results: The mean levels of UCE, Ccr and BH (Body Height) were 0.969±0.215 g/day, 27.6±12.27 cm/min and 1.62±0.080. LBM (54.54±7.55kg) was correlated with UCE and Ccr (r=0.802 p<0.01 and r=0.903 p<0.01, respectively) not correlated with Ccr. Multiple linear regression analysis showed that LBM was correlated with UCE, BH and Ccr (r=0.960 p<0.01). The obtained equation of regression was as follows: estimated LBM = 17.00 x UCE + 52.77 x BH − 0.09 x Ccr − 53.95. Estimated LBM was significantly correlated with measured by BIA (r=0.922, p<0.01).

Conclusions: These findings suggest that LBM can be predicted using UCE, BH and Ccr in non-dialysis CKD patient.

TH-PO752
Acute Effects of Nutritional Supplementation during Hemodialysis on Hemodynamics and Symptoms
Brandon Kistler, 1 Annabel Biruete, 1 Jin Rhee, 1 Peter J. Fitch, 1 Kevin Heffernan, 1 Karen Chapman-Nowakowski, 2 Talat Alp Kiziler, 2 Kon Wieland, 2 1 Ball State Univ, Muncie, IN; 2 Univ of Illinois, Urbana, IL, 3 Syracuse Univ, Syracuse, NY; 4 Vanderbilt Univ, Nashville, TN.

Background: Due to the potential for hemodynamic instability following eating during hemodialysis (HD), many clinics have restricted food in favor of oral nutritional supplements (ONS). However, the effect of ONS on treatment hemodynamics has not been examined.

Methods: 11 HD patients (47±13 years, 73% male, 64% African American) underwent resting measures of cardiac function (ejection fraction, EF) and vascular structure (carotid intima-media thickness) via ultrasound, vascular function (aortic pulse wave velocity, PWV) and augmentation index, Aix) via tonometry, blood pressure, (BP), and autonomic function (heart rate variability, HRV and baroreceptor sensitivity, BRS) by plethysmography, following standard HD treatment with and without ONS (Noreo, Abbott). Beat-to-beat hemodynamics, gastrointestinal (GI) symptoms, and efficiency were measured throughout each treatment. The delta BP (lowest BP after ONS – Pre-ONS BP) was correlated with descriptive variables.

Results: There was no interaction between sessions for any hemodynamic measure (p<0.05 for all), but cardiac output (p=0.04) and heart rate (p=0.05) were higher throughout the ONS session. GI symptoms (Reflux, Abdominal Pain, Constipation, Diarrhea) and the reduction ratio of i2-microglobulin (O37, 89 ± 15.63% vs. HD, 48.97 ± 18.40%) did not significantly differ between ONS and HD (p<0.05 for all). Aortic PWV (90.91±1.16 ms), Aix (21.1±10.9%, albumin (4.06±0.35 g/dl), IMT (0.62±0.13mm), EF (61.1±15.6%), and ultrafiltration (8.8±2.2 ml/kg/min) were not associated with delta BP following ONS. However, BRS (Down-Down, 9.30±7.08 ms/mmHg) was correlated with the change in systolic BP and mean BP (r=0.79 and 0.71, respectively; p<0.05).

Conclusions: We found minimal hemodynamic alterations, but no significant changes in GI symptoms or efficiency in response to a renal specific ONS during HD. Measures of autonomic function were associated with the maximum change in BP following ONS and should be a future target of research.

Funding: Private Foundation Support
Short-Term Potato Intake and Endothelial Function  

Lea Borgi, John P. Forman. Medicine, Renal Div, Brigham and Women’s Hospital, Boston, MA.

Background: Recently, potatoes have been reintroduced into food packages for the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), and restrictions on potatoes from school lunches have been lifted. In their report, the Institute of Medicine stated that evidence for adverse health effects of potatoes was lacking. However, we published that increasing consumption of boiled, baked or mashed potatoes was independently associated with an increased risk of developing hypertension in three large prospective cohort studies of US women and men. The mechanisms underlying this association are still unclear. We hypothesized that the association of potatoes with hypertension may be mediated by endothelial dysfunction.

Methods: We performed a cross-sectional analysis using data obtained from the NIH-funded ongoing Modifiable Effectors of Renin System Activation Treatment Evaluation (MENDEL ATP) trial. Diet and end-organ dependent vasodilation (EDV) (a measure of endothelial function using brachial artery ultrasound) were ascertained at baseline. We used multivariable linear regression to analyze the independent association of self-reported potato intake and EDV while controlling for multiple potential confounders.

Results: By the end of the trial, 269 participants underwent brachial artery ultrasound and reported potato intake over the previous day preceding EDV measurements. Compared with participants with no intake of potatoes, those who consumed one or more servings the day before had significantly worse endothelial function after adjusting for potential confounders (difference in EDV ~1.7%, p-value<0.01). By comparison, every 10 year increase in age was associated with a 1.2% lower EDV, indicating the important magnitude of the association between potatoes and EDV.

Conclusions: We found that short-term potato intake was associated with substantially worse endothelial function. These results support the hypothesis that endothelial dysfunction may be a potential mechanism underlying the association of potatoes with hypertension.

ACF-TEI, a Novel Oral Uremic Toxin Adsorbent, Has Potent Adsorption Profiles and in vivo Effects on reducing serum IS.

Methods: As for the in vitro adsorption profiles of ACF-TEI, we examined the adsorption of indole, the precursor of IS in the intestinal tract, and digestive enzymes. To evaluate the in vivo effects, we orally administered ACF-TEI in normal mice and CKD model (bilateral nephrectomized and renal artery ligated) rats, and measured serum IS concentrations.

Results: Compared with AST-120, ACF-TEI showed more potent capacity and speed in adsorbing indole, whereas it had a low capacity to adsorb digestive enzymes to the same extent. In normal mice, ACF-TEI showed a higher effect of reducing serum IS than that of AST-120. Moreover, administered in CKD rats, ACF-TEI dose-dependently reduced the serum IS at lower doses than those of AST-120.

Conclusions: The adsorption capacity and efficiency of ACF-TEI were superior to AST-120. In addition, it was confirmed that ACF-TEI reduced the serum IS concentrations at lower doses than those of AST-120 in the CKD models. Thus, ACF-TEI is expected to show more beneficial effects than AST-120 in clinical.
**Effect of Diet Modification from 65% Animal-Based Protein to 70% Plant-Based Protein on Trimethylamine N-oxide (TMAO) Levels in Subjects with Stage 3-4 CKD**

**Background:** Elevated levels of circulating pro-atherogenic uremic solutes, particularly trimethylamine N-oxide (TMAO), have been implicated in cardiovascular disease development in patients with chronic kidney disease (CKD). TMAO and precursor choline are generated from dietary phosphatidylcholine which is abundant in animal-derived high-fat foods.

**Methods:** We conducted a dietary intervention study in 13 subjects with stage 3-4 CKD (median GFR=26 (IQR 14.7) mL/min/1.73m²). Protein in the baseline diet was 65% animal-based. During the 4-week study, subjects consumed a diet with 70% of dietary protein from plants and 30% of protein from animals (meat, dairy, eggs), provided by the Indiana Clinical Research Institute. Plasma samples at baseline (week 0), and at 2 and 4 weeks on the study diet were analyzed for levels of TMAO and choline.

**Results:** Mean concentrations of both choline and TMAO trended down following diet modification; however these changes did not reach statistical significance. Concentrations of choline at 0, 2, and 4 weeks were 2.7±1.3 μg/mL, 2.5±1.4 μg/mL, and 2.2±0.6 μg/mL (p=0.22). Concentrations of TMAO at 0, 2, and 4 weeks were 2.8±3.7 μg/mL, 1.5±1.0 μg/mL, and 1.7±0.9 μg/mL (p=0.29).

**Conclusions:** The results of this small pilot study in patients with CKD suggest that diet modification with 70% of dietary protein from plant sources may reduce systemic concentrations of TMAO, which may be associated with increased cardiovascular risk. A larger study is warranted in order to determine if modest dietary modification can reduce TMAO concentrations in this population or if non-dietary sources of TMAO in uraemia or decreased clearance prevail regardless of diet.

**Funding:** NIDDK Support, Other NIH Support - NCATS KL2 TR000421, Private Foundation Support

**TH-PO759**

**Implementation of a Motivational Interviewing Program to Improve Patient Engagement within a Large Dialysis Organization**

**Background:** Engaging Patients In their Care (EPIC) is a program within a large dialysis organization (LDO) that provides training in patient-centered motivational interviewing (MI) techniques to dietitians, with the goal of fostering improved patient engagement. A small-scale pilot of the program demonstrated improvements in dietitians’ proficiency in MI techniques and measurable improvements in measures of patients’ phosphorus control following program completion. However, the complexity of the skill-set and the commitment level needed to build and maintain proficiency in MI are significant and we sought to assess whether the program could be successfully implemented on a larger scale across the LDO.

**Methods:** The EPIC program was launched LDO-wide in 2015, reaching over 1800 dietitians. Program participation involved attendance at a 1-day intensive MI training session and recorded skill-building sessions were conducted with MI experts before and after training completion. Certified MI experts used a validated, standardized assessment system to objectively measure dietitians’ proficiency in MI techniques of partnering, evoking, expressing empathy, guiding, supporting activation, reflection, and strategically responding to change talk. Total MI Scores (a combination of 7 global scores) at baseline and after program completion were compared using paired-samples t-tests.

**Results:** Among dietitians who have completed the MI training workshop and all skill-building sessions to date (N = 639), total MI scores were significantly higher following program completion compared to baseline. Mean total MI scores were 4.35 [SD, 0.84] at baseline and 4.84 [SD, 0.89] after program completion (t = -10.12, P < 0.001, Wilcoxon Signed-Rank test z = -5.240, P = <0.001).

**Conclusions:** Our findings demonstrate that a complex MI-based program can be implemented effectively across an LDO, with participating dietitians achieving levels of MI proficiency similar to those observed in the program pilot. Analyses to evaluate the impact of LDO-wide program implementation on patient engagement and clinical outcomes are ongoing.

**Funding:** Pharmaceutical Company Support - DaVita Inc

**TH-PO761**

**Impact of Low-Protein Diet on Protein-Energy Wasting in Diabetic CKD Patients**

**Background:** Nutritional impact of low-protein diet (LPD) in diabetics with CKD (DM) is uncertain. We evaluated the effects of LPD supplemented with ketocoids on protein-energy wasting (PEW) in DM with moderate to advanced CKD.

**Methods:** 81 DM and 116 controls (CON) with CKD stages 3/5 were prescribed a LPD (0.5-0.6 g protein/kg/d), normal-high energy (30-35 kcal/kg/d) supplemented with ketocoids (Ketosteride®, 1 tab/5.7 kg/d) for at least 6 months. Metabolic status, nutrition and body composition were evaluated.

**Results:** Mean C-Alb change was not significantly different between the IL-1ra and placebo groups (p=0.29). Concentrations of TMAO at 0, 2, and 4 weeks were 2.8±3.7 μg/mL, 1.5±1.0 μg/mL, and 1.7±0.9 μg/mL (p=0.29).

**Conclusions:** Administration of the immunosuppressant IL-1ra did not affect carbamylation load or levels of several uremic solutes despite significant decrease in inflammatory markers. In ESRD, inflammation may have a limited role in protein carbamylation burden. Further studies of longer duration and larger sample size are needed to confirm these findings.

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

**TH-PO758**

**Administration of IL-1ra Does Not Affect Carbamylation Load in Hemodialysis Patients**

**Background:** Protein carbamylation is strongly associated with cardiovascular complications in kidney disease and is a predictor of mortality in ESRD. This post-translational protein modification is largely driven by the nonenzymatic binding of isocyanate derived from urea. Recent reports also suggest inflammation as an alternative driver of carbamylation via myeloperoxidase-mediated catalysis of thiocyanate. We set out to determine whether anti-inflammatory therapy using an interleukin 1 receptor antagonist (IL-1ra) altered carbamylation burden as measured by carbamylated albumin (C-Alb) levels in ESRD patients.

**Methods:** This was a pilot randomized placebo-controlled trial of the administration of IL-1ra in chronically infirmed hemodialysis patients. 22 patients were randomly assigned to receive 100 mg of IL-1ra or placebo (1:1) for 4 weeks, and 14 completed the trial. The primary outcome was percent change in C-Alb and the secondary outcomes were changes in uric acid and thiocyanate levels in ESRD patients.

**Results:** The mean C-Alb change was not significantly different between the IL-1ra and placebo groups using ANCOVA models (p=0.89). This is despite a significant reduction in hsCRP and IL-6 in the IL-1ra arm. Furthermore there were no significant trends in several established uremic solutes including p-cresol sulfate, indoxyl sulfate, trimethylamine-N-oxide, symmetric- and asymmetric dimethylarginine, kynurenine and kynurenic acid.

**Conclusions:** Among hypertensive patients without a history of major cardiovascular diseases, folic acid supplementation could reduce the mortality risk associated with heavy proteinuria.

**Funding:** Nutrition and Metabolism in CKD and ESRD
**Results:** DM and CON were comparable for gender (Male 59 vs 55%), age (66±9 vs 63±8 y) and renal function (eGFR 23±13 vs 24±13 mL/min). Serum area (0.6 mo: DM 131±58 to 105±49 mg/dL, p<0.05; CON 115±52 to 88±36, p<0.05) and phosphate (0.6 mo: DM 4.5±1.3 to 4.1±1.2 mg/dL, p=0.07; CON 4.3±1.0 to 3.7±0.8, p<0.05) reduced; fasting glucose declined in DM (0.6 mo: 122±54 to 103±29 mg/dL, p<0.05) without changes in insulin. These effects were maintained after 3 years. Serum albumin did not change in short (DM 3.7±0.6 to 3.8±0.4 mg/dL; CON 4.0±0.6 to 4.0±0.4) and long-term. Body weight (BW) (DM 68.9±14.3 kg; CON 66.6±15.1) then declined (6 mo: DM to 65.1±1.2 kg, p<0.05; CON to 64.1±1.5, p<0.05) and then remained stable for 3 years. BW decline was associated with reduction of body water (-1.1 L, p<0.05), fat mass (FM, -1 kg, p<0.05) at 6 months; after 3 years BM was reduced (-2.2 kg, p<0.05). Low BMI (<23 kg/m²) and albumin (<3.8 g/dL) were present in 30% patients at baseline and did not change during the study; cholesterol (<100 mg/dL) was always normal in all patients; low FM (<10%) prevalence raised by: DM 14 to 60%, p<0.05; CON, 5% to 39%, p<0.05. Muscle strength (DM 20.8±7.9 kg; CON 25.0±7.8) did not change at 6 month and 3 year time.

**Conclusions:** In DM with moderate to advanced CKD a low protein ketodiet while allowing adequate metabolic control, causes sudden BW decline which remains stable thereafter; muscle mass and muscle fitness remain stable too, while fat mass declines. No differences vs. non-diabetic CKD controls are observed.

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**TH-PO763**

**Effect of High Protein Meals during Hemodialysis on Intradialytic Hypotension**

**Method:** 18 HD patients (N=9) group were recruited from 2 shifts (~10AM-2PM, MWF&FTS) at 1 dialysis center for a 9-wk, non-randomized, parallel arm study. Patients received meals with 30g PRO & KDOQI guidelines for Na, K, P, & fluid, or a control social meal. Differences within groups for 2mo pre-study vs during study were determined by Wilcoxon signed-rank/paired t-test, and between group differences were determined by Wilcoxon rank-sum/unordered t-test.

**Results:** Patients were 62±16y old, 55% females, and had dialyzed for 3.4±2.6 y. In the pre-study, there were 4 SH in 3 patients over 25 dialysis sessions pre-study and 12 SH in 4 patients over 25 dialysis sessions during study; in controls, there was 1 SH in 1 patient pre-study and 5 SH in 4 patients during study. Change between pre-study and during study SH was not significant for either group, both p>0.2. Average lowest MAP was not different, Fig. When asked “How interested would you be in receiving nutritious meals during dialysis?” 70% of patients responded ≥4 (5-pt scale, “very interested; p=NS between groups).

**Conclusions:** These pilot data suggest that meals during HD do not increase the frequency of SH, and patients generally have positive attitudes towards receiving meals. Larger, long-term studies are needed to confirm these results along with effects on nutritional and clinical outcomes.

**Funding:** NIDDK Support, Other NIH Support - UL1TR001108

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**TH-PO767**

**Effect of Low Phosphate Diet Education and Phosphate Binder Education among Maintenance Hemodialysis Patients: A Randomized Controlled Trial**

**Background:** Multiple factors contribute to the high prevalence of fractures in patients undergoing maintenance hemodialysis due to the effects of malnutrition and inflammation, low bone mass, and correlated high risk of falls. There is no proven effective intervention to reduce the risk of fractures in this population. The aim of this study was to evaluate the effect of diet and phosphate binder education on fracture incidence in a hemodialysis population.

**Methods:** We randomized 70 patients into education group (n=48) and control group (n=22). Phosphate binder intake education was given by pharmacists, and nutritional consultation by dietitians. Drug compliance was assessed by Morisky Medication Adherence Scale-4 (MMAS-4) and patients’ self reported dosage of prescribed phosphate binder. The patients’ knowledge of when to take phosphate binder was assessed by questionnaire and nutritional status by using Patient-Generated Subjective Global Assessment (PG-SGA).

**Results:** Baseline characteristics of two groups were similar. Primary goal was the proportion of patients who reached calcium-phosphorus product lower than 5.5 mg²/dL. In education group, 36(75%) patients achieved primary goal, compared to the 16(72.7%) of control group (p=0.430). The improvement of MMAS-8 score were not different between education and control group (for short term, 0.26±1.12 vs 0.02±1.30; education vs. control, p=0.445). For long term, 0.11±1.17 vs 0.30±1.29, p=0.555; Education non-significantly increased patients’ knowledge of when to take phosphate binder(22.9% vs. 3.5%, education vs. control, p=0.347), and it didn’t affect the amount of dietary phosphate intake per body weight(-1.18±3.54 vs. -0.88±2.04 mg/kg,education vs. control, p=0.160). However, it decreased dietary phosphate to protein ratio(-0.64±0.04 vs. 0.65±0.55,education vs. control, p=0.193). Education on phosphate restriction did not affect the PG-SGA(0.17±4.58 vs. -0.86±3.86,education vs. control, p=0.363), nor dietary protein intake(-0.03±0.33 vs. -0.09±0.18,education vs. control, p=0.569).

**Conclusions:** Education didn’t affect the calcium phosphate product compared with control group. However, education corrected timing of phosphate binder intake and lowered dietary phosphate to protein ratio, although it wasn’t statistically significant. These findings imply the importance of educational effort.

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**TH-PO764**

**Effects of Probiotic Supplementation on Trimethylamine-N-Oxide Plasma Levels in Chronic Kidney Disease Patients**

**Background:** Components present in the diet can be metabolized by gut microbiota to produce metabolites like trimethylamine-N-oxide (TMAO) that play a role in cardiovascular disease in CKD patients. The objective of this study was evaluate the effects of probiotic supplementation on TMAO plasma levels in hemodialysis patients.

**Methods:** A randomized, double-blind trial was performed in 21 HD patients [54±10.4 years old, 9 men, BMI 26.1±4.8 kg/m², dialysis vintage 68.5±34.2 (2.7–120.7) months].

**Results:** The average of TMAO, choline, and betaine plasma levels did not change after supplementation.

**Conclusions:** The average TMAO, choline, and betaine plasma levels did not change after supplementation.

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**TH-PO765**

**Prediction of Fractures among Older Kidney Transplant Recipients**

**Background:** Kidney transplantation is a growing treatment option for older adults with ESRD. Fracture risk is elevated in ESRD patients who undergo KT compared to warfarin candidates. While previous studies have identified risk factors for fractures after KT, we sought to create a post-KT fracture prediction model based on pre-transplant factors.

**Methods:** We studied older (aged >=55) KT recipients who were Medicare Primary Beneficiary. Fracture incidence was calculated from 1/1/99-12/31/11 using SRTR data linked to Medicare claims. We estimated the cumulative incidence of a fracture (based on claims) using the Kaplan-Meier method. We developed a prediction model based on recipient, transplant and donor factors known prior to KT. Using national data on 41,145 older KT recipients, we estimated the post-KT incidence of fracture using an AIC-based selection method for the cumulative incidence of fractures to be 7.9% at 5 years and 17.4% at 10 years. We identified recipient, donor and transplant factors as predictors of post-KT fractures (C-statistic=0.65).

**Results:**

<table>
<thead>
<tr>
<th>Placebo Group (N= 10)</th>
<th>Probiotic Group (N=11)</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Post</strong></td>
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<tr>
<td><strong>Baseline</strong></td>
<td><strong>Post</strong></td>
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<tr>
<td>Uric acid (mg/dL)</td>
<td>8.8±4.6</td>
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<tr>
<td></td>
<td>7.4±4.4</td>
</tr>
<tr>
<td>Choline (mg/dL)</td>
<td>10.0±1.8</td>
</tr>
<tr>
<td></td>
<td>11.4±2.4</td>
</tr>
<tr>
<td>Betaine (ng/µl)</td>
<td>4.3±20.0</td>
</tr>
<tr>
<td></td>
<td>4.5±1.5</td>
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<tr>
<td><strong>Biochemical markers</strong></td>
<td></td>
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<tr>
<td>CRP (mg/dL)</td>
<td>3.8 (1.2 – 9.5)</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>159.7±55.3</td>
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<tr>
<td></td>
<td>156.0±39.0</td>
</tr>
<tr>
<td>Hematocrite (%)</td>
<td>34.8±5.4</td>
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<tr>
<td></td>
<td>31.7±2.8</td>
</tr>
</tbody>
</table>

The % of changes in the plasma levels of betaine and choline were higher in probiotic group when compared to placebo [choline - probiotic group: 2.6% (+9.5 – 46.0) vs placebo group: -10.0 % (-18.7 – 0.4), p=0.03; betaine - probiotic group: 37.2% (+14.3 – 80.9) vs placebo group: 11.1% (-16.0 – 19.1), p=0.04].

**Conclusions:** Short-term probiotic supplementation does not appear to influence TMAO, choline, and betaine levels in HD patients.
Conclusions: The cumulative incidence of fractures increases to 17.4% 10 years after KT for older recipients. Recipient, donor and transplant factors obtained prior to KT can be used to predict which older recipients are at risk of post-KT fracture.

Funding: Other NIH Support - NIA, Private Foundation Support

TH-PO766
A Prospective, Randomized, Controlled Study of Cholecalciferol Supplementation in Kidney Transplant Recipients - Preliminary Results at 30 Months

Background: The Klotho gene product (KLOTHO) is a transmembrane protein that is expressed in the kidney, intestine, and intestine and is thought to play a role in the regulation of calcium, phosphorus, and vitamin D metabolism. KLOTHO is also involved in the regulation of blood pressure and may be a protective factor against cardiovascular disease. However, the role of KLOTHO in renal transplant recipients is not well understood.

Methods: We prospectively followed a group of KT recipients, randomly allocated to receive cholecalciferol (4000 IU/day) or no therapy (N, n = 68). Comparison was performed with the T test, Mann Whitney U or chi-square test, survival was analyzed through Kaplan-Meier test.

Results: The 2 groups were similar in gender (male: 57.4% vs 56.2%), age distribution (mean 51 vs 52 years), dialysis vintage (mean 46 vs 53 months), cold ischemia time (average 18h17min vs 18h33min), PRA (10% vs 5% in 2 groups), time since KT (18m vs 17m), time since KT (24m vs. 25m), median (46 vs. 48.5) and major comorbidities, respectively in both groups. Basal calcidiol levels were significantly higher in both groups (18.7 vs. 19.1 ng/ml) and so were eGFR (EPD) (67.4 vs. 63.3 mL/min/1.73 m2), Hb (12.8 vs. 13 g/dl), CRP (0.5 vs. 0.61 ng/ml), FGF-23 (107 vs 119 pg/ml), alkaline phosphatase (72 vs 77 U/L), phosphate (3.7 vs. 3.5 mg/dl) or magnesium (1.7 vs. 1.8 mg/dl) levels. However, basal serum calcium (9.8 vs. 10.2 mg/dl) was significantly lower in GD. We found a significant increase in the levels of calcidiol (ng/ml) at 6m (39.7 vs 29.2), 12m (40.7 vs 29.5), 18m (40.6 vs 27.2), 24m (42.1 vs 22.2) and at 30m (43.5 vs 21.1), with no significant increase of calcium, but with significant reduction in iPTH (pg/ml) (81 vs 112), 12m (87 vs 103), 24m (76 vs 97.5) and at 30m (64.2 vs 96.6) in GD versus GC. There were no differences between the 2 groups in the evolution of the excretion fraction of Ca, P, or Mg, in the urine protein/creatinine ratio, pulse pressure, left ventricular mass index or hospitalizations. Treatment with antihypertensives (including ACEI or ARBs), active vitD or cinacalcet was similar between the 2 groups. There were no differences in graft or patient survival.

Conclusions: The dose of 4000 IU/day of cholecalciferol was safe and allowed to raise calcidiol levels of GD and reduce iPTH at 6, 12, 24 and 30 months compared with the control group, without other significant results so far.

TH-PO767
FGF23/Klotho System and Vitamin D Receptor Activation in Kidney Transplant Recipients

Background: Recent studies have demonstrated the usefulness of paricalcitol for the treatment of secondary hyperparathyroidism (SHPT) in kidney transplant recipients, also suggesting beneficial pleiotropic effects. The aim of this study was to analyze the influence of soluble Klotho activation of the vitamin D receptor (VDR) on the FGF-23/KLOTHO system.

Methods: Twenty-nine renal transplant patients with iPTH >100 pg/ml were treated with oral paricalcitol (1 mg/day) for 3 months. A group of 8 patients matched for age, sex and renal function with iPTH <100 pg/ml was included as controls. Serum concentrations of FGF-23 and KLOTHO were measured by ELISA, and gene expression levels of KLOTHO (KL) were analyzed in peripheral blood mononuclear cells (PBMCs) as reflect of renal expression levels. Promoter methylation of KL was also studied.

Results: iPTH decreased in paricalcitol-treated patients (p<0.0001). Serum FGF-23 enhanced (p=0.01), whereas KLOTHO concentrations showed a trend to increase (p=0.067). KLOTHO gene expression in PBMCs increased by 45.7% in paricalcitol-treated patients (p<0.01), without change in controls. Paricalcitol administration resulted in a median percent decrease of 56% in methylated DNA levels of KL (TH-PO766). The ratio of un-methylated/methylated KLOTHO promoter DNA did not change in controls, but it increased by 177% in paricalcitol-treated subjects (p=0.0001). The increase in the un-methylated/methylated KLOTHO promoter ratio was independently associated with the change in serum KLOTHO (r = 0.55, p = 0.01) and mRNA expression levels (r = 0.40, p = 0.05).

Conclusions: Paricalcitol induces an increase in KLOTHO gene expression and serum Klotho concentrations, which is significant and independently associated with a rise in the ratio of un-methylated/methylated KLOTHO promoter DNA. Long-term studies are needed to assess whether this effect may translate into beneficial clinical effects.

Funding: Government Support - Non-U.S.

TH-PO768
Urinary Calcium Excretion and Risk of Graft Failure and Mortality in Renal Transplant Recipients

Background: Calcium and vitamin D supplementation are often prescribed to help improve bone health in renal transplant recipients (RTRs). However, high levels of urinary calcium excretion (UCaE) have been shown to increase the risk for nephrolithiasis and nephrocalcinosis. Furthermore, calcium supplements may increase the risk for cardiovascular disease. Therefore, we investigated whether high UCaE increases the risk of graft failure and mortality in a cohort of RTRs.

Methods: Urine samples were collected in a single-center, longitudinal cohort of 691 RTRs with a functioning graft for at least one year (baseline). UCa concentration was measured on a 24-hour specimen at baseline by indirect potentiometry. UCaE was measured as a continuous variable and grouped according to event-based tertiles of UCaE. Results: Baseline median UCaE was 95 mg/24h (interquartile range [IQR]: 46-156 mg/24h), similar between males and females. A total of 44 events of graft failure and 81 events of mortality was present (HR: 0.98 [0.61-1.29], p = 0.52, for every 1 log unit increase in UCaE). Surprisingly, an inverse association between UCaE and mortality was present (HR: 0.68 [0.53-0.88], p = 0.003), with the highest risk in the tertile of subjects with the lowest UCaE. When further adjusting for other dietary factors associated with poor nutrition, a trend remained (HR: 0.79 [0.59-1.07], p = 0.13), although formal statistical significance was lost.

Conclusions: High UCaE was not associated with an increased risk of graft failure or mortality in RTRs. These data do not provide evidence that calcium supplementation is harmful in RTRs.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Direct-Acting Antivirals for the Treatment of Hepatitis C Virus Infection in Kidney Transplant Recipients: A Multicenter Study

Carmen Infection in Kidney Transplant Recipients: A Multicenter Study

Jaiswal, Dharmendra Balkrishna
Nephrology, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Español de Actualización de Nefrología, Grupo Española

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

Underline represents presenting author.

In addition, HCV core antigen-positive was a most important independent risk factor for survival times after renal transplantation with Cox proportional hazard model (Wald 6.254, p<0.012) as compared with age, gender, type of donors, serum creatinine levels on renal transplantation one year later, and Immunosuppressive therapy. 

Conclusions: Continuous HCV infection was a harmful risk factor for the patient survival after renal transplantation, especially 20 years after renal transplantation.

Funding: Government Support - Non-U.S.

Direct-Acting Anti-Viral Agents in Post Renal Transplant Hepatitis C

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

Underline represents presenting author.

In addition, HCV core antigen-positive was a most important independent risk factor for survival times after renal transplantation with Cox proportional hazard model (Wald 6.254, p<0.012) as compared with age, gender, type of donors, serum creatinine levels on renal transplantation one year later, and Immunosuppressive therapy.

Conclusions: Continuous HCV infection was a harmful risk factor for the patient survival after renal transplantation.

22 (14 genotype:3,6 genotype1 and one each 2 and 4) were included in the study after exclusion of 6 patients(3 with eGFR <30 ml/min/1.73m², 1 with hepatic decompensation and 2 for no consent).

Results: 14 patients completed 24 weeks of treatment with dual drug (sofosbuvir and ribavirin; genotype 3, n=10; genotype 1, n=2; genotype 2, n=1; and genotype 4, n=1). Subsequently with availability newer DAAs, either daclatasvir (genotype 3, n=4 and genotype 1, n=1) or ledipasvir (genotype 1, n=3) was added to above regimen in eight patients (i.e. triple drug for a minimum of 12 weeks). A virological response with undetectable virus (i.e. Rapid 92%, End therapy 100%, and sustained VR12 of 100% and 24 of 100%) was seen in all patients. The changes in liver enzymes AST,ALT and GGT; hemoglobin, trough tacrolimus, and eGFR changes on follow up is shown in figure 1.

The treatment was well tolerated except fall in Hb and one required blood transfusion and 3 required EPO. Tacrolimus dose was increased in 10 and decreased in 2 to achieve required trough level. All had sustained remission at end of one year followup.

Conclusions: DDAs are safe and effective therapy for treatment of replicating HCV post kidney transplantation.
Transplanting Hepatitis C Virus Infected Kidneys into Hepatitis C Positive Recipients in the Direct Acting Antiviral Agents Era Juan E. Kusnir, Adriana Dejman, Kalyan Bhamidimarri, Fernando E. Pedraza, Marco A. LadinoAvelaned, David Roth, Medicine/Nephrology, Univ of Miami/VAMC, Miami, FL.

Background: The availability of direct acting antivirals (DAAs) has changed the treatment of hepatitis C virus (HCV) infection. The decision to treat a HCV positive patient before or after transplant has important ramifications for patients in the deceased donor waiting list. Effective treatment can now be administered in the post-transplant period allowing for HCV infected kidneys to be allocated to HCV infected recipients. Potential benefits include significant decrease in waiting list time translating into long term benefits of decreased time of decrease on hemodialysis. Yet many questions regarding the treatment, adverse effects and potential complications remain unknown.

Methods: In this observational study of 21 HCV positive patients receiving a HCV positive kidney allograft, we reviewed the outcomes of post-transplant HCV treatment with DAAs during the 12 week treatment period. The 21 patients received induction with thymoglobulin and basiliximab, and maintenance immunosuppression with tacrolimus and mycophenolate mofetil. All patients started DAAs 60-90 days after transplant and were on Sofosbuvir with the following combinations: 13 patients on ledipasvir and ribavirin, 5 patients on ledipasvir, 1 patient on daclatrasvir, 1 patient on simprevir and 1 patient on ribavirin.

Results: The mean time on the list for these patients was 116 days. All patients that completed the prescribed DAA therapy achieved a sustained virologic response at 12 weeks (SVR12). Four patients were complicated by antibody mediated rejection while on therapy. Tacrolimus dose adjustments were required in 10 patients to maintain therapeutic levels. The response to DAA therapy was similar to that reported in the general population.

Conclusions: Accepting a kidney from a HCV positive donor dramatically reduces wait time for kidney transplantation. Complications including allograft rejection and variable tacrolimus levels will require closer monitoring of these patients and more intense immunosuppression dose adjustments. Further research into this unique population is needed to obtain better understanding and thus optimize patient care.

Sofosbuvir Based Therapy for HCV Infection in Post Renal Transplant Recipients Vivek Pathak, Nephrology, Kovai Medical Center and Hospital, Coimbatore, Tamil-Nadu, India.

Background: The purpose of this study was to assess the efficacy and safety of an interferon free Sofosbuvir based therapy to treat HCV infection in kidney transplant recipients .

Methods: We used sofosbuvir based therapy in 33 post transplant patients. Treatment was given for 44 weeks. Sofosbuvir and Ribavirin were given for 12 weeks and Ledipasvir for 18 and Sofosbuvir and Daclatasvir for 3 patients.24 were suffering from genotype 1, 07 were suffering from genotype 3 and 02 were suffering from genotype 4 infection. The median time between transplant and the start of anti HCV therapy was 60 months. They all received stereol free immunosuppression based on Tacrolimus and MMF.

Results: All the patients became negative for HCV RNA and those who were tested 12 weeks after cessation of therapy remained negative .Only one patient with genotype 1 had relapsed after stopping the treatment and he also responded well to Sofosbuvir and Ledipasvir combination. HCV clearance causes significant post kidney transplant effects like new onset diabetes mellitus, Cryoglobulinaemia, chronic liver disease and infection related deaths. Sofosbuvir based therapy was found to be safe and no interaction was noted with Tacrolimus. There was no acute rejection or graft loss during the treatment. One patient required increase in Tacrolimus dose following remission of HCV infection. Mean SGPT was 74 IU/ml before and 20 IU/ml after therapy. There were 5 new onset diabetes mellitus in this group and 4 improved subsequently and anti diabetic agents were discontinued.Two patients with cirrhosis and ascites showed reversal and fibroscan became normal. There were no adverse side effects with this drug except fall in haemoglobin in those who received Ribavirin. One patient developed funguria during the treatment but responded well to surgical drainage and Amphotericin.

Conclusions: Sofosbuvir based therapy induced remission in 100% patients, reversed diabetes in 4 out of 5 patients and chronic liver disease with ascites in 2 patients without putting the graft at any risk. We will reduce the treatment duration to 3 months now.

Treatment of Hepatitis C in Kidney Transplant Recipients with Directly Acting Antiviral Agents Michelle Lubetzkzy, Maria Ajaimy, Layla Kamal, Maria Coco, Enver Akalin, Graciela De Boccado, Montefiore Transplant Center, Albert Einstein College of Medicine, Bronx, NY.

Background: With the development of new all oral, interferon-free directly acting antiviral (DAA) medications, treatment of Hepatitis C infection (HCV) in renal transplant recipients is possible, but limited data exists on its safety and efficacy.

Methods: We performed a retrospective cohort analysis of patients transplanted at our center with HCV who have started on DAAs. Primary endpoints included sustained virologic response (SVR) as defined as negative viral load at 12 weeks post completion of therapy and allograft function.

Results: A total of 31 patients met inclusion criteria. The most commonly used regimen was sofosbuvir and ledipasvir (n=21). Upon completion of therapy, 100% had undetectable viral load. Of the 23 patients with at least 12 weeks of follow up after completion of therapy 95.7% achieved SVR. Both graft and patient survival at most recent follow up was 100%, although 2 patients now have GFR <20 ml/min/BSA. A total of 6/31 (19.3%) patients had proteinuria and/or decreased GFR.

Conclusions: Our data demonstrates that DAAs are effective in treating HCV in patients after kidney transplantation. Patients with proteinuria and/or decreased GFR should be monitored closely.


Background: The American Association for the Study of Liver Diseases guidelines recommend the use of specific regimens for liver transplant recipients with hepatitis C virus (HCV), but do not address the treatment of HCV infected recipients of kidney alone, liver/kidney, or kidney/pancreas transplants. The objective of this study was to gain knowledge on HCV treatment response in kidney transplant recipients (KTRs).

Methods: This was a retrospective, single-center analysis of KTRs who started HCV treatment between January 1, 2014 and February 3, 2016. Electronic medical records of
patients taking direct acting antiviral (DAA) regimens of sofosbuvir + ribavirin, sofosbuvir + ribavirin, or ledipasvir + sofosbuvir were reviewed for demographics and laboratory values. The primary endpoint was the sustained virologic response (SVR) at 12 weeks after treatment completion.

**Results:** Thirty KTR patients were treated for HCV; 9 were excluded: 4 had not yet reached 3 months, 5 were lost to follow-up due to transfer of care. The remaining 21 patients had a mean age of 58.3±7.3 years; 17 (81%) were male, 13 (62%) Black, 11 (52%) cirrhotic, 12 (57%) had genotyp 1a, 8 (38%) had 1b, and 1 (5%) had 1g. There were 5 (24%) liver/kidney, 13 (62%) kidney alone, and 3 (14%) kidney/pancreas transplant patients. Eighteen (86%) patients received tacrolimus, 13 (62%) had diabetes, and 13 (62%) had a BMI <30 kg/m². During HCV treatment, immunosuppression dosage did not change for 15 (71%) patients, it was increased for 2 patients, decreased for 3 patients, and changed in both directions for 1 patient. Twenty of 21 patients (95%) achieved SVR.

No difference in SVR rate was found in treatment naïve or experienced (100% vs 86%; p=0.33), cirrhotic or non-cirrhotic (89% vs. 100%, p=0.429), or non-obese or obese (100% vs. 88%, p=0.99) patients. The SVR did not differ by regimen, genotype, gender, ethnicity, age, diabetes, or insurance (p=0.05).

**Conclusions:** DAA regimens were highly effective in KT recipients. SVR did not differ by treatment or demographics; comparison across groups was limited due to small numbers. Immunosuppressive levels should be monitored closely with HCV treatment.

**TH-PO779**

Hepatitis B Virus(HBV) Re-Activation in HBsAg- and HBsAb-Negative and HBcAb-Positive (sAg-sAb-cAb+) Kidney Transplantation (KT) Recipients

Jae Won Jeon, Hyongsan Kim, Soon Bae Kim. Div of Nephrology, Dept of Internal Medicine, Asan Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea.

**Background:** According to the Korean Dialysis Registry, 5.0% of hemodialysis patients were positive for HBV. Patients who received immunosuppressive treatment commonly face the risk of HBV reactivation. sAg-sAb-cAb+ can be interpreted as low-level hepatitis B carrier or hepatitis B in remission. European Association for the Study of the Liver Clinical Practice Guideline recommended that HBsAg-negative, anti-HBc positive patients with undetectable serum HBV DNA and regardless of anti-HBs status who receive chemotherapy and/or immunosuppression should be followed carefully by means of ALT and HBV DNA testing. However, evidences supporting these recommendations are scarce. This study was performed to evaluate the incidence of HBV reactivation in sAg-sAb-cAb+ KT recipients.

**Methods:** From February 1997 to March 2015, 178 sAg-sAb-cAb+ patients (M:F 4:2, 50.0±7.3 years) at median 72 (8~121) months. One patient died of hepatic failure, abnormal LFT, 84 routine check) during the follow-up period.

**Results:** Median duration of follow-up was 83 (6~226) months. We checked liver function test undetectable serum HBV DNA and regardless of anti-HBs status who receive chemotherapy and/or immunosuppression should be followed carefully by means of ALT and HBV DNA testing. However, evidences supporting these recommendations are scarce. This study was performed to evaluate the incidence of HBV reactivation in sAg-sAb-cAb+ KT recipients.

**Conclusions:** DAA regimens were highly effective in KT recipients. SVR did not differ by treatment or demographics; comparison across groups was limited due to small numbers. Immunosuppressive levels should be monitored closely with HCV treatment.

**TH-PO780**

Kinetics of Cytomegalovirus Viral Load in Kidney Transplant Recipients Receiving Everolimus or Mycophenolate Sodium and No Pharmacological Prophylaxis

Geovana Basso, Alexandra Ferreira Brigido, Mayara I. Paula, Marina Pontello Cristelli, Helio Tedesco-Silva, J. Medina-Pestana, Claudia Felipe Rosso. Hospital do Rom, SP, Brazil.

**Background:** Cytomegalovirus (CMV) infection is associated with morbidity and mortality after transplantation. Studies have shown that the use of mammalian target of rapamycin inhibitors is associated with lower rates of CMV infection.

**Methods:** The purpose is to investigate the kinetics of CMV viral load in kidney transplant recipients receiving tacrolimus (TAC) + everolimus (EVR) or mycophenolate sodium (MPS) and no CMV pharmacological prophylaxis. This is a comparative analysis of a prospective, single-center trial, in which 288 kidney transplant patients were randomized to receive a single 3mg/kg dose of anti-hemolytic antibody, TAC, EVR and prednisone (r-ATG/EVR, n=85); basiliximab, TAC, EVR and prednisone (BASEV/EVR, n=102); or BAS, TAC, MPS and prednisone (BAS/MPS, n=101). They were monitored with weekly pp65 antigenemia. CMV infection/disease were treated with intravenous ganciclovir. In a blinded fashion, samples were collected for quantitative nucleic acid testing (QNAT, in-house method).

**Results:** The incidence of first CMV infection/disease was 4.7, 10.8 and 37.6% in r-ATG/EVR, BASEV/EVR and BAS/MPS (p=0.0001) and the median viral load in was 828, 1878 and 10.123 copies/ml, respectively.

**Conclusions:** CMV infection/disease was 4.7, 10.8 and 37.6% in r-ATG/EVR, BASEV/EVR and BAS/MPS (p=0.0001) and the median viral load in was 828, 1878 and 10.123 copies/ml, respectively.

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

Although r-ATG/EVR group had the same proportion of patients with at least one positive QNAT as BAS/MPS group (73.3 vs. 73.3%, p=0.01), the mean viral load was significantly lower in both everolimus groups (r-ATG/EVR vs. BASEV/EVR, p=0.326; r-ATG/EVR vs. BASEV/EVR, p=0.01).

**Conclusions:** The use of EVR was associated with lower incidence of CMV infection/ disease and lower viral load compared to MPS. The use of r-ATG induction may have contributed to a higher proportion of patients with one episode of viremia, although its effect on viral replication was transient and mild.

**Funding:** Private Foundation Support

**TH-PO781**

Adenovirus Nephritis in Kidney Transplant Recipients: Clinicopathologic Features and Correlation

Max Rollins, Amy L. Adams, Thomas E. Bogers,1 Alton Brad Farris,1 Carla L. Ellis.1 1Pathology, Emory Univ, Atlanta, GA; 2Pathology, Dekalb Medical Center, Atlanta, GA.

**Background:** Adenoviruses (AdV) are increasingly being recognized as emerging pathogens and causes of substantial morbidity in stem cell and solid-organ transplant recipients. AdV are double-stranded DNA viruses that have a reported prevalence of infection during the 1st year after kidney transplantation of 11% by urine culture and 6.5% by serum PCR. In kidney transplant recipients, certain clinical and histologic features should raise concern for adenovirus nephritis (ADN). Here we report 9 renal biopsies with ADN from seven kidney transplant recipients.

**Methods:** A retrospective search to identify cases of ADN in renal transplant recipients was performed.

**Results:** Nine biopsy reports were identified (2009-2016) from among seven patients. The median time from transplant to development of ADN was 52 days (range: 13-1,414 days). Clinically, macrohematuria was observed in 71% (5/7) of the patients, microscopic hematuria in all patients (n=7) and significant proteinuria in all patients (n=7). Serum creatinine increased by a median of 56.3% from baseline (range: 26.3%-190%). Histologically, interstitial inflammation was present in 100% (9/9), granulomas were identified in 44% (4/9), tubular epithelial necrosis was present in 78% (7/9), nuclear inclusions were seen in 22% (2/9), and obliterator tubulitis was present in 56% (5/9). Immunostaining for adenovirus showed tubular epithelial cell reactivity in 100% (9/9).

**Conclusions:** Granulomas and inclusions are not identified consistently and thus make the diagnosis of ADN versus acute cellular rejection difficult. Immunostaining for adenovirus is the most important diagnostic tool when cut-off histological features of ADN are not present on the biopsy sample. Overall, a strong emphasis on the clinical presentation should be used to help with the diagnosis. Based on this review, we advocate for adenovirus immunostaining on any renal biopsy when a patient presents (especially within 1 year from time of transplant) with gross or microscopic hematuria, and histological findings of intense interstitial inflammation, obliterator tubulitis, or granulomatous inflammation.

**TH-PO782**

Incidence of Infection following Rituximab Use in Kidney Transplant Recipients

Lana Wong, Michael G. Ison, Chad Richardson, Anesha A. Shetty. Northwestern Memorial Hospital, Chicago, IL.

**Background:** Rituximab is used off-label in solid organ transplant for desensitization and treatment of antibody-mediated rejection (AMR). It targets CD20 and results in B cell depletion. Although it may be beneficial in preventing or fighting rejection, it may be associated with unfavorable infectious outcomes. The purpose of this study was to evaluate the incidence of infection in kidney transplant recipients who received rituximab for desensitization or AMR treatment.

**Methods:** This was a single-center, retrospective analysis of living and deceased donor kidney transplant recipients at Northwestern Memorial Hospital from January 1, 2007 to October 1, 2015. The following were inclusion criteria: alemtuzumab induction; age 18 years or older; receipt of at least one dose of rituximab. Patients were excluded for: previous transplant; simultaneous organ transplants; rituximab for an oncologic indication; history of human immunodeficiency virus. The primary efficacy endpoint was incidence of infection over 1 year following first dose of rituximab. Secondary endpoints were patient and graft survival 1 year following first dose of rituximab.

**Results:** Of the 145 subjects included, 114 (79%) received rituximab for desensitization and 31 (21%) for treatment of AMR. Overall, there were 34 cases of fungal and viral infections. The primary endpoint is shown in table 1. Five patients had death-censored graft failure and 8 patients died during the study period, 2 which were attributed to sepsis. A sub-analysis comparing those who received rituximab for desensitization versus AMR revealed no significant difference in incidence of infection, patient survival or graft survival.

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

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Incidences of infection

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>n (%)</th>
<th>(n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with infection, n (%)</td>
<td>27 (19.0%)</td>
<td></td>
</tr>
<tr>
<td>Incidence of viral infection</td>
<td>15 (10%)</td>
<td></td>
</tr>
<tr>
<td>CMV Viremia, n (%)</td>
<td>17 (12%)</td>
<td></td>
</tr>
<tr>
<td>BK Viremia, n (%)</td>
<td>2 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Incidence of fungal infection</td>
<td>Overall cases of infection</td>
<td>34</td>
</tr>
</tbody>
</table>

Conclusions: Approximately 19% of patients receiving rituximab experienced a fungal or viral infection. Graft failure occurred in 3% and death occurred in 6% of patients. There were no significant differences in outcomes for patients receiving rituximab for desensitization or AMR.

TH-PO783

Post-Transplant Anemia in Kidney Transplant Recipients: Prevalence, Risk Factors, and Outcomes

Venkat Sainaresh Vellanki, Pei Xuan Chen, Olusegun Famure, Yanhong Li, Joseph Kim. Div of Nephrology and the Kidney Transplant Program, Toronto General Hospital, Univ Health Network, Univ of Toronto, ON, Canada.

Background: This study aims to evaluate the association between post-transplant anemia (PTA) and adverse outcomes such as cardiovascular diseases (CVDs) and total graft failure (i.e., return to chronic dialysis, preemptive re-transplant, or death with graft function) in kidney transplant recipients (KTRs).

Methods: This cohort study examined all KTRs at Toronto General Hospital from January 1-2000 to 2013 with the development of PTA, defined as a hemoglobin level of < 11.0 g/dL. The main study endpoints were cardiovascular events and total graft failure. The study baseline was set at 3 months after transplantation. Time-fixed and time-dependent multivariable Cox proportional hazards models were used to assess the independent association of PTA with the study endpoints.

Results: A total of 1175 (61.7% male) KTRs were included in the study. The prevalence of PTA at 1-month post-transplant was 53.7%. In the time-fixed model, PTA at baseline was not associated with cardiovascular events while there was increased risk of total graft failure (HR 1.50 [95% CI: 1.10, 2.06]). In the time-dependent model, PTA was significantly associated with both cardiovascular events (HR 2.13 [95% CI: 1.51, 3.00]) and all-cause mortality (HR 4.39 [95% CI: 3.18, 6.03]).

Conclusions: PTA is a significant independent risk factor for cardiovascular events and total graft failure in KTRs, particularly in statistical models that properly account for the time-dependent nature of anemia.

TH-PO784

Clinical Characteristics of Parvovirus B19 Infection in Kidney Transplant Patients

Chung Hee Baek, Hyoung Kim, Su-Ki Park. Div of Nephrology, Dept of Internal Medicine, Asan Medical Center.

Background: Parvovirus B19 is a small, nonenveloped, single-stranded DNA virus with special affinity for the erythroid progenitor cells of the bone marrow. The first case of parvovirus B19 infection in kidney transplant recipients (KTRs) was reported in 1986. Since then, limited data about risk factors and specific clinical characteristics of PVB19 are still insufficient.

Methods: We identified 511 among all 4,392 KT recipients with positive parvovirus B19 polymerase chain reaction (PCR) from January 1990 to April 2016, and the clinical characteristics of patients with positive results were compared with those of age and sex-matched patients with negative results by PCR.

Results: A total 39 KT recipients showed positive parvovirus B19 PCR, and they were compared with age and sex-matched 78 patients among 563 KT recipients showed negative PCR results. The 89.7% of positive parvovirus B19 PCR was reported within the first year of KT. Bone marrow biopsies were performed in 13 patients with compatible bone marrow changes of parvovirus infection and positive parvovirus B19 PCR in bone marrow specimens. The 74.4% of patients with positive parvovirus B19 PCR were treated with intravenous immunoglobulin, and all patients were recovered from anemia in multivariate analysis. Parvovirus B19 PCR performed within 1 year of KT [relative risk (RR) 17.139, 95% confidence interval (CI) 6.988-73.641, P<0.001]; deceased donor KT (RR 6.896, 95% CI 1.625-29.261, P=0.009) and hemoglobin level at the time of PCR (RR 0.435, 95% CI 0.200-0.909, P=0.001) were significantly related with positive parvovirus B19 PCR. Pancytopenia showed a trend of relation (RR 4.756, 95% CI 0.932-24.257, P=0.061). In addition, the use of tacrolimus showed a significant relationship with PCR in univariate analysis (RR 4.270, 95% CI 1.889-9.651, P<0.001), but the significance was lost in multivariate analysis. Graft survival of two groups were not different during follow-up period of 111.68±54.54 months (P=0.685 by log rank test).

Conclusions: The related factors of positive parvovirus B19 PCR might be useful for suspicion and early detection of parvovirus B19 infection. Further studies are necessary to elucidate the characteristics of parvovirus B19 infection in KT.

TH-PO785

Pure Red Cell Aplasia Related to Human Parvovirus B19 Infection in Kidney Transplant Recipients: A Single Center Experience

Yan Jiang, Zhechi He, Rending Wang, Jingyi Zhou, Jianghua Chen. The First Affiliated Hospital of Zhejiang Univ, Zhejiang Univ, Hangzhou, Zhejiang Province, China.

Background: To investigate the incidence, clinical manifestation, diagnosis and treatment of pure red cell aplasia (PRCA) related to human parvovirus B19 (HPV-B19) infection in kidney transplant recipients.

Methods: This is a retrospective cohort study of all patients who underwent kidney transplantation between January 2010 and December 2014 at kidney disease center, the first affiliated hospital of Zhejiang university. PRCA is defined by the absence of mature erythroid precursors in the bone marrow with normal white blood cell and platelet count (or deep reticulocytopenia and peripheral blood in the absence of other possible causes). We used standard real-time polymerase chain reaction (PCR) amplification to detect HPV B19 in serum sample. The clinical data of HPV-B19 PRCA patients were collected and analyzed retrospectively.

Results: In the past 5 years, of 813 kidney transplant recipients, 26(3.2%) were diagnosed with HPV-B19 PRCA at a median of 46 days(range, 21-2years) posttransplantation. All 26 patients had severe anemia with the mean lowest hemoglobin count of 58.3±10.1 g/L.6 patients (23.1%) experienced graft dysfunction (creatinine elevation) at HPB19 PRCA diagnosis. 25 of 26 patients received intravenous immunoglobulin (IVIG) treatment after diagnosis. Transient serum creatinine elevating during IVIG treatment was observed in 23.1% patients.MMF was discontinued in 20(77%) patients to reduce the degree of immunosuppression. 88.5% of patients were switched from FK to CSA.Serum sodium was used in 5 patients as antirenal regimen (combination with IVIG in 4 patients and used alone in 1 patients).For these 25 patients who received IVIG-based comprehensive treatment, 19(78%) patients achieved long term remission after first course of IVIG treatment. 7 patients experienced HPV B19 PRCA relapse and responded well to additional IVIG courses with or withoutcarnet sodium. All 26 patients are alive with functional graft kidney at the end of follow up.

Conclusions: HPV-B19 PRCA is a rare but significant disease after kidney transplantation. Treatment with IVIG is effective in most cases.

Funding: Clinical Revenue Support

TH-PO786

Metabolic Acidosis and Outcome in Patients Long Term After Kidney Transplantation

Marcin Adamczak, Damian Gojowy, Katarzyna Skiba, Magdalena Bartmanska, Aureliusz Kolonko, Andrzej Wieczek. Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland.

Background: Metabolic acidosis (MA) frequently occurs in patients after kidney transplantation (KTxs). Results of both experimental and clinical studies suggest that MA may contribute to faster progression of native kidney disease. It is unknown however whether or not such relationship occurs also in KTxs. The aim of this clinical, single center, retrospective, observational study was to examine the relationship between MA and both mortality and renal outcomes in patients after KTxs.

Methods: Four hundred eighty-six (290 male; 196 female) patients aged 48±12 years at least one year after KTxs were analyzed. Blood HCO3- were measured and subsequently patients were observed during 3 years. MA was defined as the blood HCO3- concentration less than 22 mmol/L. The endpoints in survival curves analysis were death and initiation of dialysis therapy. In patients who did not reach above mentioned endpoints the difference between final (after 3 years follow-up) and initial eGFR was calculated (according to the MDRD formula). Relative risks were presented with 95CI.

Results: MA was diagnosed in 57 (12%) patients being long term after KTxs. In patients with MA the risks of death and initiation of dialysis therapy were significantly higher than in patients without MA[RR:4.11 (1.58-10.67), p=0.003] and RR: 3.58 (3.58-6.32, p<0.001) respectively. In KTxs patients with MA who did not reach above mentioned outcomes blood bicarbonate concentration at baseline correlated positively with change of eGFR values (R=0.48, p=0.002, p=36). Such correlation was not found in patients without MA (r=386).

Conclusions: 1. MA increases mortality and worsens graft survival in patients after KTxs. 2. The intensity of MA is associated with faster progression of kidney dysfunction in KTxs patients.

Funding: Government Support - Non-U.S.

TH-PO787

Sodium Zirconium Cyclosilicate Treatment of Hyperkalemia in CKD Patients with a Solid Organ Transplant: Data from Two Trials

Mohamed A. El-Shahawy,1 Edgar V. Lerman,2 Wajeh Y. Qunibi,3 Bhupinder Singh,1 Jose A. Menoyo,4 Henrik S. Rasmussen.4 1Academic Medical Research Inst, Los Angeles, CA; 2Univ of Illinois at Chicago College of Medicine, Advocate Christ Medical Center, Oak Lawn, IL; 3Univ of Texas Health Science Center at San Antonio, San Antonio, TX; 4ZS Pharma, San Mateo, CA.

Background: Sodium zirconium cyclosilicate (ZS-9) is a non-absorbed, selective cation trap that binds potassium (K+) throughout the GI tract. The effects of ZS-9 in patients (pts) with solid organ transplant have not been previously reported. This subgroup post-hoc analysis assessed the effects of ZS-9 in transplant pts with hyperkalemia (HK).

Methods: Data were pooled from two completed phase 3 prospective, randomized, placebo-controlled trials: ZS-003 and HARMONIZE. Both trials had an induction phase, where pts received 10g ZS-9 TID for 48h, and a maintenance phase.
Results: In the ZS-003 and HARMONIZE studies, 9 CKD pts had previously undergone solid organ transplants (5 kidney, 3 liver, 1 dual kidney/liver) and were receiving various immunosuppressive therapies including calcineurin inhibitors, antiprofiletive agents and corticosteroids; 4 pts had heart failure and diabetes, and 5 were on RAASi therapy. Mean serum K^+ declined from 5.76 mEq/L at baseline to 4.63 mEq/L at 48h in these pts (figure); 67% and 100% of pts achieved normal serum K^+ by 24h and 48h, respectively. Median time to serum K^+ normalization was 4.0h. None of the transplant pts experienced an adverse event (AE) during the induction phase. In the overall pt population who received 10g ZS-9 during the induction phase (n=401), the most common AEs were GI disorders (3.7%).

Figure. Mean Serum K^+ Over Time in Transplant Pts.

Conclusions: ZS-9 appeared to restore K^+ to the normal range in transplant pts with IK, the response to ZS-9 in these pts appeared to be similar to that observed in the general pt population in the trials.

Funding: Pharmaceutical Company Support - ZS Pharma

TH-PO788
Effect of Renal Transplantation on Carotid Intimal Medial Thickness and Left Ventricular Mass Index-A Longitudinal Study Sandeep Mahajan, Sucheta Yadav, Yogesh Kumar Chhabra. Nephrology, A.I.I.M.S, Delhi, India.

Background: Various nontraditional risk factors (NTRFs) and increased left ventricular mass index (LVMI) have been implicated for high cardiovascular (CV) mortality in CKD. Renal transplantation (RT) by correcting uremic milieu improves most NTRFs, however CV mortality remains high post RT. This has been scarcely evaluated but could be due to exacerbation of traditional & NTRFs by drugs or legacy effect of previous CKD related risk factors. Carotid intimal medial thickness (CIMT) is established marker of structural and functional modifications of arterial wall. The aim of this study is to assess the change in CIMT and LVMI at baseline and after renal transplantation 

Methods: 131 consecutive, eligible & consenting adults undergoing live RT were enrolled from March 2014-15, of which 31 couldn’t complete 1-year follow-up. All investigations, CIMT & LVMI assessments were done at baseline (≤1 week prior to RT) & 1-year post RT. Patients with established coronary & valvular heart disease were excluded.

Results: In study population 85.5% subjects were male, mean age was 31.8±10.7 years & median dialysis vintage was 227 days. Basic disease was unclassified in 72.5% & 6.1% were diabetic. All were on 3-drug immunosuppression of mycophenolate mofetil, steroids & calcineurin inhibitors (94.6% Tacrolimus, 4.6% Cyclosporine). Mean Serum creatinine was 1.41±0.6 mg% at 1 year Mean CIMT (mm) & LVMI (g/m²) at baseline & after 1 year post RT were 0.51±0.01 & 0.49±0.1 (p=0.05) & 0±31±48 & 173±44 (p<0.001) respectively. CIMT correlated significantly only with age, BMI & LVMI (r=0.001), while LVMI was significantly increased only in patients with history of hypertension & those on >2 anti-hypertensive drugs (p=0.01).

Conclusions: In younger, low risk population we document no significant change in CIMT at 1 year post RT, while LVMI decreased by 14.7%. Further studies including more diabetic & elderly patients with longer follow up are therefore warranted.

Funding: Government Support - Non-U.S.

TH-PO791

Background: The incidence and characteristics of kidney stones in kidney transplant recipients are not well studied. The objective of this meta-analysis was to evaluate the incidence and types of kidney stones after kidney transplantation.

Methods: A literature search was performed using MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews from the inception of the databases through March 2016. Studies assessing the incidence of kidney stones in kidney transplant recipients were included. We used a random-effects model to estimate the incidence of kidney stones.

Results: Eighteen studies with 61,785 kidney transplant patients were included in the analysis. The incidence of kidney stones was 3% at 1 year post RT. Logistic regression analysis showed that the estimated incidence of kidney stones was 0.9% (95% CI, 0.6%–1.4%). The mean duration to diagnosis of kidney stones after kidney transplantation was 28 ± 22 months. The mean age of patients with kidney stones was 42 ± 8 years. Within reported studies, approximately 40% of kidney transplant recipients had kidney stones. Kidney stones were made of 62% calcium oxalate, 24% struvite, 13% calcium phosphate, 6% uric acid, and 2% cystine. None of the studies included were randomized controlled trials.

Conclusions: The incidence of kidney stones in patients after kidney transplantation is 0.9%. Although calcium based stones are the most common kidney stones after transplantation, struvite stones (also known as “infection stones”) are not uncommon in kidney transplant recipients. These findings may impact the prevention and clinical management of kidney stones after kidney transplantation.

TH-PO790
Association between Cardio-Ankle Vascular Index, Carotid IMT and Level of FGF-21 in Renal Transplant Patients Thanaand Trakarnvanich, Yingchit Wang. Renal Unit, Dept of Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj Univ, Bangkok, Thailand; Renal Unit, Dept of Medicine, Renal Unit, Dept of Medicine, Navamindradhiraj Univ, Bangkok, Thailand.

Background: Cardiovascular disease is the major cause of death in patients with CKD, even after renal transplantation. The major risk factor is arterial stiffness. The cardio-anke vascular index (CAVI) was developed as an indicator of arterial wall stiffness. Fibroblast growth factor 21 (FGF-21) is a metabolic regulator and elevated FGF-21 levels have been reported in coronary heart disease and carotid artery plaque. We aimed to study the association of CAVI with FGF-21 and their relationship to cardio-ankle vascular index (CAI), carotid IMT, FGF-21, medication after renal transplantation, and incidence of cardiovascular disease.

Methods: A total of 90 participants who underwent renal transplant were included in the study. The following measurements were done and laboratory data collected: CAVI, echocardiogram, homocysteine, hs-CRP, carotid IMT, FGF-21, medication after renal transplantation, and incidence of cardiovascular disease.

Results: The average CAVI score was 7.51±1.69. The CAVI values had a positive correlation with carotid IMT and a negative correlation with homoglobin (r=0.214, P=0.000) and r=-0.219, P=0.044, respectively. No association was observed between CAVI and FGF-21. FGF-21 had a positive correlation with hs-CRP, urine protein excretion, triglyceride, and a negative correlation with renal function. The average carotid IMT score in this study was 0.57±0.18. Patients with age above 60, low cholesterol and HDL, and high BMI had significantly higher carotid IMT.

Conclusions: CAVI values after renal transplantation were within normal range and showed an association with carotid IMT. Despite the negative association with FGF-21 in this study, FGF-21 still had a positive correlation with hs-CRP, lipid profile and urinary protein.

Background: Adiponectin has antiatherogenic effects and prevents the development and recurrence of cardiovascular events. However, few long-term studies have been conducted on changes in serum adiponectin levels and arterial calcification in renal allograft recipients.

Methods: The effects of serum ADPN fractions on renal functions and serum lipid markers were examined in 51 Japanese patients. The calcification of abdominal aorta was examined by CT scan based on aortic calcification index (ACAI) and aortic calcification area index (ACAI), in order to reveal the relationship in the rate of change between arterial calcification and serum high- and low-molecular weight (HMW-LMW-ADPN) fractions during 8 years. Furthermore, factors influencing vascular calcification such as age were also examined.

Results: The rates of change of ACM and ACAI at the abdominal aorta were grouped into quartiles for comparison with the alteration of ADPN fractions for 8 years. As a result, the rate of change of ACM and ACAI were much lower in the highly HMW-ADPN elevated group (p=0.001). In the multiple regression analysis, an advanced age at transplantation increased the rate of changes in ACM, while the increased the rate of changes in HMW-ADPN concentrations decreased it. In addition, an advanced age at transplantation and a history of cardiovascular complications increased the rate of changes in ACAI, while both the increase of HMW-ADPN concentrations and the improvement of transplant resulted in lower rate of changes. In this model, eGFR was negatively correlated with HMW-LMW-ADPN concentrations (r=−0.300, p<0.033 and r=−0.380, p<0.006, respectively). BMI was positively correlated with the LDL-C/HDL-C ratio and negatively correlated with the HDL-C values (r=0.412, p=0.003 and r=−0.379, p=0.006, respectively). In a multiple regression analysis, the increased rate of changes in HDL-C was a significant factor improving the HMW-ADPN concentrations.

Conclusions: The increase of HMW-ADPN associated with HDL-C may inhibit the progression of vascular calcification at the abdominal aorta in Japanese renal allograft recipients during 8 years follow-up.

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

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Improvement of Arterial Stiffness Parameters after Kidney Transplantation: A Systematic Review and Meta-Analysis

Aim: To evaluate the impact of kidney transplantation (KT) on arterial stiffness and the association with cardiovascular outcomes.

Methods: We conducted a systematic review and meta-analysis of observational studies examining the effects of KT on arterial stiffness parameters.

Results: A total of 32 studies were included, encompassing 1,964 KT recipients and 3,318 non-KT controls. KT was associated with a significant decrease in pulse wave velocity (PWV) and augmentation index (AI) compared to controls. The overall mean difference in PWV was -1.58 m/s (95% CI: -2.97 to -0.20, I²=0%) post-KT. In subgroup analyses, this reduction was observed in both brachial-ankle PWV (3 studies, 151 patients) and aortic PWV (5 studies, 160 patients). Aortic PWV was lower in KT recipients compared to controls (WMD = -1.59 m/s, 95% CI: -2.97 to -0.20, I²=0%).

Conclusions: Kidney transplantation is associated with a significant decrease in arterial stiffness, particularly in aortic PWV, which may contribute to improved cardiovascular outcomes.

Endovascular Management of Transplant Renal Artery Stenosis: A Safe and Effective Procedure

Aim: To evaluate the safety and efficacy of endovascular stent placement for transplant renal artery stenosis (TRAS).

Methods: We conducted a retrospective review of all cases of TRAS from January 2011 to April 2016.

Results: From 519 renal transplant patients, 26 percutaneous procedures were performed on 24 patients (46%). In all patients, renal function improved with 92% recovering of renal function before 30 days. One patient died from unrelated causes to the procedure. No immediate complications were observed.

Conclusions: Endovascular stent placement for TRAS is a safe and effective procedure for restoring and maintaining graft function.

Detection of Silent Myocardial Ischaemia Using Radionuclide Imaging

Aim: To assess the role of radionuclide imaging in detecting silent myocardial ischemia (SMI) in kidney transplant recipients (KTRs).

Methods: A retrospective cohort study of KTRs without pre-transplant coronary artery disease (CAD) was conducted.

Results: Of 135 KTRs underwent 226 MPIs post-transplantation with 1.5 (1.1–2.6) years of follow-up. 91 patients had two serial MPIs, with a scan interval of 2.2 (2.0–2.5) years. SMI was observed in 10 (4.2%) patients, with an incidence of 2.2% per year. SMI was associated with a higher risk of MACE and death.

Conclusions: MPI is useful in detecting silent myocardial ischemia in KTRs, and may predict adverse cardiovascular outcomes.

The Nocturnal BP Profile and Sleep Disordered Breathing (SDB) in Renal Transplant Patients

Aim: To investigate the relationship between nocturnal blood pressure (BP) and sleep disordered breathing (SDB) in renal transplant patients.

Methods: 24-hour ABPM and polysomnography were performed in 24 patients with a median time to presentation of 101.9 months. Night-time systolic BP and the night/day SBP ratio were linearly related with AHI and to a weaker extent with severe SDB (AHI >15). Night-time systolic BP (r=0.19, P=0.005) and the night/day SBP ratio (r=0.18, P=0.01) were linearly related with AHI and to weaker extent with severe SDB (AHI >15).

Conclusions: Nocturnal hypertension and the non-dipping BP profile in renal transplant patients capture exposure to vascular barotrauma which is not apparent when BP is measured in the office or when the average 24h ABPM is considered. Further risk factors for the altered nocturnal BP profile in renal transplant patients are still undefined.

Detection of Silent Myocardial Ischaemia (SMI) using Radionuclide Imaging and Long-Term Outcomes after Kidney Transplantation

Aim: To evaluate the association between SMI and long-term outcomes in KTRs.

Methods: A retrospective cohort study was conducted.

Results: Of 135 KTRs undergoing 226 MPIs post-transplantation, 10 (4.2%) had SMI, with an incidence of 2.2% per year. SMI was associated with a higher risk of MACE and death.

Conclusions: MPI is useful in detecting silent myocardial ischemia in KTRs, and may predict adverse cardiovascular outcomes.

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Conclusions: MPI is useful in detecting silent myocardial ischemia in KTRs, and may predict adverse cardiovascular outcomes.
Conclusions: Sleep disordered breathing, as measured by the AHI, is the most powerful correlate of a nine altered nocturnal BP profile in renal transplant patients. Since sleep disordered breathing is highly prevalent in dialysis patients and in part regresses after renal transplantation, these associations suggest that persistence of this disturbance is a major player for the excessive nocturnal BP burden in transplant patients.

Funding: Government Support - Non-U.S.

TH-PO797
Post-Transplant Hypertension: A Potential Role of Genetic Kidney Disease
Ekamol Tanitsattam1, Weiwa Sukhumthammarat2, Prapat Putthapiban1, Wassawat Vuthikrai2. 1Oakland Univ William Beaumont School of Medicine, William Beaumont Hospital, 2Mahidol Univ.

Background: Genetic factor plays a role in hypertension(HTN). Kidney transplantation from non-hypertensive donors may improve post-transplant HTN.

Methods: A total of 103 kidney transplantations were reviewed. There were 32 living-donor renal transplant(LDRT), 15 living-related and 17 living-unrelated) and 12 deceased donor renal transplant(DDRT) recipients, who received paired deceased donor kidneys (derived from the same donor transplanted to different recipients) leading to 5 “mate” recipient pairs.

Results: Of 44 recipients, mean age was 53.3 yrs(odd(21.4-79.5)) and 57% were female. Mean duration of follow-up was 7.93 mo(6.10-16.3). Mean serum creatinine(SCr) was 1.4+/−0.1(LDRT 1.23+/−0.05 vs. DDRT 1.95+/−0.29;p=0.0006). Up to 93% of recipients had pre-transplant HTN, and 45% became non-hypertensive-post-transplant-SBP≥140, DBP≥90, or on ≤2 BP agents regardless SBP or DBP. Mean pre-transplant SBP was lower than mean post-transplant SBP but not statistically significant(132±2.63 vs. 135±2.42;p=0.3526) as same as DBP(77±1.74 vs. 80±2.13; p=0.2406). Among 13 LRRT recipients with pretransplant HTN, 5 patients were non-hypertensive-post-transplant; whereas 16 of 29(55%) recipients of unrelated recipients (LURT+DDRT) became non-hypertensive(Figure1A). Among 11 DDRT recipients with pretransplant HTN, only 4 patients(2 mate pairs) had the same post-transplant BP outcomes(Figure1B). Pretransplant BP, the number of BP medications, and normotensive kidneys were not determinants of post-transplant HTN in a logistic regression model.

Conclusions: Pre-transplant HTN may be resolved post-transplantation. Since the prevalence of post-transplant HTN trends to be lower in recipients receiving kidneys from unrelated donors (LURT+DDRT) compared to those recipient of LRRT, genetic factors may play an important role in pathogenesis of post-transplant HTN.

TH-PO798
Renal Angioplasty Improves Short-Term Blood Pressure and Renal Autograft Function in Transplant Renal Artery Stenosis
Ekamol Tanitsattam1, Aneesa A. Shetty2, Lorenzo G. Gallon2. 1Oakland Univ William Beaumont School of Medicine, William Beaumont Hospital, 2Northwestern Univ.

Background: Similar to non-kidney transplant patients, the favorable outcomes of renal angioplasty/stenting on blood pressure(BP) control and renal function are unclear. We aim to describe these outcomes after this procedure and identify risk factors of transplant renal artery stenosis(TRAS).

Methods: Of 225 medical records(2008-2015), 209 kidney transplant recipients in whom angiography-proven TRAS was diagnosed in 19. Each of the 19 patients was individually matched to 3 subjects without TRAS based on age, gender, diabetes, and year of kidney transplantation.

Results: The TRAS group had a mean age of 50.3 years old and was 63% diabetic, 84% male, and 42% white. About 1/3 of the patients had HTN as the cause of ESRD. Median time to TRAS onset after transplant was 3.4 months(0.4-6.3), and median duration of follow-up after diagnosed TRAS was 2.16 years(0.36-3.5). SBP and serum creatinine(SCr), but not DBP were lower after transplant renal artery angioplasty/stenting (1-mo post- minus pre-angiographic differences: mean SBP 19±4.29 mmHg-55 to 65±0.01), median SCr 0.16+/−0.14 to 9.57+/−0.008, and mean DBP 67.1±14.4 mmHg-12 to 35+/−0.06). Median duration of follow-up from transplantation to the time when the most recent SCr was measured was 2.8 and 2.5 years in TRAS and control groups, respectively. In TRAS group, graft survival was 95% and all patients survived, whereas, graft and patient survival in control group were 93% and 91%, respectively. Compared to non-TRAS patients, history of BK virus(OR 2.1+/−0.19) may increase the risk of TRAS; however, neither history of CMV viremia nor other potential risk factors (serum Ca, PO4,PTH, vitamin D or donor age) was a statistically significant risk factor in a univariate conditional logistic regression.

Conclusions: Although limited to short-term follow-up, renal angioplasty/stenting improved BP and renal autograft function in TRAS patients. In addition, graft and patient survival do not appear lower than in non-TRAS patients. Potential risk factors of TRAS are still unclear given the small number of TRAS patients.

TH-PO799
Renal and Obstetrical Outcomes of Pregnancy in Kidney Transplant under Calcineurin Inhibitors
Juliette Perche. Nephrology, CHRU Lille, Lille, France.

Background: The management of calcineurin inhibitors(CNI) in renal transplant patients during pregnancy is still not clearly codified. Their per-partum CNI levels physiologically decrease leading to a frequent adjustment of dose, although without evidence of a concomitant decline of the therapeutic efficiency. We here report the features of pregnancies during which CNI doses were unchanged.

Methods: This retrospective study identified 34 pregnancies with unchanged dose of CNI in 27 renal transplant patients in a French single-center from 1987 to 2014. We studied their nephrologist, obstetrical characteristics and outcome.

Results: The mean age at pregnancy was 28.5 (±4.7). The creatinine level was lower than 1.5 mg/dl in 23 patients before pregnancy (mean: 1.28mg/dl; ±0.16). Immunosuppression regimen included tacrolimus or cyclosporine in 12 and 22 pregnancies, respectively. Mean residual levels decreased 48% for tacrolimus and 55% for cyclosporine (nadir: 30 weeks of amenorrhea, WA). Gestational hypertension occurred in 13 (38%) patients, complicated with pre-eclampsia in 6 of them. Prematurity was 44% (mean birth term: 35±3.7 WA) and 15 infants (47%) had a hypotrophy (mean birth weight: 2247±925 grams). HLA alloimmunization were identified in 6 patients (23%) at one year postpartum, including donor specific anti-HLA antibodies in 1 case. None acute rejection was reported and 1 (30%) developed a graft dysfunction within 2 years postpartum, related to immunological process, CNI toxicity or unidentified cause in 2, 2 and 4 cases respectively.

Conclusions: The no-adaptation of CNI dose according to their residual do not seems to induce more immunological complications or a poorer renal outcome. This can be explained by the fact that circulating free drug is increased during pregnancy due to hypalbuminemia. Considering the small size of our sample, more studies are nevertheless necessary to confirm these results.

TH-PO800
A Trial-Based Algorithm for Insulin Pump Therapy in Hyperglycemic Patients Early after Kidney Transplantation
Manfred Hecking1, Marcus Saemann1, Johannes Werzowa1,2. 1Nephrology, Medical Univ of Vienna, Austria; 2First Medical Dept, Hanusch Hospital Vienna, Austria.

Background: Correction of early postoperative hyperglycemia prevented posttransplantation diabetes mellitus in our previous proof-of-concept clinical trial. We hypothesized that insulin pump therapy with maximal dosing during the afternoon, in consequence of the morning administration of glucocorticoids, would further flatten the daily glucose profiles in comparison with insulin isophane.

Methods: In our multicentre study of insulin isophane versus standard of care (NCT01685331), we added a third treatment arm at a single center (NCT01680185), employing continuous subcutaneous short-acting insulin infusion therapy (CSII, Medtronic) in 24 previously non-diabetic kidney transplant recipients who had developed pre-supper hyperglycemia ≥140mg/dL.

Results: The final insulin lispro dose after up-titration of each patient was 9.6±6.0IU daily on average ± standard deviation, compared to 17.0±11.4IU overall in the previous insulin isophane group. The insulin algorithm below shows, 75.4% of the total daily dose were administered from 11am-7pm.

Conclusions: The no-adaptation of CNI dose according to their residual do not seems to induce more immunological complications or a poorer renal outcome. This can be explained by the fact that circulating free drug is increased during pregnancy due to hypalbuminemia. Considering the small size of our sample, more studies are nevertheless necessary to confirm these results.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Hypoglycemia ≥52mg/dL was observed twice. Glucose profiles in CSII patients were flatter than in the previous insulin subcutaneous group, and lower, on average, the greatest decrease in glucose occurred fasting.

Conclusions: The first algorithm for CSII therapy against early postoperative hyperglycemia in previously non-diabetic kidney transplant recipients was safe, employed less insulin, but provided better efficiency than previous insulin subcutaneous treatment.

Funding: Pharmaceutical Company Support - Astellas Pharma, Private Foundation Support, Government Support - Non-U.S.

TH-PO801
B-Trace Protein as Predictor of Cardiovascular Risk in Patients with Renal Transplantation Carola-Ellen Ruiner, Roxana Werberich, Louisa Werberich, Miranda Leunga Mboouamba, Rainer Woitas. Nephrology, Bonn Univ Hospital, Bonn, Germany.

Background: b-Trace protein (BTP) is an alternative marker for renal function. Furthermore, it has been suggested as predictor of mortality and coronary artery disease (CAD). We determined the prognostic value of BTP for cardiovascular risk and major adverse cardiac events (MACE) in patients following kidney transplantation.

Methods: The cohort consisted of 585 consecutive patients that were kidney transplanted between March 1996 and May 2015. MACE was defined as either myocardial infarction (ST-segment elevation (STEMI) or non ST-segment elevation (NSTEMI)), stroke, intervention requiring CAD or death for cardiovascular reasons. Blood samples were drawn prior to the kidney transplantation. BTP was measured by routine methods. Median observation time was 2.6 years. Data were analyzed by Mann-Whitney U tests, Kaplan-Meier survival and Cox regression analysis.

Results: MACE occurred in 17% of kidney transplant recipients on average after mean (±SD) 5.1 ± 4.4 years. Incidence of MACE in the first year following kidney transplant was highest (0.088%). Most frequently patients suffered from NSTEMI (11.7%), followed by STEMI (1.9%) and CAD (1.6%). Only 0.6% patients died due to cardiovascular reasons. BTP was significantly higher in patients with MACE compared to the other recipients (mean (±SD) 14.4 ± 5.7 vs 11.2 ± 5.2, p<0.001). BTP was a predictor of MACE in univariate analysis (HR 1.08, 95% CI 1.03-1.12, p=0.01). Serum BTP was divided into quartiles: Recipients with preoperative BTP ranging from 14.8 to 32 mg/l (4th quartile, mean ± SD 19.2 ± 3.9 mg/l) had an average time to event of 7 years (95% CI 6.1-8.3), while patients with BTP ranging from 11.2 to 14.7 mg/l (3rd quartile, mean ± SD 12.7 ± 0.1 mg/l) showed a mean time to event of 10 years (95% CI 8.9-11.3) (p=0.005). BTP remained an independent risk factor (HR 1.11, 95% CI 1.06-1.16, p<0.001) after adjustment for potential confounders' creatinine, e-reactive protein, gender and nicotine dependence.

Conclusions: Within the first year of kidney transplantation the incidence of MACE was the highest. BTP may be used to assess renal function, also to predict cardiovascular risk in in kidney transplant recipients' patients.

TH-PO802
Adverse Weight Gain after Kidney Transplantation Biruh Workeneh,1 Ahmed Osama Gaber,2 William E. Mitch,1 1Medicine/Nephrology, Baylor College of Medicine, Houston, TX; 2Surgery, Houston Methodist Hospital, Houston, TX.

Background: Among the most serious complications to these patients are adverse weight gain and the development of diabetes, commonly termed New-Onset Diabetes After Transplantation (NODAT) with consequent CV mortality. However, there is no consensus about the cause of post-transplant weight gain and the metabolic determinants of body composition change.

Methods: Our aims were to determine the nature of the weight gain after Tx (i.e., relative changes in fat vs. muscle vs. fluid volume) using DXA and total body potassium and nitrogen counters, and to determine effect on insulin sensitivity. We enrolled 22 subjects who have had pre-transplant and 3mo characterization and 8 subjects who have completed the protocol.

Results:

The cumulative weight gain after 1 year in 8 subjects was 6.8kg p=0.01. Fig 1 shows changes in body fat in 8 subjects who completed 1 year of follow-up and all but one had a significant increase in fat mass. The fat gain is primarily in the trunk (android fat distribution) than in the appendages, which has been linked to poorer cardiovascular outcomes. Insulin sensitivity quantified by Matsuda index show statistical and clinically significant worsening of insulin resistance. Changes in muscle mass does not contribute substantially to the gain of weight.

Conclusions: The results of this study will permit us to elucidate the complex metabolic underpinnings of excessive weight gain and insulin resistance that occurs frequently in kidney transplant patients and to potentially identify those at risk for adverse weight gain and develop effective interventions.

Funding: Private Foundation Support

TH-PO803
Prolonged Fluoroquinolone Prophylaxis to Prevent BK Viremia in Kidney Transplant Recipients Marie Jacobs, Jaclyn Daigneault, Margaret V. Thomas, Kerry Crisalli, David Wojciechowski. Massachusetts General Hospital.

Background: Prophylaxis regimens for renal transplant recipients have successfully lowered the early incidence of infections such as CMV. However, 1 and 3 months courses of fluoroquinolone prophylaxis have not proven decisively successful for BK virus, despite positive in vitro evidence. It is possible that the prophylaxis duration was too short.

Methods: We retrospectively evaluated the 1 year incidence of BK viremia in a cohort of patients transplanted from 7/1/2004 to 6/30/2014 who received 6 months of ciprofloxacin or levofloxacin post kidney transplant due to a sulfa allergy (n=10) compared to a no prophylaxis cohort transplanted from 7/1/2012 to 6/30/2014 (n=69). Inclusion criteria included BK viremia screening performed at least once in months 1-6 and months 7-11, and at one year post-transplant. We compared patient and transplant demographics and immunosuppression regimens between the groups. The primary outcome was the 1 year incidence of BK viremia.

Results: The groups did not differ significantly in demographic or transplant variables or immunosuppression regimens.

The incidence of BK viremia at one year was 10% and 24.6% in the prophylaxis and no prophylaxis group, respectively (p=0.64). There were no cases of BK viremia associated nephropathy in either group. Three cases of acute rejection developed in the no prophylaxis group, while none developed in the prophylaxis group (p=1.00).

Conclusions: A 6 month course of fluoroquinolone prophylaxis resulted in a numerically lower incidence of BK vireemia. Our data suggest that there may be a benefit of this strategy which warrants evaluation in a larger cohort of patients. The safety of this strategy must also be assessed.

Funding: Clinical Revenue Support

TH-PO804
Low Level Serum BK Viremia Is Not Associated with Increased Risk of Rejections, Infections or Poor Graft Survival Amber Hertz-Tang,1 Brad C. Astor,2 Maha A. Mohamed,2 Didier A. Mandelbrot,2 Arjang Djamali,2 Sandesh Parajuli,3 1Internal Medicine, Univ of Wisconsin, Madison, WI; 2Nephrology, Univ of Wisconsin, Madison, WI.

Background: BK virus infection is considered to be a risk factor for additional infections, increased risk of rejections and graft failure. There is limited data about association of low level BK viremia and graft outcomes.

Methods: This is a retrospective study among kidney transplant recipients (KTR) at our institution transplanted between 2006 and 2013. Serum BK polymerase chain reaction (PCR) is monitored every 2 weeks for first 3 months then every month from month 3-6 and then monthly from 6-12 months post-transplant. BK level is also checked prior to allograft biopsy. Patients were divided into three groups based on their BK level during the first year post transplant: no detectable BK level (G1), low level BK (G2(< 1000 copies/ml) and high level of BK (G3 (> 1000 copies/ml).A level of 1000 was chosen, as this is a generally accepted cutoff for adjusting immunosuppression at our institution.Results were adjusted for donor and recipient age, gender, and race, as well as, live vs. deceased donor, HLA mismatch, CMV status, cause of ESRD, prior transplant, induction, and DGF.

Results: There were a total of 1126 KTR, 841 were in G1, 51 in G2 and 234 in G3. Comparing between G1 and G2, there were no statistically significant differences in donor or recipient age, gender, race, or type of transplants. Incidence of rejections, CMV disease, rate of graft loss and mortality were also not significantly different. Comparing between G2 and G3, G3 had significantly higher rates of infections (p=0.004). The majority of infections were urinary tract infections. G3 had a higher trend toward increased rate of death and graft failure though not statistically significant.

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

279A
TH-PO805
Prevalence of BK Nephropathy Post Allogeneic Stem Cell Transplantation: Autopsy Evidence
Abu Alabdulbeye,1 Rima N. Pai,1 Ankita Tandon,2 Miao Zhang,1 Asha S. Mulkami,1 William F. Glass,2 1The Univ of Texas MD Anderson Cancer Center; 2The Univ of Texas Medical School at Houston.

Background: BK virus (BKV) is known to be causally related to chronic kidney disease (CKD) in renal transplant recipients. In hematopoietic stem cell transplant (HSCT) recipients, BKV is associated with hemorhagocytic syndromes. The relationship between BKV and CKD in HSCT recipients, however, is not as well established. We chose to investigate the prevalence of BKV in kidneys obtained at autopsy of patients that have undergone HSCT.

Methods: We retrospectively for patients that had undergone a HSCT and had an autopsy performed between 2004 and 2014. Formalin fixed paraffin embedded kidney tissue blocks from these patients were analyzed by light microscopy and anti-SV40 immunohistochemistry (IHC) for detection of BKV. Cases were considered positive for BKV if moderate-to-strong staining was present in nuclei of tubular epithelial cells with appropriate controls and semi-quantitated based on percentage of total tubular epithelial cells affected (<25% vs. >25%). Additional clinicopathologic parameters were collected.

Results: A total of 46 patients were included in the study. Sixteen patients (35%) had positive SV40 staining in ≥ 25% of tubular epithelial cells. In situ hybridization using a BK Biotin-labeled DNA probe further confirmed the prevalence of BK in the kidney.

Conclusions: We have demonstrated tissue evidence of the prevalence of BKV in renal tissue of stem cell transplant patients. The results of this study will help shed more light on the role of BK post SCT and progression to CKD. Further research in looking to understand predictors of the infection and a grading system to guide early intervention would be needed to improve SCT renal outcomes.

TH-PO806
Serum Levels of Uric Acid and Progression of Arteriolar Hyalinosis after Kidney Transplantation Yasuyuki Nakada,1 Izumi Yamamoto,1 Mayuko Kawanabe,1 Takafumi Yamakawa,2 Haruki Katsusuma,1 Ai Katsusuma,1 Akimitsu Kobayashi,1 Yudo Tanno,1 Ichiro Ohkido,2 Hiroyasu Yamamoto,1 Masayoshi Okumi,1 Hideki Ishida,2 Takashi Yokoko,1 Kazuunari Tanabe.1 Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan; 2Dept of Urology, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Arteriolar hyalinosis (AH) of the kidney is considered to be strongly associated with progression of chronic kidney disease (CKD). Aging, hypertension, and diabetes mellitus generally exacerbate the extent of AH in the native kidney. In addition, in allograft kidney, nephrotoxicity attributable to the calcineurin inhibitor (CNI) can also develop, increasing the severity of AH progression. In recent years, it has often been claimed that hyperuricemia induces AH progression and accelerates the nephrotoxicity caused by CNI. We postulated that, over time, the uric acid (UA) burden in allograft kidney recipients could influence AH progression and interstitial fibrosis/tubular atrophy (IFTA).

Methods: We evaluated 126 recipients who received kidney transplants from January 2005 to December 2009 at the Department of Urology, Tokyo Women’s Medical University. Patients with diabetes mellitus were excluded. Progression of AH and IFTA were considered present if the Banff scores increased by two or more. To evaluate factors associated with such pathological progression, we subjected clinical parameters (age, gender, blood pressure, serum CNI concentration, baseline UA in serum[s-UA]) to logistic regression modeling and considered positive for BKV if moderate-to-strong staining was present in nuclei of renal tubular epithelial cells affected (<25% vs. >25%). Additional clinicopathologic parameters were collected.

Results: The baseline s-UA was correlated with progression of IFTA (p=0.03) but not AH (p=0.86). However, the UA burden over time was associated with progression of both AH (p=0.03) and IFTA (p=0.01). Of other clinical parameters, donor age was strongly associated with AH progression (p<0.01).

Conclusions: Although IFTA progression was correlated with the UA burden over the whole course of disease, the UA burden over time, but not the baseline value, induced AH progression in transplanted kidney. Therefore, we suggest that monitoring s-UA after transplantation is important to prevent AH and IFTA progression.

TH-PO807
The Mammalian Target of Rapamycin Inhibitors and Post-Transplant Malignancy in Kidney Transplantation Lee-Mooy Lim,1 Hung-Tien Kuo.2 1Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan; 2Faculty of Rural Care, College of Medicine, Kaohsiung Medical Univ, Kaohsiung, Taiwan.

Background: Improving long-term graft and patient survival is a major challenge in kidney transplantation due to prolonged immunosuppression significantly increasing the risk of malignancy, contributing to the overall morbidity and mortality. The aim of our study was to investigate the association of Mammalian Target of Rapamycin Inhibitors (mTORI) usage (early and late) with major transplant outcomes and post-transplant malignancy in kidney transplant recipients from a medical center in Taiwan.

Methods: A total of 201 adult kidney transplant recipients surviving with a functioning graft for 1 year or more were included. The mean follow-up days were 2,306. mTORI users were categorized into early and late users at the cut-off of 6 months duration after transplantation. Odds ratios for malignancy were examined using multivariate logistic regression analysis while hazard ratios for clinical outcomes were analyzed using multivariate Cox regression analysis.

Results: The major causes of death in our cohort were cardiovascular disease, malignancy and infection. Urinary tract urothelial carcinoma (UTUC) and hepatoma comprised the major malignancy after transplantation. After adjusting for confounding factors, mTORI users had lower risk of post-transplant malignancy (adjusted OR=0.28, P=0.04).

Conclusions: In our renal transplant recipients, the leading causes of death were cardiovascular disease, infection, and malignancy. The most common post-transplant malignancy were UTUC and hepatoma. The usage of mTORI was associated with a decreased risk of post-transplant malignancy.

TH-PO808
Chemoprevention of Cutaneous Squamous Cell Carcinoma (cSCC) in Long Term Renal Transplant Recipients (LRTR): A Case-Controlled Analysis Rachel Hung,1 Rakesh Anand,2 Mary Wain,2 Antonia Cronin.1 Renal, UCL Centre of Nephrology, Royal Free Hospital, London, United Kingdom; 1Renal, MRC Centre of Transplantation, Guy’s and St Thomas’ Hospital, London, United Kingdom; 2Dermatology, Guy’s and St Thomas’ Hospital, London, United Kingdom.

Background: Organ transplant recipients are up to 200 times more likely to develop cSCCs than age-matched general populations. Development of NMSC in LRTR is affected by Fitzpatrick skin type, ultra-violet light exposure, and the type and duration of immunosuppressive. Systemic retinoids have shown promising preventative effects against the development of cSCC; however this is associated with adverse side effects including liver dysfunction, dyslipidaemia, and use in renal impairment is cautioned.

Methods: We collected retrospective data from our cohort (n=469) of LRTR (>7 years) attending our annual review clinic, of which 108 patients had been diagnosed with NMSC. We identified patients (n=12) on treatment with the acitretin and matched them to an equal number of controls by age, total years from transplant and Fitzpatrick skin type. We compared GFR, liver function and lipid profile at 1 year pre, and 1, 3 and 5 years post commencing acitretin and the total number of cSCCs pre and post acitretin.

Results: Serum total cholesterol and LDL were significantly lower (p=0.007 and p=0.012 respectively) in patients prescribed acitretin at 5 years post treatment compared with baseline measurements. There were no other statistically significant differences in lipid profile, GFR or LFTs at baseline parameters and at 1, 3 and 5 years after starting treatment within cases or comparing cases and controls. After starting acitretin treatment the median number of new cSCCs per patient was 2 (0 – 4) which was significantly lower than the median number prior to treatment of 6 (3-10) p=0.005.

Conclusions: Acitretin usage did not adversely affect renal transplant function,liver function or lipid profiles when compared with baseline or matched untreated controls and showed a statistically significant reduction in total number of new cSCCs during 5-year follow-up. Acitretin can be considered as a safe and effective chemoprevention agent in selected LRTR with multiple SCCs who are under regular dermatology surveillance.

TH-PO809
The Incidence of Non-Melanoma Skin Cancers in Renal Transplant Recipients - Polish Centre Experience Alicja Debeka-Sliżen,1 Beata Imko-Walczuk,1 Maria Luiza Piesiakow,1 Sławomir Liszkowski,1 Boleslaw Rutkowski,1 1Dept of Nephrology, Transplantology and Internal Diseases, Medical Univ of Gdansk, Gdansk, Poland; 2Dermatology Dept, Copernicus Hospital in Gdansk, Gdansk, Poland.

Background: Non-melanoma skin cancers (NMSCs), especially squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most frequent malignant neoplasms in renal transplant recipients (RTRs). SCC, due to its unusual and aggressive
clinical course in RTRs, is a diagnostic and therapeutic challenge. The aim of the study was to assess the incidence of NMSSCs in Polish population of RTRs and propose methods of prevention and early diagnosis.

Methods: We included prospectively and retrospectively 77 patients with NMSSCs in a group of 813 RTRs, who were patients of Nephrology, Transplantology and Internal Dialysis Department of Medical University of Warsaw between years 1980-2015. Majority of study group (92.2%) underwent a single transplantation (Tx) and the mean time of observation was 12.5±5.8 years. The most frequently treatment scheme was MMF (mycophenolate mofetil)-CSA (cyclosporine A)-GS (glucocorticosteroids) 33.8%, MMF- TAC (tacrolimus)-GS - 22.2%.

Results: In 77 patients, 139 NMSSCs were diagnosed. It shows more than 233-times higher risk of NMSSCs development in Polish RTRs (p=0.000001). The median time since the Tx to cancer diagnosis was 75.5±3.0 months between BCC and 80.0±13.5 months for SCC. Furthermore a single lesion was diagnosed in 61.0% patients, whereas the others presented a multifocal cancers. 73.7% SCC were noticed in RTRs who received CSA as a immunesuppressive treatment and 73.3% BCC were diagnosed in patients using MMF in treatment scheme.

Conclusions: The incidence rate of skin cancer in Polish RTRs population is more than 233-times higher compared with the immunocompetent individuals (ICs). The SCC to BCC ratio increases from 0.2:1 in general population to 0.7:1 in our study group. Skin cancers in RTRs very often develop multicentrically.

TH-PO810
The New Method of Vesico-Ureteric Reflux Prophylactic in Kidney Transplant Recipients: Randomised Clinical Study

Background: Vesico-ureteric reflux (VUR) is a common complication in renal transplant recipients. VUR is associated with increased risk of UTI and graft loss. The objectives of that study were to determine the incidence and risk factors of VUR, to create and assess the efficacy of new method of VUR prophylactic in kidney transplant recipients.

Methods: We conducted case-control survey of 68 patients to detect the risk factors for VUR in renal allograft. Voiding cystograms were performed to find the reflux. We checked the association of VUR with recipient’s gender, age, type and duration of dialysis, residual urine volume output, cold ischemia time, ureteric stent placement, kidney function and infections. The new method of antireflux defense consists of the ureteroneocystostomy by Starzl with JJ stent placement followed by the simultaneously stent removal and endovesical submucosal injection of bulking substance on POD 30. To prove the efficacy of the new antireflux defense method, we considered a randomized clinical study. The incidence of VUR in the study group of 813 RTRs, who were patients of Nephrology, Transplantology and Internal Medicine department of Medical University of Warsaw between years 1980-2015. Of the 82 patients, 27 were treated with antibiotics. Only 8 admissions to hospital were associated with AB during follow up (n=1 pylonephritis, n=4 urosepsis, n=3 symptomatic UTI). All of these patients had previously received antibiotics for AB prior to the admission. A further 12 patients during follow up later developed symptomatic UTI not requiring hospital admission (8 of which were also previously treated for AB).

Conclusions: Asymptomatic bacteriuria led to few admissions and complications. Treating patients did not seem to prevent subsequent admissions. A high proportion of ‘Heavy mixed growth’ may indicate incorrect collection. Practice varies widely amongst clinicians but the vast majority of ABs are not being treated.

TH-PO813
High Incidence of Arterial and Venous Thrombosis in Patients with AA Associated Vasculitis
Ante Ang,1 Marilina Antonelou,1 Anisha Tanna,1 Nathaniel Kulkammar,1 Vineet K. Tai1.1 Imperial College Renal and Transplant Centre, Imperial College NHS Trust, London, United Kingdom; 2Renal and Vascular Inflammation Section, Dept of Medicine, Imperial College London, London, United Kingdom.

Background: A few previous studies have shown an association between AAV and cardiovascular disease (CVD) and venous thromboembolism (VTE), which may be mediated by inflammation or anti-plaunmonogen antibody. We aimed to determine the incidence and risk factors for arterial and venous thrombosis in AAV associated vasculitis (AAV). AAV.

Methods: This single-centre retrospective cohort study presents the incidence of arterial thrombosis (defined as coronary events and ischaemic stroke), VTE and all-cause mortality in people diagnosed with AAV between 2005 -2014. We collected patient baseline characteristics, risk factors for CVD and VTE, and events of CVD, VTE, and all-cause mortality in people diagnosed with AAV between 2005 -2014. We collected patient baseline characteristics, risk factors for CVD and VTE, and events of CVD, VTE, and all-cause mortality in people diagnosed with AAV between 2005 -2014.

Results: 204 patients with AAV were identified with a median follow-up of 5.3 [range: 0.08-10] years or total of 1088 person-years. The overall incidence was 2.76/100 person-years for CVD (1.65 for coronary events and 1.10 for ischaemic stroke) and 1.47/100 person-years for VTE (0.83 for DVT only and 0.64 for PE with or without DVT). Two coronary events were fatal. 71 percent of our cohort had renal involvement with a median creatinine of 117 (IQR 73-268) mmol/L. On multivariate analysis only prior ischaemic heart disease was a predictor of CV events. CVD (but not VTE) was an independent predictor of all-cause mortality. When we removed patients with prior CVD the incidence of CV events was still elevated at 2.32/100 person-years (1.26 for coronary events and 1.06 for ischaemic stroke). When we compared these results with reported rates for the UK population, the rates in AAV patients were 17 times higher for coronary events, 10 times higher for acute myocardial infarction and 20 times higher for VTE.

Conclusions: Patients with AAV have a high incidence of arterial and venous thrombosis. These results may aid in the development of protocols to minimise thrombotic risk and improve prognosis for patients with AAV.

TH-PO814
Risk Factors of Severe Infections following Rituximab in ANCA-Associated Vasculitis
Andreas Kronbach,1 Julia Kerschbaum,2 Federico Alberici,1 Rachel Jones,1 David R. Wordsworth,1 1Addenbrooke’s Hospital, University of Cambridge, Vasculitis and Lupus Clinic, Cambridge, United Kingdom; 2Internal Medicine IV (Nephrology and Hypertension), Medical Univ Innsbruck, Innsbruck, Austria; 3Renal Medicine and Vasculitis, San Carlo Borromeo Hospital, Milan, Italy.

Background: Severe infections potentially leading to hospitalization are frequently observed in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The aim of our study was to investigate potential risk factors having an impact on severe infections in AAV.

Conclusions: Treatment of asymptomatic bacteriuria in the first year post-transplant may be beneficial to prevent subsequent episodes of symptomatic UTIs.

TH-PO812
Asymptomatic Bacteriuria in Renal Transplant Patients
Anna Price, Lukas Fogegetinner. Renal Dept, Queen Elizabeth Hospital Birmingham, Birmingham, West Midlands, United Kingdom.

Background: Patients with renal transplant are vulnerable to post-operative infection, particularly urinary tract infection (UTI). UTIs are linked with acute cellular rejection, graft loss, sepsis and death. The management of asymptomatic bacteriuria (AB) however, remains a clinical conundrum in these patients. The risk of untreated AB vs. the risk of antimicrobial side effects or overuse is unclear.

Methods: Aims: 1. Quantify the frequency and nature of AB amongst renal transplant population. 2. Determine our management of these cases and any adverse outcomes.

Methods: Between 1st January 2013 and 31st December 2013 132 renal transplant patients with AB were identified and followed up for 12 months. Demographic data was collected from electronic patient records. The urinary pathogen, bacterial count and white blood cell count of each AB was recorded following return to the clinic. Patient management, admissions and subsequent urine results were retrospectively reviewed.

Results: Of the 132 patients identified, 82 patients met inclusion criteria. There were more females (n=55) than males (n=27). The mean age was 50.8 yrs. (range 17-79yrs). All ABs had greater than 80 white blood cells (WBC) or 10³ bacterial organisms. Most ABs were ‘Heavy mixed growth’ or E.coli. Only 14 patients had complete resolution, 56 patients had AB recurrence and 12 patients had persistent AB throughout follow up. Of the 82 patients, 27 were treated with antibiotics. There were no related deaths or episodes of sepsis. Only 8 admissions to hospital were associated with AB during follow up (n=1 pylonephritis, n=4 urosepsis, n=3 symptomatic UTI). All of these patients had previously received antibiotics for AB prior to the admission. A further 12 patients during follow up later developed symptomatic UTI not requiring hospital admission (8 of which were also previously treated for AB).

Conclusions: Asymptomatic bacteriuria led to few admissions and complications. Treating patients did not seem to prevent subsequent admissions. A high proportion of ‘Heavy mixed growth’ may indicate incorrect collection. Practice varies widely amongst clinicians but the vast majority of ABs are not being treated.
**Valaciclovir to Prevent Cytomegalovirus Mediated Adverse Modulation in ANCA-Associated Vasculitis (CAVAS)**

 Valaciclovir treatment there was a significant reduction in both the mean percentage of CD4+CD28- cells (mean reduction 23% (95% confidence interval (CI) 3-39%; p=0.039) and the absolute count of CD4+CD28- cells (mean reduction 27% (95%CI 17%-37%;p=0.013) whereas no significant change was seen in the control group (mean change -5% (95%CI -18% to -11%) p=0.449 and -7% (95%CI -25% to -16%; p=0.523) respectively. The reduction in CD4+CD28- cells in the valaciclovir treated group persisted 6 months after cessation of treatment. Valaciclovir was well tolerated. None of the patients had clinical CMV reactivation.

**Conclusions:** Blocking subclinical CMV reactivation led to a persistent reduction in CD4+CD28- cells suggesting CMV causes the expansion of this cytotoxic T-cell subset and offering novel therapeutic opportunities in AAV to reduce the risk of infection, CVD and mortality.

**TH-PO817**

**High Incidence of ANCA-Associated Vasculitis after the Great East Japan Earthquake**

**Background:** ANCA-associated vasculitis including microscopic polyangiitis (MPA) is triggered by silica exposure. After the Great East Japan earthquake on March 11 in 2011, tsunami waves produced a huge volume of silica-containing sludge. We aimed to determine if the incidence of the MPA increased following the serious disaster.

**Methods:** This is an observational retrospective population-based study in a single institute. Forty-three consecutive patients were selected through the CHCC2012 criteria for the MPA from 2007 to 2015. We fitted the Poisson regression model to the incidence with the annual population of the medical district. The participants were selected during 3-year period from before (13 people) to after the disaster (20 people). The differences between the groups were analyzed by using Fisher’s exact test and the Mann-Whitney U test. Overall survival was calculated according to the Kaplan-Meier method. All statistical data were analyzed by using EZR.

**Results:** The incidence of MPA per million increased after the disaster (λ= 17.4 [95% CI: 7.60 to 36.8]) in the disaster group compared to the non-disaster group (λ= 3.1 [95% CI: 17.7 to 61.7]) after the disaster. (P = 0.004). High Birmingham Activity Score was associated with a high incidence of MPA after the disaster (16.0 [12.0 - 18.0]) before the disaster and 18.0 [16.0 - 22.0] after the disaster, (P = 0.019). The overall survival of the patients with MPA declined after the disaster (P = 0.01 by log rank test).

**Conclusions:** The incidence of MPA increased after the Great East Japan earthquake. The patients enrolled after the disaster had severe symptoms and a high mortality rate.

**TH-PO818**

**Reestablishment of Immune Tolerance in ANCA-Associated Vasculitis: A Cohort with Both Sustained Undetectable Antibody, and Disease Free Remission**

**Background:** ANCA associated vasculitis (AAV) is associated with disease relapse in up to 50% of patients despite immunosuppression (IS). We studied patients who became persistently AANA negative off IS without relapse to define a tolerant phenotype.

**Methods:** Patients at 3 centres were identified who became AANA negative and were off IS therapy for 2 years or more. Clinical, and laboratory data were analysed. A subset of tolerant patients were compared to other remission patients and healthy controls.

**Results:** 35 tolerant patients were identified. Baseline characteristics are shown in Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, median (range))</td>
<td>59 (14-74)</td>
</tr>
<tr>
<td>Female/Male</td>
<td>22/13</td>
</tr>
<tr>
<td>MPO/PR3/both</td>
<td>17/17</td>
</tr>
<tr>
<td>UK/China/Netherlands</td>
<td>7/11/17</td>
</tr>
<tr>
<td>System</td>
<td>MPO/PR3 (%)</td>
</tr>
<tr>
<td>Renal</td>
<td>82/59</td>
</tr>
<tr>
<td>Lung</td>
<td>47/56</td>
</tr>
<tr>
<td>ENT</td>
<td>29/61</td>
</tr>
<tr>
<td>Eyes</td>
<td>6/33</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>18/17</td>
</tr>
</tbody>
</table>

**Induction regimens included steroids (97% patients) and cyclophosphamide (88%).** During maintenance, 67% received azathioprine. All patients became AANA negative and ceased IS. Median time to AANA -ve was 5.5 months (ms) and was similar in CANCA negative AANA-ve (6m; P=0.59). The cohort proportion who were AANA -ve at 6ms was similar to patients analysed in the IMPROVE trial (P=0.67). Median time to stop therapy was 30.5ms and did not differ according to AANA type (P=0.60). Median duration of AANA -ve follow-up is 61ms with median duration off IS of 46ms. Analysis of PBMC in a subset of these patients (n=4) demonstrated significantly higher proportion of CD24CD38+ regulatory B cells compared to non-tolerant remission patients (n=33; p=0.002) and similar levels to healthy controls (n=9). Proportions of regulatory T cells did not differ significantly. Analysis of leukocyte subsets is ongoing and may provide insight into cellular mechanisms underpinning restoration of tolerance.

**Conclusions:** AAV patients who remain persistently AANA -ve off IS are uncommon, are clinically similar to other remission patients, but display different molecular phenotypes. **Funding:** Government Support - Non-U.S.

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

**Underline represents presenting author.**
**TH-PO819**

**Risk Factors of Treatment-Related Diabetes Mellitus in ANCA Vasculitis**  
**Patrick H. Nachman,** Yichun Hu, Caroline J. Pouton, William Franklin Pendergraff, Ronald J. Falk, Susan L. Hogan. *UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC.*

**Background:** Diabetes mellitus (DM) is a complication of glucocorticoid treatment which affects a third of patients with ANCA-associated vasculitis (ANCA-V). We describe the time course and complications of treatment-related DM and identify the independent risk factors in a large cohort of patients with ANCA-V.

**Methods:** Patients with ANCA-V and no prior history of DM were selected from the Glomerular Disease Collaborative Network. The association of induction IV methylprednisolone (MP) with DM was evaluated as a categorical (exposure vs no) and as continuous (cumulative dose). Several multivariable proportional hazard models were explored to identify independent risk factors of DM [results reported as hazards ratios (HR) with 95% confidence intervals (CI) and p-values].

**Results:** 454 patients were identified (median age 59 years (IQR 45, 70), 55% MPO-ANCA positive). Median follow up was 2.8 years (IQR 1, 2, 6.2), 153 (34%) developed DM in a median of 0.69 months (IQR 0.07, 4.05). DM was associated with a higher frequency of severe infections. By multivariable analysis, exposure to, cumulative dose of MP, PR3-ANCA, and the combination of family history of DM and BMI ≥ 26.5 kg/m² were associated with an increased risk of DM. ENTER disease was associated with an increased risk.

**Variable** | **HR (95% CI)** | **P value**
--- | --- | ---
Age (per year) | 1.021 (0.99, 1.05) | 0.012
Female Sex | 1.450 (0.92, 2.34) | 0.125
MP (exposure vs no) | 1.751 (1.08, 2.84) | 0.024
MP (cumulative dose, per g) | 1.241 (1.05, 1.47) | 0.012
No Family Hx & BMI ≥ 26.5* | 1.590 (0.88, 2.88) | 0.126
Family Hx & BMI < 26.5* | 1.830 (0.85, 4.18) | 0.118
Family Hx & BMI ≥ 26.5* | 2.701 (4.55, 50.2) | 0.002
PR3- vs MPO-ANCA | 1.781 (10.2, 8.88) | 0.019
ENT (vs no) | 0.500 (30.38, 0.85) | 0.01

*vs No Family Hx & BMI < 26.5.

**Conclusions:** In addition to combined obesity and family history, treatment-related DM in ANCA-V is independently associated with PR3-ANCA and exposure to induction MP. The relative benefits and risks of IV MP in treating ANCA-V are not well established. Our results support using IV MP sparingly in patients at risk of DM.

**Funding:** NIDDK Support

**TH-PO820**

**Immunoglobulin Levels and Infection Risk with Rituximab Induction for ANCA Associated Vasculitis**  
**Shivani Shah,** Keckio I. Greenberg, Duvuru Geetha. *Johns Hopkins Univ.*

**Background:** Rituximab (RTX), a B cell depleting anti-CD20 monoclonal antibody, is approved for treatment of ANCA associated vasculitis (AAV). Low immunoglobulin (Ig) levels have been observed surrounding RTX treatment. The association between the degree of Ig deficiency and infection risk is unclear in AAV patients.

**Methods:** AAV patients treated with RTX for remission induction in a single center (2005 to 2015) with serum Ig measurements were included. Patient characteristics, serum Ig levels, and occurrence of infections were collected retrospectively. Logistic regression models were adjusted for age at RTX administration and race.

**Results:** Our cohort of 28 patients had a median age of 65 years; 23 were women; 15 had GPA; and 13 were PR3 ANCA positive. Ten received concomitant cyclophosphamide. Mean IgG, IgM and IgA Ig levels were 569.8 mg/dL, 47.8 mg/dL, and 123.1 mg/dL, respectively. Twenty one patients had low serum IgG levels (<750 mg/dL) following RTX treatment. Over 2.4 years of follow up, 5 individuals developed infections requiring hospitalization (3 bacterial pneumonia, 1 PJP pneumonia, and 1 C. difficile colitis). IgG level ≤375 mg/dL was associated with higher odds of infection requiring hospitalization compared to IgG level >375 mg/dL (odds ratio 26.7, 95% CI: 1.0-452, p=0.023). Similarly, low IgM and IgA levels were also associated with infection.

**Conclusions:** Lower Ig levels were associated with increased odds of infection requiring hospitalization in this cohort. Further investigation is warranted given our study is limited by small sample size, concomitant cyclophosphamide use, and variable timing of Ig measurement.

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

**283A**
Methods: Retrospective review of all patients identified as MPO-ANCA positive, as determined by Luminex testing in our laboratory over a 4 year period. Case notes and laboratory results were reviewed subsequently to establish if they had a diagnosis of AAV or alternate diagnoses.

Results: Two hundred and eight patients were positive for MPO-ANCA, of whom 121 (58.2%) had primary AAV. Seventy nine (37.9%) patients were anti-MPO positive without AAV. Clinical associations included other autoimmune disorders (69.6%), infections (8.9%), malignancy (5.1%) and other miscellaneous conditions (16.4%). The median (IQR) MPO-ANCA titre in this group was 16 (12-30) mU/ml vs 66 (24-100) mU/ml in the group with primary AAV (p<0.001). Thirty eight (40%) patients without known AAV had renal impairment defined as eGFR<60mL/min or/and uPCR>0.1g/gCr ≥100. Twenty two of these two patients had a kidney biopsy that ruled out the diagnosis of primary AAV. The characteristics of the 16 patients that were not biopsied are shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>n=16</th>
<th>Age, mean(SD)</th>
<th>Male/Female</th>
<th>Anti-PR3 positive</th>
<th>Anti-MPO positive</th>
</tr>
</thead>
</table>

Conclusions: In patients with MPO-ANCA positivity, 37.9% showed a variety of underlying non-vasculitic conditions, much higher than that reported for PR3-ANCA, in which 9.7% of patients did not have AAV(1). As detectable antibodies may predate the onset of disease, unexplained ANCA findings require long-term follow up and often warrant tissue diagnosis.

TH-PO824
Therapeutic Effect of Plasma Exchange in the Treatment of Severe Renal Damage in Anti-Neutrophil Cytoplasm Antibody Associated Vasculitis
Liping Wang, Div of Nephrology, Fuzhou Dongfang Hospital, Fuzhou, Fujian, China.

Background: Anti-neutrophil cytoplasm antibody-associated vasculitis (AAV) is associated with high rates of mortality due to uncontrolled disease and treatment toxicity. Small randomized trials suggest adjunctive plasma exchange(PE) may improve disease control.

Methods: ALL AAV patients presenting between 2011 and 2013 were retrospectively analyzed. The patients were divided into two groups according to the presence of PE or not. The two groups in age, sex, BVAS, serum creatinine and the level of ANCA have no statistical difference (P > 0.05). Patients were treated with corticosteroids, and intravenous CYP.

Conclusions: Therapeutic effect of Plasma exchange in the Treatment of Severe Renal Damage in Anti-Neutrophil Cytoplasm Antibody Associated Vasculitis

Results: Forty-six patients were included. The two groups in age, sex, BVAS, serum creatinine and the level of ANCA have no statistical difference (P > 0.05). PE group had a higher level of serum creatinine in the 6 months (1.9±1.8 vs 1.6±1.8)RU/mL(P<0.05), serum creatinine from [570.8±206.1] to [465.7±191.0]mU/mL(P<0.05). In control group, the level of serum creatinine from [169.0±86.4] to [146.9±61.8]RU/mL(P<0.05), serum creatinine from [570.8±206.1] to [465.7±191.0]mU/mL(P<0.05). In control group, the level of serum creatinine from [169.0±86.4] to [146.9±61.8]RU/mL(P<0.05), serum creatinine from [570.8±206.1] to [465.7±191.0]mU/mL(P<0.05). In control group, the level of serum creatinine from [169.0±86.4] to [146.9±61.8]RU/mL(P<0.05). Serum creatinine from [570.8±206.1] to [465.7±191.0]mU/mL(P<0.05).

Conclusions: PE combined corticosteroids and intravenous CYP could effectively reduce the level of AAV and improve renal function rate, delay of dialysis independence at 3 months was higher than control group, but the long-term survival In PE group was no difference from the control group.

Funding: Government funding - Non-U.S.

TH-PO825

Background: ANCA associated vasculitis is classically associated with a necrotizing crescentic glomerulonephritis with a lack of immune deposits on immunofluorescent microscopy. We studied the prevalence and characteristics of immunofluorescent deposits in a cohort of patients with known ANCA associated vasculitis.

Methods: We performed a retrospective, single centre cohort study in Hamilton, Canada. We identified patients with a clinical diagnosis of granulomatosis with polyangiitis or microscopic polyangiitis and a renal biopsy. Biopsy records were reviewed for reports of the type, location and intensity of immune deposits on immunofluorescence. Patient characteristics were extracted from clinical charts with a standardized case report form. Biopsy and clinical characteristics were summarized using descriptive statistics. We used multivariable logistic regression to determine if there was an association between immunofluorescent staining and age, sex, ANCA type or need for dialysis at time of biopsy.

Results: We identified 69 patients with ANCA associated vasculitis and a renal biopsy. The median age at biopsy of the 69 patients was 57 (range 21-70) years old. Case notes and laboratory results were reviewed subsequently to establish if they had a diagnosis of AAV or alternate diagnoses.

Conclusions: Although the glomerulonephritis in ANCA associated vasculitis is classically described as pauci-immune, 30-40% of patients have immunofluorescence staining, most often men.

TH-PO826
Distribution of Neutrophil Extracellular Traps in the Kidney Suffering from Myeloperoxidase-ANCA Associated Vasculitis with Peritubular Capillaritis
Naoko Tsui, Takayuki Tsujii, Naro Ohashi, Akihiko Kato, Hideo Yasuda. Internal Medicine 1, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan.

Background: Neutrophil extracellular traps (NETs) have been shown to contribute to development of MPO-AAV. We previously reported that peritubular capillaritis (PTC) was accompanied by 55% of patients with myeloperoxidase-ANCA associated vasculitis (MPO-AAV). We hypothesized that NETs could be found around PTC as well as crescentic formation in MPO-AAV. The purpose of this study is to reveal the distribution of intrarenal NETs in MPO-AAV with PTC.

Methods: We evaluated the distribution of NETs by immunofluorescence in paraffin-embedded tissue sections of 24 patients with MPO-AAV diagnosed by kidney needle biopsies at Hamamatsu University Hospital from January 2011 to January 2016. PTC was defined by histological findings of inflammatory cells accumulated in the peritubular capillary in association with the disruption of the capillary wall that was stained by anti-C34 antibody. NETs were identified by colocalization of DNA and citrullinated histone and MPO with confocal immunofluorescence microscopy.

Results: NETs were found around 13 (54.2%) of 24 patients with MPO-AAV. There were no significant difference in ages (70.0±17.1 vs 63.1±19.1), serum creatinine (1.62 ± 1.08 vs 2.15 ± 1.52 mg/dl), MPO-ANCA titers (156.5±108.8 vs 170.1±205.4 IU/ml) between MPO-AAV with and without PTC. NETs were seen more outside glomeruli especially in and/or around PTC. At last follow-up (median 5 years; range 1-10), 10 patients (15%) experienced development of PTC.

Conclusions: NETs were found around PTC in MPO-AAV with capillaritis, suggesting NETs might contribute to development of PTC.

TH-PO827
Long-Term Follow-Up of a Combined Rituximab and Low-Dose Cyclophosphamide Regimen for Remission Induction in Renal ANCA-Associated Vasculitis
Stephen Paul McAdoo,1 Nicholas R. Medjerda-Thomas,1 Anisha Tanna,1 Megan Griffith,1 Jeremy B. Levy,1 H. Terence Cook,1 Tom Cairns,1 Alan D. Salama,2 Charles D. Pusey,2 Imperial College Kidney and Transplant Centre, United Kingdom; Univ College Centre for Nephrology, United Kingdom.

Background: We have previously reported prolonged relapse-free survival in a cohort of 23 patients with renal AAV, following remission-induction treatment with a rituximab-based, cyclophosphamide-sparing regimen. We now report long-term outcomes using this protocol in an extended cohort of 66 patients.

Methods: We report long-term follow-up of consecutive patients presenting with new or relapsing renal AAV at our centre since 2006, who were treated with our published regimen of oral steroids, rituximab and low-dose pulsed intravenous cyclophosphamide. Patients who presented with alveolar haemorrhage, renal-failure requiring dialysis, or other severe disease manifestations requiring addition of plasma exchange were not included. Maintenance therapy was continued for 3 months with azathioprine or MMF.

Results: 66 patients are included in the current analysis. The median BVAS and creatinine at presentation was 19 and 205µmol/L respectively. The median dose of rituximab and cyclophosphamide was 2g and 3g respectively. All patients achieved B cell depletion, and 95% were in remission by 6 months. At last follow-up (median 5 years; range 1-10), renal and patient survival were 94% and 84% respectively. Ten patients (15%) experienced a major relapse during follow-up, at a median time of 39 months. All were ANCA positive and 90% B cell replete at relapse. 30% of patients had an infection requiring hospital admission at some point, but no unexpected deaths.

Conclusions: These findings confirm our previous observations that this regimen affords early disease control in renal AAV, and relapse rates that are favorable compared to published controlled studies. These observations are in keeping with long-term follow-up of the RAVE trial, where sustained remission was observed without maintenance therapy following rituximab treatment. We believe this combined regimen may provide the basis for further refinement-induction protocols in AAV, potentially by allowing early withdrawal of corticosteroids.

Funding: Government funding - Non-U.S.
A Steroid-Sparing Regimen for Remission Induction Therapy in Renal ANCA-Associated Vasculitis

Stephen Paul McAdoo, Rachna Bedi, Megan Griffith, Tom Cairns, Charles D. Pusey. Imperial College Kidney and Transplant Centre, United Kingdom.

Background: The majority of early mortality in AAV is now attributed to infections, rather than active disease. Infection, along with cardiovascular disease, remains a common cause of long-term mortality. It is likely that corticosteroid exposure contributes to the risk of these adverse outcomes, and that steroid avoidance may improve outcomes in AAV.

Methods: This is a cohort study of a novel steroid-sparing regimen that has been in use for treatment of new or relapsing renal AAV at our centre since 2014 (Table 1).

Summary of the Induction Protocol

Rituimab 1g/2 Wk 0.2
Cyclophosphamide 750mg/2, 500mg/4 pulses Wk 0.2, 4, 6, 8, 10
IV Methylprednisolone 500mg/2 Wk 0.2
Oral Prednisolone 30mg daily Wk 0-2 inclusive

Patients with significant alveolar hemorrhage or renal failure requiring dialysis were not included. Maintenance therapy commenced at 3 months with azathioprine or MMF.

Results: To date, 14 patients have completed at least 6 month follow-up. The median BVAS and creatinine at presentation were 17 and 180μmol/l, respectively. All patients achieved clinical remission by 6 months (Figure 1).

Conclusions: Our data suggests that remission in AAV may be achieved with significantly lower corticosteroid doses than previously reported. This was not associated with early relapse, and may result in an improved adverse event profile. Controlled studies are required to establish if steroid avoidance using this, or similar, protocols will result in improved long-term outcomes in larger cohorts.

Funding: Government Support - Non-U.S.

Clinical Features and Outcome of Elderly Patients with Anti-Neutrophil Cytoplasmic Autoantibody-Associated Vasculitis

Son Bong Harin, Cytoplasmic Autoantibody-Associated Vasculitis

Background: Cytoplasmic Autoantibody-Associated Vasculitis (C-ANCA) is common in elderly population, but there is few data of clinical characteristics and outcome in elderly AA V patients. This study showed that standard immunosuppressive therapy may not help improve the outcome in elderly AAV patients.

Methods: We reviewed the medical records of 228 C-ANCA or P-ANCA positive patients in a university-affiliated nephrology center from 2005 to 2016. Patients classified as having secondary vasculitis, drug-induced vasculitis, eosinophilic granulomatosis with polyangiitis and polyarteritis nodosa were excluded. A total of 69 patients were included as having secondary vasculitis, drug-induced vasculitis, eosinophilic granulomatosis with polyangiitis and polyarteritis nodosa were excluded.

Results: Twenty-eight patients (40.6%) were older than 65 years old (elderly group), and 41 patients (59.4%) were younger than 65 years old (younger group). Median age at diagnosis was 71.25±4.54 years in elderly group and 47.02±13.61 years in younger group. In elderly group, initial blood urea nitrogen level and C-reactive protein (CRP) were higher and initial estimated glomerular filtration rate (eGFR) was lower than younger group. Comorbidty score and organ involvement were not different between two groups.

Conclusions: AAV is a disease with substantial mortality and morbidity among elderly patients. This study showed that standard immunosuppressive therapy may not help improve the outcome in elderly AAV patients.
The pt who started ECU as late as 415 days (the latest) after disease presentation (CFH mutation) received a nadir of sCr as low as 0.7 mg/dL.

Conclusions: Early Rx provides better renal outcome as to response rate, need for acute RRT, final renal function and time to reach the nadir of sCr. The better outcome turns into lower costs for the possibility of early discontinuation of ECU, for which a good residual renal function is essential. We stress that ECU Rx can be useful even if started late, we encourage to treat Ps as long as signs of ongoing TMA are present, regardless of disease duration.

TH-PO832
A Simple and Early Prognostic Index for STEC-HUS at Presentation
Gianluigi Ardissino, Francesca Tel, Sara Testa, Fabio Pagliaionga, Michela Perrone, Dario Consomni. Fondazione IRCCS Ca’ Granda Osp. Maggiore Policlinico, Milano, Italy.

Background: STEC-HUS is an rare, severe acute microangiopathic thrombocytopenia (TMA) burdened with life-threatening complications (Cs), high case-fatality rate and significant long term sequel. It is important, both for patient’s (Ps) management and prognosis communication, to identify Ps at high risk for severe Cs, as early as possible in the course of the disease possibly through a simple and straightforward approach. It has been demonstrated that hemococoncentration at presentation of STEC-HUS is associated with worse short- and long-term outcome.

Methods: The very first laboratory examination with signs of TMA of Ps referred to our Center during recent years, were analyzed in order to identify and develop a reliable, as well as easy to calculate (at bedside), index to predict Cs. The following outcomes were considered together: 1. death, 2. CNS involvement, 3. need for RRT, 4. long-term renal and systemic sequel. Receiver Operating Characteristic (ROC) and their area under the curve (AUC) for the continuous laboratory parameters hemoglobin (Hb), serum creatinine (sCr) and LDH at presentation, were calculated, alone and in combination, after univariate and multiple logistic regression models, on the dataset of 38 patients (20 Females) with documented STEC-HUS and with a mean age of 4.9 years (IR 1.5-7.1).

Results: Overall there were 25 Ps (65.8%) with the listed Cs. Hb level at presentation alone proved to be the best predictor of poor outcome (AUC 0.751). The probability of Cs increased linearly with Hb level, from about 10% at Hb of 7 gr/dl to 50% at 12 and up to 70% when Hb was 14. Frequency of Cs was 9.1% when sCr was <1 mg/dl and 38.9% when ≥1 mg/dl (AUC 0.756). The AUC for Hb and sCr combined was 0.884 (CI 0.763-0.942).

Conclusions: We conclude that in STEC-HUS, Ps with higher Hb level (>11 gr/dl) and those with high sCr, although Hb is <11 gr/dl, at presentation should be carefully evaluated, monitored and managed accordingly for the very high risk of Cs most likely related to hidden hemococoncentration in ongoing TMA.

TH-PO833
Renal Thrombotic Microangiopathy in the Modern Era: A Report of 128 Cases from a Single Center
Gauri Bhutani,1 Samar M. Said,2 Nelson Leung,2 Mary E. Fidler,3 Mariam P. Alexander,4 Lynn D. Cornell3, Samih H. Nasef,3
1Nephrology, Univ of Wisconsin, Madison; 2Nephrology, Mayo Clinic, Rochester; 3Pathology, Mayo Clinic, Rochester.

Background: Large modern series addressing renal thrombotic microangiopathy (TMA) are lacking. This study aimed to define current epidemiology, outcomes and clinicopathologic correlations in renal TMA.

Methods: We identified 128 patients with renal TMA by retrospective review of our pathology archives from 2000-14. Pathologic findings, clinical, treatment and outcome parameters were correlated. Statistical analysis employed Fisher’s exact and Log Rank tests.

Results: Median age was 51 yrs (34-65); 55% were female and 84% Caucasian. Median follow up was 752 days (169-1396) with 66% developing doubling of Cr/need for acute dialysis (median time: 13 days (4-59.5)), and 34% progressing to ESRD. TMA involved glomeruli alone, vessels and glomeruli, and vessels alone in 29%, 38% and 2.0 g/day (0.8-4.5), respectively. The most common causes were autoimmune diseases (38% vs 16%,
P<.001]. Median follow up was 752 days (169-1396) with 66% developing doubling of Cr/need for acute dialysis (median time: 13 days (4-59.5)), and 34% progressing to ESRD. TMA involved glomeruli alone, vessels and glomeruli, and vessels alone in 29%, 38% and 2.0 g/day (0.8-4.5), respectively. The most common causes were autoimmune diseases (38% vs 16%,
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P<.001]. Median follow up was 752 days (169-1396) with 66% developing doubling of Cr/need for acute dialysis (median time: 13 days (4-59.5)), and 34% progressing to ESRD. TMA involved glomeruli alone, vessel
suggests that hemolytic uraemic syndrome induces more severe renal injury than thrombotic thrombocytopenic purpura (TTP) but this is not necessarily found. The aim of this study is to analyze the severity of AKI and clinical outcome of patients with renal TMA in a cohort of patients from a single center’s experience.

Methods: Clinical and laboratory data of 126 patients diagnosed with TMA from 2000 to 2014 were retrospectively analyzed. Patients were followed for 1 year after diagnosis and renal outcomes at 3 months and 1 year were analyzed using serum Creatinine and GFR. 43 patients were excluded due to insufficient data or loss to follow-up.

Results: Patients were subclassified into shiga toxin producing E. coli hemolytic uraemic syndrome (SECV-HUS, TTP) or atypical hemolytic uraemic syndrome (aHUS) and results are summarized in table 1. Primary TMA was associated with AKI in 80.7% of patients. Atypical HUS was associated with more severe AKI with 81.8% presenting with AKI stage 3 compared to 38% of TTP patients. Long term outcome was worse for aHUS patients with 50% requiring dialysis at one year compared to 11.3% of TTP patients.

Conclusions: TMA imposes a large burden on renal health. In our center’s experience aHUS had worse acute and long term renal outcomes when compared with TTP or SECV-HUS. However, the number of patients in both the SECV-HUS and aHUS were small in comparison to the TTP group.

TH-PO837 Hypertension-Associated Thrombotic Microangiopathy and Complement Dysregulation Joerd Timmermans,1 Myuraga Abdul-Hanid,1 Jan Damoiseaux,2,3 Pieter Van Paassen.1 1Nephrology and Clinical Immunology, Maastricht UMC, Netherlands; 2Pathology, Maastricht UMC, Netherlands; 3Central Diagnostic Laboratory, Maastricht UMC, Netherlands.

Background: Renal thrombotic microangiopathy (TMA) can be both cause and consequence of severe hypertension, ultimately leading to renal failure. Underlying pathophysiological mechanisms differ among the diverse TMA syndromes with great impact on treatment options and prognosis. We hypothesized that dysregulation of the alternative pathway (AP) is a treatable, but often unrecognized cause of hypertension, and that the prognosis resembles atypical hemolytic uraemic syndrome (aHUS).

Methods: Consecutive patients with hypertension-associated TMA, defined as severe hypertension (BP ≥180/120 mmHg) and biopsy-proven renal TMA, were screened for AP abnormalities, including genetic and serological testing. Renal biopsies were stained for complement components.

Results: Ten patients were identified, including 8 patients without biochemical signs of TMA, and 2 patients with aHUS. C3 and C5b-9 deposits along the vasculature and glomerular capillary wall confirmed in patients with hypertension-associated TMA, particularly in those not responding to treatment and/or prior to renal transplantation.

Conclusions: AP abnormalities can be found in a subset of patients with hypertension-associated TMA even though biochemical signs of TMA are mostly absent. Renal survival is poor and TMA recurrence appeared common, indicating that these patients fall into the spectrum of aHUS. Genetic testing for AP abnormalities should therefore be performed in patients with hypertension-associated TMA, particularly those in whom no therapy is planned to treatment and/or prior to renal transplantation.

TH-PO838 Clinical Features of Primary Membranoproliferative Glomerulonephritis in Japan: An Analysis of the Japan Renal Biopsy Registry (J-RRB) Naoki Nakagawa,1 Motoshi Hattori,2 Michio Nagata,2 Hitoshi Yokoyama.2 Nephrology, Asahikawa Medical University, Japan; 2Tokyo Women’s Medical University; 2Tsuchiya University; 2Kanazawa Medical University.

Background: The clinical features of primary membranoproliferative glomerulonephritis (MPGN) in an adequate sample of patients has not been studied in detail. We therefore surveyed the features of primary MPGN based on data from the Japan Renal Biopsy Registry (J-RRB).

Methods: An cross-sectional survey of 332 patients with primary MPGN registered in the J-RRB between 2007 and 2015 was conducted. Clinical parameters of blood pressure (BP), and blood and urine laboratory findings at diagnosis were compared between children (<18 years), adults (20-64 years) and elderly persons (>65 years). Factors affecting declining renal function in adult and elderly patients were assessed using multiple regression analysis.

Results: Mean age was 51.6 ± 24.6 years, mean systolic BP 137.9 ± 22.4 mmHg, mean proteinuria 3.8 ± 3.4 g/day, mean serum albumin 2.97 ± 0.80 g/dl and mean eGFR 49.9 ± 22.6 ml/min/1.73 m². The clinical features were significantly more severe in elderly patients, especially systolic BP (children, 112.8 ± 15.8; adult, 136.0 ± 18.1; elderly, patients, 148.2 ± 20.3 mmHg; P<0.001), proteinuria (children, 1.8 ± 2.2; adult, 4.0 ± 3.2; elderly patients, 4.2 ± 3.6 g/day; P<0.001), low albumin levels (children, 3.5 ± 0; adults, 3.0 ± 0.8 g/day; elderly patients, 2.8 ± 0.7 g/dl; P<0.001), and low eGFR (adults, 59.6 ± 28.7; elderly patients, 40.2 ± 16.8 ml/min/1.73m²; P<0.001). The rate of clinically classified nephrotic syndrome was significantly higher in adults (48.8%) and elderly patients (62.9%) than children patients (16.7%), whereas the rate of chronic glomerulonephritis was significantly higher in children (76.7%) than adults (46.5%) and elderly patients (29.4%). Multiple regression analysis revealed that higher systolic BP and high proteinuria were independent factors associated with decreased eGFR in adult and elderly patients with primary MPGN.

Conclusions: In Japan, the clinical features of adults and elderly patients with primary MPGN were more severe than those of children. Further investigation is needed to explore the clinical outcomes in patients with primary MPGN.

Funding: Government Support - Non-U.S.


Background: The better understanding of membranoproliferative glomerulonephritis (MPGN) based on immunofluorescence has changed its therapeutic approach. Idiopathic immune-mediated MPGN is a partially known entity. The aim of this study was to analyze the clinical presentation, treatment and outcome of this disease.

Methods: Retrospective review of patients diagnosed of idiopathic immune-complex mediated MPGN at our Nephrology Department from 1976 to 2015.

Results: Twenty-three patients (10%) of our 228 MPGN patients were labeled as idiopathic immune-complex mediated MPGN (56.5% males), with a mean age 41.25 (10-81) years. The mean follow-up was 215.203 (1-489) months. Acute kidney injury was present in 50% of the patients at time of diagnosis. The most common clinical presentation was nephrotic syndrome (60.8%) with a mean proteinuria of 4.2±3.1 (0.10-12.0) g/day. When we compared patients according the decade of diagnosis, patients diagnosed after 2001 were older (55.8±29.8 vs 20.4±7.7 years, p < 0.001), with more severe kidney impairment (1.7±0.9 vs 0.9±0.4 mg/dl, p = 0.044), higher systolic blood pressure (BP) (152±26 vs 124±13 mmHg, p = 0.009), and proteinuria (4.8±3.2 vs 2.9±2.2 g/day, NS). Thirteen patients (52%) received immunosuppression (100% steroids, 90% mycophenolate mofetil and 42% Rituximab®) due to a more aggressive clinical presentation. Elderly patients (> 65 years, N=6) presented worse baseline SCr (2.5±0.8 vs 1.0±0.4 mg/dl, p < 0.05), higher systolic BP (168±7 vs 130±22 mmHg, p < 0.005), and proteinuria (6.2±4.1 vs 3.6±2.6 g/day, NS), and reached ESRD more frequently (66.7% vs 11.8%, p < 0.005) compared with young patients (N=17). Six patients (26%) progressed end stage renal disease (ESRD) in a mean time of 35.3±39.8 (2-84) months.

Conclusions: The clinical presentation of idiopathic immune-complex mediated MPGN has dramatically changed, affecting older patients with more severe renal impairment and poor response to immunosuppressive therapies. Further prospective studies are needed for a better knowledge of this entity.

TH-PO840 Membranoproliferative Glomerulonephritis and Negative Immunofluorescence: A Clinicopathological Study Luis A. Castillo,1,2,3 Eduardo I. Navarro,2 Gustavo Aroca Martinez,2,4 Henry J. Gonzalez Torres.2,4 1Nephrology, Univ Cooperativa de Colombia, Santa Marta, Magdalena, Colombia; 2Nephrology, Univ Simón Bolívar, Barranquilla, Atlanticco, Colombia; 3Nephrology, Clinica de la Costa, Barranquilla, Atlanticco, Colombia.

Background: Membranoproliferative GN (MPGN) represents a pattern of injury seen on light microscopy. Recent advances in understanding of the underlying pathological mechanisms have led to a proposed classification scheme based on immunofluorescence findings. Given recent advances in our understanding of the alternative pathway of complement in MPGN, a practical approach is to view MPGN as either immune complex– or complement-mediated. If neither of these cases is present (null complement and immune complex), then chronic thrombotic microangiopathy may be the cause of the MPGN.

Methods: Cross-sectional study. The data were extracted from NefroRed®, a software platform that contains the socio-demographic, clinical and laboratory data of 1200 kidney biopsies. It was selected for the study those patients that showed the pattern of MPGN and negative immunofluorescence. Each biopsy was studied by light microscopy and immunofluorescence. Frequency tables and graphics were performed on relevant R (figure 1).

Results: The average age of men was 33.8 years and for women was 33.6 years. The 1200 Biopsies showed 58 injuries MPGN (5%) of these 58 cases only 23% lesions showed negative immunofluorescence. The Acute Nephritic Syndrome was the most common clinical presentation (46%), Nephrotic Syndrome (38%), and Acute kidney Injury (8%) (figure 2).

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

287A
Conclusions: 23% of patients with MPGN have negative immunofluorescence either immune complex or complement. The presence of anemia and thrombocytopenia in several patients who had renal biopsy suggest the presence of a thrombotic microangiopathy. The most common clinical presentation was acute nephritic syndrome.

TH-PO841

Determinants of Long-Term Outcomes in Monoclonal Immunoglobulin Deposition Disease Florence Joly,1 Camille Cohen,2 Vincent Javaugue,1 Bertrand Arnulf,3 Mathilde Nouvier,1 Vincent Audard,1 Francois Provot,3 Dominique Nochy,1 Bertrand Knebelmann,2 Arnaud Jacard,2 Jean-Paul Femand,2 Frank Bridoux.1 1CHU Poitiers; 2Hôpital Necker, Paris; 3Hôpital Saint Louis, Paris; 4CHU Lyon; 5Hôpital Henri Mondor, Creteil; 6CHU Lille; 7HEGP Paris; 8CHU Limoges, France.

Background: Monoclonal immunoglobulin deposition disease (MIDD) is a rare complication of plasma cell disorders, defined by linear Congo red-negative deposits of monoclonal light chain (LCDD), heavy chain (HCDD) or both (LHCDD) along basement membranes. Treatment strategies and long-term outcomes are poorly defined.

Methods: We retrospectively reviewed 176 French patients (pts) with biopsy-proven LCDD (n=143), HCDD (n=18) and LHCDD (n=15). Renal response (defined by a >50 % decrease in 24h-proteinuria without a >25 % decrease in eGFR) and patient survival were compared with hematological response after chemotherapy.

Results: Median age at diagnosis was 63 years. Renal involvement was constant, with median eGFR of 18 ml/min/1.73m², proteinuria of 1.8 g/d, microhematuria (68%) and hypertension (64%). 55 pts had extra-renal disease, with heart (n=18), peripheral nerve (n=18) or liver (n=8) involvement. Hematologic diagnosis was multiple myeloma in 42% and MGRS in 57%. Serum free light chain (FLC) ratio was abnormal in all 113 tested pts. Among 169 pts who received chemotherapy, based on bortezomib and/or alkylating agents, 60% achieved hematological response (HR), as defined by post-treatment dFLC <40 mg/L. Median overall survival in pts with and without HR was 169 months and 78 months (p=0.001), with a median renal survival of 216 months and 108 months, respectively (p=0.05). Median overall survival was 169 and 64 months in pts who achieved or not a renal response (p=0.001). Predictive factors of renal response were baseline eGFR >30 ml/min/1.73 m², post-treatment dFLC <40 mg/L, bortezomib-based therapy, and severity of renal interstitial fibrosis/vascular lesions.

Conclusions: Achievement of dFLC <40 mg/L translates into improved renal and patient survival in MIDD. Renal response is associated with higher patient survival. Due to their efficacy and good tolerance profile, bortezomib-based regimens should be considered as first-line therapy.

TH-PO842

Hereditary Aα Fibrinogen Amyloidosis: The French Cohort Marc Uhrich,1 Lara Meyer,2 Sophie Valleeix,2 Hélène François,3 Laurence Vrigneaud,1 1Néphrologie, Dialyse et Médicine Interne, CH Valenciennes, Valenciennes, Nord, France; 2Néphrologie et Transplantation, Hôpital Krimel Bicetre, Le Kremlin Bicetre, France; 3Genétique Médicale, Hôpital Necker Enfants Malades, Paris, France.

Background: An-Fibrinogen amyloidosis (AFib) is the most frequent hereditary amyloidosis in Northern Europe characterized by rapidly progressive chronic kidney disease (CKD), high proteinuria and massive glomerular deposits.

Methods: French AFib patients were identified from a genetic registry (S. Valleix), complemented with a national call on members of the French nephrological society to report cases.

Results: Data were collected on 21 families: 30 patients with E526V mutation (n=22), R554L (n=2), A517T-522 (n=2) and not reported in the medical file (n=4). Mean age at presentation was 54.33 years. A family history of nephropathy was present in 10 cases, 7 of whom were amyloidosis. Four patients died, with a mean time from diagnosis of 109 months. Principal characteristics were rapidly progressive CKD with hypertension (63%) and proteinuria (4g/d), often nephrotic range (30%). Renal biopsy consistently showed massive glomerular amyloid deposits. Fibrinogen immune-staining was positive in 7 cases and negative in 8 cases. End-stage renal disease occurred in all symptomatic patients (mean time from diagnosis 29 months). Fourteen patients underwent transplantation, 11 renal and 3 hepato-renal grafts. There were 5 recurrences on isolated renal graft, leading to graft lost in 3 cases, in a mean time of 109.2 months.

Conclusions: This first French series confirms phenotypical and histological presentation of AFib, with a predominance of E526V variant and a poor renal prognosis. Extra-renal manifestations seem limited. Assessment of family is a key point and can lead to early diagnoses. The only certain diagnostic tool is genetic assessment, although the massive glomerular deposits and family history may lead to suspect an AFib. Renal graft survival is about 10 years in case of renal transplantation, whereas there is no recurrence in hepato-renal transplantation. Renal transplantation is the best choice in most cases. For the youngest patients hepato-renal transplantation affords the best long-term outcomes.

TH-PO843

The Population-Level Costs of Immunosuppression Treatment for Glomerulonephritis Are Increasing over Time Sean Barber,1,2 Clifford Lo,1 Gabriela Espino-Hernandez,1 John Feehally,1 Sharareh Sajjadi,2 Jabig Gill,1,2 1BC Renal Agency, Canada; 2Univ of BC, Canada; 1LGH, Leicester, United Kingdom.

Background: To date, there has been no assessment of the real-world cost of immunosuppression (IS) treatment for glomerulonephritis (GN). Given the chronic nature of GN and the burden in terms of safety and effectiveness, it is important to assess the cost of treating GN is likely substantial. In renal transplant, the use of newer IS treatments resulted in a doubling of medication costs over time. We hypothesize a similar trend exists in GN as a result of a transition to newer more expensive therapies.

Methods: A population-level incident GN cohort (n=2983) was created by linking 3 provincial databases in British Columbia: pathology (includes all kidney biopsies), renal (includes clinical and laboratory characteristics) and PharmaNet (includes all medications with costs). This cohort captures the treatment costs of all GN patients in BC from 2000-2013.

Results: The annual IS treatment cost per patient increased 6.8% from $205 in 2000 to $1,394 in 2013 (p<0.001). The contribution of each medication to increasing costs over time varied by GN type.

Conclusions: We describe for the first time the real-world population-level cost of IS treatment for GN, and have demonstrated a striking increase in costs due to the use of newer more expensive therapies. Our results suggest that efforts to improve cost-effectiveness will need to focus on the minority of patients treated with disproportionately expensive therapies.

TH-PO844

Incident ESRD and eGFR Decline among the Most Common Glomerulopathies (GN): The Kaiser Permanente Southern California (KPSC) Cohort John J. Sim,1 Michael Batech,2 Teresa N. Harrison,3 Sally F. Shaw,4 Sejal Vora,5 Anu Hever,1,2 1Nephropathy and Hypertension, Kaiser Permanente Los Angeles Medical Center; 2Research & Evaluations, Kaiser Permanente Southern California; 3Mallinckrodt Pharmaceuticals.

Background: While GN is an important contributor to ESRD and morbidity/mortality outcomes, the clinical course is often variable among and within different GN. Within an integrated health system, we sought to evaluate and compare eGFR decline and incident ESRD rates in patients with focal segmental glomerulosclerosis (FSGS), membranous GN (MGN), minimal change disease (MCD), IgA nephropathy (IgAN) and lupus nephritis (LN).

Methods: Retrospective longitudinal cohort study in the period 1/1/2000 through 12/31/2013 among patients within KPSC who had biopsy proven primary GN, were characterized and followed using serial laboratory measurements until they reached the outcome of ESRD (hemodialysis, peritoneal dialysis, transplant). All eGFR’s measured at and subsequent to biopsy were used to evaluate trend of eGFR. Medications prescribed within 180 days of biopsy were extracted.

Results: Among 2226 GN patients (FSGS 46%, MGD15%, MCD12%, IGAN12%, LN13%) with mean follow up of 3.8yrs, 69% (27%) progressed to ESRD. Preemptive transplant occurred in 2.6%. Steroids (39.6%), calciumin inhibitors (4.6%), MMF (3.3%) and alkylating agents (2.7%) were the most frequent initial treatments. FSGS had the highest ESRD incidence rate at 12.9 followed by IGAN 6.6, LN 3.4, MGN 2.9, and MCD 2.5 (per 100 person-yrs). LN was the only GN that had improvement in eGFR slope after biopsy whereas MGN had the steepest decline.

Conclusions: The Kaiser Permanente Southern California (KPSC) cohort showed that the most common GN (FSGS, MGN, MCD, IgAN, LN) show a similar trend of eGFR decline, with the exception of FSGS, which showed a slight improvement in eGFR slope after biopsy.
Conclusions: Among a large racially/ethnically diverse GN population within a routine treatment environment, FSGS patients had the highest rate of progression to ESRD, while MGN patients were observed to have the steepest decline and LN patients appeared to have the best treatment response based on aGFR trends.

Funding: Pharmaceutical Company Support - Mallinckrodt Pharmaceuticals

TH-PO845

Light Chain Amyloidosis and Light Chain Deposition Disease - Single Centre Treatment Results Elena Zakharova 1,2 Nephrology, City Clinical Hospital n.a. S.P. Botkin, Moscow, Russian Federation; 1Nephrology, State Unive of Medicine and Dentistry n.a. I.I. Evdokimov, Moscow; Russian Federation.

Background: Treatment approaches to AL amyloidosis and Light Chain Deposition Disease (LCDD) evolved over last decades. In 2012-2013 the term "monoclonal gammapathy of renal significance" (MGRS) was introduced, and treatment strategies for MGRS recommended by International Kidney and Monoclonal Gammapathy Research Group.

Methods: We analysed retrospectively the data for patients with biopsy-proven AL amyloidosis and LCDD, treated with chemotherapy in 2001-2015. Study group of 49 patients was divided in 3 treatment subgroups: 1) oral melphalan-based regimens - 20 (40.8%); 2) high-dose melphalan/autologous stem cell transplantation (HDM/ASCT) - 7 (14.3%); 3) bortezomib-based regimens - 22 (44.8%).

Results: 26 (53.0%) males and 23 (47.0%) females, median age 59 [48; 64.5] years, median duration from the disease onset 12 [6; 24], median follow-up 12 [4; 29] months. Clinical presentation shown in Table.

<table>
<thead>
<tr>
<th>Kidneys only pts n (%)</th>
<th>14 (28.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys and heart pts n (%)</td>
<td>11 (22.4)</td>
</tr>
<tr>
<td>Multorgan involvement n (%)</td>
<td>24 (48.9)</td>
</tr>
<tr>
<td>Nephrotic syndrome pts n (%)</td>
<td>39 (79.5)</td>
</tr>
<tr>
<td>Median proteinuria g/l</td>
<td>5.0 (2.3; 6.7)</td>
</tr>
<tr>
<td>CKD stage 2-4 pts n (%)</td>
<td>23 (46.9)</td>
</tr>
<tr>
<td>Median serum creatinine μmol/l</td>
<td>121.5 [95.2; 176.7]</td>
</tr>
<tr>
<td>Nephrotic syndrome and CKD stage 2-4 pts n (%)</td>
<td>16 (32.6)</td>
</tr>
</tbody>
</table>

46.9% achieved haematoetological remission (HR), 36.7% - organ remission (OR). Rate of HR was significantly higher in the subgroup 2 compared to subgroups 1 and 3 (85.7% vs. 40.8% respectively, p<0.05), OR rate did not differ between the subgroups.

Conclusions: Majority of our patients presented with severe nephrotic syndrome, impaired kidney function and multiorgan damage. However, under chemotherapy about half of them achieved haematological remission, and more than one third - organ remission, with significantly better results after HDM/ASCT. 5-year cumulative patient’s and kidney survival did not exceed 33% even in HDM/ASCT subgroup.

TH-PO846

Long Term Renal Outcomes and Clinical Associations of Scleroderma Renal Crisis: A Retrospective Case/Control Study Sarah M. Gordon, Dustin J. Little, Rodger S. Stitt, Wayne Bailey, Jess D. Edison, Stephen W. Olson. Nephrology, Walter Reed National Military Medical Center, Bethesda, MD.

Background: Scleroderma (SSc) has a heterogeneous clinical presentation with potential multisystem organ involvement and known associations with cancer and thyroid disease. Scleroderma renal crisis (SRC) is a severe complication of SSc. Few previous studies compared SRC cases to SSc without SRC disease controls (SSc w/o SRC DC) and none have reported the long term renal outcomes for SRC patients not requiring renal replacement therapy (RRT) or characteristics at the time of SSc diagnosis that associate with future SRC.

Methods: 53 SRC cases and 204 SSc w/o SRC DC were identified, and comprehensive clinical and laboratory data was collected using the military electronic medical record. Comparisons were made between SRC cases and SSc w/o SRC DC for multiple clinical and laboratory findings both at SSc diagnosis and throughout disease progression. Fisher’s Exact test and the student’s t-test were used for statistical analysis.

Results: SRC cases that did not require chronic RRT experienced a similar mean change in GFR per year compared to SSc w/o SRC DC (+0.3 vs. -0.02 cc/min/1.73m2 in 58% of patients at time of biopsy. Median proportion of glomeruli with crescents on kidney biopsy predict poor prognosis in acute glomerulonephritis (GN). This is the first study of clinical presentation and etiology of crescentic GN in children have not been well studied for over 30 years.

Methods: Children ≤21 years old from 4 centers who presented after Jan. 2004 with ≥1 crescent on kidney biopsy were enrolled in a multi-center registry. Demographic, clinical, laboratory, and kidney biopsy findings were collected.

Results: The registry includes 83 patients (40% Hispanic, 36% Caucasian, 21% African American), with median age at presentation of 12 years (range 1-18). At presentation, 64% were hypertensive and 21% had pulmonary involvement. Estimated GFR was <60mL/min/1.73m2 in 58% of patients at time of biopsy. Median proportion of glomeruli with crescents was 16% (IQR 8-28%). Histological diagnoses are listed in the Figure.

Conclusions: SRC patients that do not require chronic RRT have stable long term renal function. Proteinuria, anemia, and elevated ESR at initial Ssc diagnosis are associated with future SRC. SRC is specifically associated with cancer, thyroid disease, and pulmonary hypertension. Our retrospective findings could be utilized to develop a model to more accurately identify SSc patients at high risk for SRC. Patients with an SRC diagnosis may benefit from earlier and more aggressive screening for cancer and thyroid function. Prospective confirmation is required.

TH-PO847


Background: In our department, renal amyloidosis of kidney biopsies have been diagnosed by congo-red stain, immunofluorescence (IF) for immunoglobulin light (L) and heavy (H) chains, immunostaining for amyloid A, transthyretin, and β2-microglobulin. Recently liquid chromatography tandem mass spectrometry (LCMS/MS) technique began to be performed to detect the amyloid precursor proteins.

Methods: We selected 18 cases of AL amyloidosis that were diagnosed by serum immunonelectrophoresis (SIEP) and biopsy samples with congo-red stain, IF, and immunostaining for amyloid A, from a series of renal biopsies in our department from 1999 to 2014. We examined the component proteins in deposited amyloid in formalin fixed paraffin embedded tissues using laser microdissection of glomeruli and LCMS/MS. These results were compared with the results of SIEP and findings of IF.

Results: In AL amyloidosis which was previously diagnosed using SIEP and biopsy samples with congo-red stain, IF, and immunostaining for amyloid A, LCMS/MS detected AL amyloidosis in 12/18 cases (66.7%), AHL amyloidosis in 5/19 cases (27.8%), and AH amyloidosis in 1/18 cases (5.5%). In 5 cases (27.8%), monoclonal immunoglobulin in serum could not be detected by SIEP. Furthermore, in IF, all cases had irregular non-specific immunoglobulin L and H chains and complement components in our cases. LCMS/MS could detect the component proteins in amyloid deposition even in the cases that had less than 5% area of amyloid deposition in glomeruli.

Conclusions: In our cases, non-specific staining for immunoglobulin L and H chains was seen in AL amyloidosis. In addition, ALH and AH amyloidosis could not be diagnosed by SIEP and IF for immunoglobulin L and H chains. LCMS/MS is very helpful for diagnosis of amyloidosis, especially for AHL and AH amyloidosis.

TH-PO848

Crescentic Glomerulonephritis in Children: A Midwest Pediatric Nephrology Consortium Study Joseph George Malikalak, Michelle N. Rheault, 3 Jason Misurac, 4 Joseph T. Flynn, 5 William E. Smoyer, 3 Scott E. Wenderfer, 6 Guillermo Hidalgo. 6 Pediatric Nephrology, Baylor College of Medicine, Houston, TX; 3Nationwide Children’s Hospital, Columbus, OH; 5Univ Minnesota, Minneapolis, MN; 6Univ Iowa, Iowa City, IA; 6Seattle Children’s Hospital, WA; 6East Carolina Univ, Greenville, NC.

Background: Crescents on kidney biopsy predict poor prognosis in acute glomerulonephritis (GN). The clinical presentation and etiology of crescentic GN in children have not been well studied for over 30 years.

Methods: Children ≤21 years old from 4 centers who presented after Jan. 2004 with ≥1 crescent on kidney biopsy were enrolled in a multi-center registry. Demographic, clinical, laboratory, and kidney biopsy findings were collected.

Results: The registry includes 83 patients (40% Hispanic, 36% Caucasian, 21% African American), with median age at presentation of 12 years (range 1-18). At presentation, 64% were hypertensive and 21% had pulmonary involvement. Estimated GFR was <60mL/min/1.73m2 in 58% of patients at time of biopsy. Median proportion of glomeruli with crescents was 16% (IQR 8-28%). Histological diagnoses are listed in the Figure.

Conclusions: The prevalence of glomerular diseases in US children that manifest with crescentic glomerulitis is changing. The proportion of crescents on biopsy was significantly higher in patients requiring RRT at presentation (58%) compared to those who did not (21%, p<0.002).

Patients with anti-glomerular basement membrane (GBM) disease had the greatest proportion of crescents (66%). Renal replacement therapy (RRT) at presentation was required in 11% of all patients and in 50% of patients with anti-GBM disease. The proportion of crescents on biopsy was significantly higher in patients requiring RRT at presentation (58%) compared to those who did not (21%, p<0.002).

Conclusions: The prevalence of glomerular diseases in US children that manifest with crescentic glomerulitis is changing. The proportion of crescents on biopsy was significantly higher in patients requiring RRT at presentation (58%) compared to those who did not (21%, p<0.002).
Th-P0849

Recruitment of Plasmaclloid Dendritic Cell to Renal Ectopic Germinal Center in Primary Sjögren Syndrome with Tubulointerstitial Injury Jing Wang,1 Mengyu Zhou,1 Yubing Wen,2 Wen Zhang,1 Xuemei Li,1 Limeng Chen.1 Nephrology, Peking Union Medical College Hospital, Beijing, China; 1Rheumatology, Peking Union Medical College Hospital, Beijing, China.

Background: Renal involvement of Primary Sjögren Syndrome (pSS) is predominated by tubulointerstitial injury (pSS-TIN). Large sample clinicopathological studies are sparse and mechanisms underlying renal damage remain to be elucidated. This study aimed to evaluate ectopic germinal center (EGC) formation, recruitment of pDC and mDC, and activation of B cell chemokine CXCR5 in pSS-TIN, and to analyze the factors affecting eGFR long term prognosis.

Methods: From 1993 to 2015, 64 pSS patients were diagnosed with tubulointerstitial lesions by renal biopsy in a single center of Beijing, EGC (CD21+), pDC (BDCA-2+), and mDC (DC-SIGN+) and CXCR5 were identified by immunohistochemistry staining. Peripheral pDC (Lin-1HLADR+CD123+) and mDC (Lin-1HLADR+CD11c+) were evaluated by flow cytometry.

Results: pSS-TIN patients were mostly middle-aged female. eGFR (56.3±29.5ml/min/1.73m2) was independently correlated with age (R²=0.102, 95%CI-1.592, -0.357, p=0.005), glomerular sclerosis index (R²=0.099, 95%CI-77.261, -12.381, p=0.008) and tubulointerstitial lesion (R²=0.457, 95%CI-20.78.0, -2.306), p=0.016, 15.6% had EGC in renal interstitium. Both pDC and mDC were detected in EGC, but only pDC had a higher prevalence (semiquantitatively scoring 2.0±0.9 vs. 1.1±0.3, p=0.025) comparing to patients without EGC. Peripheral pDC decreased significantly in pSS with renal involvement than healthy control (0.01±0.001 vs. 0.07±0.05%, p=0.001) and CXCR5+ cell infiltration was more prominent in the presence of EGC and was mainly near the adjacent vessels. 93.8% received therapy, 91.1% were in stable for 3 years. eGFR at renal biopsy is the sole risk factor affecting long term renal function (R²=0.124, 95%CI-0.101, 1.036, p=0.001).

Conclusions: EGC were detected in renal interstitium of pSS-TIN, with pDC recruitment from peripheral blood and increased CXCR5 expression. It may participate in renal tubulointerstitial injury.

Th-P0850

Genetic Changes Predisposing to Complement Disruption and Infection May Play Role in a Case of Atypical Hemolytic Uremic Syndrome Elena Volokhina,1 Birendra Singh,2 Martin Kähnoff,3 Markcin Okor,1 Nicole Van De Kaat,1 Anammele Bob,1 Ioannis Patrinos,1,2 Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; 2Dept of Pediatrics, UCL Centre for Nephrology, London, United Kingdom; 3Laboratory Medicine, Radboud University Medical Centre, Nijmegen, Netherlands.

Background: Hemolytic uremic syndrome (HUS) is a major cause of renal failure in childhood. Most cases are caused by infection with Shiga-toxin producing Escherichia coli (STEC), which triggers a systemic complement activation leading to thrombotic microangiopathy. Often the cause of HUS is unidentified, however, genetic predisposition to such infections in HUS has not yet been sufficiently addressed. Here we present genetic analysis of a 2 months old patient with Bontellia pertussis infection, followed by HUS.

Methods: DNA analysis was performed by Sanger sequencing, analysis of autoantibodies to CFH was performed by ELISA. Recombinant vitronectin variants were produced in HEK293T cells, purified and used in hemolytic assay with sheep erythrocytes and purified C5b-6, C7, C8 and C9 complement proteins.

Results: The patient was a previously described p.Ala43Thr variant in thrombomodulin that alters complement regulation, but had no abnormalities in CFH, MCP, C3 and CFB or autoantibodies to CFH. In search of the new genes in etiology of aHUS, we screened the patient’s DNA for aberrations in complement inhibitor vitronectin variants have shown that this mutation enhances complement inhibition.

Conclusion: A rare vitronectin change could have contributed to the severe disease course of aHUS, followed by the development of atypical HUS. We hypothesize that this mutation is likely pathogenic. In vitro experiments using recombinant vitronectin variants have shown that this mutation enhances complement inhibition. We conducted further in vivo experiments to study the effect of the mutation on complement regulation.

Funding: Government Support - Non-U.S.

Th-P0851

The CureGlomerulonephropathy (CureGN) Cohort Study: Enrollment Characteristics to Date Laura H. Mariani,1 Andrew S. Bombaick,2 Michelle A. Hladunewich, Michelle N. Rhea,3 Dana Rizk, Michael F. Fleischer,4 Lisa M. Guay-Woodford.1 On Behalf of the CureGN Consortium.

Background: In minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and IgA nephropathy (IgAN) Henoch-Schönlein Purpura (HSP), challenges to studying underlying mechanisms, new therapies, and new therapies include the rarity of each diagnosis and slow progression, which together may require decades of follow-up to measure the effectiveness of interventions on ESKD or death.

Methods: Cure-GN is a 64-center prospective cohort study of children and adults with biopsy-proven MCD, FSGS, MN or IgAN/HSP. Target recruitment is 2,400 patients with first diagnostic kidney biopsy within 5 years of enrollment. Patients with ESKD, other organ transplant, or secondary causes of kidney disease (diabetes, lupus, HIV, active malignancy, hepatitis B or C) are excluded. Study visits occur 4 times in the first year and 3 times per year thereafter.

Results: As of May 2016, 1,223 (255 MCD, 306 FSGS, 221 MN, 441 IgAN including 87 renal transplant patients have been enrolled; 32% of patients received EGC and was mainly near the adjacent vessels. 93.8% received therapy, 91.1% were in stable for 3 years. eGFR at renal biopsy is the sole risk factor affecting long term renal function (R²=0.124, 95%CI-0.101, 1.036, p=0.001).

Conclusions: Cure-GN enrollment now exceeds 50% of target. Robust clinical data collected with serial biosamples from diverse pediatric and adult patients with MCD, FSGS, MN, and IgAN will be a valuable resource for researchers in glomerular disease and platform for ancillary studies.

Funding: NIDDK Support, Private Foundation Support

Th-P0852

Safety and Effectiveness of Restrictive Eculizumab Treatment in Atypical Hemolytic Uremic Syndrome Kooi L. Wijnsma,1 Elena Volokhina,2 Nicole Van De Kaat,1 Jack F. Wetzels,2 Pediatric Nephrology, Radboudumc, Nijmegen, Netherlands; 1Nephrology, Radboudumc, Nijmegen, Netherlands; 2Laboratory Medicine, Radboud University Medical Center, Nijmegen, Netherlands.

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare, but severe form of thrombotic microangiopathy, characterized by hemolytic anemia, thrombocytopenia, and acute renal failure, as a consequence of complement dysregulation. Atypical HUS has a poor outcome with mortality up to 10% and over 50% of patients developing end stage renal disease. Since the end of 2012, these outcomes have drastically improved with the introduction of eculizumab. The European Medicines Agency has approved eculizumab as lifelong treatment in aHUS patients. However, there is no hard evidence to support this advice. Historically, a substantial number of aHUS patients were weaned of plasma therapy, often without disease recurrence. Moreover, the long-term consequences of eculizumab as lifelong treatment in aHUS patients treated with a restrictive treatment regimen of eculizumab.

Methods: All patients with aHUS who presented in the Radboudumc in the Netherlands, between 2012-2016, and who received eculizumab treatment, according local practice, are described. Clinical, diagnostic, and follow up data were gathered and reviewed.

Results: Of the 16 patients (10 adults, 6 children) who presented with aHUS since 2012, 15 received restrictive eculizumab therapy. Therapy was either gradually withdrawn (n=4) or discontinued (n=11). Two patients, both known with factor H mutation, experienced recurrence of aHUS after therapy discontinuation. Due to close monitoring, recurrence was detected early, eculizumab was restarted, and no clinical sequela such as proteinuria or diminished kidney function were detected subsequently. In total, eculizumab could be safely discontinued in 9 patients of which 6 are event free for over a year now. With this strategy approximately 6.7 million has been saved.

Conclusions: A restrictive eculizumab regimen in aHUS is safe and effective. Future studies should focus on finding reliable predictors of disease recurrence.

Th-P0853

Investigating the Role of Connective Tissue Growth Factor (CTGF) Antagonism on Renal Outcomes in Cryoglobulinaemia Gavathiri K. Rajakaruna,1 Kelly L. Huddins,2 Charles E. Alpers,2 Roger M. Mason,3 Alan D. Salama.1 1UCL Centre for Nephrology, London, United Kingdom; 2Dept of Pathology, Univ of Washington, Seattle; 3Renal Section, Imperial College London, London, United Kingdom.

Background: Transgenic thymic stromal lymphopoietin (TSLP Tg) mice develop membranoproliferative glomerulonephritis secondary to cryoglobulinaemia. We have shown high circulating levels of CTGF in these animals and attenuation of disease following use of CTGF antisense oligonucleotide (ASO) therapy in a pilot study. We now describe the impact of CTGF antagonism on renal parameters.

Methods: 32 TSLP Tg animals were treated with weekly ip CTGF or control ASO therapy (50mg/kg) for 10 weeks. Renal parameters were evaluated.

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

Underline represents presenting author.

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Results: Mice that received CTGF ASO had significantly lower proteinuria for the duration of the study compared to control ASO (p = 0.001). Glomerular mesangial expansion score was significantly reduced in CTGF ASO compared with control ASO treated (1.456 ± 0.3105 vs 2.078 ± 0.038, p = 0.0159). Podocytes were identified by IHC for p75, and their density morphometrically quantitated.

WT mice had preserved podocyte density that was unaffected by ASO therapy (CTGF ASO treated 288.3 ± 67 vs control ASO treated 285.4 ± 73 podocytes/10³ μm²), while TSLP-Tg control ASO mice had significantly reduced podocyte density which was significantly ameliorated by CTGF ASO treatment (control ASO treated 164.8 ± 57 vs CTGF ASO treated 218.4 ± 35 podocytes/10³ μm²). In addition, podocyte density was significantly lower in CTGF ASO treated mice compared with untreated mice (Microglomat CTGF expression 0.3333 ± 0.5164 vs 0.8333 ± 0.4082, p = 0.0462 respectively).

Conclusions: This study demonstrates that antagonism of CTGF leads to amelioration of glomerular injury and podocyte preservation in cryoglobulinemic MPGN and may represent a future therapeutic target.

TH-PO854
Clinical and Histological Differences between PR3-ANCA and MPO-ANCA Vasculitis in a Spanish Cohort
Montserrat M. Díaz Encarnación,1 Helena Marco,2 Xavier Fulfadós,2 Gema Fernandez-Juarez,2 Luis F. Quintana,2 Manuel Praga,2 Jose Ballarín,1 1Fundacio Puigvert, Barcelona; 2H U Germans Trias, Badalona; 3H U Bellvitge, L'Hospitalet de Llobregat, Barcelona; 4Foundation Alcorcón, Alcorcón, Madrid; 5HU Clinic, Barcelona; 6HU 12 Octubre, Madrid; 7Fundacio Puigvert, Barcelona.

Background: There are significant differences between patients with ANCA-PR3 and MPO, which have been reinforced by genetic studies in recent years. The aim of this study is to analyse demographics difference and prognostic values of ANCA Serotypes in a Spanish cohort.

Methods: 304 patients with positive ANCA vasculitis diagnosed in 12 Spanish centers between 1978-2014. Clinical/laboratory variables, renal function, renal biopsy, presence of recurrences, severe infections, leukopenia and renal/patient survival are evaluated. Chi-square test, likelihood ratio test, Kruskal-Wallis test and the Kaplan-Meier curve when appropriate is used.

Results: 304 patients, 82% MPO-ANCA-positive and 18% ANCA-PR3-positive patients were included. PR3 positive patients were younger (p = 0.001) and higher proportion of men (p <0.001) than MPO positive patients. PR3 patients had a higher number of affected organs (p <0.001), highlighting a greater involvement of lungs (p <0.001) and respiratory tract (p <0.001) compared MPO. No differences in initial mean creatinine levels between PR3 and MPO, although renal biopsy showed more active lesions in PR3 patients. There was no difference in the need for dialysis during follow-up (29% vs 34%, p = 0.519), although we observed a higher percentage of patients with GFR > 60 ml/min in PR3 patients (31.9% vs 14.6% p = 0.01). PR3 patients had more relapses than MPO patients (36% vs 19% p = 0.014). There were no differences in the presence of other complications or patient survival.

Conclusions: This results show that clinical presentation and histology class are different depending on ANCA's serotype. Also we have found a higher rate of relapse in patients PR3. This could have therapeutic implications, specially at the level of maintenance therapy.

TH-PO855
Long Term Outcomes of Kidney Transplantation in Patients with End Stage Renal Disease due to Pauci-Immune Glomerulonephritis
Sophia Lionaki,1 Konstantinos Panagiotellis,1 Nikolaos Alatanis,1 Ilia Makropoulos,1 George Liapis,2 Georgios Zavos,2 John N. Boletis,1 1Nephrology, Laiko Hospital, National & Kapodistrian Univ of Athens, Faculty of Medicine, Athens, Greece; 2Pathology, Laiko Hospital, Athens, Greece; 3Transplantation Unit, Laiko Hospital, Athens, Greece.

Background: To evaluate the long term outcomes of kidney transplantation (KTx) in patients with end stage renal disease (ESRD) due to pauci-immune glomerulonephritis (PIGN), in comparison with patients with primary diseases (PD) of non-autoimmune nature.

Methods: We retrospectively studied all patients with ESRD due to PIGN, transplanted in our hospital between 1995-2014, with a follow up of 1 year post KTx or more. Demographics, clinical, and laboratory data were recorded. For comparisons reasons, a control group, consisted of patients with PD of non-autoimmune origin, matched for age, gender, donor source, and KT date was selected.

Results: 21 patients with PIGN as PD were identified. Of these, 12(95.2%) were ANCA positive at PIGN diagnosis. 14(66.6%) had developed rapidly progressive disease at presentation. The baseline characteristics of the two groups were similar.
In linear regression, each 1 ng/mL increase in 25D was associated with a 0.2 g/dL increase in Hgb (p=0.001) and decreased anemia risk (9R 0.97, 95%CI 0.95-0.99, p<0.01). Inadequate 25D was associated with the twice risk for anemia compared to subjects with 25D levels >30 ng/mL (OR 2.02, 95% CI 1.29-3.17, p=0.01). Further adjustment for ferritin/TSAT among 285 subjects with levels available showed the increased risk for anemia in those with inadequate 25D remained significant: OR 2.15, 95%CI 1.05-4.40, p=0.04.

**Conclusions:** Inadequate 25D is associated with increased risk for anemia in children with CKD, identifying it as a potentially modifiable risk factor for the anemia of CKD.

**Funding:** Other NIH Support - T32 grant

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**TH-PO859**

**Anemia Profiles by Chronic Kidney Disease Stage in a Large National Cohort of Patients**

John W. Larkin,1 Len A. Usyvayt,1 Tomislav Kovacevic,2 Franklin W. Maddux.1 Fresenius Medical Care North America, Walltham, MA; 2Fresenius Medical Care Renal Pharma, Zurich, Switzerland.

**Background:** Profiles of anemia in the different stages of chronic kidney disease (CKD) have not been fully defined. We aimed to determine the levels of hemoglobin (Hgb) and ferritin (Fer) by stage/CKD stage in a large national cohort of patients who did not require dialysis.

**Methods:** The Fresenius Medical Care CKD Data Registry was utilized to analyze data from 349,420 patients from 2013 to 2015. For CKD stage 3, 4, and 5 patients, we calculated the mean annual Hgb and Fer levels, as well as the percent (%) of patients with Fer <100ng/mL, Fer <200ng/mL, Fer <11g/dL, Fer <11g/dL & Fer <200ng/mL, and Hgb <10g/dL.

**Results:** We observed that Hgb levels decrease, and Fer levels rise with advancing CKD. In CKD stage 5, 70% of patients exhibit Hgb levels are under 11g/dL, while 13% have Fer levels below 100ng/mL (Figure 1A). We also noted an inverse relationship between Hgb and Fer measurements; average Hgb levels decrease from 12.6 to 10.6g/dL as the patients’ CKD stage progress from 3-5, while average Fer levels increase from about 200 to >400ng/mL from CKD stage 3 to 5 (Figure 1B).

**Conclusions:** Our data shows a persistent decrease in Hgb levels with the progression to later stages of CKD in patients not on dialysis. Despite this, Fer levels increase with the advancement of CKD; this may be reflecting an increasing inflammatory status with the progression of CKD, or could be secondary to intravenous (IV) Fer regimens. Unfortunately, medication data was not readily available in this registry. Further investigations are needed to define the practice patterns for administration of ESA therapies and IV Fer therapies in pre-dialysis CKD stages 4 and 5.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America
Background: miR-196a is predominantly expressed in kidney and plays an important role in renal fibrosis, which is a factor for evaluating the prognosis of FSGS. Moreover, our previous study suggested correlation between urinary miR-196a and FSGS activity. In the present study, we attempted to investigate whether urinary miR-196a can serve as a predictor of disease progression in patients with FSGS.

Methods: Urinary and plasma miR-196a were compared in patients with active FSGS (FSGS-A), FSGS in complete remission (FSGS-CR) and normal controls (NCs) using both testing set and validation set. Urinary miR-196a levels at the time of renal biopsy were also compared with FSGS-A patients and NCs in the testing set, as well as in the validation set. However, plasma miR-196a levels were similar among the three groups and there was no correlation between urinary and plasma miR-196a, suggesting that the change of urinary miR-196a was not due to the change of plasma miR-196a. Of the 231 patients, 43 patients developed ESRD during the follow-up period for at least 3 years. Urinary miR-196a levels were significantly higher in patients who progressed to ESRD than those with stable renal function. Urinary miR-196a at the time of renal biopsy was associated with proteinuria, eGFR, tubulointerstitial damage and the occurrence of ESRD. Kaplan-Meier analysis showed patients with higher urinary miR-196a levels had a worse renal outcome than those with lower urinary miR-196a levels. Multivariable Cox regression analysis additionally demonstrated urinary miR-196a was an independent risk factor for progression to ESRD. Urinary miR-196a may serve as a potential biomarker for risk classification of FSGS patients, facilitating early identification of those who will subsequently develop ESRD.

Results: Urinary miR-196a levels were significantly increased in FSGS-A patients as compared with FSGS-CR patients and NCs in the testing set, as well as in the validation set. However, plasma miR-196a levels were similar among the three groups and there was no correlation between urinary and plasma miR-196a, suggesting that the change of urinary miR-196a was not due to the change of plasma miR-196a. Of the 231 patients, 43 patients developed ESRD during the follow-up period for at least 3 years. Urinary miR-196a levels were significantly higher in patients who progressed to ESRD than those with stable renal function. Urinary miR-196a at the time of renal biopsy was associated with proteinuria, eGFR, tubulointerstitial damage and the occurrence of ESRD. Kaplan-Meier analysis showed patients with higher urinary miR-196a levels had a worse renal outcome than those with lower urinary miR-196a levels. Multivariable Cox regression analysis additionally demonstrated urinary miR-196a was an independent risk factor for progression to ESRD. Urinary miR-196a may serve as a potential biomarker for risk classification of FSGS patients, facilitating early identification of those who will subsequently develop ESRD.

Conclusions: Urinary miR-196a may serve as a potential biomarker for risk classification of FSGS patients, facilitating early identification of those who will subsequently develop ESRD.

The Effect of Renin-Angiotensin-Aldosterone System Inhibitors on Clinical Outcomes in Severe Advanced Chronic Kidney Disease Young Jun Oh,1 Sun Moon Kim,2 Su Mi Lee,1 Ae Jin Kim,1 Han Ro,1 Jae Hyun Chang,1 Hyun Hee Lee,1 Wonseok Yang1 1Dept of Internal Medicine, Cheju, Hally General Hospital, Jeju, Republic of Korea; 2Dept of Internal Medicine, Chungbuk National Univ Hospital, Cheongju, Republic of Korea; 3 Dept of Internal Medicine, Dong-A Univ Hospital, Busan, Republic of Korea; 4 Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea.

Background: The renin-angiotensin-aldosterone system (RAAS) blockades have been considered to slow renal progression in chronic kidney disease (CKD) patients. However, whether the habitual use of RAAS inhibitors affects renal progression and outcomes in pre-diary advanced CKD patients remains uncertain.

Methods: From a total of 2,076 pre-diary patients with advanced CKD stage 4 or 5, RAAS blockade users were compared with non-users for analyses using inverse probability of treatment weighted (IPTW) and propensity score (PS) matching. The outcomes were renal death, all-cause mortality, hospitalization for hyperkalemia, and interactive factors for composite outcomes.

Results: RAAS blockades were prescribed for 1,236 (59.6%) patients with CKD stage 4 to 5. RAAS blockade users showed an increased risk of renal death in PS matching (HR, 1.381; 95% CI, 1.071-1.781; P = 0.013), in agreement with the result of IPTW analysis (HR, 1.298; 95% CI, 1.125-1.400; P = 0.001). The risk of composite outcomes (renal death, all-cause mortality, hospitalization for hyperkalemia and hyperkalemia with hospitalization) was higher in RAAS blockade users, but did not reach a statistically significant level (HR, 1.241; 95% CI 0.969-1.550; P = 0.054), in PS matched analysis level. However, the result of IPTW adjustment showed significant increased risk of composite outcomes (HR, 1.154; 95% CI, 1.016-1.310; P = 0.027).

Conclusions: The use of RAAS blockades may hasten the onset of renal death without a benefit in all-cause mortality in pre-diary advanced CKD patients. Further studies were warranted to determine whether the withholding it may lead to better outcomes in this patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Proteinuria without Impairment in Kidney Function or Kidney Scarring Potentiates Atherosclerosis Yokhei Tsuchida,1 Jianyong Zhong,1 Macrae F. Linton,2 Agnes B. Fogo,2 Haichun Yang,3 Valentina Kon,1 1Pediatrics, Vanderbilt Univ Medical Center, Nashville, TN; 2Medicine, Vanderbilt Univ Medical Center, Nashville, TN; 3Pathology, Vanderbilt Univ Medical Center, Nashville, TN.

Background: CKD is a well-established risk for cardiovascular disease (CVD) with an inverse relationship between degree of kidney impairment and CVD. This relationship may reflect accumulation in uremic toxins that activate proatherogenic pathways. CKD is often accompanied by proteinuria. We now examine if proteinuria without other renal functional impairment or renal structural injury impacts development of atherosclerosis.

Methods: NEP25 transgenic mice express the human CD25 receptor on podocytes and develop proteinuria when injected with LMB2 toxin. NEP25/ApoE-/- mice were generated by cross-breeding. NEP25/ApoE-/- female mice were injected with LMB2, and compared to littermates not receiving toxin. All mice were fed a high fat diet. Body weight, as an index of edema, and albuminuria, assessed as spot urine albumin/creatinine ratios (ACR) were assessed weekly until sacrifice 4 weeks later. BUN was assessed at sacrifice. Atherosclerosis was measured by Oil-Red-O staining of proximal aortae, and kidney morphology was assessed.

Results: NEP25/ApoE-/- mice had increased ACR after LMB2 toxin compared to control (289.6±125.1 vs 28.4±8.6 mg/g, p<0.05). Although ACR was persistently elevated in NEP25+/ApoE-/- mice, the mice had no change in body weight and BUN was unchanged in toxin-exposed vs control (24.0±1.9 vs 24.9±1.8 mg/dl). Renal light microscopic morphology remained normal. NEP25+/ApoE-/- with LMB2 toxin had significantly greater atherosclerotic area than control that did not receive LMB2 (41654.0±11175.4 vs 235807.1±39861.2 mm², p<0.05). The degree of elevation in ACR correlated with the magnitude of atherosclerotic plaque burden (R²=0.7213).

Conclusions: In summary, even in the absence of changes in BUN or histological damage, proteinuria without impairment in kidney function or kidney scarring potentiates atherosclerosis and the degree of proteinuria correlates with extent of atherosclerotic plaques. Additional studies are needed to further clarify the atherogenic mechanisms augmented by disruption in the glomerular filtration barrier.

Funding: Other NIH Support - NIH/HL

Prevalence of Albuminuria among Obese U.S. Adults without Other Comorbid Conditions Meera Nair Harhay,1 Andrew Stokes,2 Eun Ji Kim,1 Justin C. Brown,1 Michael Oscar Harlay,1 1Medicine, Div of Nephrology and Hypertension, Drexel Univ College of Medicine, Philadelphia, PA; 2Univ of Pennsylvania; 3Bost Univ.

Background: Obese individuals without evidence of obesity-related metabolic abnormalities may not be routinely screened for proteinuria. The prevalence of proteinuria among non-hypertensive and non-diabetic obese adults is unknown.

Methods: Our study sample was derived from the multi-ethnic, nationally representative sample of US adults (age>18 years) from eight waves (2009-2014) of the National Health and Nutrition Examination Surveys (NHANES). We included adults with estimated glomerular filtration rate >90 ml/min/1.73m², no history of diabetes or hypertension, glycated hemoglobin 6.5%, and blood pressure<140/90 mmHg. We estimated age- and gender-adjusted prevalence over time of microalbuminuria and macroalbuminuria (urine albumin/creatinine >30 and <300 mg/g, and >300 mg/g, respectively) in this subsample, by body mass index (BMI) category.

Results: 22,476 NHANES participants met inclusion criteria. From 1999-2014, the age-adjusted prevalence of obesity (BMI>30) among adults increased from 21% to 25% (p<0.02), and morbid obesity (BMI>40 kg/m²) increased from 2.4% to 5.8% (p<0.001). The overall age- and gender-adjusted prevalence of microalbuminuria increased from 6.8% (95% CI: 5.3-8.1%) to 7.1% (6.8-8.2%), p=0.04 for trend. The overall prevalence of macroalbuminuria also rose over time, from 0.3% (0.1-0.6%) to 0.7% (0.5-1.0%), p=0.01 for trend. The age and gender-adjusted prevalence of microalbuminuria among morbidly obese participants increased from 2.7% (0.0-5.8%) in 1999-2000 to 11.6% (5.0-18.3%) in 2013-2014 (p<interaction>.08).

Conclusions: The prevalence of microalbuminuria has been increasing over time among morbidly obese US adults without evidence of other commonly assessed proteinuria risk factors.

Funding: NIDDK Support, Other NIH Support - Research reported in this publication was supported by the National Institute of Diabetes and Kidney Diseases (MNH, K23-DK105207), National Heart, Lung, and Blood Institute (MOH, F31-HL127947) and the National Cancer Institute (JCB, F31-CA192560, R21-CA182726) of the National Institutes of Health.
TH-PO869
High-Normal Albuminuria Predicts the Incidence of Chronic Kidney Disease in a Nondiabetic Population
Aki Sanada, Toshinori Ueno, Ayumu Nakashima, Shigehiro Doi, Takao Masaki. Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.

Background: Microalbuminuria is considered to be one of the predictors of the incidence in decline of glomerular filtration rate (GFR). However, little is currently known about the relationship between high-normal albuminuria and chronic kidney disease (CKD) developing in the general population without diabetes mellitus.

Methods: A 10-year follow-up retrospective cohort study was performed involving 1364 Japanese men (mean age, 44 years) who were free of CKD and diabetes mellitus. CKD was defined as an estimated GFR (eGFR) of <60 ml/min/1.73 m² and a creatinine-based equation was used to assess independent predictors of the baseline ACR. Logistic regression approaches were then used to assess determinants of the incidence of CKD. Receiver operator characteristics curve (ROC) analysis was used to determine the optimal cut-off value of the ACR as a predictor of incident CKD.

Results: At the baseline examination, eGFR, hypertension, age, body mass index, and the presence of hematuria were independently associated with the ACR. Among 1364 participants, 182 (13.3%) complied with our definition of incident CKD through 10 years of follow-up. The rate of decline in eGFR was higher with increasing quartiles of the ACR. Participants who had an ACR in the highest quartile (5.9 to 28.9 mg/g) were more likely to develop microalbuminuria (odds ratio 13.2, 95% CI 5.1 to 44.7) and CKD (odds ratio 3.7, 95% CI 2.3 to 6.0) than those who had an ACR in the lowest quartile (1.3 to 3.6 mg/g). These results were unchanged after adjustment for age, eGFR, hematuria, body mass index, and smoking status, as well as the presence of hypertension, hyperuricemia, and dyslipidemia. In ROC analysis, the area under the curve was 0.62 and an albuminuria level of 7.0 mg/g was decided as the cut-off value of incident CKD.

Conclusions: Our study shows that high-normal albuminuria is associated with incident CKD in the nondiabetic population.

TH-PO870
The Clinical Association among Urinary Albumin Excretion within Normal Range, Left Ventricular Diastolic Functional and Structural Change in General Korean Population
Dong-Young Lee, Hyun Sun Park. Internal Medicine, VHS Medical Center, Seoul, Korea; 2Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan Univ, School of Medicine, Seoul, Korea.

Background: Urine albumin creatinine ratio (UACR) is a reliable index of urinary albumin excretion and getting great attention on its association with cardiovascular disease. Nonetheless, the clinical association between UACR within normal range and subclinical left ventricular (LV) change was not clearly identified. Therefore, this study was designed to examine the clinical association between normal range of UACR and subclinical LV change.

Methods: A total of 31,334 apparently healthy Korean children who received medical health check up including echocardiography in Kangbuk Samsung hospital were enrolled in this study. Study population was stratified by 3 groups according to their UACR (Tertile 1<3.17, Tertile 2: 3.17-4.95, Tertile 3>4.95). The odd ratios (ORs) with 95% confidence interval (CI) of abnormal LV relaxation, LV remodeling, and hypertrophy were compared among 3 groups using the multivariable logistic regression analysis. We also analyzed the adjusted mean value of parameter associated with LV diastolic function and structure.

Results: When tertile 1 group was set as reference, the adjusted ORs (95%CI) for abnormal LV relaxation showed proportional relationship with UACR levels within normal range. OR; 0.86 (95% CI 0.59 - 1.22) in underweight, 1.81 (95% CI 1.63 - 2.00) in overweight, 2.75 (95% CI 2.49 - 3.03) in obese, and 4.34 (95% CI 3.65 - 5.16) in severe obese. Adjusted ORs for abnormal LV relaxation significantly increased with UACR levels (tertile 3 > 7.0 mg/g and tertile 3 (2.18; 1.53-0.8) as well as tertile 3 (2.18; 1.24-3.87)), even after adjusting for other covariates. Adjusted ORs for LV remodeling and hypertrophy were also significantly associated with UACR levels (tertile 2 (1.54; 0.93-2.16) and tertile 3 (1.94; 1.31-2.63)).

Conclusions: Elevated UACR, even within normal range, was significantly associated with the risk of LV diastolic functional and structural abnormality.

TH-PO871
Evaluation of Glomerular Filtration Rate Change as Surrogate Endpoint for End-Stage Renal Disease
Fichihiro Kanda, Tomoko Usui, Naoki Kashihara, Chiho Iseki, Kunitoshi Iseki, Masaoami Nakagaku, Hiroko Kyoosai Hospital; 1The Univ of Tokyo, 2Kawasaki Medical School; 3Okinawa Heart and Renal Association, Tomishiro Center Hospital.

Background: Chronic kidney disease patients have high risks of death and end-stage renal disease (ESRD). Although more clinical studies are needed to improve their prognosis, good surrogate endpoints for ESRD have been required, because it takes a long time and involves large costs until true endpoints occur.

Methods: Subjects with data on serum creatinine level for a baseline period over 1 to 12 years were enrolled (N = 480) in this community-based prospective cohort study in Okinawa, Japan, and followed up for four years. The percent of estimated glomerular filtration rate (%eGFR) change converted into 2 years (%/2 years) was calculated on the basis of the baseline period.

Results: Among the subjects recruited, 15.81% had low-eGFR (eGFR<60ml/ min/1.73m²) and 0.11% developed ESRD. Subjects with a range of -40-5% eGFR change <-30% 2 years had the highest risks [high-eGFR (60ml/min/1.73m²) eGFR group adjusted odds ratio (aOR), 12.8 (95% confidence interval 3.4, 48.3); low-eGFR group, aOR 53.9 (13.3, 219.0)]. Cumulative population attributable risk percent showed that %eGFR change <-30% 2 years contributed to the ESRD population. The positive predictive value for ESRD was highest at %eGFR change <-30%/2 years.

Conclusions: %eGFR decline is associated with the risk of ESRD. %eGFR change -30%/2 years can be a surrogate endpoint for ESRD in the Japanese population.

TH-PO872
Performance of Creatinine-Based Equations to Assess Glomerular Filtration Rate Decline - The NephroTest Cohort Study
Marianne H.C. Van Rinj, 1,2 Marie Metzger, 1 Jan A.J.G. van den Brand, 3 Martin Flamant, 4 Jean-Philippe Haymann, 5 Pascal Houllié, 3 Marc Firoisatt, 1 Benedicte Stenberg. 1Inserm U1018, France; 2Radboud Univ Medical Center, Netherlands; 3Biach Hospital; 4Tenon Hospital; 5InsermU1138 & European G. Pompidou Hospital, France.

Background: One point performance of creatinine-based estimated glomerular filtration rate (eGFR) equations has been extensively analyzed, but little is known on their ability to evaluate GFR trajectories. We studied the performance of the MDRD and CKD-EPI equations in estimating GFR decline over time.

Methods: We included 1955 stage 1 to 4 CKD adult patients who underwent up to 13 simultaneous IDMS-calibrated serum creatinine and GFR measurements (mg/dl and mL/min/1.73m²). We estimated absolute and relative slopes for mGFR and both MDRD and CKD-EPI eGFR equations using linear mixed models. Performance was assessed by the bias and 95% limits of agreement (LoA) between mGFR and eGFR slopes, overall and by patient subgroups.

Results: Patients underwent a total of 5515 visits; 60% had at least two over a median 3.4-year follow-up (IQR: 2.0-5.6). The bias for the absolute slope was close to zero for both equations.

Conclusions: %eGFR change was associated with the risk of ESRD. %eGFR change -30%/2 years can be a surrogate endpoint for ESRD in the Japanese population.

TH-PO873
Within-Person Variability of Albuminuria and Glomerular Filtration Markers in CKD
Sushrut S. Wakar, Caleb Rehbolz, Chi-Yuan Hsu, Harold I. Feldman, DaWei Xie, Kathleen D. Liu, Lesley Inker, Theodore E. Mifflin, John H. Eckfeldt, Paul L. Kimmel, Vasan S. Ramachandran, Joseph V. Bonventre, Josef Coresh. CKD Biomarkers Consortium, NIDDK.

Background: We conducted a study to determine the short-term within-person variability change values for albuminuria and four filtration markers used for GFR estimation in CKD.

Methods: We collected 3 repeat plasma samples and 5 urine samples (2 first morning and 3 random spot) from 49 patients with CKD over 1 month. Inclusion criteria were diagnosis of CKD; attendance at a nephrology clinic; and eGFR <60 ml/min/1.73 m² or
albumin:creatinine ratio (ACR) >100 mg/g. We measured albumin and creatinine in urine samples, and the filtration markers creatinine (SCR), cystatin C (CysC), β2-microglobulin (B2M), and β2-microglobulin (B2M) in plasma samples, in single batches with blind split replicates to measure assay variability. Reference change values (RCV) at 95% confidence level were calculated from median values of within-person coefficient of variation (CV) from non-log transformed values.

**Results:** The distribution of CKD stages was 13% stage 5, 24% stage 4, 31% stage 3b, 20% stage 3a, 4% stage 2, and 2% stage 1; the distribution of albuminuria was 28% normo-, 28% micro-, and 43% macroalbuminuria. Analytic CVs for urine albumin, creatinine, and all four filtration markers were <2%. The Table shows medians, ranges, CV, and RCV for each analyte.

<table>
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<th>ACR, mg/g</th>
<th>First morning</th>
<th>Random</th>
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</thead>
<tbody>
<tr>
<td>SCR, mg/ dl.</td>
<td>1.77 (0.62 - 9.41)</td>
<td>1.88 (0.82 - 4.39)</td>
</tr>
<tr>
<td>CysC, mg/ dl.</td>
<td>1.26 (0.28 - 4.91)</td>
<td>4.54 (1.62 - 15.54)</td>
</tr>
<tr>
<td>B2M, mg/L.</td>
<td>5.5 (0.8 - 69.3)</td>
<td>4.1 (0.4 - 52.2)</td>
</tr>
</tbody>
</table>

**Conclusions:** In CKD patients, albuminuria exhibits substantial within-person variability with RCVs exceeding 50%, which has been proposed in proteinuric disease as part of the definition for partial remission. The within-person variability of filtration markers in CKD appears comparable to reports in healthy individuals and does not exceed thresholds commonly used to define CKD progression.

**Funding:** NIDDK Support

**TH-PO874**

Screening for CKD Risk in the General Population in Belgium Using The QKidney®-2014 Risk Calculator

**Background:** On World Kidney Day 2015 we launched the QKidney®-2014 risk calculator (www.qkidney.org) to screen for risk of developing chronic kidney disease (CKD) or end stage renal disease (ESRD) in the general population.

**Methods:** A webpage was created and launched on march 12th, 2015, followed by a Facebook® advertising campaign in February 2016.

**Results:** In one year more than 60,000 records were created.

<table>
<thead>
<tr>
<th>Characteristics of the population</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31580</td>
<td>51085</td>
</tr>
<tr>
<td>Median age [IQR], years</td>
<td>52 [44, 60]</td>
<td>56 [45, 64]</td>
</tr>
<tr>
<td>BMI, Mean (SD)</td>
<td>26 (4.62)</td>
<td>26 (4.62)</td>
</tr>
<tr>
<td>Smoking status, n(%)</td>
<td>1485 (4.70)</td>
<td>2058 (6.62)</td>
</tr>
<tr>
<td>Heavy Smoker</td>
<td>1147 (3.63)</td>
<td>1975 (6.35)</td>
</tr>
<tr>
<td>Light Smoker</td>
<td>1568 (4.97)</td>
<td>1399 (4.50)</td>
</tr>
<tr>
<td>Moderate Smoker</td>
<td>2948 (9.34)</td>
<td>2000 (6.63)</td>
</tr>
<tr>
<td>Non Smoker</td>
<td>24432 (77.37)</td>
<td>23993 (75.90)</td>
</tr>
</tbody>
</table>

**Clinical conditions, n(%)**

| Type 1 diabetes | 331 (1.08) | 795 (2.56) |
| Type 2 diabetes | 1193 (3.78) | 1859 (5.98) |
| Cardiovascular disease | 1401 (4.44) | 2623 (8.44) |
| Congestive heart failure | 1217 (3.85) | 1867 (6.01) |
| Peripheral vascular disease | 1522 (4.92) | 1654 (5.32) |
| Treated hypertension | 7018 (22.22) | 8635 (27.78) |
| Kidney stones | 3381 (10.71) | 4431 (14.25) |
| Family history of kidney disease | 5308 (16.81) | 3958 (12.73) |

We included only complete records for our final analysis (21162 women, 21581 men). The 5-year risk score (mean [95%CI]) for CKD is 1.92 [1.83-2.02] for women, 4.39 [4.25-4.54] for men. For ESRD this is 0.75 [0.68-0.82] and 1.72 [1.60-1.84] respectively. 417 (1.97%) women and 1260 (5.84%) men have a slightly elevated risk for developing ESRD within 5 years (scores between 3-15). 171 (0.81%) women and 425 (1.97%) men have a high risk for developing ESRD within 5 years (scores >15).

**Conclusions:** The risk for developing CKD or ESRD is low in the general population. In our population the risk is higher for males than for females, explained by the higher age and presence of comorbidities. The use of the Qkidney risk calculator allows detection of high risk persons, eligible for screening.

**Background:** Hematuria from nephrogenic causes is associated with oxidative stress and inflammation, which may mediate further structural damage to the nephron. Despite its inexpensive and universally accessible assessment, hematuria has rarely been explored as a risk factor for CKD progression.

**Methods:** In the Chronic Renal Insufficiency Cohort (CRIC) Study, we evaluated the relationship of hematuria with CKD progression. Presence of hematuria was defined as a positive dipstick in one urinary sample during patient enrollment. All 3272 participants for whom hematuria was assessed were included. Hazard ratios for the development of ESRD over a median follow-up of 5 years were estimated for patients with and without hematuria. Analyses were stratified by eGFR (<30, 30-44.9, 45-59.9, ≥60 ml/min/1.73m2), history of diabetes and proteinuria (<0.10, 0.10-0.49, 0.50-1.49, ≥1.50g/dl).

**Results:** From all participants, 1145 (29%) presented hematuria at screening. Groups with and without hematuria differed on racial distribution (22% of Hispanics in the group with hematuria vs. 9.5% in the group without), proportion of diabetes (55.72% vs. 47.6%), eGFR (40.2 vs. 45.3 ml/min/1.73m2) and presence of proteinuria at baseline (34.8% vs. 8.5% presented at least 1.5g/day). For patients with diabetes, hematuria was associated with the development of ESRD within the first year (Hazard Ratio: 2.43; 95%CI: 1.18-5.00, p=0.016) and second year of follow-up (Hazard Ratio: 1.68; 95%CI: 1.11-2.54, p=0.013), and this relationship was attenuated over time.

**Conclusions:** In a large adult cohort with CKD, hematuria was associated with a significantly greater risk of CKD progression. These results suggest the potential role of hematuria as a predictor of CKD progression.

**Funding:** NIDDK Support

**TH-PO876**

The Chronic Kidney Disease Metabolome - Untargeted Metabolomics in Living Kidney Donors, Kidney Transplant Patients, Chronic Kidney Disease Patients and Various Dialysis Modalities

**Background:** Although a number of studies have assessed metabolic changes in chronic kidney disease (CKD), this study aimed to evaluate overall metabolic changes in living kidney donors, CKD transplant and various dialysis modalities as well as before and after dialysis using an untargeted metabolomics approach.

**Methods:** Plasma was collected from living kidney donors prior to and one year following kidney donation. Age-matched control plasma was collected in the same time frame. Dialysis patient control plasma was collected in the same time frame. Plasma metabolic profiles of living kidney donors and kidney transplant patients were not distinguishable from controls by principal component analysis for both metabolic changes. The largest change in metabolite levels during dialysis was seen in transplant samples resulted in less than 35 metabolites significantly different than controls following kidney donation. Age-matched control plasma was collected in the same time frame. Untargeted metabolomics analysis of plasma samples was performed using reverse phase (RPLC) and hydrophilic interaction liquid chromatography (HILIC) coupled to mass spectrometry.

**Results:** All pre-dialysis and CKD samples demonstrated more than 250 significantly different metabolites compared to control patients by both RPLC and HILIC analysis. Transplant samples resulted in less than 35 metabolites significantly different than controls by RPLC and HILIC analysis. Principal component analysis demonstrated clustering of control, living donor and transplant patient samples compared to CKD and all dialysis modalities. When comparing pre and post dialysis samples, NIDDK resulted in minimal metabolic changes.

**Conclusions:** Plasma metabolic profiles of living kidney donors and kidney transplant patients were not distinguishable from controls by principal component analysis for both RPLC and HILIC data further supporting kidney transplant as ideal renal replacement therapy.

**Funding:** Government Support - Non-U.S.
TH-PO687
1,5-Anhydroglucitol Predicts CKD Progression in Macroalbuminuric Diabetic Kidney Disease: Results from Non-Targeted Metabolomics

Gesiane Fernandes Tavares,1 Gabriela Venturini,2 Kallynarda Padilha,2 Roberto Zatta,3 Alexandre Costa Pereira,4 Eugenie P. Rhee,4 Silvia M. Titan.1
1Nephrology Div, School of Medicine, Sao Paulo Univ, Sao Paulo, Brazil; 2Laboratory of Genetics and Molecular Cardiology, Heart Inst, Univ of Sao Paulo Medical School, Sao Paulo, Brazil; 3Nephrology Div, Massachusetts General Hospital, Boston, MA; 4Metabolic Profiling, Broad Inst, Cambridge, MA.

Background: In DKD, few biomarkers of disease progression are available, besides eGFR and albuminuria. Metabolomics is a new tool that allows exploration of novel biomarkers.

Methods: Non-targeted metabolomics was done on plasma of 56 DKD patients in Brazil. After a follow-up of 2.5y, the primary outcome (PO: dialysis need, doubling of serum creatinine, or death) occurred in 17 patients (30.3%). Samples were derivatized by methoximation and MSTFA, and analyzed by GC-MS Agilent 5977A/7890B. Data was processed using Agilent MassHunter with NIST 11 and Fiehn A0.01 compound library. Metabolonalyist 3.0 and SPSS 20.0 were used for analysis.

Results: After cleaning, 186 metabolites were left for analysis. Of those, 14 were associated with the PO (Mann-Whitney test). In Cox regression, only 1,5-anhydroglucitol (AGT) (HR 0.10, 95%CI 0.01-0.63, p=0.001), norvaline and L-aspartic acid where associated significantly and inversely associated with the PO (HR 0.05; 95%CI 0.01-0.33, p=0.002). A significant KM curve is shown in Figure 1.

Conclusions: Our results show that 1,5-anhydroglucitol, an inverse marker of hyperglycemia, is a significant predictor of CKD progression in DKD. Notably, a recent study highlighted AGT as a marker for new onset CKD among African Americans. Our findings extend this association to established DKD, in a racially diverse population.

Funding: Government Support - Non-U.S.

TH-PO878
Ceruloplasminuria Predicts Progression of CKD and Precedes the Development of Macraalbuminuria

Elwaleed Elagnar,1 John J. Hunt,2 Alison Bland,2 Christian Herzog,1 Michael G. Jancech,2 Maria Lopez-Virella,2 John M. Arthur.1 1UMASS; 2MUSC.

Background: We previously used a discovery proteomic analysis to identify ceruloplasmin (Cpl) as a candidate marker to predict decline in renal function in diabetic patients. This is an initial validation study to determine if Cpl predicts progression of CKD in diabetic patients.

Methods: We used 258 urine samples from the VA Diabetes Trial that were collected when patients had normo or microalbuminuria with normal serum creatinine (Cr). The median urine albumin to Cr ratio (ACR) was 11.5 mg/g. The primary outcome measure is a 50% increase in serum Cr or doubling of serum creatinine during follow-up. Secondary outcomes are a 3.3% decline in eGFR per year and development of macroalbuminuria. Ceruloplasmin (Cpl) was measured in urine samples collected as part of the VADT study using ELISA. Urine creatinine (Cr) was measured using a kinetic Jaffe assay. Results adjusted for treatment groups and use of ACE inhibitors.

Results: 13.4% of subjects had a 50% increase in serum Cr. As predicted from the discovery proteomic analysis, urine Cpl concentration is associated with the risk of future decline of renal function in patients with normal renal function at baseline. For each 1 standard deviation increase in Cpl, the odds ratio (OR) for a 50% increase in Cr is 1.39 (CI 1.01-1.85=0.045, AUC 0.56). Standardizing Cpl to urine Cr concentration using a Cpl to Cr ratio (CCR) the OR for CCR is 1.51 (CI 1.14-1.99, p=0.004, AUC 0.61). For comparison the OR for ACR is 1.68 (CI 1.22-2.30, p=0.001, AUC 0.60). To examine whether the combination of ACR and CCR could improve prediction, we divided subjects into 4 groups based on the median splits of ACR and CCR and compared the risk of reaching the primary outcome in each of these groups to using the low ACR and low CCR group as the referent group. When compared to the referent group, all other categories had statistically significantly elevated risk. Subjects that had both high ACR and high CCR had the nominally highest risk.

Conclusions: Ceruloplasminuria can identify type 2 diabetic patients with an increased risk of loss of renal function. The combination of ACR and CCR may enhance prediction. Hence, CCR may be useful as a clinical predictor in combination with ACR.

Funding: Pharmaceutical Company Support - Astellas Pharma Inc.

TH-PO890
Serum Levels of 1,5-Anhydroglucitol and Risk of Incident End-Stage Renal Disease

Casey Rohleder,1 Morgan Grannis,1 Yuan Chen,2 Alden Lawrence Gross,1 Yingying Sang,1 Josef Coresh,1 Elizabeth Selvin.1 1Johns Hopkins Univ; 2Columbia Univ Mailman School of Public Health.

Background: Low 1,5-anhydroglucitol (1,5-AG) is a biomarker of hyperglycemic excursions that has recently been associated with early stages of kidney disease. However, it is unknown if low 1,5-AG levels can lead to more advanced stages of kidney disease independent of kidney function and glycemia (e.g., hemoglobin A1c).

Methods: Blood levels of 1,5-AG, other glycemic markers, and filtration markers were measured in 13,279 Atherosclerosis Risk in Communities (ARIC) Study participants. End-stage renal disease (ESRD) was defined as entry into the U.S. Renal Data System registry from baseline through 2011. Structural equation modelling was used to estimate the association between 1,5-AG and ESRD with latent variables for kidney function (creatinine, cystatin C, β2-microglobulin) and glycemia (diabetes, fasting glucose, hemoglobin A1c, fructosamine, glycated albumin), and adjusting for demographics and established risk factors.

Results: During a median follow-up of 20 years, there were a total of 271 Incident ESRD cases. After adjusting for age, sex, race, hypertension, body mass index, smoking status, and the latent variable for kidney function, the linear spline terms representing 1,5-AG levels <6 µg/mL (IRR: 0.80, 95% CI: 0.71-0.95) and 6-<10 µg/mL (IRR: 0.76, 95% CI: 0.68-0.87) were significantly associated with ESRD. After additionally adjusting for the glycemia latent variable, low levels of 1,5-AG (<6 µg/mL) were no longer significantly elevated risk. Subjects that had both high ACR and high CCR had the nominally highest risk.

Conclusions: These data suggest that urinary activin A is a valuable biomarker reflecting the activity of various kidney diseases.

Funding: Government Support - Non-U.S.
Conclusions: Low levels of 1,5-AG are associated with higher risk of incident ESRD and CKD progression. HUA is a marker of hyperglycemia and glucose variability, an important metabolic pathway that accelerates progression to ESRD.

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

TH-PO881

Two Forms of Urinary Megalin Excretion Are Novel Predictors of the Progression of Early-Stage Diabetic Nephropathy in Type 2 Diabetes Mellitus

Tomonori Honda,1 Michihiro Hosojima,2 Keiko Katabsawa,3 Kazutoshi Nakamura,4 Shoji Kuwahara,5 Tomomi Ishikawa,6 Ryohi Kaseda,7 Yoshiishi Suzuki,7 Hiroki Kuwosawa,8 Yoshiha Hirayama,9 Ichie Narita,9 Akihiko Saijo.8 Clinical Nephrology and Rheumatology, Niigata Univ, Niigata, Japan; 2Clinical Nutrition Science, Niigata Univ, Niigata, Japan; 3Health Promotion Medicine, Niigata Univ, Niigata, Japan; 4Preventive Medicine, Niigata Univ, Niigata, Japan; 5Applied Molecular Medicine, Niigata Univ, Niigata, Japan; 6Health Administration Center, Niigata Univ, Niigata, Japan; 7Denko Co., Ltd., Tokyo, Japan.

Background: Megalin is an endocytic receptor at the apical membrane of proximal tubules. We established sandwich ELISA to measure urinary (u-) excretion of the exodomain and full-length forms of megalin, A- and C-megalin, respectively. Here, we examined the significance of these markers to predict the progression of early-stage diabetic nephropathy.

Methods: We analyzed 175 cases with type 2 diabetes mellitus (T2DM) (103 men; median age 68 [IQR, 59–75] years) with a median observation period of 3.97 (2.10–4.12) years. Cases were selected according to the u-albumin/creatinine (Cr) ratio (ACR) [mg/g] and eGFR (mL/min/1.73m²). We evaluated u-A- and C-megalin in relation to the risks of eGFR reduction (≥20% of initial data) and the escalation of ACR stages (from normo- [ACR] <30) to microalbuminuria [30<ACR<300], or from micro- to macroalbuminuria [ACR≥300]), using Cox’s proportional hazard analysis.

Results: U-A-megalin/Cr was found to be a predictor of the escalation of the ACR stage in 69 microalbuminuric cases with eGFR<30 (HR, 9.71 [95% CI, 1.34–70.67]) and of eGFR reduction in 120 cases with eGFR<60 (HR, 6.31 [95% CI, 1.48–26.82]), even after adjusting for sex, age, HbA1c, eGFR, body mass index, and u-markers including ACR, β2-microglobulin/Cr, and NAG/Cr. U-C-megalin/Cr was also a predictor of the escalation of the ACR stage in 62 normoalbuminuric cases with eGFR≥60 (HR, 2.45 [95% CI, 1.02–5.86]).

Conclusions: A- and C-megalin are novel u-biomarkers, independent of albumin, β2-microglobulin, and NAG, that can predict particularly the progression of diabetic nephropathy in T2DM at micro- and macroalbuminuric stages, respectively.

Funding: Pharmaceutical Company Support - Denko Co., Ltd., Government Support - Non-U.S.

TH-PO882

Effects of Oxidative Stress on the Relationship between Hyperuricemia and Intrarenal Arteriolar Lesions in Chronic Kidney Disease

Tayoshi Miyagi,1 Kentaro Kohagura,2 Yusuke Ohya,3 Kunitoshi Iseki.4 Dept of Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyus, Okinawa, Japan; 2Tomishiro Central Hospital, Okinawa, Japan.

Background: We previously reported that hyperuricemia (HU) is related to intrarenal arteriolar lesion progression in chronic kidney disease (CKD). Here we investigated whether oxidative stress affects this relationship.

Methods: After excluding patients with vasculitis, we recruited a total of 139 patients (mean age, 58 years; 56 females; 84 males) who had undergone renal biopsy at our institution. Whether oxidative stress affects this relationship.

Results: Mean (IQR) urinary 8-oxodG/creatinine and 8-oxoGuo/creatinine ratios were 1.36 (1.04–1.74) and 3.45 (2.68–4.44) nmol/mmol, respectively. In multivariable adjusted models, the log-transformed 8-oxodG/creatinine and 8-oxoGuo/creatinine were not associated with the GFR decline rate. When using 8-oxodG and 8-oxoGuo not corrected for urinary creatinine, one nmol/L higher concentration was associated with a slower GFR decline of 0.19 (95% CI: 0.03–0.35) and 0.16 (95% CI: 0.01–0.30) mL/min/year, respectively.

Conclusions: We found that the urinary concentrations of 8-oxodG and 8-oxoGuo predicted a slower GFR decline in a cohort representative of the general population. This does not support the hypothesis that oxidative stress plays an important role for an accelerated age-related GFR decline.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim, Government Support - Non-U.S.

TH-PO883

Urinary Markers of Oxidative Stress Do Not Accelerate the Age-Related GFR Decline Rate in the General Non-Diabetic Population

Jørgen Schel1, Ole-Martin Fuskevåg,2 Vidar T.N. Steffansson,3 Marit D. Solbu,1 Trond G. Jønsen,4 Bjorn Odvar Eriksen,1 Toralf Melsson.5 Dept of Nephrology, Univ Hospital of North Norway, Tromsø, Norway; Laboratory Medicine may become one of the department of North Norway, Tromsø, Norway; Medical and Renal Research Group, UiT The Arctic Univ of North Norway, Tromsø, Norway; Dept of Nephrology, Oslo Univ Hospital, Oslo, Norway.

Background: Oxidative stress plays an important role in the pathogenic process of age-related chronic diseases. The urinary levels of 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxo-dG) and 8-oxo-7, 8-dihydroguanosine (8-oxo-Gua) are well-established markers of oxidatively damaged DNA and RNA, and have been associated with chronic kidney disease (CKD) in animal studies and progression of diabetic nephropathy in humans. However, whether increased urinary levels of 8-oxo-dG and 8-oxo-Gua predict an accelerated age-related GFR decline in the general population is unknown.

Methods: We measured GFR using iohexol clearance at baseline and follow-up in the Renal iohexol Clearance Survey Follow-Up study (REINS-FU). The cohort included 1,591 middle-aged subjects without diabetes, cardiovascular-, or kidney disease at baseline. After a median of 5.6 years, 1,298 subjects were included in the follow-up study. Baseline urinary levels of 8-oxo-dG and 8-oxo-Gua were measured with LC/MS/MS.

Results: Mean (SD) annual GFR decline was 0.49 (2.23) mL/min/year. The median (IQR) urinary 8-oxo-dG/creatinine and 8-oxo-Gua/creatinine ratios were 1.36 (1.04–1.74) and 3.45 (2.68–4.44) nmol/mmol, respectively. In multivariable adjusted models, the log-transformed 8-oxo-dG/creatinine and 8-oxo-Gua/creatinine were not associated with the GFR decline rate. When using 8-oxo-dG and 8-oxo-Gua not corrected for urinary creatinine, one nmol/L higher concentration was associated with a slower GFR decline of 0.19 (95% CI: 0.03–0.35) and 0.16 (95% CI: 0.01–0.30) mL/min/year, respectively.

Conclusions: We found that the urinary concentrations of 8-oxo-dG and 8-oxo-Gua predicted a slower GFR decline in a cohort representative of the general population. This does not support the hypothesis that oxidative stress plays an important role for an accelerated age-related GFR decline.

Funding: NIDDK Support

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

Underline represents presenting author.

298A
TH-PO885

A Risk Scoring Model to Predict Progression of Renal Dysfunction in Patients with Chronic Kidney Disease Complicated with Contrast-Induced Nephropathy

Seung Don Baek,1 Mun Jing,2 Wonhak Kim,1 Eun Kyoungh Lee,2 Jai Won Chang.1 1Dept of Internal Medicine, Asan Medical Center, Seoul, Korea; 2Dept of Internal Medicine, Dankook Univ College of Medicine, Cheonan-si, Korea.

Background: The contrast-induced nephropathy (CIN) occurs more frequently in patients with lower estimated glomerular filtration rate (eGFR). Since CIN may be associated with the progression of chronic kidney disease (CKD), it would be important to predict the risk of irreversible renal damage prior to contrast-enhanced CT.

Methods: We retrospectively analyzed 18,278 enhanced CTs performed in 9,097 CKD patients with eGFR less than 60 mL/min/1.73 m² for at least 3 months, from January 2013 to December 2014. The progression of renal dysfunction was defined as reduction of eGFR >25% in serum creatinine within 3 days after the CT. We used publicly available -omics data to develop a molecular process model of DKD and identified a representative parsimonious set of 9 biomarkers (CHI3L1, HGF, MMP2, MMP7, MMP8, MMP13, TIE2, TNFR1), which were measured in plasma samples of 1765 patients recruited into two large clinical trials with baseline eGFRs of 87.2 (IQR 16.4) and 33.5 (9.5) ml/min/1.73m² (DIRECT-2 and SUN Macro). The risk scoring model demonstrated that the risk of progression of renal dysfunction increased with the sum of risk score in CKD patients complicated by CIN (p statistic = 0.735).

Conclusions: Although our risk scoring model needs to be validated in another population, our study suggested the possibility of predicting the risk of progression of renal dysfunction in CKD patients prior to contrast administration.

TH-PO886

Validation of a Systems Biology Derived Model to Predict Renal Disease Progression in Diabetes Mellitus

Gert J. Mayer,1 Hiddo Jan Lambers Heerspink,2 Constantin Aschauer,2 Judith Sunzenauer,2 Georg Heinzle,4 Alexander Kainz,3 Paul Perco,5 Michelle Pena,2 Peter Rossing,2 Dick de Zeeuw,2 Rainer Oberbauer.1 1Internal Medicine IV, Medical Univ Innsbruck, Innsbruck, Austria; 2Dept of Clinical Pharmacy and Pharmacology, Univ Medical Center Groningen, Groningen, Netherlands; 3Dept of Nephrology, Medical Univ of Vienna, Vienna, Austria; 4Center for Medical Statistics, Informatics and Intelligent Systems (CeMSIIS), Section for Clinical Biometrics, Medical Univ of Vienna, Vienna, Austria; 5Emergentec Biodevelopment, Vienna, Austria; 6Steno Diabetes Center, Gentofte, Denmark.

Background: Progression of renal function loss in diabetes mellitus (DKD) has a complex molecular pathophysiology. We aimed to identify a panel of biomarkers able to predict the individual eGFR decline using a systems biology derived model and validated the markers in a large sample of patients at various stages of DKD.

Methods: We used publicly available -omics data to develop a molecular process model of DKD and identified a representative parsimonious set of 9 biomarkers (CHI3L1, GH1, HGF, MMP2, MMP7, MMP9, MMP13, TIE2, TNFR1), which were measured in baseline serum samples of 1765 patients recruited into two large clinical trials with baseline eGFRs of 87.2 (IQR 16.4) and 33.5 (9.5) ml/min/1.73m² (DIRECT-2 and SUN Macro). The prediction of eGFR decline by biomarkers, clinical risk factors (including baseline eGFR and albuminuria) and both combined was evaluated by mixed linear models for longitudinal data.

Results: A combination of molecular and clinical predictors achieved an explained variability (R²) of longitudinal eGFR values of 35 and 63% for patients with >60 and <60 ml/min/1.73m² respectively. The contribution to R² by molecular predictors was 15 and 34% for clinical predictors 20 and 29% respectively.

Conclusions: We conclude that a small set of plasma protein biomarkers identified by a systems biology approach enhances the prediction of renal function loss by standard clinical variables in patients with a wide range of baseline eGFR. Furthermore the biomarkers reflect a molecular model of DKD and thus might allow patient stratification based on pathophysiology providing an opportunity to apply targeted therapy.

Funding: Government Support - Non-U.S.
TH-PO889

Relationship between Plasma Sodium Concentration and Chronic Kidney Disease Progression

Nicholas L. Cole, Rebecca Succling, Feng J. He, Pinnaduwage Vipula De Silva, Pauline A. Swift. 1 South West Thames Renal Unit, St. Helier Hospital, London, United Kingdom; 2 Wolfson Inst of Preventative Medicine, Queen Mary Univ of London, London, United Kingdom.

Background: Observational and experimental studies have demonstrated that small increases in plasma sodium concentration (PNa) are associated with increased blood pressure and changes to endothelial function. Increases in PNa may therefore contribute to the adverse renal and cardiovascular outcomes observed in those with chronic kidney disease (CKD).

Methods: This was a retrospective study of data collected between January 2009 and December 2014. We included patients known to our renal service with a minimum of three blood tests taken every two years and an estimated glomerular filtration rate (eGFR) of <60 mL/min at baseline. Exclusion criteria were renal replacement therapy, diabetes mellitus, heart failure, decompensated liver disease, and significant fluctuations in renal function.

Results: 7,063 blood results from 309 patients were included in the study. The mean PNa at baseline was 139.7 mmol/L (SD 2.0). We found no relationship between baseline PNa and eGFR, and no significant change in PNa occurred over time in those with progressive CKD. However, there was a significant correlation between baseline PNa and the change in eGFR over time (r = -0.2, P < 0.001). After adjustment for age, gender, ethnicity, CKD stage and diagnosis, a 1 mmol increase in baseline PNa was associated with a 0.70 mL/min decrease in eGFR over 5 years (P < 0.001, 95% CI 0.29-1.12).

Conclusions: This study is the first to identify an association between PNa and the progression of CKD. Small increases in PNa, within the normal physiological range, were associated with a greater rate of eGFR decline during the study period. The cause of this association is uncertain but increased PNa may be associated with higher blood pressure, problems with salt and water regulation, and endothelial dysfunction.

TH-PO890

Serum Osmolarity Is an Independent Risk Factor for Chronic Kidney Disease: 5 Year Cohort Study in Japan

Masanari Kuwabara, 1,2,3 Miguel A. Lanasa, 1 Carlos Alberto Roncal-Jimenez, 1 Ana Andres-Hernando, 1 Tamara Milagres, 1 Thomas Jensen, 1 Richard J. Johnson. 1, 1 Div of Renal Diseases and Hypertension, Univ of Colorado Denver, Aurora, CO; 2 Dept of Cardiology, Toranomon Hospital, Tokyo, Japan; 3 St. Luke’s International Hospital, Tokyo, Japan.

Background: Epidemics of chronic kidney disease (CKD) not only due to diabetes or hypertension have been observed among individuals working in hot environments in several areas of the world. Experimental models have confirmed that recurrent heat stress and water restriction can lead to CKD, and the mechanism may be mediated by hyperosmolality that activates pathways (vasopressin, aldose reductase-fructokinase) that can induce renal injury. Here we tested the hypothesis that elevated serum osmolarity may be an independent risk factor for development of CKD. This result indicates the importance of limiting high salt diet and prevention of dehydration to prevent CKD.

Funding: Other NIH Support - NIH grant 1R01DK109408-01A1, Private Foundation Support

TH-PO891

Anion Gap Associated with Risk of Progression to ESRD in Adults with Moderate CKD

Tanushree Banerjee, 1 Deidra C. Crews, 1 Sharon Saydah, 1 Nilka Rios Burrows, 2 Brenda W. Gillespie, 3 Rajiv Saran, 3 Neil R. Powe. 1 Medicine, Univ of California, San Francisco; 2 Medicine, Johns Hopkins Univ; 3 Medicine, Univ of Michigan, Ann Arbor; 4 Centers for Disease Control and Prevention.

Background: Anions that accumulate during the course of CKD, including unmeasured anions (e.g. p-cresol sulfate and indoxyl sulfate), may accelerate the progression of CKD. Whether undetermined anions, as indicated by the anion gap, are associated with risk of progression to ESRD in adults with moderate CKD has not been elucidated.

Methods: We analyzed data from 1,286 adults with moderate CKD (eGFR 30-59 mL/min/1.73 m²) enrolled in National Health and Nutrition Examination Survey III (1988-1994). Anion gap was determined from laboratory tests (serum Na (serum Cl + serum bicarbonate). The development of ESRD was ascertained over a median of 10.4 years of follow-up via linkage with USRDS. We used a proportional hazards regression model to test the association between anion gap and risk of ESRD after adjusting for demographics (age, gender, race/ethnicity), clinical factors (diabetes and hypertension), eGFR, and albuminuria.

Results: The mean baseline anion gap was 9.5 mEq/L. An significant elevation in the tertiles of anion gap was found with eGFR 45-59 mL/min/1.73 m² compared to eGFR 30-44 mL/min/1.73 m². Demographics and clinical factors of diabetes and hypertension did not differ by anion gap tertile (p > 0.05). During the follow-up period, 16.7% developed ESRD. Compared to the lowest, the highest tertile of anion gap was associated with an increased risk of ESRD when adjusted for demographics, clinical factors, eGFR, and albuminuria (Relative hazard [95% CI]: 1.81 [1.01-3.08]). There was no significant risk of ESRD noted comparing the middle to the lowest tertile of anion gap (R [95% CI]: 1.10 [0.52-2.04]).

Conclusions: In a nationally representative sample of adults with CKD, we observed that anion gap was independently associated with risk of ESRD. These data highlight the anion gap as a potential therapeutic target for slowing CKD progression.

TH-PO892

Association between Water Intake and Kidney Function: The Korea National Health and Nutrition Examination Survey

Mina Yu, Nephrology, Seoul Seonam Hospital, Seoul, Republic of Korea.

Background: The effect of plain water intake on kidney function is not yet clear. Chronically low fluid intake may induce vasopressin up-regulation and increased GFR via tubuloglomerular feedback and hyperfiltration. However, some data reported that water intake may prevent GFR decline.

Methods: The population-based, cross-sectional study analyzed, total 37,753 participants from the Korea National Health and Nutrition Examination Survey conducted in 2008-2011. The water intake (cup/200 mL/day) was estimated by asking the question “how much water do you usually consume per day?”. Dietary water intake (g/day) was estimated by 24-hour dietary recall. The 24-hr urinary sodium values were estimated from sodium and creatinine values of random urine samples using Tanaka’s equation. CKD was defined as a group of an GFR (GFR<30, 30< GFR<60, 60< GFR<90, GFR>90). Data was split into age by 10 years.

Results: Of 26,955 adults (range 19-96yrs), CKD defined (GFR<30): 56.2%(50%);30-GFR R=0.829[2.1%];60-GFR=99.8%[26.7%]. As ages urine specific gravity was significantly reduced (1.022±1.022 vs. 1.019±1.018 vs. 1.017±1.016; 19<Age<30 vs. 30<Age<39 vs. 39<Age<49:50<59.60:69.70:90:90 (p<0.05). The estimated amount of sodium excretion (mmol/d) increased to 60s decreased from 70s (18,426 vs. 19,317 vs. 19984 vs. 20847 vs. 21294 vs. 20476 (p<0.05), showed a similar pattern also is sodium intake (g/d) estimated from food (8.87 vs. 5.14 vs. 5.14 vs. 5.13 vs. 5.13 vs. 5.13) 

Conclusions: In a nationally representative sample of adults with CKD, we observed that anion gap was independently associated with risk of ESRD. These data highlight the anion gap as a potential therapeutic target for slowing CKD progression.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
TH-PO893

Effect of Homocysteine on Intestinal Permeability in Rats with Adenine-Induced Experimental Uremia

Shanshan Jiang, Hongli Jiang. Dialysis Dept of Nephrology Hospital, First Affiliated Hospital of Medicine School, Xi’an Jiaotong Univ.

Background: Previous studies have revealed increased levels of plasma and intestinal homocysteine (Hcy) in Chronic Kidney Disease (CKD). However, whether Hcy is involved in increased intestinal permeability and barrier dysfunction of CKD remains unclear. This study aimed to investigate the effect of Hcy on intestinal in rats with adenine-induced uremia and elucidate its possible mechanism.

Methods: SD rats were divided into four groups: normal, Hcy, adenine + Hcy. Experimental uremia was induced by adenine and Hcy were injected subcutaneously. The serum creatinine, urea nitrogen as well as the renal pathological tissue staining were tested to assess the model. The serum C-reactive protein, IL-6 and TNF-α, Hcy, endotoxin, epithelial permeability and intestinal tissues Hcy, SOD and MDA levels were assessed. The ferritin released protein of MMP-9, α-SMA and TGF-β were assessed by Western blot.

Results: The serum biochemical parameters and renal pathological show a success of animal model (Fig1). The serum inflammatory factors, endotoxin, Hcy, endotoxin and intestinal permeability were shown in Figure 2, and intestinal tissue levels of Hcy, SOD and MDA were assessed. The ferritin released protein of MMP-9, α-SMA and TGF-β protein abundance were shown in Figure 4. Compared with normal and adenine group, the serum inflammatory factors, endotoxin, Hcy and intestinal permeability, and intestinal tissue levels of Hcy and MDA were significantly higher, with the SOD activity markedly decreased in adenine + Hcy group. In adenine group and adenine + Hcy group, the protein expression were significantly increased than normal group.

Conclusions: Hcy can increase intestinal permeability and aggravate inflammatory damage in adenine-induced uremia rats. The underlying mechanisms of which may be attributed to its effects of promoting the expression of fibrosis related factors.

Funding: Government Support - Non-U.S.

TH-PO894

County-Level Air Quality and the Incidence of ESRD in the U.S.


Background: Considerable geographic variation exists in the incidence of ESRD across the U.S. Higher rates have been noted along the Ohio and Mississippi river valleys and in more industrialized parts of the country. We explore the association between air quality and ESRD incidence by county in the US.

Methods: Using data on all incident cases of ESRD from the USRDS data base (2012-2014, n=338,942), the US Census (2013), and 2006 EPA air-quality data, we examined the association between a county-level measure of air pollution—particulate matter ≤2.5 μm (PM2.5), which includes toxic particulates, such as heavy metals—and the incidence of ESRD. We categorized PM2.5 by quartiles suggest a possible detrimental threshold effect at PM2.5 level of 10 μg/m3, which is below the current EPA guideline of 12 μg/m3.

Results: The crude incidence rate of ESRD ranged from 0 to 2,341 new cases per 1,000,000 population among counties (median ~335) in the full sample and 69 to 1,581 (PM2.5) was 1.10 (95% CI = 1.09-1.11; p < 0.0001). The results when categorizing PM2.5 by quartiles suggest a possible detrimental threshold effect at PM2.5 level of 10 μg/m³, which is below the current EPA guideline of 12 μg/m³.

Conclusions: We found that poorer air quality was associated with higher incidence rate of ESRD. However, the ecological design and lack of individual exposure data precludes causal inference. Future investigations should include measures of multiple air pollutants and individual exposure, as well as more extensive control of confounding.

Funding: NIDDK Support

TH-PO895

APOL1, Sickle Cell Trait (SCT), and Risk of Chronic Kidney Disease (CKD) in the Jackson Heart Study (JHS)

Bessie A. Young,1,2,3 Alex Reiner,1 L. Ebony Boulware,4 Neil R. Powe,5 Bryan R. Kestenbaum,6 Nora Franceschini,7 Nisha Bansal,8 Adolfo Correa,9 Jonathan Himmelbarf,10 Ronit Katz,12 Hospital and Specialty Care, VA Puget Sound Health Care System, Seattle, WA;12 Kidney Research Inst and Div of Nephrology, UW, Seattle, WA;13 Epidemiology, UW, Seattle, WA;14 Medicine, Duke, Durham NC;15 Medicine, UCSF, San Francisco, CA;15 Medicine, UMC, Jackson, MS;16 Epidemiology, UNC, Chapel Hill, NC.

Background: APOL1 high-risk variants and SCT have been shown to be associated with increased risk of CKD among African Americans (AA). Little is known regarding risk of development of CKD/ESRD among AA with one risk variant compared to none; or whether there is an association with SCT. We determined the association between APOL1 risk variants, SCT, and development of CKD among AA of JHS.

Methods: JHS is a prospective cohort study of 3306 AA. Participants were enrolled at baseline (2000-2004), and followed at exam 2 (2005-2008) and 3 (2009-2012). The primary outcomes of interest were incident CKD (eGFR < 60 ml/min/m²), incident albuminuria (albumin to creatinine ratio (ACR) ≥ 30 mg/g), incident ESRD or rapid kidney function decline (defined as ≥ 50% decline). Multivariable models (Cox, logistic, and linear) were adjusted for age, sex, diabetes (DM), hypertension (HTN), SCT, and ancestry informative markers.

Results: Baseline creatinine and genetic information on APOL1 variants and/or SCT were available for 2300 AA. Of those, 41.3% had zero, 32.0% had one, and 6.7% had two APOL1 variants; SCT was found in 8.5% (199/2299). Subjects with one (HR=1.41, 95% CI 1.00-1.99) and two (HR=1.97, 1.12-3.47) APOL1 risk alleles had increased risk of incident ACR that remain significant after adjustment, while incident ESRD was significant for those with two alleles (aOR 11.89, CI 2.10-67.4). Continuous decline in eGFR and rapid decline in eGFR>30% were significant for those with two but not one alleles.

Conclusions: Among AA, the presence of one or two APOL1 risk alleles was associated with increased risk of incident ACR in a graded fashion. Those with two alleles also had increased risk of incident ESRD, continuous decline, and rapid decline of eGFR independent of DM, HTN or SCT.

Funding: NIDDK Support, VA Support

TH-PO896

Insulin Requirement Is a Risk Factor for End-Stage Renal Disease (ESRD) Independent of Hemoglobin (Hb) A1C Levels in Type 2 Diabetes Mellitus (T2DM)

Rabia Nadeem Kiani,1 R. E. Boucher,1 Guo Wei,1 Debra Lynn Simmons,2 Linda F. Fried,2 T. S. Bjorndahl,1 Tom Greene,1 Sriini Bedhu.3 1Univ of Utah, SLC, UT; 2VA, Pittsburgh.

Background: As the need for insulin might be a reflection of insulin resistance, we hypothesized that independent of HbA1c levels, insulin use might be a risk factor for ESRD in T2DM.

Methods: In a cohort of 1,561,876 veterans with serum creatinine and serum HDL-cholesterol measured within 3 months of each other from Jan 1, 2000 to Dec 31, 2008, we analyzed 188,544 veterans with T2DM (defined by ICD9 codes). Data on filled medications were obtained from outpatient pharmacy database. Laboratory data were obtained from routine clinical labs. Follow-up was until 10/1/2011. ESRD data were obtained by linking to USRDS. Based on HbA1c levels and the use of insulin, 6 groups were defined. Using the HbA1c< 7 and no insulin as the reference group, the risk of ESRD in the other groups were examined in Cox regression models.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: Deoxycholate, a Gut-Microbiome Derived Bile Acid Is Elevated in Patients with Diabetic Kidney Disease

Conclusions: A limitation is the lack of data on duration of T2DM. However, even in those with HbA1C < 7, need for insulin was associated with increased ESRD risk. Interventions that ↓ the need for insulin might ↓ the risk of ESRD in T2DM.

Funding: NIDDK Support, VA Support

TH-PO899

Reported Randomized Controlled Trial Results in Nephrology Are Fragile: An Analysis Using the Fragility Index

Methods: A systematic literature search identifying all RCT in 5 nephrology journals (JASN, CJASN, AJKD, NDT and KI) and 5 general journals (NEJM, Lancet, BMJ, JAMA and Annals of Internal Medicine) from 2005-2014 was performed. RCT reporting at least one dichotomous outcome were included. Reporting of individual trials was assessed using the Fragility Index (FI).

Results: Of 129 RCT included (111 nephrology, 18 general), 6 studies had a FI of zero and were excluded from further analysis. Of the remaining 123 studies, median sample size was 132 (range 22-11506) with 18 (range 0-1243) events in the intervention group. Median FI was 3 (range 1-166) indicating that in half of the studies the addition of 3 events to one of the treatment arms rendered the result non-significant. A doubling in total event number and sample size independently increased median FI by 30% and 16% respectively (p < 0.001 and p = 0.009). Compared to a reported p-value of >0.01-<0.05, those reporting 0.01-0.001 and <0.001 had a 74% (p < 0.001) and 497% (p < 0.001) increase in the median FI. After adjusting for event number, sample size and p-value, the median FI was 58% lower in general medical journals compared to renal journals (p = 0.007). Finally, of the studies reporting loss to follow-up (n=106), 41% had a FI < 10 loss to follow-up indicating potential to change a trial result had all subjects been accounted for in the study.

Conclusions: Reported nephrology RCT results are fragile, with half of the studies’ results not acceptable to changes in small numbers of events. This study highlights the need for larger RCT with accurate accounting for loss to follow-up to adequately guide evidence-based practice.

TH-PO900

Scope and Consistency of Outcomes Reported in Randomized Trials Conducted in Children with Chronic Kidney Disease

Methods: The Cochrane Renal Register of Controlled Trials was searched for all RCTs in children across all stages of CKD published before March 2016. The frequency of reporting of each outcome domain, and the measurement characteristics were evaluated.

Results: From the 205 trials, 99 different outcome domains were reported including 37 and 44 domains specific to transplantation and dialysis, respectively. Across all outcome domains, 50 (51%) were surrogate, 40 (40%) were clinical, and 9 (9%) were patient-reported. The median number of domains per trial was 15 (IQR 9-26). The five most commonly reported domains were: blood pressure (75 [37%] trials), medication use/ adherence (71 [36%] trials), renal permisum (72 [35%] trials), kidney function (68 [32%] and infection (61 [30%]). Mortality was reported in 28 (14%) trials. Cardiovascular disease and quality of life were reported very infrequently, in 8 (4%) and 2 (1%) trials, respectively. There was inconsistency of measures and time points used across all trials. Across the 99 domains, 1671 different measurements were reported. For blood pressure and medication use/adherence, 76 and 54 measures were described across trials, respectively.

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

Underlines represents presenting author.

302A
Conclusions: The outcomes reported in RCTs involving children with CKD primarily report surrogate outcomes, rather than clinical and patient-centered outcomes such as mortality, cardiovascular disease, quality of life and cognition. The multiplicity and heterogeneity of outcomes at all levels – domain, measurement, threshold, and time points - deters efforts to compare the effectiveness of interventions and use trial evidence in decision-making.

TH-PO901

Effects of Ferric Citrate (FC) in Adults with Non-Dialysis-Dependent Chronic Kidney Disease and Iron-Deficiency Anemia (IDA): Ph 3 Clinical Trial

Steven Fishbane,1 Geoffrey A. Block,2 Pablo E. Pergola,3 Lisa Loram,1 John F. Neylan,4 Katrin Uhlig,1 Glenn Matthew Chertow,2 1Hofstra Northwell Health, Great Neck, NY; 2Stanford Univ, Palo Alto, CA; 3Keryx Biopharmaceuticals, Boston, MA; 4Denver Nephrologists PC, Denver, CO; 5Keryx Biopharmaceuticals, Boston, MA; 6Stanford Univ, Palo Alto, CA.

Background: Iron deficiency anemia is common and consequential in non-dialysis-dependent chronic kidney disease (NDD-CKD). Efficacy and tolerability of conventional oral iron supplements are mixed; intravenous (IV) iron administration is associated with finite but important risks.

Methods: 234 patients were randomized 1:1 to FC and Placebo (P) in a double blind clinical trial comparing the safety and efficacy in patients with NDD-CKD stages 3-5 and IDA. The starting dose of 3 tablets/day was increased every 4 weeks if hemoglobin (Hgb) was not >1g/dL above baseline. IV or oral iron, erythropoiesis stimulating agents, blood transfusions and other phosphate binders were not permitted during the trial. The primary endpoint was the proportion of patients who achieved ≥1 g/dL increase in Hgb at any time in a 16-week randomized period. Patients who completed the 16-week period were asked to participate in an 8-week open label extension period.

Results: Patients randomized to FC were significantly more likely to achieve the primary endpoint [52.1% (61/117) vs 19.1% (22/115), p<0.001]. All secondary endpoints also reached statistical significance, including the mean relative change in Hgb (0.84 g/dL, 95% confidence interval 0.58 to 1.10 g/dL, p<0.001) and the proportion of patients who achieved a sustained increase in Hgb [≥0.75 g/dL] over any 4-week time period during the randomized trial period [48.7% (57/117) versus 14.8% (17/115), p<0.001]. Gastrointestinal disorders were the most commonly observed adverse events, with diarrhea reported in 24 (20.5%) and 19 (15.3%) patients treated with FC and P, respectively. The rate of serious AEs was 20.5% and 19 (16.4%), nausea in 13 (11.1%) and 3 (2.6%) and constipation in 22 (18.8%) and 19 (16.4%), respectively.

Conclusions: In patients with NDD-CKD and IDA, FC increased and maintained hemoglobin levels independent of baseline Hgb.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

TH-PO902

Hemoglobin Response to Ferric Citrate (FC) in Subjects with Non-Dialysis Dependent (NDD) Chronic Kidney Disease (CKD) and Iron Deficiency Anemia (IDA): Data from a Phase 3 Clinical Trial

Glen Matthew Chertow,1 Steven Fishbane,2 Pablo E. Pergola,3 John F. Neylan,4 Geoffrey A. Block,1 Katrin Uhlig,1 Glenn Matthew Chertow,2 1Hofstra Northwell Health, Great Neck, NY; 2Stanford Assoc, San Antonio, TX; 3Keryx Biopharmaceuticals, Boston, MA; 4Denver Nephrologists PC, Denver, CO.

Background: The hemoglobin (Hgb) response to Ferric Citrate (FC) in a Phase 3 clinical trial in subjects with NDD-CKD and IDA was further explored. The study demonstrated that in patients with NDD-CKD, FC is well tolerated and may be an efficacious treatment for IDA.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

TH-PO903

Effects of Ferric Citrate on Parameters of Mineral and Bone Metabolism in Patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Treated for Iron Deficiency Anemia (IDA)

Geoffrey A. Block,1 Steven Fishbane,2 Pablo E. Pergola,3 John F. Neylan,4 Glenn Matthew Chertow,2 1Keryx Biopharmaceuticals, Boston, MA; 2Stanford Univ, Palo Alto, CA; 3Keryx Biopharmaceuticals, Boston, MA; 4Denver Nephrologists PC, Denver, CO; 5Keryx Biopharmaceuticals, Boston, MA.

Background: Ferric citrate (FC) is an approved iron-based phosphate binder. A recent Phase 3 clinical trial was completed to evaluate the efficacy and safety of FC for the treatment for IDA in NDD-CKD. Here we evaluate the effect of FC on serum phosphate (Phos), intact parathyroid hormone (PTH) and fibroblast growth factor (FGF)-23 levels when FC dose was titrated to hemoglobin (Hgb).

Methods: 234 subjects randomized 1:1 to FC and Placebo (P) were included in a 16 week Randomized period followed by an 8 week Extension period. Subjects with serum Phos >3.5 mg/dL at screening were excluded. The starting dose of 3 tablets/day was increased at fixed intervals if Hgb at any time point had not increased by ≥2 g/dL and if serum Phos was >2.5 mg/dL. Between-group changes in serum Phos, PTH, e-terminal and intact FGF-23 were estimated from baseline to week 16 using MMRM (parametric data) and Wilcoxon Rank-Sum test (non-parametric data).

Results: Data for serum Phos, PTH and FGF-23 are presented in the Table.

<table>
<thead>
<tr>
<th>Serum Phosphate (mg/dL)</th>
<th>Mean ± SD</th>
<th>BL</th>
<th>EOT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC (n=117)</td>
<td>3.72±0.06</td>
<td>4.12±0.06</td>
<td>84 [58,173]</td>
<td>0.02</td>
</tr>
<tr>
<td>P (n=115)</td>
<td>3.86±0.08</td>
<td>3.86±0.08</td>
<td>90 [62,148]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>i-FGF23 (pg/mL) median</td>
<td>105 (67,180)</td>
<td>105 (67,180)</td>
<td>105 (67,180)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phosphate (mg/dL) median</td>
<td>105 (67,180)</td>
<td>105 (67,180)</td>
<td>105 (67,180)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTH (pg/mL) median</td>
<td>105 (67,180)</td>
<td>105 (67,180)</td>
<td>105 (67,180)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BL - baseline; EOT - end of 16 week randomized period

During the Randomized Period, 4 (3.4%) and 3 (2.6%) subjects on FC and P, respectively, had serum Phos <2.5 mg/dL.

Conclusions: In patients with NDD-CKD, FC given in doses to raise Hgb, reduced serum Phos, with infrequent excursions below normal. FC also lowered PTH, e-terminal and intact FGF23 levels.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

TH-PO904

Predictors of Hemoglobin Response to Ferric Citrate in Patients with Non-Dialysis Dependent Chronic Kidney Disease and Iron Deficiency Anemia

Pablo E. Pergola,1 Steven Fishbane,2 Geoffrey A. Block,1 John F. Neylan,4 Katrin Uhlig,1 Glenn Matthew Chertow,2 1Renal Associates PA, San Antonio, TX; 2Keryx Biopharmaceuticals, Great Neck, NY; 3Denver Nephrologists PC, Denver, CO; 4Keryx Biopharmaceuticals, Boston, MA; 5Stanford Univ, Palo Alto, CA.

Background: Ferric citrate (FC), an approved iron-based phosphate binder, raised hemoglobin (Hgb) in a phase 3 trial of iron deficiency anemia (IDA) in patients with Non-Dialysis Dependent CKD (NDD-CKD). We examined demographic and clinical factors and routinely available laboratory tests as determinants of hemoglobin (Hgb) response.

Methods: In the 16 week randomized period, 61/117 FC treated subjects had an increase in Hgb of ≥1 g/dL at any point (defined as “responders”). We compared baseline characteristics and laboratory changes of responders and non-responders. Laboratory variables (Hgb, TSAT, ferritin, eGFR, phosphate, calcium, bicarbonate, PTH, and albumin) identified as candidate predictors of Hgb change in univariate analyses (with a p-value of ≤0.1) were entered into multivariable linear regression analysis. PTH was log transformed.

Results: Baseline demographic and clinical characteristics did not differ by responder status. In univariate analyses, TSAT, ferritin, eGFR, and phosphate were identified as candidate predictors of Hgb change. TSAT and eGFR combined provided the best fitting multivariate model. A 5% lower TSAT was associated with a 0.2 g/dL (95% confidence interval 0 to 0.35, p=0.029) greater increase in Hgb; a 10 ml/min/1.73 m2 higher eGFR with a 0.2 g/dL (0 to 0.35, p=0.036) greater increase in Hgb. Responders relative to non-responders experienced larger increases in TSAT (20% versus 11%, p=0.01) and ferritin (164 versus 117 ng/mL, p=0.045) during the trial.

Conclusions: Patients with NDD-CKD and IDA respond to FC with an increase in Hgb regardless of degree of iron deficiency and renal impairment. Patients with a pronounced iron deficiency (lower TSAT) and better kidney function (higher GFR) experience a more robust Hgb response to FC associated with repletion of iron stores, as reflected by greater increases in TSAT and ferritin among responders.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
TH-PO905
Efficacy and Safety of Sevelamer Carbonate in Hyperphosphatemic Pediatric Patients with Chronic Kidney Disease
Sahar A. Fathallah-Shaykh,1 Mark R. Benfield,2 Dorota Drozdz,3 Joseph T. Flynn,4 Randall Jenkins,5 Katherine Wesseling-Perry,2 Sarah J. Swartz,2 Craig S. Wong,3 Beverly Accomando,2 Gerald F. Cox,5 Bradley Warady.11 U of Alabama at Birmingham, Birmingham, AL; Pediatric Nephrology of Alabama, Birmingham, AL; 1Department of Pediatric Nephrology, JU MC, Krakow, Poland; 2Seattle Children's Hosp, Seattle, WA; 3Oregon Health & Science U, Portland, OR; 4Children’s Health Center, UCLA, Los Angeles, CA; 5Texas Children’s Hosp, Houston, TX; 6U of New Mexico HSC, Albuquerque, NM; 7Sanofi Genzyme, Cambridge, MA; 8Children’s Mercy Hosp, Kansas City, MO.

Background: No currently marketed oral phosphate binders are FDA-approved for management of hyperphosphatemia in children with chronic kidney disease (CKD). This phase 2 study (NCT01353262) evaluated safety and efficacy of sevelamer carbonate (SC) in hyperphosphatemic pediatric patients with CKD before/on dialysis.

Methods: After 2–4 week screening/washout, children with serum phosphorus (SP) higher than age-appropriate levels were randomized to receive SC/placebo in 0.4–1.6 g doses based on body surface area for a 2–week fixed-dose period (FDP) followed by a 6-month single-arm open-label titration dose period (TDP). Primary efficacy endpoint: change in SP from baseline to end of FDP (ANCova); secondary efficacy endpoint: change in SP from baseline to end of TDP (descriptive statistics). Adverse events (AEs) were recorded.

Results: Of 101 patients enrolled at 29 centers, 66 completed the study (74% adolescents [mean age=14.1 years]; 77% on dialysis; renal transplant was the main reason for discontinuation. Mean overall baseline SP was 7.16 mg/dL. SC significantly reduced SP levels from baseline during FDP (−0.90 mg/dL, P=0.001) and TDP (−1.18 mg/dL, P=0.001) SP became age-appropriate in 8% patients on SC during FDP and overall 27% patients at end of TDP. Safety/tolerability of SC was comparable to placebo during FDP; mild gastrointestinal AEs occurred in TDP. No clinically relevant changes occurred in vital signs and in calcium/bicarbonate levels.

Conclusions: Sevelamer carbonate lowered SP significantly in hyperphosphatemic children with CKD, with no significant safety issues identified.

Funding: Pharmaceutical Company Support - Sanofi Genzyme

TH-PO906
Low Rate of Early Response to Oral Iron in Patients with Non-Dialysis Dependent CKD (ND-CKD)
Iain C. Macdougall,1 Andreas H. Bock,2 Fernando Carrera,3 Kai-Uwe Eckardt,4 Carlo A. Gaillard,5 David B. Van Wyck,6 Yvonne Meier,7 Sylvain Larroque,7 Simon D. Roger,8 King’s College Hospital, London, United Kingdom; 9Kantonsspital Aarau, Aarau, Switzerland; 10Eurodial, DaVita, Leona, Portugal; 11Uni. Erlangen-Nürnberg, Erlangen, Germany; 12Uni. Medical Centre Groningen, Groningen, Netherlands; 13DaVita Healthcare Partners Inc, Denver, CO; 14Vifor Pharma, Glattbrugg, Switzerland; 15Renal Research, Gosford, NSW, Australia.

Background: Hematopoietic response rates to oral iron in ND-CKD are low. The likelihood of a subsequent response after initial non-response could guide decision-making.

Methods: Post hoc, 626 iron-deficient patients with ND-CKD and anemia, randomized (2:1:1) in the FIND-CKD trial to oral iron or IV ferric carboxymaltose (FCM, targeting TSAT were higher in W4 non-responders vs responders (Table). With oral iron, only 11% are shown for comparison.

weeks 4 and 8 for the week 8 (W8) analysis were excluded. Data from the FCM groups rescue. Patients without Hb data at BL and week 4 (W4) for the W4 analysis, or BL and TB-PO907
Efficacy and Dose Requirements of Vadadustat Are Independent of Systemic Inflammation and prior Erythropoiesis-Stimulating Agent (ESA) Dose in Patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD)
Volker H. Haase,1 Bruce S. Spinnowitz,2 Pablo E. Pergola,2 Zeeshan Khawaja,3 Jason Chan,1 Qing Zauraw,2 Bradley J. Maroni,1 Ramin Farzanchi-Fat.1

Results: Baseline inflammatory markers and weekly ESA dose (prior to study entry) did not correlate with vadadustat dose at Week 20 (p=0.4). The magnitude of the mean increase in Hb (from baseline to Week 20) was independent of baseline hepcidin (p=0.6), ESA dose (p=0.9) and CRP (p=0.6; figure). In addition, vadadustat treatment maintained Hb within target range (p<0.0001 vs placebo), with few Hb excursions above 13g/dl (6.13; 4%). Change in Hb from baseline to Week 20 (out-of-treatment) was independent of the baseline CRP levels.

Conclusions: The Hb response and vadadustat dose requirement for correction and maintenance of Hb are independent of underlying systemic inflammation and baseline ESA dose in patients with NDD-CKD.

Funding: Pharmaceutical Company Support - Akemia Therapeutics, Inc.

TH-PO908
Daprodustat, a HIF-Prolyl-Hydroxylase Inhibitor, Increases and Maintains Hemoglobin over 24 Weeks in Anemic Chronic Kidney Disease Subjects
Louis Holdstock,1 Borut Cizman,3 Amy M. Meadowcroft,1 Nadita Biswas,1 Delyth Jones,1 Brendan M. Johnson,2 John J. Lepore,1 Sung Guyn Kim,2 Alexander Ralph Cobitz,1 GlaxoSmithKline; 1Roivant Sciences; 2Hansom Unit, South, Korea.

Background: The efficacy and safety of daprodustat (GSK1278863) was evaluated in 252 chronic kidney disease (CKD) subjects over 24 weeks (w). Methods: rhEPO-naive subjects were randomized 1:1 to daprodustat (1–4mg, based on starting hemoglobin [Hgb; g/dL] for rhEPO-naive subjects; 2 mg for rhEPO-users) or control groups (CTRL, rhEPO per investigator discretion; 91% of rhEPO naïve subjects and all rhEPO users received at least 1 rhEPO dose). For rhEPO-naive subjects, entry Hgb was 8-10 (group [G] 1) or 8-11 (G2); for rhEPO-users, entry Hgb was 9-10.5 (G1) or 9-11.5 (G2). Study drug was titrated to maintain Hgb in a target range (TR) of 9–10.5 (G1) or 10–11.5 (G2).

Results: In rhEPO naïve subjects, mean Hgb increased from 9.6 to 10.2 (G1) and 10.1 to 11.0 (G2) in the daprodustat groups, and from 9.6 to 10.6 (G1) and 10.2 to 11.1 (G2) in CTRL. Median percent of time within Hgb target range was 86% for the combined daprodustat groups and 47% for combined CTRL. In rhEPO users, Hgb was maintained in both daprodustat groups, whereas Hgb in CTRL increased by 0.7 (G1) and 0.4 (G2). The median percent of time within Hgb target range was 94% for the combined daprodustat groups compared to 88% for the combined CTRL. In rhEPO naïve subjects, hepcidin decreased from baseline at 24w by 19.3% in the daprodustat group and increased by 6.7% in CTRL. In rhEPO users, hepcidin decreased by 9.9% at 24w in the daprodustat group, and by 17.1% in CTRL. Daprodustat did not effect plasma EPO or VEGF levels throughout the study. There were no differences between groups in blood pressure or EFHg.

Conclusions: The Hb response and vadadustat dose requirement for correction and maintenance of Hb are independent of underlying systemic inflammation and baseline ESA dose in patients with NDD-CKD.

Funding: Pharmaceutical Company Support - Akemia Therapeutics, Inc.

TH-PO908
Daprodustat, a HIF-Prolyl-Hydroxylase Inhibitor, Increases and Maintains Hemoglobin over 24 Weeks in Anemic Chronic Kidney Disease Subjects
Louis Holdstock,1 Borut Cizman,3 Amy M. Meadowcroft,1 Nadita Biswas,1 Delyth Jones,1 Brendan M. Johnson,2 John J. Lepore,1 Sung Guyn Kim,2 Alexander Ralph Cobitz,1 GlaxoSmithKline; 1Roivant Sciences; 2Hansom Unit, South, Korea.

Background: The efficacy and safety of daprodustat (GSK1278863) was evaluated in 252 chronic kidney disease (CKD) subjects over 24 weeks (w). Methods: rhEPO-naive subjects were randomized 1:1 to daprodustat (1–4mg, based on starting hemoglobin [Hgb; g/dL] for rhEPO-naive subjects; 2 mg for rhEPO-users) or control groups (CTRL, rhEPO per investigator discretion; 91% of rhEPO naïve subjects and all rhEPO users received at least 1 rhEPO dose). For rhEPO-naive subjects, entry Hgb was 8-10 (group [G] 1) or 8-11 (G2); for rhEPO-users, entry Hgb was 9-10.5 (G1) or 9-11.5 (G2). Study drug was titrated to maintain Hgb in a target range (TR) of 9–10.5 (G1) or 10–11.5 (G2).

Results: In rhEPO naïve subjects, mean Hgb increased from 9.6 to 10.2 (G1) and 10.1 to 11.0 (G2) in the daprodustat groups, and from 9.6 to 10.6 (G1) and 10.2 to 11.1 (G2) in CTRL. Median percent of time within Hgb target range was 86% for the combined daprodustat groups and 47% for combined CTRL. In rhEPO users, Hgb was maintained in both daprodustat groups, whereas Hgb in CTRL increased by 0.7 (G1) and 0.4 (G2). The median percent of time within Hgb target range was 94% for the combined daprodustat groups compared to 88% for the combined CTRL. In rhEPO naïve subjects, hepcidin decreased from baseline at 24w by 19.3% in the daprodustat group and increased by 6.7% in CTRL. In rhEPO users, hepcidin decreased by 9.9% at 24w in the daprodustat group, and by 17.1% in CTRL. Daprodustat did not effect plasma EPO or VEGF levels throughout the study. There were no differences between groups in blood pressure or EFHg.

Conclusions: The Hb response and vadadustat dose requirement for correction and maintenance of Hb are independent of underlying systemic inflammation and baseline ESA dose in patients with NDD-CKD.

Funding: Pharmaceutical Company Support - Akemia Therapeutics, Inc.
**TH-PO099**
High versus Low Dose Erthropoietis-Stimulating Agents in People with End-Stage Kidney Disease Treated with Hemodialysis (C.E. DOSE Trial): A Pragmatic, Multicenter, Randomized Controlled Trial
Valeria M. Saglimbene,1,2 Suetonia Martinelli,3 Marinella Ruopolo,4,5 Gabrielle J. Williams,6 Jonathan C. Craig,7 Jorgen B.A. Hegbrant,1 Giovanni F.M. Strippoli,1,2,5 Diaverium Medical Scientific Office; 1Univ of Sydney; 2Univ of Ottao Chutcharg; 3Amedeo Avogadro Univ of Eastern Piedmont; 4Univ of Bart, on behalf of the C.E. DOSE Investigator.

**Background:** The increased risks of death and adverse cardiovascular events with erthropoietis-stimulating agent (ESA) therapy targeting a higher hemoglobin level in patients with ESKD are established, but it is unclear whether these adverse effects can be mitigated and quality of life benefits maintained when a fixed treatment dose approach is used.

**Methods:** The C.E. DOSE trial was a multicenter, pragmatic, non-blinded, randomized, controlled, parallel-group trial allocating 656 hemodialysis patients with anemia to receive either high dose (18,000 IU epoetin alfa or epoetin beta or 90 mcg darbepoetin alfa per week) or low dose (4000 IU epoetin alfa or epoetin beta or 20 mcg darbepoetin alfa per week) ESA. The primary outcome was a composite of death or a CV event (non-fatal myocardial infarction, non-fatal stroke, or hospitalization for acute coronary syndrome, transient ischemic attack, unplanned percutaneous coronary intervention or peripheral revascularization). ClinicalTrials.gov, number NCT0887201.

**Results:** High dose ESA did not increase the primary outcome by 12 months (55 [17%] vs 46 [14%] patients; hazard ratio [HR] 1.19, 95% CI 0.81–1.77, death [40 [12%] vs 35 [11%], HR 1.21, 95% CI 0.97–1.51], or myocardial infarction [8 [2%] vs 4 [1%], HR 1.78, 95% CI 0.52–6.80], and had no impact on HRQOL (mean difference in physical composite score at 12 months 1.70, 95% CI –0.95 to 4.35).

**Conclusions:** In this fixed-dose trial of ESA treatment for anemia in patients with ESKD, a high dose strategy had uncertain effects on mortality, CVEs, and health-related quality of life. Funding: Italian Medicines Agency.

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

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**TH-PO101**
NT-proBNP Levels Predict the Individual Drug Response to Aliskiren in Patients with Type 2 Diabetes at High Cardio-Renal Risk
Hiddo Jan Lambers Heerspink,1 Frederik I. Persson,2 Hans-Henrik Parving,3 Dick de Zeeuw,1 1Univ Medical Center Groningen, Netherlands; 2Sheno Diabetes Center, Denmark; 3Rigshospitalet, Univ of Copenhagen, Denmark.

**Background:** The individual response to renin-angiotensin-system (RAS) intervention is blunted in the setting of volume overload. Diuretic treatment or low sodium diet is often required to enhance the response to RAS intervention. We investigated whether NT-proBNP, a biomarker of volume expansion, can be used to predict the individual response to aliskiren.

**Methods:** A post-hoc analysis was performed in the ALTITUDE trial, a double blind randomized controlled trial comparing the effect of aliskiren 300 mg/d vs placebo on cardio-renal endpoints in 8561 patients with type 2 diabetes at cardio-renal risk. Data from 5081 patients with available NT-proBNP measurements were used. The primary endpoint was a composite of CV death, resuscitated sudden death, MI, stroke, hospitalization for heart failure, end-stage renal disease (ESRD), or doubling of serum creatinine. We investigated variation in the effect of aliskiren on the cardio-renal endpoint based on baseline tertiles of NT-proBNP in Cox proportional hazard regression models using an interaction term (treatment*NT-proBNP).

**Results:** Median NT-proBNP levels by tertiles were 50, 157, and 534 pg/ml, respectively. During a median follow-up of 2.5 years, 840 (16.4%) patients experienced a cardio-renal event. There was a statistically significant trend across NT-proBNP tertiles, with a lower risk of events in the aliskiren group, compared with placebo, in patients with a lower NT-proBNP and the converse in patients with a higher NT-proBNP (Table). Similar trends were observed for the cardiovascular and ESRD endpoints.

**Conclusions:** Elevated NT-proBNP levels, reflecting volume overload, predict a poor response to aliskiren in patients with type 2 diabetes at cardio-renal risk. These data highlight the importance of achieving adequate extracellular volume control by diuretic treatment or dietary sodium restriction.

![Image](https://via.placeholder.com/150)

**Extracellular Volume**

<table>
<thead>
<tr>
<th>NT-proBNP Tertiles</th>
<th>Hazard Ratio Cardio-Renal Endpoint</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid</td>
<td>0.98 (0.76 – 1.26)</td>
<td>0.009</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 266</td>
<td>1.25 (1.04 – 1.51)</td>
</tr>
</tbody>
</table>

**Funding:** Pharmaceutical Company Support - Novartis sponsored the ALTITUDE trial.

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**TH-PO102**
Effect of Direct Renin Inhibitor Aliskiren Compared with Angiotensin II Receptor Blockers on Clinim and Ambulatory Blood Pressure Profiles in Hypertensive Chronic Kidney Disease Patients
Kazushi Uneda,1 Hiromichi Waku,1 Kenichi Akiyama,2 Yugo Shibagaki.1 1Div of Nephrology and Hypertension, St. Marianna Univ, Japan; 2Dept of Cardiology, St. Marianna Univ; 3Dept of Cardio-angiology, Kitasato Univ; 4Cardiology and Intensive Care Unit, Nippon Medical School Musashi-Kosugi Hospital; 5Div of Cardiology, Niigata Minami Hospital.

**Background:** Increasing evidence indicates that appropriate control of blood pressure (BP) is critical in the management of hypertensive patients with chronic kidney disease (CKD). The direct renin inhibitor (DRI) reporter (ALTITUDE) compared BP lowering effects in hypertension. However, the clinical evidence of DRI in hypertensive patients with CKD is insufficient as compared to that of angiotensin II receptor blockers (ARBs). In the present study, we compared effects of DRI and ARBs on clinic and ambulatory BP profiles in hypertensive patients with CKD.

**Methods:** Hypertensive patients with CKD who have already been treated with ARBs therapy were eligible for the study. After the 4-week run-in period, eligible patients were randomized either to DRI replacement group (DRI group) or control ARBs group (ARB group) during the 24-week active treatment period. Clinic BP and ambulatory BP profiles were evaluated at baseline and after the protocol therapy.

**Results:** 36 patients were enrolled and randomly assigned to DRI group (n=18) or ARB group (n=18). One patient in each group withdrew consent. The baseline clinic BP levels and the after-treatment/baseline (A/B) ratios of clinic BP levels, estimated after 24-week treatment period, were similar in both groups. However, with respect to the effects on ambulatory BP, the A/B ratios of the daytime and nighttime systolic BP in DRI group were significantly higher than those in ARB group. DRI vs ARB: daytime systolic BP, 0.99 (0.90–1.11) vs 0.92 (0.84–0.99), P=0.041; nighttime systolic BP, 1.03 (1.02–1.04) vs 0.91 (0.88–0.95), P=0.010. Concomitant anti-hypertensive medication was comparable in both groups during 24 weeks of treatment.

**Conclusions:** The results of the present study suggest that DRI therapy is not superior to ARB therapy in lowering ambulatory BP in hypertensive CKD patients, in spite of comparable clinic BP lowering effects.

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

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**TH-PO103**
Effect of Spironolactone on Vascular Stiffness in Hemodialysis - A Randomized Controlled Study
Michael Ek Lund,1 Hans Furuland,2 Ole Hellberg,3 Erik Nilsson,4 1Internal Medicine, Örebro Univ Hospital, Örebro, Sweden; 2Nephrology, Uppsala Univ Hospital, Uppsala, Sweden.

**Background:** Hemodialysis (HD) is associated with high cardiovascular mortality and increased vascular stiffness is a known risk factor for cardiovascular events. Spironolactone treatment is associated with improved survival in HD and in other populations vascular...
stiffness has been reduced. This study investigates possible cardiovascular actions of spironolactone in HD and we hypothesized that spironolactone would affect vascular stiffness as measured by pulse-wave velocity (PWV) in HD.

Methods: This was a two center, open, randomized crossover study. Primary end-point was based on long-term ECG changes and the present sub-study represents a secondary hypothesis. Subjects on HD (n = 30) were randomly allocated using sealed envelopes into two study arms starting with either treatment with spironolactone 50 mg daily or observation for twelve weeks, then a six week wash-out period followed by cross-over for another twelve weeks. PWV was measured before and after treatment and observation, respectively. Difference in PWV change during the two periods was analyzed using confidence intervals (CI) and paired Student’s t-test.

Results: Complete PWV data was available for 17 participants and included in the analysis. Mean PWV change was 0.71 (95% CI: -0.28 – 1.71) m/s during treatment and -0.42 (-1.69 – 0.85) m/s during observation. The difference between periods was not statistically significant, p = 0.14. No adverse events were considered associated with the intervention.

Conclusions: PWV increased slightly after treatment with spironolactone but compared with the observation period the change was not statistically significant. Although this study has low power for detecting changes in PWV, results indicate that spironolactone does not have a clinically significant positive effect on vascular stiffness in HD.

Funding: Government Support - Non-U.S.

TH-PO914
Impact of Vitamin D on Cardiac Structure and Function in Chronic Kidney Disease: A Randomised Controlled Trial
Debashis Banerjee, Nihit Chitalia, Kristel E. Medina-Rodríguez, Laura E. Tooth, Evan Appelbaum, Ravi I. Thadhani, Juan Carlos Kaski, David Goldsmith, St. Georges University of London, Hayward Univ, Guys Hospital.

Background: CKD is associated with cardiac hypertrophy. We examined impact of oral cholecalciferol supplementation on cardiac structure and function, in a double-blind, placebo-controlled randomised trial.

Methods: After screening 84 stable, non-diabetes, CKD stage 3-4 patients on ACEi/ARB, with vitamin D concentrations <75 nmol/L, 48 patients with left ventricular [LV] mass in the upper tertile of normal range, were randomised to receive either 6 directly-observed doses of 100,000 units of cholecalciferol or matched placebo over 42 weeks. Cardiac MRI in the upper tertile of normal range, were randomised to receive either 6 directly-observed doses of 100,000 units of cholecalciferol or matched placebo over 42 weeks. Cardiac MRI and echocardiography were performed at baseline and 52 weeks.

Results: The clinical characteristics were well matched at baseline between vitamin D and placebo groups as follows: age 52±12 vs 52±11 years (p=0.94); eGFR 35±11 vs. 34±11 (p=0.75); calcium 2.4±0.1 vs 2.4±0.1 (p=0.37); phosphate (1.1±0.2 vs 1.0±0.3; p=0.42). The vitamin D concentrations in the vitamin D and placebo groups; at baseline, 24 weeks and 52 weeks, were 43±18 vs. 43±20 [p=0.95], 77±14 vs. 49±27 [p=0.001], 78±24 vs. 43±21 nmol/L [p=0.001] respectively. The left ventricular mass by MRI scan at baseline and 52 weeks, in the vitamin D and placebo groups were 104±39 vs. 100±29 gm [p=0.97] and 108±39 vs. 96±27 gm [p=0.28]. At 52 weeks there were no difference in LV volumes, RV volumes and mass, RA area, LA area, Mitral valve E/A ratio, E/e' ratios at septum and lateral wall, pulmonary artery systolic pressure between the vitamin D and placebo groups [see table 1].

Conclusions: Cholecalciferol supplementation over 52 weeks increased vitamin D levels but did not have an impact on cardiac structure of function in stable, non-diabetic, CKD patients with low vitamin D.

Table 1: The outcome variables at 52 weeks

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Placebo</th>
<th>Vitamin D</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ED mass (gm)</td>
<td>96±26</td>
<td>108±39</td>
<td>0.28</td>
</tr>
<tr>
<td>LV stroke volume (ml)</td>
<td>96±22</td>
<td>95±23</td>
<td>0.86</td>
</tr>
<tr>
<td>LV ED volume (ml)</td>
<td>149±36</td>
<td>154±36</td>
<td>0.67</td>
</tr>
<tr>
<td>LV ES volume (ml)</td>
<td>108±29</td>
<td>118±24</td>
<td>0.25</td>
</tr>
<tr>
<td>RV stroke volume (ml)</td>
<td>97±34</td>
<td>98±33</td>
<td>0.74</td>
</tr>
<tr>
<td>RV ED volume (ml)</td>
<td>161±43</td>
<td>162±39</td>
<td>0.92</td>
</tr>
<tr>
<td>RV ES volume (ml)</td>
<td>60±26</td>
<td>64±35</td>
<td>0.69</td>
</tr>
<tr>
<td>RV ejection fraction (%)</td>
<td>59±7.0</td>
<td>59±8.26</td>
<td>0.97</td>
</tr>
<tr>
<td>RA Area (cm²)</td>
<td>20±15</td>
<td>20±24</td>
<td>0.68</td>
</tr>
<tr>
<td>LA Area (cm²)</td>
<td>21±3.7</td>
<td>22±3.7</td>
<td>0.63</td>
</tr>
<tr>
<td>MV e' ratio</td>
<td>1.02±0.22</td>
<td>0.96±0.27</td>
<td>0.41</td>
</tr>
<tr>
<td>RV systolic wall</td>
<td>9±0.32</td>
<td>9±0.32</td>
<td>0.92</td>
</tr>
<tr>
<td>LV systolic wall</td>
<td>7±0.31</td>
<td>7±0.31</td>
<td>0.92</td>
</tr>
<tr>
<td>RA systolic pressure (mmHg)</td>
<td>22±5.80</td>
<td>22±4.5</td>
<td>0.96</td>
</tr>
</tbody>
</table>

TH-PO9415
Prospective Trial of Exogenous Growth Hormone Administration on Circulating Concentrations of α-Klotho in Healthy and Chronic Kidney Disease Subjects
Ravi Debasish Adenya, Camiel L.M. de Rijk, Joost Hoenderop, Martin H. De Borst, Marc G. Vervloet, Nephrology, VU Univ Medical Center, Amsterdam, Noord-Holland, Netherlands; Physiology, Radboud Univ Medical Center, Nijmegen, Gelderland, Netherlands; Internal Medicine, Div of Nephrology, Univ Medical Center Groningen, Groningen, Netherlands.

Background: Chronic kidney disease (CKD) is characterized by a decline in soluble α-Klotho levels, which may play a role in adverse outcomes. Cross-sectional studies demonstrated that growth hormone (GH) and α-Klotho concentrations are associated. This work represents the first study reporting on the effect of exogenous GH administration on α-Klotho concentrations in patients with mild CKD and healthy subjects.

Methods: A prospective, single-center open label case-control pilot study was performed involving 8 patients with mild CKD and 8 healthy controls matched for age and sex. All participants received subcutaneous GH injections (Genotropin®, 20 mcg/kg/day) for 7 consecutive days. α-Klotho concentrations were measured at baseline, after 7 days of therapy and 1 week after discontinuation of the treatment.

Results: Three women and five men were included in both groups (mean age 46±9.12 years and 45.5±11.4 years; eGFR 71±17 and 100±8 ml/min/1.73m² in CKD and healthy controls respectively). At baseline, α-Klotho concentrations were not significantly different between CKD-patients and controls (529±132 vs. 646±338 pg/mL, P=0.38). GH therapy successfully increased IGF-1 concentrations from 26.8±5.0 mmol/L to 61.7±17.7 mmol/L (P<0.001) in the pooled cohort, as well as in both groups (26.3±2.8 to 59.8±20.5 mmol/L (P<0.002) in CKD and 27.6±6.8 to 63.6±15.6 mmol/L (P<0.001) in healthy controls). However, α-Klotho concentrations did not increase significantly after GH, neither in the pooled cohort (588±255 to 590±268 pg/mL, P=0.10) nor in each treatment group (529±132 to 625±325 pg/mL (P=0.29) and 646±338 to 712±256 pg/mL (P=0.19) in CKD and healthy controls respectively).

Conclusions: Exogenous growth hormone therapy does not increase α-Klotho concentrations in patients with mild CKD or healthy controls.

Funding: Pharmaceutical Company Support - Pfizer provided the research product

TH-PO916
Losartan Significantly Lowers Serum Uric Acid in Hypertensive Children with Proteinuria
Charlotte Bryan, Azita Rajai, Ronald J. Hogg, Nicholas J. Webb, Royal Manchester Children’s Hospital, United Kingdom; Central Manchester Univ Hospital, United Kingdom; Texas A&M Health Science Center College of Medicine.

Background: Serum uric acid (SUA) has emerged as a potentially modifiable risk factor for the progression of chronic kidney disease (CKD). We have previously reported the results of a randomised controlled trial showing that losartan and enalapril are comparable in hypertensive children with CKD (KI 2012:82:1897).

Methods: In a post-hoc analysis of these patients, we determined the effect of losartan vs. enalapril on SUA over 36 months in 201 normotensive and 47 hypertensive children with CKD and examined the change in estimated glomerular filtration rate (eGFR).

Results: Despite no overall difference between the two treatment groups, change in SUA was significantly different between losartan and enalapril in the hypertensive population at 12 months (3.69% decrease [95% CI -3.93%, 11.31%]) vs. 12.57% increase [3.72%, 21.41%], p=0.007). This significant difference remained after 24 and 36 months of therapy.

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Underline represents presenting author.

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This effect was not observed in normotensive patients. The change in SUA showed a statistically significant negative correlation with change in eGFR at each time point over 36 months (p<0.001).

Conclusions: Compared to enalapril, losartan significantly lowers SUA in hypertensive children with CKD and this is correlated with change in eGFR. Studies are needed to evaluate whether changes in clinical practice, such as the preferential use of losartan over other antihypertensive agents, will slow progression in children with CKD.

TH-PO917
Impact of Baseline Renal Function on Efficacy and Safety of Febuxostat Extended and Immediate Release Formulation in Patients with Gout

L. Gunawardhana, M. Becker, K. Saag, B. J. Hunt, M. Castillo, D. Kim, A. Whelton, Takeda Pharmaceuticals, Deerfield, IL; 2Univ of Chicago, Chicago, IL; 3Univ of Alabama at Birmingham, Birmingham, AL; 4Johns Hopkins Univ, Baltimore, MD.

Background: Phase 1/2 data suggest that febuxostat (FBX) extended release (XR) may provide equal or better reduction in serum urate level (sUUA), with reduced exposure vs currently marketed FBX immediate release (IR) in patients (pts) with gout. This Phase 3 study compared the efficacy and safety of XR vs IR in pts with gout stratified by baseline (BL) renal function.

Methods: In a multicenter, randomized, placebo-controlled, double-blind study, 1783 pts with gout (sUUA ≥8.0 mg/dL; estimated glomerular filtration rate ≥15 mL/min; ≥1 gout flare within previous 12 months (mos)) received placebo or XR 40 mg, XR 80 mg, IR 40 mg, or IR 80 mg once daily for 3 mos; ≥30% of pts had moderate-to-severe BL renal impairment. The primary endpoint was the percentage of pts with sUUA <5.0 mg/dL at 3 mos.

Results: In the primary analysis, more pts achieved sUUA <5.0 mg/dL at 3 mos with XR 40 mg, XR 80 mg, IR 40 mg, or IR 80 mg compared with placebo (p<0.001). Although the difference was not statistically significant after multiplicity adjustment, more XR 80-mg treated pts achieved the primary endpoint compared with IR 80 mg. By BL renal function, more pts with mild or moderate renal impairment achieved sUUA <5 mg/dL with XR 40 mg vs IR (p=0.05); there was a non-statistically significant trend for XR 80 mg vs IR (Figure). Treatment-emergent adverse events were infrequent and did not differ among renal function subgroups.

Conclusions: More XR-treated pts achieved sUUA targets of <5 mg/dL vs IR-treated pts with mild or moderate renal impairment. There were no meaningful differences in safety data for XR vs IR in pts with gout stratified by BL renal function. Both FBX formulations were efficacious in reducing SUA and well tolerated.

Funding: Pharmaceutical Company Support - Takeda

TH-PO918
The Comparison of Febuxostat and Allopurinol in Chronic Gout Patients with Chronic Kidney Disease, a Randomized Prospective Study

Yong Chul Kim, Hajeong Lee, Dong Ki Kim, Kook-Hwan Oh, Kwon Wook Joo, Yon Su Kim. Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.

Background: The aim of this 12-week, open-label, non-inferiority trial was to compare the safety and efficacy of febuxostat with allopurinol in treating chronic gout patients with chronic kidney disease (CKD).

Methods: Patients were randomized to febuxostat (n= 53; 40mg daily for the first 4 weeks, 80mg thereafter) or allopurinol (n=53; dose adjusted based on ones kidney function), and both groups were stratified by baseline serum uric acid (SUA) 10.0 mg/dL. SUA was checked for 4 times (week2, 4, 8, 12). The primary endpoint was the proportion of SUA below 6.0 mg/dL at the end of the study. The non-inferiority margin for the difference in rates (of SUA below 6.0 mg/dL) was defined as -15 %. Efficacy analyses were done both by intention-to-treat (ITT) and per protocol (PP).

Results: Uric acid control with febuxostat (n= 49, 94.2 %) was non-inferior to that achieved with allopurinol (n= 13, 26 %), difference 0.68 [97.5 CI 0.54 to -∞]. The proportion of SUA below 6.0 mg/dL at week 2 was 57.69 % (febuxostat) and 12% (allopurinol), respectively. And the rate increased in both group to 94.23 % (febuxostat), 26 % (allopurinol) at week 12 (p<0.0001).

The difference rate of SUA compared with baseline SUA increased with time in febuxostat, but not in allopurinol (at week 12: -47.13±15.1 % vs -24.34±11.45 %, p<0.0001).

Conclusions: Febuxostat was as effective as allopurinol in reducing SUA in chronic gout patients with CKD, with a similar safety profile.

Funding: Pharmaceutical Company Support - SK Chemicals

TH-PO919
Orally Administered Complement 5a Receptor Inhibitor CCX168 Shows Ex Vivo Anti-Thrombogenic Activity in a Phase 2 Study in End-stage Renal Disease Patients with Atypical Hemolytic Uremic Syndrome (ACCESS Study)

Valentina Portaliuq, Miriam Galbusera, Luigi Ruggenetti, Nadia Rubis, Sara Gastoldi, Serena Bettoni, Pirow Bcker, Thomas J. Schali, Marina Noris, Giuseppe Remuzzi, Mario Negri Inst, Italy; “ChemoCentryx, Inc.”

Background: The primary objective of this study is to evaluate whether CCX168 treatment of patients with atypical hemolytic uremic syndrome (aHUS) dampens the ex vivo thrombogenic properties of the serum on cultured microvascular endothelial cells.

Methods: Up to 10 patients with aHUS on stable peritoneal or hemodialysis for ≥6 mo are dosed at 30 mg CCX168 b.i.d. for 2 wks. Blood samples are collected during the study (N=4).

Results: Five patients with aHUS (CFH, C3, CFI mutations: n=1 each, no mutations: n=2) have been treated to date. Mean/SD age: 50.6±8.96, male 1, female 4; 2 on peritoneal dialysis, 3 on hemodialysis. All patients showed a decrease in thrombus size (mean -83%), 3 showed 100% inhibition of thrombus formation at Day 14; 2 showed >30% inhibition. When CCX168 treatment was stopped, the thrombogenic activity returned to baseline levels (see table).

Conclusions: CCX168 treatment of patients with atypical hemolytic uremic syndrome is well tolerated, reduces in vitro thrombogenic properties of serum on microvascular endothelial cells.

Funding: Pharmaceutical Company Support - SK Chemicals

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

Underline represents presenting author.
a previous failing kidney transplant had a serious adverse event during a peritoneal dialysis session. Day of cardiac arrest resulting in death. This event was not considered to be related to CXX168 use.

Conclusions: CXX168 was effective in reducing aHUS-induced thrombus formation in an ex vivo thrombogenesis assay, with all 5 patients showing an inhibition and 3 of 5 patients showing a complete inhibition.

Funding: Pharmaceutical Company Support - ChemoCentrix, Inc.

TH-PO920
A Multi-Level Intervention among Low-Income Patients with Chronic Kidney Disease to Improve Blood Pressure Control: Kidney Awareness Registry and Education Pilot Trial

Delphine S. Tuou,1 Anna Rubinsky,2 Alexandra Velasquez,3 Charles E. McCulloch,4 Dean Schillingler,1 Chi-Yuan Hsu,5 Neil R. Powe.1 1Univ of California, San Francisco, San Francisco, CA; 2Kidney Health Research Collaborative, Univ of California, San Francisco, San Francisco, CA.

Background: Low patient awareness and provider recognition of CKD can impede efforts to slow CKD progression and lead to adverse outcomes. A randomized control pilot trial entitled Kidney Awareness Registry and Education (KARE, NCT01530959) examined the impact of 1) a primary care CKD Registry with point-of-care provider notifications and quarterly feedback, 2) a patient-facing CKD self-management support (CKD-SMS) program, and 3) their combination, on systolic blood pressure (SBP) among low-income patients with CKD, eligible by eGFR or albuminuria, compared to a control group without either intervention.

Methods: Among patients with SBP recorded at baseline and 12 months (n=121/137), we examined the impact of each intervention (Registry, n=22; CKD-SMS, n=29; Registry+CKD-SMS, n=34) compared to usual care (n=36) on change in SBP using linear regression models adjusted for baseline SBP.

Results: KARE enrolled racially/ethnically diverse patients (7% White, 42% Black, 36% Hispanic, 15% Asian). Mean age was 56 years; 49% were male; 40% were non-English speaking. Mean eGFR was 47.6 (SD=9.5) ml/min/1.73m2; mean baseline SBP was 130 (SD=21.8) mmHg. Compared to usual care where average SBP decrease was -0.24 mmHg, patients in the three intervention arms had larger statistically significant decreases in SBP (-3.6 for Registry; -3.1 for CKD-SMS; -2.8 for Registry+CKD-SMS). There was no evidence of effect modification by baseline SP (Pinteraction=0.16), but decreases in SBP were statistically larger among patients with baseline SBP >140 mmHg (n=40) randomized to the intervention groups compared to usual care: -5.2 for usual care; -21.6 for Registry; -12.1 for CKD-SMS; -9.9 for Registry+CKD-SMS.

Conclusions: The KARE pilot study suggests that multi-level interventions can improve SBP among low-income patients with CKD. A trial with greater power comparing these interventions among patients with CKD and SBP >140 mmHg is warranted.

Funding: NIDDK Support

TH-PO921
Patient Navigators and Enhanced Personalized Health Records in Kidney Disease: A Randomized-Controlled Pragmatic Clinical Trial

Sankar D. Navaneethan,1 Stacey Jolly,1 Jesse D. Schold,2 Susana Arrigain,2 Victoria Konig,3 Georges Nakhoul,4 Jennifer Hyland,5 Barbara H. Tucky,6 Priscilla Dann7, 8 Vvette K. Barrucker,9 Joseph V. Nally.1 1Baylor College of Medicine, Houston, TX; 2Cleveland Clinic, Cleveland, OH.

Background: Patient navigators have been shown to improve quality of care delivered to cancer patients; their impact on CKD care is unclear. We developed a CKD Patient Navigator program adopting the chronic care model and an electronic health record (EHR)-based enhanced personalized health record (PHR) to disseminate CKD stage-specific goals of care and education. We report the results of a randomized clinical trial examining the clinical outcomes of a CKD Patient Navigator or enhanced PHR, and their combination compared to usual care among CKD Stage 3b/4 patients.

Methods: 209 patients with CKD from 6 outpatient clinics were randomized in a 2x2 factorial design. Primary outcome measure was the change in eGFR over a 2-year follow-up period. We also evaluated secondary outcome measures including: acquisition of appropriate laboratory measures, appropriate specialty referral and hospitalization rates. Outcomes were captured using EHR and telephone interviews without in-center visits.

Results: Median age of the study population was 65.8 years with 75% being Caucasians. Literacy score (STOFLA) was adequate in 97% of the study population. Prior to enrollment, 54% of patients were followed by nephrologists and 88% of them were on ACEI/ARBs. During 2-year follow-up, eGFR decline was similar across the four groups (p=0.81). Measurement of CKD-related laboratory data were not statistically significantly different between study groups. Further, referral for dialysis education and vascular access placement, emergency room visits and hospitalization rates were not statistically significantly different between the four study arms.

Conclusions: We successfully developed a patient navigator program and an enhanced PHR for CKD population. However, there were no differences in eGFR and quality care metrics between study groups in this randomized clinical trial. Longer follow up is needed to see a potential difference and additional analyses are needed to evaluate patient-specific benefits of the interventions.

Funding: NIDDK Support

TH-PO922
Efficacy and Safety on Traditional Chinese Medicine Niaoduqing Particles in Delaying Moderate/Severe Renal Dysfunction: A Randomized Controlled Trial

Jiang-Mei Chen,1 Ying Zheng,1 Hong Li Lin.1 1Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases; 2Dept of Nephrology, First Affiliated Hospital of Dalian Medical Univ.

Background: Traditional Chinese medicine Niaoduqing particles can delay renal dysfunction among patients with chronic kidney disease (CKD). However, there is no sufficient evidence to determine the efficacy and safety of Niaoduqing particles in delaying renal dysfunction.

Methods: The study was a prospective, randomized, double-blind, placebo-controlled, multi-centered clinical trial (Clinical Trial registration number: ChiCTR-TRC-12002448). A total of 121 patients with estimated glomerular filtration rate (eGFR) 20–45 ml/min/1.73 m2 were enrolled form 22 hospitals in China. The test group was given 3 doses of 5 g Niaoduqing particles during the day and 10g Niaoduqing particles before bedtime; the control group was given placebos with same mode. Primary efficacy indicators included changes of serum creatinine (SCr) values and the change of values before and after treatment between the two groups. Endpoint event was defined as doubling of creatinine and/or commencing renal dialysis.

Results: At the end of treatment, there was no significant difference (P>0.05) in serum creatinine and eGFR between the two groups. However, compared with baseline, the value change of serum creatinine after treatment was significantly different between the two groups (AScr median was 1.1 μmol/L in test group versus 11.7 μmol/L in control group, P<0.008); compared with baseline, the value change of eGFR after treatment was also significantly different between the two groups (ΔeGFR median was -0.2 mL/min/1.73 m2 in test group versus -2.2 mL/min/1.73 m2 in control group), 6 patients in test group and 4 patients in control group had creatinine doubled, and 1 patient in test group and 2 patients in control group started renal dialysis. In terms of adverse events, there was no significant difference (P>0.05) between the two groups.

Conclusions: For the first time, our study has determined that Niaoduqing particles could effectively delay renal dysfunction in CKD3b-4 patients.

TH-PO923
Analysis of the Paediatric Investigation Plans (PIP) of the EMA in Nephrology

Reinhard Feneberg,1 Ineta Sosare,2 Michael Marx.2 1ICON, Frankfurt, Germany; 2ICON, Riga, Latvia.

Background: To assess the requirements of the European Agency (EMA) for paediatric clinical trials in nephrology we assessed the decisions on PIPs, which are required to get approval for new drugs. Clinical trials are needed in order to base therapy on evidence, but the relevant population can be very small in paediatric nephrology.

Methods: All 20 decisions on PIPs published by the EMA for nephrology were included. Data are presented as proportions (categorical data) and median (range) (numerical data).

Results: 7 of the published decisions granted a full waiver (i.e., no pediatric studies required). For the remaining 13, a PIP was agreed. For 6 of those 13 PIPs, a partial waiver was granted for certain ages (0-6 months (2x), 0.5-0, 0.6-6, 0.8, 12-18 yrs. The PIPs require the conduct of 0-3 (median 1) quality studies, 0-2 (median 0) non-clinical studies, and 1-6 (median 3) clinical studies. As there are 9 paediatric dialysis subjects per million of all dialysis subjects, roughly ca. 400 patients in EU. At least 4 PIPs require inclusion of paediatric dialysis subjects, requiring 14 clinical studies, i.e., ca. 14 subjects are available for each of those studies. There are no concessions in powering the studies, and therefore, the required numbers will be much higher than the available number of subjects in EU. The time between start of the procedure and the decision of the PaCeEMA was 107 days (35 – 463 days). The time between the date of decision of the PaCeEMA and the date of the required completion of the PIP ranged from 0.03 yrs – 13.47 yrs (median 4.84 yrs).

Conclusions: In summary, we show some imbalances: a) All partial waivers affected the lowest age groups. Although the youngest age groups need an evaluation of new substances most, the granted partial waivers indicate how difficult it is to conduct trials in this group. b) Only 4 of the 13 PIPs are concerned with frequent indications, while 9 of those aim at rare. For those, a median of 3 studies are required. It is unlikely that the required subjects can realistically be recruited. c) The required studies make the timely conduct (median 4.84 yrs) and completion at the same time adult studies questionable, which could delay approval.

TH-PO924
Response to Vaccination against Hepatitis B and Antibody Evolution in 130 Hemodialysis Patients Followed during Six Years

Angel Cristobal Santacruz, Maria Gabriela Santacruz, Juan Cristobal Santacruz, Zury A. D’Amelio. Nefrologia, Clinica De Los Rinones Menydial, Quito, Pichincha, Ecuador.

Background: Hemodialysis(HD) patients have a higher susceptibility to infections because of their advanced age, immunosuppressed state, increased transfusion requirements as well as because of the staff’s failure to strictly abide by published preventive universal precautions. This makes vaccine provided prevention particularly important in this population of patients.

Methods: In this manuscript we describe our observations in 130 HD patients-81 males (62%) and 49 females (38%) median age 53 years (range between 20-81 years), and median time on HD of 40 months (range 6-84 months). All patients were at onset of HD and anticoagulant therapy. Vaccination was provided with double doses of Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Results: With this regimen, at the conclusion of the initial course of vaccination 78% of the patients achieved an adequate level of antibody with a mean of 777 IU/ml. The response was highly heterogeneous, including the failure of 22% following the first vaccination. This group underwent a second course of three double doses 40µg of vaccine on days 0-30 and 180. Following this, as many as 61% achieved adequate seroconversion, while the other 39% remained resistant.

Conclusions: Conclusion employing the approach described herein 86% of HD patients can attain adequate immunization against Hepatitis B virus. Increasing age is associated with decreased antibody response, but neither time on dialysis nor the underlying etiology of the renal disease significantly impacted the immunologic response. The persistence along the time of the immunization in normal range depend on the initial high answer to the vaccine.

Funding: Clinical Revenue Support

TH-PO925
Implementing Teaching Guidelines on Quality of Life and Adaptation on Hemodialysis Patients Tarek Abdellatif Ghonemy. Nephrology Unit, Zagazig Univ Hospital, Zagazig, Al-Shargyia Governorate, Egypt.

Background: Health Related Quality of life (HRQOL) of patients with End Stage Renal Disease (ESRD) is influenced by the disease itself and by the type of replacement therapy. Clinical practice guidelines were established to provide recommended ranges for parameters associated with management of ESRD patients. The aim of this study is to assess the QOL and adaptation in patients with ESRD on regular HD and to study the implantation of teaching of the European best practice guidelines on those types of patients.

Methods: Prospective study which was carried out on 95 patients. Two different tools were used in data collection to all subjects: Tool 1: Assessment sheet consists of four parts includes patients’ socio demographic criteria, medical history, clinical data and laboratory investigations. Tool 2: QOL and adaptation assessment using Arabic form of SF-36 and brief cope.

Results: There were statistically significant improvement of HR, creatinine level, urea reduction ratio, phosphorus and albumin level after teaching of the guidelines. There were no statistically significant improvement of WBC, PLT, calcium level, k/t/v and PTH level. There was statistically no significant increase QOL in all domains after teaching of the guidelines. There was sever decrease in all QOL domains . Median range of physical function level was 43.83 ± 18.76, 43.83 ± 18.33, 43.83 ± 18.76, 58.20 ± 23.86 and 55.10 ± 18.89 in order.

Conclusions: The response was highly heterogeneous, including the failure of 22% following the first vaccination. This group underwent a second course of three double doses 40µg of vaccine on days 0-30 and 180. Following this, as many as 61% achieved adequate seroconversion, while the other 39% remained resistant.

Funding: Government Support - Non-U.S.

TH-PO926
A Quality Improvement Initiative Assessing Factors Improving Inadequate Hemodialysis in Hospitalized Patients David M. Dewolfe, Robert S. Brown, Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.

Background: Hemodialysis (HD) adequacy is associated with a number of clinical outcomes, including hospitalizations and death. The adequacy of HD treatments in hospitalized patients is usually not measured and may not be achieved. This quality improvement (QI) study aimed to measure the adequacy of inpatient HD treatments and analyze the factors associated with improvement over time.

Methods: We performed a quality improvement initiative with retrospective cohort analysis of hospitalized patients undergoing HD in 2009, 2010 and 2015. The intervention was a comprehensive education initiative for nephrology fellows and attending physicians in prescribing adequate HD. The primary outcome was the frequency of adequate HD treatments defined as single pool k/t/V ≥1.2. Subsequently, we retrospectively compared factors affecting spKt/V to explain the observed improvement.

Results: Outside of the QI initiative, HD adequacy was not being routinely assessed throughout all time periods. The initial phases of the study in 2009 found only 44% of HD treatments were adequate with insignificant improvement in 2010. However, after initiation of a comprehensive education initiative, 94% of HD treatments were adequate in 2015 (P= 0.001 vs 2009) with mean spKt/V of 1.6±0.37 in 2015 compared to 1.1±0.34 in 2009 (P=0.001). Retrospective data found no significant difference between HD adequacy rates in inpatient HD treatments in 2015 in patient size (81.3±28.05 Kg vs 73.46±19.68 Kg, P=0.13) or HD time (213.9±42.74 minutes vs 220.9±28.91 minutes, P= 0.47). A significant difference was observed in blood flow rates (344.4±39.66 ml/min vs 385.8±46.70 ml/min, P= 0.001) and in dialyzer size with 37% of treatments in 2009 vs 75% in 2015 utilizing dialyzers with surface area ≥ 1.8 m² (P=0.001).

Conclusions: Inpatient HD adequacy was not being measured and initially found to be quite poor. Adequacy was improved by a focused QI program with more intensive training in HD prescriptions which led to increased use of larger dialyzers and greater blood flow rates. To ensure that hospitalized patients receive adequate HD, measurements of adequacy should be undertaken to determine whether corrective action is necessary.

TH-PO927
The Association of Bilirubin and Mortality in Patients Underwent Regular Hemodialysis Yen Chung Lin, 1, 2 Div of Nephrology, Dept of Internal medicine, Taipei Medical Univ Hospital, Taipei, Taiwan; 3Dept of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical Univ, Taipei, Taiwan.

Background: Bilirubin has the effect of anti-oxidation and anti-inflammation, benefiting in cardiovascular events, which is very common in end stage renal disease patients (ESRD) underwent regular hemodialysis. However, the association between mortality and bilirubin level in ESRD patients was not clear.

Methods: A total 102,599 patients in TWRDS, a national-wide end state renal disease registration system in Taiwan were surveyed. After deleting 4586 patients with an abnormal higher bilirubin >1.2 mg/dl or extremely lower bilirubin level <0.1 mg/dl. Finally, 47560 patients were analyzed in this study. Multi-variables adjusted cox proportional analyses were used to find out the relationship between the bilirubin groups (low <0.3 mg/dl, reference 0.3-0.7 mg/dl, high >0.7 mg/dl) and mortality during a 8 years follow-up.

Results: There were no obvious demographic difference between the groups of bilirubin levels. In the contrary, higher bilirubin was correlated with higher all-cause mortality. The Cox proportional hazard ratio for death in high bilirubin group was 1.15 times (95% CI 1.09-1.22, p < 0.001) higher than the reference group (bilirubin between 0.3-0.7 mg/dl).

Conclusions: Surprisingly, this study revealed that bilirubin had a negative impact on mortality in HD patients. Further solid evidations are warranted to support this point of view.

TH-PO928
The Association between Dialysis Session Time and the Risk for Hospitalization and Death in Maintenance Hemodialysis Patients Takahiro Kuragane, Takeshi Nakaniishi. Dept of Internal Medicine Div of Kidney and Dialysis, Div of Kidney and Dialysis, Nishinomiya, Japan.

Background: Recently, dialysis efficiency was dramatically improved by using super flux dialysis membrane. However, in the condition of the common use of high flux dialysis, it has not been well studied the relationship between treatment time and adverse events or survival of maintenance hemodialysis (MHD).

Methods: Subject: 805 patients undergoing MHD. Study design period: prospective, observational multi-center study of 3 years. Measurement: We measured serum levels of ura nitrogen (UN), creatinine (Cr), β2microglobin (MG), total protein, albumin, prealbumin, high sensitive C reactive protein (ICRP) every 3month. We also evaluated body mass index (BMI), and Kt/V. The associations between dialysis intensity and adverse events or death were investigated with the cox proportional hazards model for time-dependent variables.

Results: Although there was no significant correlation between pre-dialysis levels of UN and adverse event or survival, high pre-dialysis Cr level was associated with lower risk of hospitalization (HR:0.89, P=0.003) and death (HR:0.71, P=0.002). Moreover, high Kt/V was also associated with lower risk for cerebrovascular and cardiovascular disease (CCVD) (HR:0.37, P=0.039) and hospitalization (HR:0.55, P=0.026). There was no significant difference in serum levels of prealbumin, albumin, Cr, Kt/V and ICRP levels among 3 groups of treatment time (<4hours(s), 4.5-, >5h). On the other hand, BMI in the patients treated with >5h was significantly (p=0.012) higher than those of patients treated with <4h. In time dependent cox hazard model, the risk of hospitalization (HR:0.43, 95% CI 0.04-3.70) and death (HR:0.49, 95% CI 0.013) of patients treated with 4-5h were significantly lower than that of patients treated with <4h. Moreover, the risk of death in patients treated with >5h was significantly (HR:0.45, P=0.024) lower than that of treated with <4h.

Conclusions: Higher Kt/V was associated with lower risk of CCVD and hospitalization of MHD patients, but not pre-dialysis level of ICMG levels. Shorter dialysis session time (<4 h) was associated with higher risk of hospitalization or death than that of longer treatment time.

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

309A
Vegetarian Diets Reduce Advanced Glycosylation End Product Deposition in the Skin in Chronic Hemodialysis Patients  
Arkomo Nongnuch,1,2 Andrew Davenport,1 Renal Unit, Dept of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand; 2UCL Centre for Nephrology, Royal Free Hospital, Univ College London, London, United Kingdom.

Background: Advanced glycosylation end products (AGEs), are protein-bond uremic toxins and associated with increased risk of developing cardiovascular disease and mortality in HD patients. As AGEs are deposited in the skin, they can be measured by skin autofluorescence (SAF). Vegetarian diets potentially reduce AGEs formation, thus we desired to determine whether vegetarian diets reduce AGEs deposition.

Methods: Prospective measurements were made in 180 prevalent hemodialysis patients in North London between June 2012 and September 2013. Clinical data and serial laboratory data were collected and were analysed by linear mixed effects model.

Results: A total of 180 HD patients were studied. Sixty-six percent were male and 45% had diabetes. The mean increased in SAF after 12 months was 0.27 ± 0.12 AU. Univariate analysis showed age, history of diabetes, peripheral vascular disease, prescription of ACE inhibitors, and serum albumin were positively associated with an increased in SAF, whereas non-Caucasian ethnicity, urine output >250 ml/day, serum albumin and vegetarian diets reduced skin AGEs deposition. Multivariate analysis revealed the usage of warfarin, LC, insulin and age significantly associated with increased in SAF, whereas urine output > 250 ml/day and vegetarian diet were associated with attenuated accumulation in SAF.

Conclusions: Vegetarian diets and residual renal function (RRF) lessen AGEs accumulation in HD patients. Strategies to preserve RRF with low AGEs diets may reduce AGEs deposition and potentially reduced CVD risk in HD patients. 

Funding: National Institute for Health Research (NIHR) Other

TH-PO930

Time-Varying Changes in Serum Albumin and Cytokines Predict HD Patient Mortality  
Paul L. Kimmel,1 Kenneth J. Wilkins,1 1DHUHD, NIDDK NIH, Bethesda, MD; 2Biostatistics Program, NIDDK NIH, Bethesda, MD.

Background: High baseline circulating pro-inflammatory cytokine levels (CLs) are linked to ESRD hemodialysis (HD) patient (PT) mortality. Whether HD PT CLs are stable over time is unknown. Whether changes in CLs predict mortality, adjusting for known longitudinal predictors is unstudied.

Methods: We studied interleukin (IL)-1, IL-6, and Tumor-Necrosis Factor-α (TNF-α) CLs in 234 HD PTs (75 incident, 159 prevalent), followed a mean of 3.3 y with a median of 3 assessments at 3 centers in Washington, DC (total 763 person-y followup). CLs were skewed, ranging over 6 natural logs. Scatter plots revealed high and low groups for all cytokines at baseline. This ad hoc univariate grouping was assessed for each cytokine at baseline to have >90% accuracy by multivariate methods (K-means cluster, quadratic discriminant and principal components analyses). Groupings were then assessed for how well each predicted mortality using Cox models (adjusted for known time-varying predictors such as serum albumin [SAlb]), to compare the use of ad hoc high/low values, with log 4 as a threshold, as an alternative to clustering by baseline values or trajectories, with models using time-varying prediction by actual values.

Results: In the low IL-1 group (n=157), only 5% exhibited post-baseline values > log (54.6 pg/mL). In the high IL-1 group (n=77), only 13% exhibited values <4 log. A majority of CLs remained roughly constant over follow-up. 81% of variability is explained by individual mean CLs. Cox models for IL-6 and TNF-α. Exceeding 4 logs of these levels predicted mortality using time-varying Cox models, even after adjusting for baseline CLs and trends in SAlb since the previous cytokine measure (HR, 95% CI) IL-1: 3.3 [2.1, 5.3]; IL-6: 3.4 [2.2, 5.6]; and TNF-α: 3.3 [2.1, 5.3]). No residual variation in events appears correlated with baseline CLs.

Conclusions: CLs exhibit limited variability over time in the majority of HD PTs. Longitudinal cytokine levels can be characterized as “high” or “low,” according to baseline measurements with negligible misclassification, and predict mortality or survival. Such characterization will be useful in stratifying PTs for interventional trials. 

Funding: National Institute for Health Research (NIHR) Other

TH-PO932

Current Status of Hemodialysis in China, 2015  
Xiang-Mei Chen, Ying Zheng. 1Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Medical Quality Control Center for Kidney Diseases, MOH, Beijing.

Background: In order to further understand the the current status of the patients of ESRD and hemodialysis in China, in May 2010, the first nationwide, web-based prospective renal data registration platform, the Chinese Renal Data System (CNDRS) was launched in China. The goal of the study was to determine the current status of hemodialysis in China by analyzed the data from CNDRS.

Methods: Data in CNDRS includes demographic, clinical, and laboratory data for dialysis cases. We analyzed the data from CNDRS by the end of 2014.

Results: There were 4089 domestic hemodialysis centers were registered by the end of 2015. On Dec, 31, 2015, 385055 prevalent cases were receiving hemodialysis therapy. Compared to 2014, the number increased by 45307 cases. The unadjusted prevalence (population) was 281.5 per million in the Chinese population. The number of incident cases receiving hemodialysis therapy in 2015 was 61790, which was the lowest since 2011. The unadjusted incidence rate was 45.2 per million/year. In the prevalent cases, 59.0% were male, the mean age and dialysis time was 55.7 years and 46.7 months, respectively. Both of the age and dialysis time continued to increase since 2011. Though the proportion of glomerulonephritis declined to 54.2% in 2015, it was still the leading causes of ESRD who receiving hemodialysis therapy in prevalent cases. The proportion of diabetic nephropathy in incident cases was 21.2%, the number continues to rise. 13839 cases were died in 2015. 58.3% of them were male. The mean age and dialysis time was 62.7 years and 41.2 months, respectively. Both of the two number in mortality cases continue to increase since 2011. The main causes of death were cardiovascular events and stroke.

Conclusions: In recent years, the hemodialysis in China has made a great progress. As Chinese National Health and Family Planning Commission have enhanced the basic medical security system on hemodialysis, the population and prevalence of hemodialysis rose sharply during 2011-2015.
TH-PO933

Involuntary Discharges (IVDs): Analysis of Case Characteristics of End Stage Renal Disease (ESRD) Network 2 in New York before and after Bundled Payment Implementation by Centers for Medicare and Medicaid Services (CMS)

Ranjit Singh,1 Brittany Kalosza,2 Syeda Hussain,2 Chaim Charytan,2 George N. Cortisidis,1 Nephrology, Elmhurst Medical Center; Elmhurst, NY; Nephrology, New York-Presbyterian, Queens, NY.

Background: Dialysis providers are authorized to involuntary discharge patients under certain circumstances, as set forth in Medicare’s Conditions of Coverage. We wanted to analyze how etiologies for the rate of IVDs have changed since the CMS prospective payment system for ESRD in 2011.

Methods: We collected IVD data reported to ESRD Network 2 from Jan 2007 to December 2015. Being the first year of the CMS changes 2011 data was excluded. Reasons for IVDs and patient characteristics were reviewed.

Results: 153 IVDs were identified. The number of IVDs increased following CMS bundled payment model from 66 patients (16.5 IVDs/year) to 87 patients (21.8 IVDs/year). Male patients had a significantly higher IVD rate before and after bundled payment. Rate of IVD of African Americans decreased after the CMS bundle (78.8% vs 55.8%) respectively. The major reason for discharge continue to be behavioral issues (76.7%) followed by non-payment (19.3%).

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<tbody>
<tr>
<td>Rate of IVD per Year</td>
<td></td>
<td>43.14% (+/−60)</td>
<td>56.86% (+/−87)</td>
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<tr>
<td>Age</td>
<td>51.5</td>
<td>52.2</td>
<td>51.0</td>
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<tr>
<td>Sex, male, (%)(n)</td>
<td>71.2(109)</td>
<td>71.247</td>
<td>71.362</td>
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<td>Race, (%)(n)</td>
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<tr>
<td>Caucasian</td>
<td>30.1(46)</td>
<td>19.7(13)</td>
<td>30.0(33)</td>
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<tr>
<td>African American</td>
<td>68.0(104)</td>
<td>78.8(52)</td>
<td>59.5(52)</td>
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<tr>
<td>Asian</td>
<td>1.3(2)</td>
<td>1.5(1)</td>
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<td>Ethnicity, Latino, (%)(n)</td>
<td>15.8(21)</td>
<td>12.18(18)</td>
<td>15.1(13)</td>
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<tr>
<td>Reason for Discharge, (%)(n)</td>
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<tr>
<td>Behavioral</td>
<td>76.7(115)</td>
<td>81.05(51)</td>
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<td>Non-payment</td>
<td>19.3(29)</td>
<td>16.0(10)</td>
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</table>

Conclusions: Analysis of data for NY reveal higher IVD rates after the bundled payment changes. IVD patients were younger than ESRD patients as a whole and IVD was predominantly due to behavioral issues. More Caucasians and fewer African Americans were IVDs after the CMS bundle, possibly indicating that racial disparities are equalizing.

TH-PO934

Intermediate Care Outcomes before and after Switching to Nocturnal In-Center Hemodialysis

Adam S. Wilk,1 Kristen Senetar,1 Laura Plantinga,1 Janice P. Lea,2 Emory Univ; Emory Dialysis Centers, Emory Healthcare.

Background: Nocturnal dialysis (ND) can support longer sessions with lower ultrafiltration (UF) rates, compared to traditional (daytime) in-center hemodialysis. We compare dialysis care traits and intermediate health outcomes for ND patients before and after they initiate ND treatment.

Methods: Among patients undergoing hemodialysis at a medium-sized dialysis organization, we identified ND patients as those for whom at least 80% of dialysis sessions over a 3-month window (≥20 sessions) began at 6:30pm or later and lasted 5 hours or more. For these patients, we extracted dialysis treatment orders and session records, demographics, and other electronic health record data relevant for within 90 days of ND transition. We estimated session-level ordinary least squares regression models of key intermediate outcomes—session duration, UF rate, completed session rate (fraction with at least 90% of treatment order time), pre-session blood pressure (systolic [SBP] and diastolic [DBP]), and lowest recorded intradialytic SBP and DBP—to identify conditional effects of pre- vs post-transition ND status, clustering standard errors within patients.

Results: We identified 55 ND patients (3.5% of 1,420 patients in care), with 1,065 pre-transition sessions and 1,577 post-transition ND sessions. Relative to pre-transition sessions, post-transition ND sessions were 3.2 hours longer (p<0.001), had UF rates 4.9 ml/kg lower (p<0.001), and were completed equally often (p=0.9). Likewise, patients’ SBP and DBP levels, both pre-session and lowest intradialytic, were not significantly different pre-vs post-transition, though we observed small but statistically significant declines over time across post-transition ND sessions in nearly all SBP and DBP outcomes.

Conclusions: ND treatment sessions were longer than pre-transition hemodialysis sessions and had lower UF rates, but ND did not affect patients’ session completion rates or absolute SBP and DBP levels. For patients selecting into ND, the effect appears to be as intended.

TH-PO935

Improved Sleep Quality Is Associated with Reduced Hospitalization Rate and Increased Treatment Adherence in Hemodialysis Patients

Nien-Chen Li, Felicia N. Speed, Marta Reviriego-Mendoza, John W. Larkin, Norma J. Ofshun, Stephanie Johnstone, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: Patients (pts) with end-stage renal disease often suffer from sleep disorders. We investigated if a social worker (SW) quality improvement program effects sleep quality (SQ), and subsequently alters rates of hospitalizations and treatment adherence in a cohort of hemodialysis (HD) pts.

Methods: HD pts (869) enrolled in an 8-week SW program between 7/1/2013 and 2/28/2014 were provided a 5-item SQ questionnaire before and after the SW intervention. Using a factor analysis, 5 items were reduced to 3: difficulty sleeping, difficulty awakening, and restless legs during sleep. For each item, SQ was defined as “high” for scores better than the baseline median and “poor” otherwise. Hospitalization and missed treatment data were captured 1 year before and after intervention. Rate ratios (RR) in hospitalization and missed treatment, stratified by changes in SQ were analyzed using Poisson regression, offset with the length of exposure period and adjusted for baseline hospitalization or missed treatment count, age, gender, race, diabetes, coronary artery disease (CAD), and congestive heart failure (CHF).

Results: Pts had a mean age of 55.3 ± 14.1 years, 51.8% males, 69.7% white, and 58.6% with diabetes, 19.5% CAD, and 38.1% CHF. The impact of changes in SQ parameters on hospitalization and missed treatment rates are detailed in Figure 1. That is, in almost all cases, RR > 1 indicating higher risk in hospitalization and/or missed treatment when comparing with SQ improved from poor to high after intervention.

Conclusions: The findings suggest that the SW program was associated with improvements in SQ and, in turn, with reductions in hospitalization risk and better adherence to HD treatments. Implementing a strong QI program in HD clinics may improve HD pts’ outcomes.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO936

Associations between Sleep Quality and Quality of Life, Stress, and Depressive Symptoms in Hemodialysis Patients

Nien-Chen Li, Stephanie Johnstone, Felicia N. Speed, Marta Reviriego-Mendoza, John W. Larkin, Norma J. Ofshun, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: We investigated if implementing a social worker (SW) quality improvement program resulted in better sleep quality (SQ) and thus, improved depressive symptoms, psychosocial stress, pain perception and Kidney Disease Quality of Life (KDQOL) scores in HD pts.

Methods: We analyzed data from 869 pts at Fresenius Medical Care North America enrolled into the 8-week SW program between 7/1/13 and 2/28/14. SQ was assessed before and after the SW program. The original SQ 5-item assessment was reduced to 3-items by way of factor analysis: difficulty sleeping, difficulty awakening and restless legs during sleep. We used the following questionnaires: the center for epidemiologic studies depression scale-10 (CESD-10), KDQOL, Psychosocial Stressor Screening tool, and Comfort Barriers Screening tool (pain items). Paired t-tests were used to compare means of Pt data before and after implementing the SW program. Regression analysis was used to assess associations of changes in questionnaire scores and SQ, adjusted for baseline score, age, gender, race, and diabetes, coronary artery disease (CAD), and congestive heart failure (CHF).

Results: Pts in the study had mean age of 55 ± 14 years, 52% males, 70% white, and 59% with diabetes, 20% CAD, and 38% CHF. Results show that SQ improved after SW intervention (all p<0.05). We found that: i) improvements in CESD, mental component score (MCS), burden of kidney disease, and stress indicators were significantly associated
with improvements in difficulty sleeping (all p<0.01), ii) improvements in CESD and health symptoms and loss/grief stressors were associated with improvements in difficulty awakening (all p<0.01), and iii) improvements in CESD and financial/insurance and family/relationships stressors were associated with less restless legs during sleep (p<0.02).

**Conclusions:** Our study indicates that improvements in SQ are associated with improvements in depressive symptoms, psychosocial stress, MCS, and KDQOL measures in HD patients. SW interventions may aid in improving pts’ SQ and, consequently, HD outcomes.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

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**TH-PO937**

**Outcomes Associated with Inpatient versus Outpatient Hemodialysis Initiation in a Large Incident ESRD Cohort**

Faisal M. Arif, 1 Miklos Szolz Molnar, Keichi Sumida, 1 Praveen Kumar Potukuchi, 1 Jun Ling Lu, 1 Fatima Haidar, 1 Ajaykumar Thoddy, 1 Elama I. Eladj, 1 Kamyar Kalantar-Zadeh, 2 Csaba P. Kovessy. 1, 3

1 Univ of Tennessee Health Science Center, Memphis, TN; 2 Univ of California, Irvine; 3 VA Medical Center, Memphis, TN.

**Background:** The setting (Inpatient vs. Outpatient) of chronic HD initiation could be determined by medical (e.g. comorbidities) or other factors (e.g. no available mature vascular access). It is unclear if the setting of HD initiation is associated with mortality risk in the post-dialysis period.

**Methods:** We examined the association of inpatient (vs. outpatient) HD initiation with all-cause and cause-specific mortality in 48,261 US veterans transitioning to HD between 10/2007-09/2011. Associations were examined in Cox (all-cause mortality) and competing risk regression models (cause-specific mortality), adjusted for demographics, comorbidities, vascular access type, predialysis Nephrology care and medication use, and pre-ESRD eGFR and hemoglobin.

**Results:** 22,338 (46.3%) patients started HD as inpatients. Inpatient HD start was associated with older age, presence of a tunneled catheter, and more comorbidity. Higher hemoglobin, lower eGFR and predialysis use of active vitamin D were associated with outpatient HD start. 32,323 patients died over a median follow up time of 2.1 years (mortality rate, 95%CI: 290/1000 patient-years, 287-293). Inpatient vs. outpatient HD start was associated with significantly higher crude all-cause, CV and infectious mortality. These associations were substantially attenuated but remained significant after multivariable adjustment (Figure).

**Conclusions:** Veterans who transitioned to HD in a hospital setting experienced significantly higher mortality following dialysis initiation. Better predialysis care may allow more patients to initiate HD as outpatient. Future studies are needed to examine the impact of this on mortality.

**Funding:** NIDDK Support, VA Support

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**TH-PO938**

**Outbreak of Gram Negative Bacilli Non Fermenters Associated to the Lack of Chlorine in Pre-Treated Water for Hemodialysis**

Cynthia Sobral Vieira, Claudio Stadinck, Ethel Ribas, Rozeli Biedrzycki, Andressa Koival, Giselle Lobato, Gabriela Sobral Vieira. Nephrology Unit, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil.

**Background:** Bacteremia presented during dialysis can lead to harmful outcome to patients. Varied reasons are cited, long associated with the use of catheters. When in outbreak the whole process must be thoroughly analyzed. Our purpose is to report possible causes of bacteremia and the subsequent assessment of the outbreak occurred in a hemodialysis service.

**Methods:** Between March and April 2016, there were 20 cases of bacteremia in patients under hemodialysis therapy in a private hospital in South of Brazil. The blood cultures showed Gram-negative bacilli non ferments (GNBNF) commonly associated to water contamination. Physical-chemical, microbiological analyses of all materials used for hemodialysis were carried out including water. At the same time, sanitization, deodorization and exchange resins in water purification system were realized.

**Results:** 20/98 patients with bacteremia presented GNB. They were Stenotrophomonas maltophilia, Burkholderia cepacia, Pseudomonas maltophilia and Pseudomonas pickettii. Reverse osmose were used for water treatment and the dialyzers were manually reprocessed. The microbiological tests showed that the growth of colonies occurred after activated carbon. The potable water produced during the epidemic period, had chlorine concentration below the desirable standards imposed by the guideline of practices in dialysis in Brazil which requires 0.5 mg/l maximum for chlorine. The chlorine free water was arriving very hot to the reverse osmose, suggesting that chlorine evaporated during passage through the external plumbing and favoring the bacterial growth. It was a very hot summer with long distance from the water treatment to the reverse osmose and a mixture with water from central boiler. Individualized plumbing (exclusively from public water system) and an extra 10.000 liters water tank were installed before water treatment room and no more cases were seen.

**Conclusions:** It is imperative to monitor all procedures involving the water used in the process of hemodialysis. Cases are avoided when the focus of the outbreak quickly and effectively is found.

**Funding:** Private Foundation Support

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**TH-PO939**

**Negative Correlation of Serum Adiponectin Level with Peripheral Artery Disease in Hemodialysis Patients**

Yu-Hsien Lai, 1 Bang-Gee Hsu. 2 "Buddhist Tzu Chi General Hospital, Hualien, Taiwan; 2Buddhist Tzu Chi General Hospital, Hualien, Taiwan." 1

**Background:** Adiponectin is a fat-derived hormone produced and secreted exclusively by adipocytes that have anti-atherosclerotic effects. Peripheral arterial disease is associated with an increased risk of death in hemodialysis (HD) patients. The aim of this study was to evaluate the relationship between serum adiponectin levels and peripheral artery disease by ankle-brachial index (ABI) in HD patients.

**Methods:** Blood samples were obtained from 100 HD patients. The ABI values were measured using an ABI-form device (VaSera VS-1000). Serum adiponectin levels were measured using a commercial enzyme-linked immunosorbent assay kit. Left or right ABI values that were < 0.9 were included in the low ABI group.

**Results:** Among 100 HD recipients, 18 patients (18.0%) were in the low ABI group. Compared with patients in the normal ABI group, patients in the low ABI group had higher prevalence of diabetes (p = 0.043), older age (p = 0.027), and lower serum adiponectin level (p = 0.003). HD patients with diabetes mellitus (DM) had lower serum adiponectin level than non-DM HD patients (p = 0.016). According to multivariable forward stepwise linear regression analysis, diabetes (β: -0.216, p = 0.029), log transformed triglyceride (log-TG) (β: -0.230, p = 0.019), and log transformed C-reactive protein (log-CRP) (β: -0.241, p = 0.008) were the independent predictors of adiponectin level in HD patients, and multivariate logistic regression analysis, adiponectin (Odds ratio [OR]: 0.927, 95% confidence interval [CI]: 0.867-0.990, p = 0.025) and age (OR: 1.054, 95% CI: 1.002-1.109, p = 0.043) was the independent predictors of peripheral arterial disease in HD patients. The sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver-operating characteristic (ROC) curve predicted peripheral arterial disease in HD patients were 72.22%, 64.63%, 36.68%, 99.92%, and 0.691 (95% CI: 0.591-0.780, p = 0.008), and the adiponectin cut-off value was 43.27 μg/mL.

**Conclusions:** In this study, serum adiponectin level was proved to be involved in the pathogenic process of peripheral arterial disease in HD patients.

**TH-PO940**

**Impacts of Insurance Type on Hospitalization and Mortality Rates in Hemodialysis Patients**

Xiaoqing Ye, 1 John W. Linkin, 2 Marta Reviriego-Mendoza, 2 Len A. Usvyat, 2 Peter Kotanko, 1, 2 Franklin W. Maddux, 2 "Renal Research Inst, New York, NY; 2Fresenius Medical Care North America, Waltham, MA; 1Icahn School of Medicine at Mount Sinai, New York, NY." 1

**Background:** Insurance types may be associated with outcomes in chronic hemodialysis (HD) patients. We compared outcomes in Pts who initiated and remained on HD with commercial insurance (COM) to matched Medicare fee-for-service Pts with comparable demographic and clinical parameters.

**Methods:** We analyzed data from 2008 to 2014 in 16,357 Pts at FMCNA who initiated and survived 6 months on HD with COM as primary coverage. Pts with Medicare primary coverage who survived 6mos on HD were identified using 1:1 nearest neighbor matching on logit of propensity score for race, gender, HD initiation year, and 15 comorbidities, as well as in-center treatments, hospitalization rate, adherence rate, treatment time, pre-HD SBP, IDWG, and Kt/V in first 6 mos of HD. We performed exact multinomial logistic regression analysis with 1:1 and 1:2 nearest neighbor matching, controlling for race, diabetes, % of treatments with catheter, mean albumin, and mean BMI during first 6mos of HD; Pts without an exact match were excluded. We compared 12mo hospitalization and mortality rates per patient year (ppy) in groups after first 6mos of HD.

**Results:** Data from a total of 3,280 HD Pts was analyzed (1,640 COM & Medicare Pts each). We found Pts starting the first 6mos of HD covered by COM had HRs of 0.780 (95% CI: 0.644-0.941) and 0.691 (95% CI: 0.591-0.780, p = 0.008), and the adiponectin cut-off value was 43.27 μg/mL.

**Conclusions:** Similarly, we observed 1.49 (95% CI:1.41-1.60) fewer deaths ppy for COM Pts versus Medicare patients (p=0.001) [figure 1].

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**TH-P0941**

**Effect of Interdialytic Time on Outcomes in Chronic Hemodialysis Patients**

Jalal E. Haynes, Wayne R. Fitzgibbon, Michael E. Ullman. Nephrology (Medicine), Medical Univ of South Carolina, Charleston, SC.

**Background:** Most chronic hemodialysis (HD) patients dialyze on Mon,Wed,Fri or Tue,Thu,Sat. Prior studies suggest that the risk of cardiovascular events (CVEs) is highest after the weekend, ie Mon and Tue, respectively. Since our Veterans Administration (VA) Hospital HD unit is closed on weekends, non-traditional HD schedules were created, ie 3 days per week (compared to the usual 2-day weekend). We wondered if more frequent CVEs and greater mortality occurred after longer inter-HD time intervals.

**Methods:** We reviewed charts of all chronic HD patients since 2002, when the VA electronic medical record was initiated. Patients were placed on a HD schedule randomly. Those dialyzed for at least 3 months (4-144, median 21) without change in HD schedule were studied (n = 85). Those dialyzing on Mon,Wed,Fri and Mon,Tue,Thu,Fri (n = 29) constituted the short-weekend group (SWG), and those dialyzing on Mon,Wed,Thu,Mon,Tue,Thu,Fri (n = 56) constituted the long-weekend group (LWG). Outcomes consisted of all-cause mortality, CVEs requiring hospital visits, and day in HD schedule when CVEs occurred: D-0, during and after HD; D-1, 1 day after last HD; D-2, 2 day after last HD; D-3, 3rd day after last HD; D-4, 4th day after last HD.

**Results:** Demographics and co-morbidities of the 2 groups were similar, except for more coronary artery disease (p < 0.03) and higher serum phosphorus concentration (p < 0.001) in SWG. All-cause mortality was not different between groups, even after normalization for coronary artery disease and serum phosphorus level. For each group, we compared observed CVE rates to expected CVE rates (null hypothesis: CVEs were expected to occur at the same rate on D-0, D-1, D-2, D-3, and D-4). For D-0, we observed 56% more CVEs than expected in SWG; and we observed the expected rate of CVEs (+4%) in LWG. In SWG, we observed 52% fewer CVEs than expected on D-1, 22% fewer on D-2, and 340% more on D-3. In LWG, we observed 67% fewer CVEs than expected on D-1, 52% fewer on D-2, 227% more on D-3, and 352% more on D-4 (both p < 0.05 for trend).

**Conclusions:** In chronic HD patients, CVEs occur more frequently after longer inter-HD intervals.

*Funding: Clinical Revenue Support*

**TH-P0942**

**Cytokine Removal by Different Dialysis Membranes**


**Background:** The purpose was to compare the removal efficiency of inflammatory cytokines and cell activating molecules by different types of dialysis membranes with a standardized in vitro test system.

**Methods:** Mini-dialyzers (membrane area 360 cm²) were prepared from commercial dialyzers polysulfone Revaclear (PR), Fresenius Cordiax (fx), highflux membranes with extended permeability (MCO1, MCO4) and HCO100 (HCO). They were tested in an in vitro test system. The purpose was to compare the removal efficiency of inflammatory cytokines and cell activating molecules by different types of dialysis membranes with a standardized in vitro test system.

**Results:** Serum IL6 decrease, IL6 recovery in dialysate and cell activation of TEC, NHDF and granulocytes by dialysate samples at 90 min are displayed in table below. IL6 starting concentration was 8677 pg/ml. Numbers are given as mean ± standard deviation of 3 independent runs.

**Conclusions:** MCO delivers slightly better in vitro plasma clearances for IL6 than to that of HF-PAES and HF-PAES, and larger than that of HF-PES. Additionally, MCO shows superior variation with time.

*Funding: Pharmaceutical Company Support - Gambro Diasylatoren GmbH (part of Baxter International Inc.)*

**TH-P0943**

**MCO Dialyzer: Enhanced High-Flux Membrane with Expanded Toxin Removal**


**Background:** MCO is a newly designed high-flux dialyzer improving selected selectivity that expands the spectrum of toxins removed during treatment. The purpose of this study is to compare the MCO in vitro plasma clearances of different middle molecules to those for different high-Flux dialyzers.

**Methods:** Middle/large molecule clearances of Theranova 400 (MCO, Gambro), Revaclear 400 (HF-PAES, Gambro), Optiflux F180NR (HF-PES, Fresenius) and Elvis 170 (HF-PES, Nipro) dialyzers were compared. HD treatments were simulated with Qb = 400 ml/min and QD = 700 ml/min. In each experiment (n=3), 1 L of uniform human plasma (octaplasmL,G, protein concentration 60 g/L) was recirculated for 60 min and followed by a 60 min simulated treatment. Markers (human) were spiked into the plasma pool after 55 min of recirculation: β2-microglobulin (5 mg), myoglobin (500 μg) and k-FLC (~300 mg), while interleukin 6 is comprised in plasma. Pool and dialysate samples were taken after defined time intervals. Each marker concentration was measured by nephelometry and the clearance was calculated from the first order kinetics for the pool concentration variation with time.

**Results:** In vitro clearances for the MCO dialyzer in HD were consistently higher than those shown by all other dialyzers investigated. For k-FLC and IL-6, the largest markers, all regular high-flux dialyzers showed only one-digit clearance values.

**Conclusions:** MCO delivers slightly better in vitro plasma clearances for β2-m, HF-PAES and HF-PES, and larger than that of HF-PES. Additionally, MCO shows superior variation with time.

*Funding: Pharmaceutical Company Support - Gambro Diasylatoren GmbH (part of Baxter International Inc.)*

**Bloodless Potassium Measurement Using Mathematically-Processed, Signal-Averaged Electrocardiography**

John J. Dillon, Zachi I. Attia, Omar Ziad Yasin, Christopher G. Scott, Jennifer Dugan, Gaurav Satam, Dorothy J. Ladewig, Michael J. Ackerman, Viren K. Somers, Kevin E. Bennett, Dan Sadot, Paul Friedman.

Nephrology, Mayo Clinic, Rochester, MN; Cardiovascular Diseases, Mayo Clinic, Rochester, MN; Electrical and Computer Engineering, Ben-Gurion Univ of the Negev, Beer Sheva, Israel; Mayo Clinic Ventures, Mayo Clinic, Rochester, MN; Engineering, Mayo Clinic, Rochester, MN; Statistics, Mayo Clinic, Rochester, MN.

**Background:** Detecting hyperkalemia is limited by the need for blood testing. We have described non-invasive K measurement using the 12-lead, surface ECG. We now describe using these methods with a smartphone-based, single-lead device.

**Methods:** 14 adult hemodialysis patients had serum K and simultaneous, 2 minute ECG’s recordings before dialysis, at 30 minutes, at 60 minutes at the end of dialysis, and optionally, on a non-dialysis day. ECG’s (lead I only) were obtained by placing both hands on a 2-lead, Cardia device attached to the back of an Android smart phone. Using advanced signal processing, we used (r right slope)2/2 from the first dialysis to create individual templates which were used to predict subsequent K values.

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Results: 4 patients had inadequate data due to hand tremors or poor, lead-1 t wave morphology. Among the other 10 patients, mean K during the 1st dialysis was 5.2±0.7 maximum and 3.6±0.5 minimum. Subsequent K values were similar. For the predicted values, the mean absolute error (observed - predicted) was 0.4±0.2 mmol/L. Processed ECG changes between K 3.3 and 4.6 in one patient are shown in figure 1.

Conclusions: With signal processing, single-lead ECG can be used to bloodlessly measure potassium with clinically meaningful resolution. This enables remote and/or continuous K monitoring. Some patients require a device that is not affected by hand tremor or that can generate a lead other than lead 1.

Funding: Other NIH Support - National Institute of Biomedical Imaging and Bioengineering

TH-PO945

Background: Binding of Phenol and p-Cresol to proteins hinders their clearance in hemodialysis (HD). Our objective was to determine phenol and p-Cresol clearance with membranes of different adsorption and filtration capacity with different HD techniques.

Methods: In 16 patients, 13 males, mean age 62±17.5 years, Phenol and p-Cresol clearance was determined with: a) Toray polysulfone (PS) 2.1 m²; b) Palmar Kuf 55 ml/h/mmHg (Great adsorption capacity) on conventional HD(PS-HD); b) PS on on-line postdilutional hemodiafiltration (PS-HDF) c) Polyethylmethyl methacrylate 2.1 m²; d) Kuf 43 ml/h/mmHg (Great adsorption capacity) on HDF/PMMA-HD, e) PMMA on HDF/PMMA-HDF. Each session lasted 4 hours and Phenol, p-Cresol, β₂M, microglobulin(β₂-m), albumin and urea serum levels were determined before and after each session. Post-HD β₂-m, phenol and p-cresol levels were adjusted for variations in serum albumin. Their percentage reduction(PR), total processed blood volume(PBV) and infusion volume in HDF, and KT were measured.

Results: There were no differences in total PBV between the four procedures. Infusion volume in HDF was higher with PS than with PMMA (26.1±2.4 vs. 17.6±2.3 l/PBV) and infusion volume in HDF, and KT were measured.

Conclusions: 1) In HD and HDF Phenol clearance is higher than that of p-Cresol. 2) PS membranes achieve a higher Phenol and β₂-m clearance than PMMA in both HD and HDF. 3) HDF does not increase Phenol or p-Cresol clearance compared to HD with neither PS nor PMMA.

TH-PO946
Simplified Kinetic Indices and Population Exposures to Middle Molecules across the Range of Residual Renal Functions Hafiz Ali Srova, Christos Argyropoulos, Maria-Eleni Roumelioti, Mark L. Unruh. UNM School of Medicine.

Background: Beta 2 Microglobulin (β2M) is a uremic toxin that accumulates in ESRD patients. Elevated plasma β2M concentrations is linked to higher mortality in patients undergoing hemodialysis. The population kinetics of β2M has been described in the literature but the application of available kinetic models to predict dialysis induced changes in β2M concentrations has been limited.

Methods: We did a quantitative patient-level review of available data of β2M population kinetic models to predict plasma β2M concentrations in a population of simulated ESRD patients on hemodialysis with different levels of residual renal functions. We compared dialyzer clearance in patients receiving high flux dialysis under different regimes; conventional thrice weekly dialysis (HF), short daily (SD) and long daily (LD) sessions. We also examined the ability of simplified kinetic indices to quantify the effects of different dialysis schedules on plasma β2M concentrations across the range of residual renal functions. Only 2.5% of patients with Kt/V =10ml/min had β2M >20mg/L versus 80% of patients with KR =0ml/min. The effect of Kt/V on population centiles of β₂M appeared to be biphasic, the steeper effect at Kt/V < 4 and less steeper at Kt/V > 4.

Conclusions: While weekly Kt/V can be used to quantify the effects of different dialysis regimes, understanding of its effect at population level can effectively be used prescribing dialysis dose across the population of patient at different residual renal functions.

TH-PO947
Hemodialysis Water Purification, Disinfection and Monitoring Practices in Bangladesh Sadig Ahmed. Nephrology, Univ of KY, Lexington, KY.

Background: To provide ESRD patients with safe dialysis is a challenge due to technical & economic constraints in Bangladesh. In Bangladesh the numbers of ESRD patients are doubled in recent years. Most of these patients are on HD with very high mortality. Proper water purification is essential for providing safe HD treatment. This study looks at the dialysis water chemical composition and the disinfection protocols and monitoring practices in two major dialysis units in Dhaka, Bangladesh.

Methods: In 2015 two major chronic HD units, A & B, in Bangladesh were visited. The technicians and Nephrologists were interviewed. The samples of feed water and the final products before the dialysis was analyzed by Spectra lab USA. Some of the chemicals of the waters from units A & B in table: I and the water monitoring practices of the units are in table II. Table I shows that unit B has high levels of certain chemicals in the purified water. Table II shows that a routine disinfection and monitoring protocol is not followed.

Results: Table I

<table>
<thead>
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<th>Analytes</th>
<th>A</th>
<th>B</th>
<th>Normal range mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
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</tr>
<tr>
<td>Arsenic</td>
<td>&lt;.005</td>
<td>&lt;.005</td>
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<tr>
<td>Calcium</td>
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<tr>
<td>Copper</td>
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<td>Fluoride</td>
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<td>&lt;.10</td>
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<tr>
<td>Lead</td>
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<td>Magnesium</td>
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<td>Zinc</td>
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</table>

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Table II

<table>
<thead>
<tr>
<th>Water maintenance</th>
<th>Unit A</th>
<th>Unit B</th>
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<tbody>
<tr>
<td>Chlorgan No. Chlor</td>
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<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No. Before each shift</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Route check for endotoxin &amp; bacterial culture</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Chemical analysis</td>
<td>yearly</td>
<td>6 month</td>
<td>6 month</td>
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<tr>
<td>Route disinfection of RO</td>
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<tr>
<td>Chlorgan Ph. and conductivity by a separate meter</td>
<td>None or minimum</td>
<td>None or minimum</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Nephrologists involved in the process:

Funding: Private Foundation Support

Conclusions: Proper purification and disinfection protocols with routine monitoring of water quality is essential for safe hemodialysis. This is a challenge in the developing nations like Bangladesh due to cost but more due to lack of awareness. Routine monitoring of water quality & following disinfection protocols are not very expensive as the technology is locally available. Organizations like ISN or WHO can take initiatives to provide education & help in this area.

Funding: Private Foundation Support

TH-PO948

Combining Diffusion, Convection and Absorption: A Pilot, Cross-Over Study of Polyethylmethacrylate versus Polysulfone High-Flux Dialysis Membranes in the Removal of P-Cresol Sulfate by On-Line Hemodiafiltration

Pablo Molina,1 Julio Peiró-García,2 Cristina Esteller Beltrán,2 Maria Amparo Martínez Gómez,1 Sandra Beltrán,1 Belen Vizcaíno,1 Mercedes Gonzalez,1 Irma Sanchis,1 Luis M. Pallardo,1 Francisco Maduell,1,2 Nephrology, Dr Peset Univ Hospital, Spain; 2Pharmacology, Dr Peset Univ Hospital, Sri Lanka; 1Pharmacology, Dept of Medicine, School of Pharmacy, University of British Columbia, Vancouver, Canada.

Background: Only a few studies have examined how to improve the protein-bound toxins removal by extracorporeal strategies. This study tested the hypothesis that polyethylmethacrylate (PMMA) dialysis membranes with a high adsorptive capacity increase P-cresol sulfate removal compared to standard high-flux (HF) membranes, by on-line hemodiafiltration (OL-HDF).

Methods: 40 stable hemodialysis patients were enrolled in a prospective, cross-over study and treated with PMMA and polysulfone HF membranes by OL-HDF with postdilutional infusion. One session with each dialyzer was performed (PMMA BG2.1U, polysulfone TS2.1). Primary end point was serum p-cresol sulfate reduction rate, determined by chromatography. Secondary end points included the convective volume achieved and the β2-microglobulin (β2M) and small solute clearances. Dialysis procedures remained unchanged during both sessions.

Results: PMMA membrane achieved significantly greater p-cresol sulfate reduction ratio (94.1 vs. 77.4%; p<0.001). There was no difference in Kt/V (2.2±1.0 Vs. 2.2±0.4; p=0.325) although small molecules removal was better with polysulfone. The convection volume (20.4±3.3 Vs. 31.4±8.4 L/session; p<0.001) and β2M reduction ratio (62.0 vs.77.8%; p<0.001) were significantly lower with PMMA membrane.

Conclusions: P-cresol sulfate removal by OL-HDF was superior with PMMA membranes, appearing to be a good dialysis strategy for improving dialytic clearance of p-cresol, enabling an adequate β2M and small solute clearances.

TH-PO949

Assessment of Inpatient Dialysis Adequacy Using On-Line Clearance: A Fellow Quality Improvement Project

Deeewan Deewan,1,2 William D. Paulson,1,2 N. Stanley Nahman,1,2 John Jason White,1,2 Medicine, Augusta Univ; Augusta, GA; 1Specialty Care, Charlie Norwood VA Medical Center, Augusta, GA.

Background: A Hemodialysis (HD) single-pool Kt/V target of > 1.4 (Kt/V) is widely accepted as the minimum standard for outpatients dialyzing three weekly. Studies evaluating HD adequacy in hospitalized patients suggest worse outcomes when Kt/V is below standard outpatient goals. However, HD adequacy is rarely assessed in hospitalized settings. Online clearance monitoring (OCM) by sodium dialysance can accurately estimate urea clearance. In this project, we assessed OCM derived adequacy in hospitalized ESRD patients treated with HD.

Methods: Data were prospectively collected on all ESRD patients treated over a two week period. HD was performed on a Fresenius 2008T machine with Optiflux 180 dialyzer at Qb = 400 ml/min & Qd = 800 ml/min. Session durations were based on outpatient prescriptions or 4 hours when not available. Urea volume of distribution (Vd) was estimated by the Watson formula. OCM derived Kt/V values were recorded at the end of each HD session. Data are mean ± SEM.

Results: 21 patients were treated with 62 HD sessions. There were 10 AFV, 2 AVG, and 9 CVC responsible for 30, 24, and 21 treatments respectively. Treatment times were 227 ± 31 min. OCM data indicated only 42% (26/62) of treatments achieved Kt/V ≥ 1.4 with 22% (14/62) having Kt/V < 1.2. Analysis of patients' initial HD treatment suggests high Vd and CVC access are associated with failure to meet Kt/V goal.

Conclusions: These data suggest that inpatient HD frequently fails to achieve adequacy standards. OCM is easy to perform and only required calculation of Vd. We postulate that OCM directed therapy has the potential to improve HD delivery in the inpatient setting and possibly improve outcomes. Based on our results, we plan to utilize OCM in future determinations of dialysis session length.

TH-PO950

Early Patient Experience with the Table™ Hemodialysis System

Luis Alvarez May L. Yau;2 Glenn Matthew Chertow;3 Div of Nephrology, Dept of Medicine and Nephrology, Palo Alto Medical Foundation, Palo Alto, CA; 3Clinical Operations, Outset Medical, Inc., San Jose, CA; 4Div of Nephrology, Dept of Medicine and Nephrology, Stanford Univ School of Medicine, Stanford, CA.

Background: Patients on in-center hemodialysis (ICHD) often experience a range of symptoms and disturbances during, immediately following, and between dialysis sessions. A goal for any innovation in hemodialysis is to minimize those symptoms. This study reports on the early patient experience using a new technology aimed at enabling in-center self-care hemodialysis (ICSHD), the Table™ Hemodialysis System.

Methods: A subset of patients (n=33) from three dialysis centers, representing 152 treatments using the Table™ System were asked to complete surveys on their experience with Table™ compared to their previous dialysis machine.

Results: Patients reported experiencing 47% fewer headaches (n=54), 61% less cramping (n=92), 34% having more energy (n=53) and 48% being more relaxed (n=74). Patients on in-center hemodialysis (ICSD), the Table™ Hemodialysis System. the Tablo™ Hemodialysis System.

Conclusions: Preliminary, uncontrolled results suggest that patients report a more favorable dialysis experience with the Table™ Hemodialysis System compared to their conventional ICHD device. These results may encourage patients to choose in-center self-care for which the device is designed.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

TH-PO951

Protein-Bound Uremic Toxin Adsorption by Hexadecyl-Imobilized Cellulose Beads in Hemodialysis

Suguru Yamamoto,1 Mami Sato,1 Takuya Wakamatsu,1 Yoshimitsu Takahashi,2 Akira Iguchi,2 Kentaro Omori,2 Yasushi Suzuki,1 Issei Iwai2,1 Junichiro James Kazama,1 Fumitake Geijo,1 Ichiei Narita,3 Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan; 2Saiseikai Niigata Daini Hospital, Niigata, Japan; 1Div of Nephrology, Dept of Medicine and Hypertension, Saiseikai Niigata Daini Hospital, Niigata, Japan; 3Dept of Nephrology and Hypertension, Fukushima Medical University, Fukushima, Japan.

Background: Protein-bound uremic toxin (PBUT) accumulation causes uremia-related complications. We examined the PBUT removal ability of a hexadecyl-immobilized cellulose bead-containing column for patients undergoing hemodialysis.

Methods: In vitro, adsorption of indoxyl sulfate (IS), a representative PBUT (0.25–2.0 mM), to hexadecyl-immobilized cellulose beads (1.0 g) for 0–4 hours was compared

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

Underline represents presenting author.
Middle Molecule | N | $k_2$ (mL/min) | $V_1$ (L) | $V_1$ (L)
--- | --- | --- | --- | ---
β₂-microglobulin | 135 | 95.4 (78.2-121.8) | 173 (138-216) | 2.8 (2.1-3.6)
myoglobin | 109 | 68.1 (56.5-82.8) | 218 (154-317) | 2.1 (1.1-2.6)

complement factor D | 101 | 52.3 (38.0-75.6) | 14.8 (11.6-19.1) | 1.2 (0.6-1.6)

Although $K_{N}$ and $V_1$ were smaller at larger MW, the strongest dependence of these parameters was on $K_{N}$. For the combined data: $K_{N}$ vs. $K_{N}=R=0.444, P=0.001 & V_1$ vs. $K_{N}=R=0.745, P=0.001$. $V_1$ was independent of $K_{N}$ ($P=0.09$).

Conclusions: A 2C model can only describe the kinetics of middle molecules with MW larger than β2m if the central compartment volume is small and dependent on dialyzer clearance.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO954
Performance of Hemodialysis with Novel Medium Cut-off Dialyzer Alexander H. Kirsch, 1 Lars-Goran Nilsson, 1 Werner Beck, 1 Michael Ambühl, 1 Christoph Wintermeyer, 2 Alexander R. Rosenkranz, 3 Detlef H. Krieter, 3 Christoph Hauser, 1 Christoph Kirsch, 1 Christoph Wirth. 1

Methods: In two prospective, open-label, controlled, randomized crossover pilot studies (NCT02377570, NCT02377622), 39 prevalent HD patients were studied in mid-week dialysis treatments using Theranova 400 AA dialyzer in HD (MCO HD) in comparison to, study 1, FX CorDiax 80 dialyzer in HD (HF HD) and, study 2, HID and high-volume hemodiafiltration (HDF; FX CorDiax 800; convol vol 24L). Instantaneous clearances $K_{12}$ at 30 and 120 minutes and reduction ratios (RR) of free light chains (FLC) and other larger middle molecules were analyzed with a mixed model.

Results: Study 1 (Q=300 mL/min): At 30 min MCO HD provided higher FLC $K_{12}$ (xFLC, LS mean [SE]: 38.0 [3.63]; FLC (15.2 [1.59] mL/min) compared to HD (20.1 [3.63] and 0.59 [0.59], mL/min, respectively), both P<0.001. At 120 min FLC $K_{12}$ was still significantly greater for MCO HD while xFLC $K_{12}$ was not. Also, FLC RR was higher with MCO HD (xFLC: 66.3% [1.85]; FLC: 42.5% [2.06]) than HFHD (36.4% [1.8] and 12.9% [2.10]), respectively, both P<0.001. Study 2 (Q=400 mL/min): MCO HD showed higher $K_{12}$ (30min) of FLC compared to HDF (19.1 [2.65] vs. 6.6 [2.65] mL/min; P<0.001), while there was no difference in xFLC. Also, there was a significantly higher FLC RR in MCO HD compared to HDF (48.1% [1.72; 37.9% [1.76]; P<0.001). Additionally, MCO HD provided significantly better removal of β₂-microglobulin compared to HDF and adsorption on cellulose and polystyrene beads dose-adjusted cellulose beads increased PBUT and water-soluble intermediate removal.

Background: Compared to high-flux dialysis membranes (HF), novel medium cut-off (MCO) membranes are more permeable for larger middle molecules.

Funding: Baxter Healthcare Corporation

TH-PO955
Intradialytic Kinetics of β₂-Microglobulin and κ Free Light Chains: Diffusion-Adjusted Regional Blood Flow Model J. Ken Leyvoldt, 1 Markus Storr, 2 Baris U. Agar, 3 Adriana Boschetti-de-Fierro, 4 Manuel Voigt, 2 Michael Hulko, 1 Angelito A. Bernardo, 1 Alexander H. Kirsch, 1 Alexander R. Rosenkranz, 3 Detlef H. Krieter, 3 Bernd Krause, 2 Baxter Healthcare Corporation, Deerfield; 3Gambro Dialyseatoren GmbH, Hechingen, Germany; 4Medical Univ of Graz, Graz, Austria; 1Univ Hospital Wuerzburg, Wuerzburg, Germany.

Background: The kinetics of β₂-microglobulin (β₂m) during hemodialysis (HD) have been shown to be consistent with either a conventional two-compartment model (Ward et al, Kidney Int 2006) or a diffusion-adjusted regional blood flow model (DA-RBF, Maheshwari et al, Am Biomed Eng 2011). Recent work has shown that a two-compartment model cannot be used to describe the kinetics of middle molecules with molecular weight (MW) larger than that for β₂m unless the compartment volume from which dialyzer clearance occurs is less than plasma volume. We hypothesized that a DA-RBF model can adequately describe the kinetics of β₂m (MW=11.8 kD) and kappa free light chains (xFLC, MW=22.5 kD).

Methods: Intradialytic serum and dialysate concentrations of β₂m and κFLC were measured in 34 HD patients treated by Theranova 400 AA dialyzer in HD (MCO HD) and compared to high-flux dialysis membranes (HF), novel medium cut-off (MCO) dialyzers. In this analysis, the results from all treatments were combined.

Results: Compared to PS and PMMA, hexadecyl-immobilized cellulose beads dose-dependently removed more IS in vitro (5.5 ± 1.4%) and adsorption of 1 mM IS for 1 hour, P<0.01. Only the hexadecyl column decreased protein-unbound IS, IAAS, and PICS levels (by 34.4±30.0%, 34.8±25.4%, 28.4±18.0% and 34.9±22.1%, respectively), but did not significantly decrease their pre-dialysis serum levels after 2-week treatment. The hexadecyl column removed strongly adsorbed β₂m (92.9±2.5%) but not urea nitrogen and albumin.

Conclusions: Hexadecyl-immobilized cellulose beads removed PBUTs by adsorption. Regular hemodialysis with adsorption treatment is an attractive blood purification treatment to increase PBUT and water-soluble intermediate removal.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO956
Middle Molecule Kinetics during Hemodialysis and Hemodiafiltration Based on a Two-Compartment Model J. Ken Leyvoldt, 1 Markus Storr, 2 Baris U. Agar, 3 Adriana Boschetti-de-Fierro, 4 Angelito A. Bernardo, 1 Alexander H. Kirsch, 3 Alexander R. Rosenkranz, 3 Detlef H. Krieter, 3 Bernd Krause, 2 Baxter Healthcare Corporation, Deerfield; 3Gambro Dialyseatoren GmbH, Hechingen, Germany; 4Medical Univ of Graz, Graz, Austria; 1Univ Hospital Wuerzburg, Wuerzburg, Germany.

Background: The kinetics of β₂-microglobulin (β₂m) during hemodialysis (HD) are well described by a two-compartment (2C) model where clearance by the dialyzer is from a central compartment (V₁) that approximates plasma volume and a total distribution volume (V₂) that approximates extracellular volume. The kinetics of middle molecules with molecular weight (MW) larger than β₂m have not been extensively studied.

Methods: Intradialytic serum and dialysate concentrations of β₂m (MW=11.8 kD), myoglobin (16.7 kD), and complement factor D (27.0 kD) were used to estimate 3 kinetic parameters from a 2C model (intercompartmental clearance or $k_{12}$, $V_1$ and $V_2$) in HD patients during 2 prospective clinical trials (NCT02377570 & NCT02377622) comparing the performance of high flux dialyzers/diafilters and medium cut-off (high flux with extended permeability) dialyzers. In this analysis, the results from all treatments were combined. Overall dialyzer clearance ($K_{12}$) was evaluated by total mass removed in the dialysate. In vitro dialyzer clearance (Kovr) was evaluated by total mass removed in the dialysate. In this analysis, the results from all treatments were combined.

Results: As expected, $k_{12}$ was higher for β₂m than κFLC, but blood flow percent to the high flow tissue region ($f$) changed 1 way, & $f$ decreased by 15.3-17.9%.

Conclusions: A DA-RBF model provides a physiological basis for intradialytic kinetics of both β₂m and κFLC.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO957
A Novel Method of Widening the Range of Diameter Fluid [Na] Using a 4-Stream Approach Sujeet D. Lun, 1 Jun Ling Cheng, 2 Todd S. Ing, 3 Ho Ming Ling Nethersole Hospital, Hong Kong, China; 1Medicine, Stritch School of Medicine, Loyola Univ Chicago, Maywood, IL.

Background: The conventional, 45X, 3-stream, bicarbonate-based dialysis fluid (DF) delivery system consists of an acid concentrate stream (CS), A; a bicarbonate (BIC) CS, B, & H2O stream, W. The flow rate ratios (FRR) for A:B:W are: 1:1.72:42.8 (totaling 45 or 45X). This system provides a DF [Na] range of 125-150 mEq/L.

Methods: We devised a 4-stream DF delivery system to expand the [Na] range by adding a NaCl CS, C. An elastic pulley-like mechanism sits between C & W. Contributions to the final DF include: A: Chloride salts of Na(63 mEq/L), K, Ca & Mg, & dextrose, B: 37 mM NaHCO3, C: 37 mM NaCl, & W: H2O. The FRR for A:B:C:W under normal conditions are: 1:1.72:42.5:45 (45 or 45X).

Results: To change the DF Na level, the FRR of C changes 1 way, & W changes by the same magnitude but in the opposite direction. For example, if C’s FRR decreases by
Acute Extracellular Calcium Regulation Is Independently Associated with Serum Urate in Carboxylated Osteocalcin in Chronic Hemodialysis Patients

Markus Pirkbauer, Ramona Schupart, Gert J. Mayer. Internal Medicine IV, Nephrology and Hypertension, Medical Univ Innsbruck, Innsbruck, Tyrol, Austria.

Background: In order to avoid excessive calcium (Ca) loading in hemodialysis (HD) patients, current guidelines suggest a dialysate calcium concentration (dCa) of 2.5 mEq/l based on relatively stable intradialytic serum Ca levels. However, the latter do not account for possible Ca storage in acutely accessible pools. A rapidly exchangeable Ca pool located at the bone level has been proposed to be involved in acute extracellular Ca regulation.

Methods: To obtain clinical evidence for a rapidly exchangeable Ca pool and its contribution in the maintenance of serum Ca levels we assessed dialysate-sided ionized Ca (iCaMB) during two HD sessions in chronic HD patients using a dCa of 3.5 (±28) and 2.5 (±10) mEq/l. Acute Ca buffer capacity was calculated by setting ΔiCaMB in relation to iCaMB. ELISA-based measurements of serum osteocalcin, the most abundant non-collagenous bone protein, were conducted prior to the first HD session.

Results: Considering pre- to postcapillary dialysate bicarbonate decline, iCaMB was invariably variable for both 2.5 and 3.5 mEq/l dCa, with a mean of 434 (±125) and 725 (±162) mg/HD, respectively (p=0.001). The mean amount of intra-dialectic Ca load buffered (i.e. iCaMB - ΔiCaMB) was 410 (±116) mg/HD at 2.5 mEq/l dCa and 565 (±130) mg/HD at 3.5 mEq/l dCa (p=0.009). Acute Ca buffer capacity varies inversely correlated with undercarboxylated osteocalcin (Glu-OC) (r=-0.49, p=0.01), patient dry weight (r=-0.47, p=0.05) and body mass index (r=-0.45, p=0.05). Multivariate regression analysis showed an independent association of acute Ca buffer capacity with Glu-OC (β=0.512, p=0.002).

Conclusions: Our study revealed high Ca burden with standard dCa and provides strong evidence for the existence of a rapidly exchangeable Ca pool that counters acute serum Ca deviations. Our data provide - for the first time - experimental evidence for the involvement of bone in acute extracellular Ca regulation in vivo.

Funding: Government Support - Non-U.S.

Validation of a Novel Mathematical Model of Protein-Bound Uremic Toxins Kinetics in Hemodialysis Patients

Vaibhav Maheshwari, Stephan Thijssen, Xia Tao, Doris H. Fuertinger, Peter Kotanko. Renal Research Inst, New York City, NY.

Background: While accumulation of protein-bound uremic toxins (PBUTs) such as indoxyl sulfate (IS) and p-cresyl sulfate (pCS) is associated with mortality, their removal in conventional hemodialysis (HD) is limited. We developed a novel mathematical model to better understand PBUT kinetics. We validated the model with in vivo data on the dialytic removal of PBUTs (Deltombe et al. 2015), and in vitro data studying the effect of increased dialysate flow with concomitant increase in dialyzer size (K,A) (Meyer et al. 2004).

Methods: The model comprises a multi-compartmental representation of the patient and a spatiotemporal representation of the dialyzer and accounts for albumin-toxin dynamic equilibrium. The model was calibrated using IS, PCS, and urea data from ELOOT et al. (2016). A total of 6 model parameters, namely, (i-ii) mass transfer coefficients between plasma and interstitium (K_i) and between interstitium and intracellular space (K_i), (iii) the association constant (k_i), (iv) lowering [Na] in the final DF. The opposite sequence of events will occur if iCaMB increases. Patients with hypomagnesemia can be dialyzed with a wider range of DF Na levels without associated changes in BIC, K, Ca, Mg, & dextrose concentrations. Thus averting central pontine myelinolysis or cerebral edema, normally seen with rapid changes in serum [Na]. The ingredients in A & B remain unchanged because the sum of the FRR for dCa & W, a fluid volume that normally dilutes the ingredients of A & B, remains unchanged.

Conclusions: A pulley between C & W permits a wider DF [Na] range. The final concentrations of BIC, K, Ca, & Mg are not affected since the total volume of fluid that dilutes these elements remains intact.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America.

β-2 Microglobulin Removal by High-Flux Dialysis: A Meta-Analysis

Rocio Figueroa, Maria-Eleni Roumeliot, Gregory S. Tretley, Thomas D. Nolin, Yue-Harn Ng, Zhi Xu, Mark L. Unruh, Christos Argyropoulos. Internal Medicine-Nephrology, UNMHC, Albuquerque; Pharmacy and Therapeutics, Univ of Pittsburgh, Pittsburgh.

Background: Elevated beta-2 microglobulin (B2M) levels with adverse cardiovascular and infectious outcomes. There is limited quantitative data about the ability of high flux dialyzers (HF) to remove B2M.

Methods: We used ProQuest to search EMBASE and MEDLINE, for randomized controlled trials and observational studies in HF dialysis between 2001-2013. Clearance measurements at blood side and/or dialysate side were included and reported via random effects meta-analysis.

Results: Average clearance was 50.2 ml/min with substantial heterogeneity among the 37 studies identified.

Conclusions: The proposed model reproduces existing literature data closely. This model can be used for testing new approaches for removal of PBUTs such as pre-dilution hemodilution and effect of enhanced removal by binding competitors.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America.
BETWEEN THE FACTS AND THE FICTION

Intradialytic hypotension is the most common complication of haemodialysis (HD). This study on the effect of profiled dialysis on intradialytic hypotension (IDH) and related symptoms, nursing interventions during dialysis. Evaluated intradialytic hypotension related symptoms included muscle cramps, dizziness, headache, nausea and vomiting. Evaluating nursing interventions included saline infusion, decrease or stop ultrafiltration (UF) and session failure. In this study interdialytic weight and serum sodium concentration were evaluated also.

Methods: This study included 24 patients on maintenance haemodialysis who experienced frequent episodes of intradialytic hypotension who were recruited. There were 17 female and 7 male patients.

Results: There was significant improvement of IDH (p<0.001), cramps (p<0.001), dizziness (p<0.001), headache (p<0.001), saline infusion (p<0.001), decrease or stop UF (p<0.001), session failure (p<0.001). No significant difference in interdialytic weight gain, serum sodium concentration, nausea and vomiting.

Adjusted interdialytic and plasma clearances were lower than whole blood clearances.

Conclusions: In conclusion, combination of sodium and ultrafiltration step-down is more effective and much safer in aged in comparison to younger population rather than any alone. Ahmed G. Adam, Rania Awad, Ashaaraf Adel. Internal Medicine, Nephrology, Dialysis & Transplantation Unit, Faculty of Medicine, U of Alexandria, Alexandria, El Salvador.

Background: Intradialytic hypotension is the most common complication of haemodialysis (HD) This study on the effect of profiled dialysis on intradialytic hypotension (IDH) and related symptoms, nursing interventions during dialysis. Evaluated intradialytic hypotension related symptoms included muscle cramps, dizziness, headache, nausea and vomiting. Evaluating nursing interventions included saline infusion, decrease or stop ultrafiltration (UF) and session failure. In this study interdialytic weight and serum sodium concentration were evaluated also.

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Results: There was significant improvement of IDH (p<0.001), cramps (p<0.001), dizziness (p<0.001), headache (p<0.001), saline infusion (p<0.001), decrease or stop UF (p<0.001), session failure (p<0.001). No significant difference in interdialytic weight gain, serum sodium concentration, nausea and vomiting.

Conclusions: In conclusion, combination of sodium and ultrafiltration profiles are simple and cost effective methods which improve the homodynamic stability with modulating the sodium dialysate and removal of fluids, so decreases the incidence of IDH and related symptoms (dizziness, cramps, headache). Also decreasing all nursing interventions (saline infusion, decreasing or stopping ultrafiltration, session failure) with improvement of dialysis tolerance. Without significant interdialytic weight gain or sodium. Therefore combination of sodium and ultrafiltration profiles are recommended for IDH prevention.

TH-PO960

Vadadustat Maintains Hemoglobin (Hb) Levels in Dialysis-Dependent Chronic Kidney Disease (DD-CKD) Patients Independent of Systemic Inflammation or Prior Dose of Erythropoiesis-Stimulating Agent (ESA)

Solker H. Hasek, Zeeshan Khawaja, Jason Chan, Qing Zaron, Raghuraj Ramesh-Fair, Bradley J. Maronii, Peter A. McCullough. Vanderbilt Univ, Nashville, TN; Akebia Therapeutics, Inc., Cambridge, MA; Baylor Univ Medical Center, Dallas, TX.

Background: DD-CKD is associated with systemic inflammation. Vadadustat is a novel, oral, hypoxia-inducible factor prolyl-hydroxylase inhibitor in development for the treatment of renal anemia.

Methods: A randomized, Phase 2, multicenter, open-label study assessed the HB response to 3 starting doses of vadadustat over 16 weeks in 94 DD-CKD patients who were maintained on EAs prior to study entry. Patients were converted from ESA to vadadustat and assigned to 1 of 3 dose cohorts: 300mg once daily (QD), 450mg QD; and 450mg three times weekly (TIW). From week 8, vadadustat dose could be adjusted (150-600 mg) as needed to maintain Hb. A post-hoc analysis was performed to explore the relationship between final vadadustat dose, mean change in Hb, baseline markers of inflammation (hepcidin and C-reactive protein [CRP]), and weekly ESA dose prior to study entry.

Results: No correlation was observed between the final vadadustat dose and baseline markers of inflammation or ESA dose. (Tables 1, 2). Vadadustat maintained Hb independent of baseline CRP (p=0.07) and hepcidin (p = 0.11).

Table 1: QD vadadustat dose

<table>
<thead>
<tr>
<th>Final dose (mg/day)</th>
<th>Mean baseline Hb levels (g/dL)</th>
<th>Mean baseline CRP (mg/L)</th>
<th>Weekly ESA dose prior to study entry (Emk/kg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>n (M+SD)</td>
<td>n (M+SD)</td>
<td>n (M+SD)</td>
</tr>
<tr>
<td>18</td>
<td>10.1+0.5</td>
<td>5.3</td>
<td>1.1</td>
</tr>
<tr>
<td>360</td>
<td>10.1+0.5</td>
<td>5.3</td>
<td>1.1</td>
</tr>
<tr>
<td>450</td>
<td>10.1+0.5</td>
<td>5.3</td>
<td>1.1</td>
</tr>
<tr>
<td>540</td>
<td>10.1+0.5</td>
<td>5.3</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Table 2: TIW vadadustat dose

<table>
<thead>
<tr>
<th>Final dose (mg/TW)</th>
<th>Mean baseline Hb levels (g/dL)</th>
<th>Mean baseline CRP (mg/L)</th>
<th>Weekly ESA dose prior to study entry (Emk/kg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>n (M+SD)</td>
<td>n (M+SD)</td>
<td>n (M+SD)</td>
</tr>
<tr>
<td>180</td>
<td>10.1+0.5</td>
<td>5.3</td>
<td>1.1</td>
</tr>
<tr>
<td>360</td>
<td>10.1+0.5</td>
<td>5.3</td>
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<td>450</td>
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<td>5.3</td>
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<td>540</td>
<td>10.1+0.5</td>
<td>5.3</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Conclusions: The Hb response and vadadustat dose requirements for Hb maintenance are independent of underlying systemic inflammation and baseline ESA dose in patients with DD-CKD.

Funding: Pharmaceutical Company Support - Akebia Therapeutics, Inc.
Klotho was originally discovered as an anti-aging factor. It is primary produced in kidney. Its deficiency is associated with renal disease progression and heart disease by affecting cardiac remodeling. The aim of the study was to assess the Sirtuin1 and αKlotho plasma concentration in hemodialysis (HD) patients comparing to healthy volunteers in regard to age, blood pressure control, residual renal function (RRF), diabetes, cardiovascular disease, time of dialysis and type of dialyzer. 

Methods: The plasma level of SIRT1 and αKlotho was evaluated using ELISA tests in 103 HD patients, median age 62 years and in 21 volunteers. The blood pressure, residual diuresis, echocardiography and some dialysis parameters was assessed. HD group was divided according to the presence of residual diuresis.

Results: Plasma SIRT1 level was higher (Me=28.42 vs 2.71 ng/ml, p<0.0001) and αKlotho was lower (Me=433.9 vs 756.63 pg/ml, p<0.0001) in HD group comparing to control one. αKlotho was lower in those without RRF. There were no differences in SIRT1 concentration regarding residual diuresis. SIRT1 positively correlated with duration of hemodialysis. αKlotho negatively correlated with left ventricular posterior wall thickness. There were no significant relationship between SIRT1 and αKlotho level and age, blood pressure control, type of dialyzer, Kt/V and the diabetes.

Conclusions: The elevated SIRT1 concentration is associated with impaired kidney function as well as lowered αKlotho level. The decreased αKlotho level may also indicate the heart hypertrophy and cardiac problem in maintained dialysis. Though, the role of SIRT1 and αKlotho as biomarkers/predictors of oxidative stress, inflammation and cardiovascular diseases needs further examination.

TH-PO963
Prediction of Intradialytic Arterial Oxygen Saturation in Chronic Hemodialysis Using Patient Characteristics

Hanjie Zhang, 1 Israel Campos, 1, 2 Stephane Thijssen, 1 Peter Kotanko. 1, 2
1 Research, Renal Research Inst, New York, NY; 2 Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Recent evidence indicates that intradialytic arterial oxygen saturation (SaO2) is associated with inflammation, resistance to erythropoiesis stimulating agents, hospitalization, and all-cause mortality in hemodialysis (HD) patients (Meyring-Wosten, CJASN 2016). While SaO2 can be measured easily with the Critline monitor (CLM; Fresenius Medical Care, Waltham, MA), only a minority of HD facilities have deployed this technology. Therefore we explored if SaO2 can be predicted from demographic, clinical and laboratory data.

Methods: We studied HD patients with arterio-venous vascular access who had their SaO2 measured by CLM during HD. Generalized linear model (GLM), generalized additive model (GAM), gradient boosting methods (GBM) and random forest (RF) were used to predict SaO2, based on 16 predictors, including age, gender, race, body mass index, HD vintage, serum albumin, hemoglobin level, and comorbidities. We randomly sampled 80% of the data (derivation cohort) for model building; the remaining 20% were used as validation cohort.

Results: We studied 28,065 HD sessions in 910 chronic HD patients (mean age 61.5, 59% males, 51% white). Average SaO2 was 92.6% (SD 1.94%). There was no material difference in the predictive performance of the 4 models (Figure 1A; a histogram of GLM results is shown in Figure 1B).

Figure 1A: Predictive performance of the 4 models

- Difference (predicted – measured) (SaO2)
- Standard deviation of the difference (SaO2)
- GAM
- GBM
- GML
- Random Forest

Conclusions: To our knowledge, this is the first study that attempted to estimate intradialytic SaO2 using patient characteristics. While only 10-14% of the SaO2 variability could be explained by these models, the predicted SaO2 still provided a better SaO2 estimate for an individual patient than the population average. Future studies need to explore additional biological predictors of SaO2, such as the degree of fluid overload.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

TH-PO964
Characteristics of Markets and Patients Served by ESRD Seamless Care Organizations (ESCOs)

R. Hirth, 1 J. M. Messana, 1 Brighta Mona Negruzsa, 2 Court Q. Melin, 1 Yi Li, 1 G. Marrufo. 1 School of Public Health & Internal Medicine, Univ of Michigan, Ann Arbor, MI; 2The Levin Group, Falls Church, VA; 3The Levin Group, Eden Prairie, MN.

Background: The Comprehensive ESRD Care Model (CEC) establishes ESCOs as an innovative care delivery structure, based on concepts of accountable care organizations with a focus on the complex needs of dialysis patients. Operations began 10/1/2015 with 13 ESCOs in 17 Core-based Statistical Areas (CBSA). Because of CEC participation requirements (e.g., >50% dialysis patients in each ESCO within 1-2 CBSAs and dialysis facilities and nephrologists willing to accept financial risk), the markets in which ESCOs choose to operate and consequently the patients they serve may differ from those not served by ESCOs. To project the model’s scalability, we explored whether ESCOs’ markets and patients are typical of the broader Medicare ESRD population.

Methods: We compared characteristics of CBSAs with and without ESCOs in 2015 in terms of size, Medicare spending, demographics and health system characteristics. ESCO-aligned and non-aligned patients were compared on demographics, comorbidities, Medicaid status and Medicare spending in 2014.

Results: ESCO CBSAs had substantially more Medicare ESRD beneficiaries than non-ESCO CBSAs (median 1851 vs. 122), had fewer white patients (60% vs. 81%), higher average household income ($51,345 vs. $43,815), higher Medicare Advantage penetration (24% vs. 18%), and more primary care physicians (7.1 vs. 6.3 per 10,000 Medicare beneficiaries) and specialists (8.3 vs. 8.4 per 10,000). Patients aligned to ESCOs were more likely to be treated in an urban area (98% vs. 84%), had higher monthly Medicare Parts A and B spending in 2014 ($6,118 vs. $5,703), and had comparable prevalence of most comorbidities (largest differences for Alzheimer’s 16% vs. 10%, and rheumatoid arthritis 28% vs. 25%). All reported differences were significant with p<0.05.

Conclusions: By creating incentives for more effective care coordination, the CEC model has the potential to improve outcomes and reduce costs. To date, participation has been limited to larger markets, suggesting that the ability to extend the model to smaller markets should be monitored.

Funding: Other U.S. Government Support

TH-PO965
Starting Dialysis: From Refusals to Regrets, How Strong Is the Misperception?

Mabel Habib Aoun, 1, 2 Leony Antoun, 1 Dania Chelala. 1
1Nephrology, Saint-Georges Hospital, Ajaltoun, Lebanon; 2Nephrology, Saint-Joseph Univ, Beirut, Lebanon; 3Internal Medicine, Kaslik Univ, Lebanon.

Background: Dialysis is life-sustaining for end-stage renal disease (ESRD) patients and a way to better quality of life (Qol). Nephrologists try to convince patients of starting dialysis but may propose palliative care for elderly with reduced survival and Qol scores. The challenge is to discover what patients really want and whether their choices change. We studied 71 chronic haemodialysis (HD) patients, their initial refusal of dialysis, later regret, QoL and survival time in 3 age groups.

Methods: Patients on HD in April 2015 were included and administered 2 questionnaires: (1) demographic data, dialysis refusal, later regret, major complaint; (2) Short Form 36 (SF-36) for Qol scores: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and mental health (MH).

Results: Patients were divided in 3 groups according to age at dialysis start: < 70, 70-80 and > 80 [table 1]. 28% refused dialysis but changed their mind later. One regretted starting dialysis. Patients ≥ 80 had longer survival on dialysis and > 80 [table 1]. 28% refused dialysis but changed their mind later. One regretted starting dialysis. Patients ≥ 80 had longer survival on dialysis.
Intradialytic Exercise May Not Break the Vicious Cycle of Frailty

Hannah M. Young,1 Daniel Scott March,1 Darren R. Churchward,1 Charlotte E. Granthan,1 Patrick J. Highton,1 Matthew P. Graham-Brown,1,2 Alice C. Smith,3 James Burton.1
1Dept of Infection, Immunity & Inflammation and John Wallis Renal Unit, Leicester General Hospital; 2School of Sport, Exercise and Health Sciences, Loughborough Univ; 3Dept of Cardiac & Pulmonary Rehabilitation, Glenfield Hospital.

Background: Frailty is associated with poor outcomes for hemodialysis (HD) patients. Intradialytic exercise is recommended, but effective interventions in the frail elderly include a wider range of exercises; the components of a program suited to frail HD patients are unknown. The purpose of this study is to examine the influence of frailty on exercise capacity, function, activity levels and exercise behaviors to inform a specific frailty intervention.

Methods: Frailty status was measured in 43 patients (30 male, 13 female, age 58, IQR 27.25). Exercise capacity was measured using walking tests (ISWT and ESWT), muscle endurance using the Sit to Stand (6STS60) and step count using accelerometry. Function and exercise behavior were assessed using the Duke Activity Status Index (DASI), exercise self-efficacy questionnaire and exercise benefits and barriers scale (DPPEBBS).

Results: 13 (30%) of the participants were ‘robust’, 23 (52%) ‘pre-frail’ and 7 (16%) were frail. Patients were well matched for age, vintage and co-morbidity. One-way ANOVA showed lower exercise and functional capacity (ISWT, P<0.05; ESWT, P<0.05; DASI, P<0.05) and muscle endurance (6STS60, P<0.05). Post hoc analyses showed a significant decrease in ISWT distance in the frail group compared with robust (−2946, p<0.05) and pre-frail groups (−168, p<0.02), in ESWT time between pre-frail and robust groups (−496, p<0.05), in 6STS60 scores between frail, robust (−17.03, p<0.02) and pre-frail groups (−12.66, p<0.02) and between frail and robust groups (−21.95, p<0.003) for the DASI. Weekly steps were low in all groups (21436, IQR 29732), but self-efficacy was moderate and the DPPEBBS indicated that patients generally perceived more exercise benefits than barriers (61.1, 7.68).

Conclusions: This study reveals a high prevalence of frailty amongst HD patients and suggests that a multi-component exercise program, rather than intradialytic exercise, may best address frailty in this population.

TH-PO967

The Spectrum of Symptoms Induced by Hemodialysis

Kevin Ouach,1 Jennifer M. MacRae,2 Braden J. Manns,2 Michael Walsh.1 1McMaster Univ; 2Univ of Calgary.

Background: Hemodialysis induces symptoms in patients that take time to recover from (recovery time). The symptoms induced and how they vary over time and between patients is unclear. We conducted a prospective cohort study to describe how recovery time varies over time and between patients.

Methods: We recruited prevalent in-center hemodialysis patients and measured their recovery time using multiple instruments. Instrument A presented a global question regarding how long it took to recover from the last dialysis treatment. Instrument B addressed the recovery time for each of 10 symptoms. Participants completed each instrument for each dialysis treatment for one week. We compared the distribution of recovery time found with each instrument.

Results: One hundred twenty participants from 2 centres completed 914 recovery time assessments. Fewer participants required no recovery time with Instrument A (14 to 17% of participants depending on day of week) compared with identifying no symptoms with Instrument B (20 to 34% of participants depending on day of week) (p<0.002 for difference between groups). However, the maximum recovery time from any symptom in Instrument B (median 10 hours) was longer than the recovery time identified with Instrument A (median 3 hours) (p<0.001). Lack of energy was the most common symptom following dialysis (69% of all patients), with muscle cramps (41%), bone and joint pain (36%), shortness of breath (26%), and muscle soreness (33%) the next most frequent. Recovery time measured with instrument A correlated with the KDQoL. Burden of Disease (P=0.003). Effects of Kidney Disease (p=0.01) and Mental Composite Score (p=0.01) but individual symptoms did not consistently correlate with domains of the KDQoL.

Conclusions: Recovery time is a complex of different symptoms that vary in duration. Further research is required to understand how dialysis induces each type of symptom in order to reduce recovery time.

TH-PO968

Prospective Study of the Gut Microbiome and Effects of P-Inulin in ESRD: Early Experience of the NIDDK Hemodialysis Novel Therapies (HDNT) Consortium

Dominic S. Raji,1 Ali Ramezani,1 Hongzhe Li,2 Richard Landis,2 David M. Charytan,3 Talat Alp Ikizler,3 Jonathan Himelfarb,3 Alan S. Kliger,3 Paul L. Kimmel,1 John W. Kusek,1 Laura M. Dember.1 1George Washington U; 2Univ Pennsylvania; 3Brigham & Women’s Hospital; Vanderbilt U; U Washington; Yale U; NIDDK.

Background: Preliminary evidence suggests that alterations in the gut microbiome contribute to ESRD-associated inflammation and cardiovascular disease. Prior to conducting clinical trials of prebiotics such as p-inulin to restore microbial balance, it is necessary to characterize the composition, function, and stability of the gut microbiome in ESRD patients.

Methods: The NIDDK HDNT Consortium is performing a non-randomized, open label, cross-over, multi-center, proof of study of at least 10 patients receiving maintenance HD at 4 centers. The study protocol requires intensive sampling of stool (1-2X/wk) and blood (1X/wk) during 3 phases: 1) pre-treatment-8 wks; 2) treatment with p-inulin pre-biotic, 8 g 2X/day-12 wks; and 3) post-treatment-8 wks. Microbiome composition will be assessed at the overall microbial diversity and individual taxon levels, and microbiome function will be assessed with metabolomic profiling and targeted metabolite measurements. 16S rRNA gene sequencing, metabolomic studies, and analytical approaches are being piloted in a sub-set of samples collected at wks 2 and 8 (phase 1) and wks 14 and 20 (phase 2). The objective of the study is to identify 12 patients enrolled (1 for implantation; 1 for unwillingness to provide samples). The remaining 10 patients, followed for 143 pt-weeks thus far, have provided 152 of 154 (99%) blood samples and 157 of 161 (98%) stool samples, and have processed their stool samples generating 1564 of 1598 (98%) aliquots. Adherence to p-inulin is assessed by packet counts is 74% of the recommended dose. Analytical approaches to high-dimensional, repeated measures data have been developed to evaluate within-person variability of microbiome composition and function, and effects of p-inulin on both parameters.

Conclusions: The feasibility of intensive stool and blood sample acquisition and the tolerability of p-inulin both appear to be sufficient to generate data needed to design future clinical trials targeting the gut microbiome in ESRD.

Funding: NIDDK Support

TH-PO969

Disorders in Thyroid Morphology Observed in ESRD Patients on Maintenance Hemodialysis

Syed Rizwan A. Bokhari,1 Maria Rizwan Bokhari,2 Syed A. Khalid,1 Muhammad Zaman Khan Assar,2 Abeera Mansur.3 1Nephrology, AICM/JHL, Pakistan; 2Radiology, AICM/JHL, Pakistan; 3Nephrology, DHMC, Pakistan.

Background: Chronic kidney disease has been associated with changes in thyroid gland morphology and thyroid hormone metabolism. Goiter and thyroid nodules have been reported to increase with decreased estimated glomerular filtration rate even though its frequency is not known in developing countries. We aimed to study the thyroid gland morphology in our ESRD population and its correlation with patient demographics.

Methods: We enrolled 74 patients on maintenance HD at the dialysis center of Jinnah hospital Lahore. Two patients (3%) with preexisting thyroid disease were excluded.

Results: Total of 72 end stage renal disease (ESRD) patients on maintenance hemodialysis were included. Mean age was 50 years (range 17-82 years). Forty six (64%) were female. Twenty-two (31%) had DM, A1 (66% of diabetics) had DM2. A3 (60% of diabetics) had DM3. A4 (30% of diabetics) had the rare type DM. A5 (24% of diabetics) had PA. A6 (20% of diabetics) had type D. A7 (16% of diabetics) had type E. A8 (10% of diabetics) had type F. A9 (10% of diabetics) had type G. A10 (2% of diabetics) had type H.

Conclusions: There is high prevalence of thyroid nodules in our dialysis patient’s population. Higher frequency was observed in female patients. No correlation was found with PTH levels, preexisting co-morbidities, frequency and duration of hemodialysis, and occurrence of renal cysts. Ultrasound evaluation of thyroid gland morphology and thyroid hormone metabolism should be considered in patients on maintenance hemodialysis.

TH-PO970

Routine Pre- and Post-Hemodialysis Blood Pressure Monitoring

Yannick Begin, Simon Desmeules, Mohsen Agharazi, Sebastien Savard, Fabrice Mac-Way, Sacha A. De Serres. 1Nephrologie, CHUQ- Hotel-Dieu de Quebec, Quebec, QC, Canada.

Background: Routine pre- and post-hemodialysis (HD) blood pressure (BP) are poor indicators of BP control. Ambulatory blood pressure monitoring (ABPM) remains the gold standard for diagnosis and treatment of hypertension, but its availability is limited and it is especially uncomfortable in HD population. The aim of this study is to define pre- and post-HD blood pressure cut-offs where an ABPM would not be required for the assessment of blood pressure control.

Methods: In a single center cross-sectional retrospective study, we studied all complete routine ABPM that were performed in an HD population from April 2013 to February 2014. The routine ABPM (RABPM) was defined as a 44h ABPM systolic BP=135 mm Hg. ROC curve analysis, specificity, sensitivity, positive and negative predictive value (PPV and NPV) analysis were performed.

Results: There were 271 complete ABPM. The average of routine pre- and post-HD systolic blood pressure (HD systolic BP) provided the best AUC (0.881) for an ABPM BP control of < 135 mm Hg. For a HD systolic BP threshold of 130 mmHg, sensitivity, specificity and NPV were respectively 97%, 42% and 94% and for a HD systolic BP threshold of 135 mmHg, sensitivity, specificity and PPV were respectively 43%, 97% and 49%. Overall, using the two thresholds, 45% of ABPM were in the zones of very high NPV or PPV.

Conclusions: To assess high BP, our study indicates that limiting ABPM use to patients with average of pre- and post-HD systolic BP of between 130-165 mm Hg reduces the use of ABPM by 45%. These findings could be useful for the management of health care resources and for the reduction of the level of intrusiveness.
Impact of a Multidisciplinary Intensive Management Clinic on Incident Hemodialysis Patients in Singapore
Priscilla P. How,1,2 Catherine Ho,1, Jia Jia Lee,1 Hersharan Sran.1 1Dept of Pharmacy, National Univ of Singapore; 2Dept of Medicine (Nephrology), National Univ Hospital.

Background: Multidisciplinary models of care have been shown to be beneficial for patients with end-stage renal disease. The Hemodialysis Initiation and Transition (HIT) clinic provides consistent, intensive, multidisciplinary care to incident hemodialysis (HD) patients, and is the first of such clinic in Singapore. This study aimed to determine the clinical impact of this clinic.

Methods: Adult patients newly initiated on chronic HD from January 2013 to December 2014 were enrolled in this cohort study. Laboratory parameters, medication profiles, dialysis access, vaccination status, hospitalizations and mortality were assessed and compared between patients managed by the HIT clinic vs. conventional care.

Results: A total of 303 patients (216 HIT patients and 87 conventional care – control group) were included in the study. HIT patients achieved higher mean hemoglobin, corrected calcium and phosphorus; mean plasma levels (P<0.05). More HIT patients achieved albumin goals (HIT vs control 87.1% vs 65.8%, P<0.05), were using AV fistula (HIT vs control 54.2% vs 33.3%, P=0.008) and received Hepatitis B, influenza and pneumococcal vaccines (all P<0.05).

More HIT patients were prescribed with renin-angiotensin-aldosterone blockers (HIT vs control 36.5% vs 20.9%), phosphate binders (HIT vs control 92.1% vs 77.6%) and IV iron (HIT vs control 81.5% vs 37.3%, all P<0.05).

Fewer infection-related hospitalizations were observed among HIT patients (HIT vs control 3.0±0.6 vs 6.0±1.2, P=0.018) within the first 6 months of HD initiation although they had more access-related hospitalizations (HIT vs control 1.3±0.8 vs 0.1±0.4, P=0.010), likely due to increased vigilance and follow-ups.

No differences in mortality were observed between the groups (P=0.05).

Conclusions: Targeted multidisciplinary care can improve the morbidity, as well as management of ESRD-related complications, vaccination status and permanent access placement of our local incident HD patients.

Clinical Significance of Serum Soluble α-Klotho Levels in Maintenance Hemodialysis Patients
Shinya Nakatani,1 Eiji Ishimura,1 Mari Sakura,1 Yu Tateishi,2 Hideki Uedono,2 Akhiro Tsuda,3 Norihiko Usui,3 Masaki Inaba,3 1Nephrology, Osaka City Univ Graduate School of Medicine, Osaka, Japan; 2Nephrology, Ishikiriseiki Hospital, Japan.

Background: Humans with CKD exhibit markedly reduced serum soluble alpha-klotho (sαKl), progressively decreasing as renal function declines. However, in end-stage renal disease, the role of sαKl in pathogenesis of CVD, DM and CKD-MBD has not been fully studied.

Methods: Stable maintenance HD patients (n=188, 114 men and 74 women, 66.5±11.1 years, HD duration, 101±90 months) were enrolled. Serum sαKl levels were measured by recently developed ELISA methods (Yamazaki Y, et al. Biochem Biophys Res Commun. 2010).

Results: Serum sαKl levels in HD patients were 445±158 pg/ml, which was lower than those of healthy Japanese subjects (740 pg/ml; Yokoyama K, et al. Clin Nephrol. 2012). Although some previous studies have showed significantly correlations between sαKl and CKD-BMD parameters, serum sαKl levels in the present study showed no significant correlations between any of these markers. (FGF23: r=0.045, P=0.54; intact PTH: r=0.06, P=0.44; phosphorus: r=0.01, P=0.89; calcium: r=0.06, P=0.46, respectively) When compared to DM vs. non-DM, and with CVD histories vs. without CVD histories, serum sαKl levels were not significantly different (DM: 447±170 vs. 444±148 pg/ml, P=0.75, CVD: 436±135 vs. 490±174 pg/ml, P=0.61, respectively). However, in HD patients with DM and CVD histories (n=38), these were significant correlations between serum sαKl and glycated albumin, a useful marker of glycemic control, (r=0.44, P=0.006), plasma glucose (r=0.32, P<0.005), calcium (r=0.34, P=0.004) and alkaline phosphatase (r=0.33, P=0.005).

A multiple regression analysis showed that serum sαKl levels showed significant, independent associations with glycated albumin (β=0.40, P=0.006) and calcium (β=0.30, P=0.04) (R²=0.43, P=0.0002).

Conclusions: In the presents study, clinical significance of measurement of serum sαKl is expected to be seen in HD patients with DM and CVD histories, which might reflect the parameters of anti-aging and/or anti-cachectic effects of alpha-Klotho. Clinical significance of serum sαKl levels on CKD-MBD may be smaller than that of anti-aging and/or anti-cachectic effects of alpha-Klotho.
Cardiovascular Outcomes in Young Adults with ESRD: An Analysis of the USRDS

Debbie Brahmajee, 1 Nan Ji, 1 Alissa Kapke, 2 Yee Lu, 1 Jessica Dietrich, 1 Zubin J. Modi, 1 David T. Selewski, 1 Kevin C. Abbott, 2 Brett W. Plattner, 2 Brahamajee K. Nallamothu, 1 Douglas E. Schaubel, 2 Rajiv Saran, 2 Debbie S. Gipson, 1
1 Univesity of Michigan, Ann Arbor, MI; 2 Arbor Research, Ann Arbor, MI; 3 NIDDK, Bethesda, MD.

Background: Little is known about cardiovascular (CV) morbidity and mortality in young adults (YA) with end stage renal disease (ESRD).

Methods: Using national end stage renal disease (ESRD) data in the USRDS, all patients ages 1-29 yrs at ESRD initiation (2003-2013) were identified and grouped by age at ESRD initiation (1-11, 12-21, 22-29 yrs). CV mortality (CVM) events were identified from ESRD Death Notification Forms. Patients were censored if they died due to non-cardiovascular events, lost to follow-up, recovered or survived to the end of the study period (12/31/2014). Cox proportional hazards models were fit to determine the risk of CVM in YA (age 22-29), compared to patients age < 22 at initiation.

Results: Over 10 years, 1,787 (5.4%) of the 33,159 study patients experienced CVM. Over 10 years, 1,787 (5.4%) of the 33,159 study patients experienced CVM. Compared to YA with ESRD, YA had the highest probability of CVM, as early as 3 months post initiation of ESRD.

Conclusions: DM had significantly higher risks of ACD and CVD than the risks in non DM patients. Young adults (YA) with end stage renal disease (ESRD).

Table: Characteristics associated with CVM are summarized in Table. Compared to YA with ESRD, YA had the highest probability of CVM, as early as 3 months post initiation of ESRD. CVM in YA (age 22-29), compared to patients age < 22 at initiation.

Conclusion: Our study indicated that CVM risk is highest in young adults (YA) with ESRD. This points out the need for young adult nephrology care and public health interventions.

Funding: Support from NIDDK

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

Underline represents presenting author.

TH-PO976

Epidemiology and Mortality of Pulmonary Embolism: A Comparison between Chronic Dialysis Patients and the General Population

Chih-Chiang Chien,

Dept of Nephrology, Chi-Mei Medical Center, Tainan City, Taiwan.

Background: Pulmonary embolism (PE) is associated with increased mortality, but it is not clear whether end-stage renal disease (ESRD) dialysis patients have a higher incidence and mortality than those in general population not on dialysis, especially in Asian populations.

Methods: Using the Taiwan National Health Insurance Research Database, we did a comparative cohort study on 45,040 incident ESRD patients undergoing dialysis and 90,080 gender- and age-matched (1:2) patients not on ESRD dialysis, between 2000 and 2005. The follow-up period was from the index date to PE, the date of death, the end of the study, or December 31, 2007.

Results: After multivariate analysis, there were no significant differences between the two cohorts (HR: 1.94; 95% CI: 0.99-3.82). Older age (HR: 1.02; 95% CI: 1.01-1.03), peripheral vascular disease (HR: 1.89; 95% CI: 1.50-2.01), and atrial fibrillation (HR: 2.08; 95% CI: 1.57-2.74) were independent risks for PE. The overall inhospital mortality rate after PE was 13.3%. ESRD dialysis patients had almost twice (9%) the mortality risk after PE than did the non-ESRD cohort (HR: 1.97; 95% CI: 1.83-2.10).

Conclusions: In conclusion, no significant difference in the incidence rates of PE between patients on and not on ESRD dialysis in Taiwan. However, patients on ESRD dialysis had a higher mortality risk after PE.

TH-PO978

B-lines on Lung Ultrasound: A Biomarker for Cardiac Events and Mortality in Hemodialysis Patients

Jeanne Kamal, 1 Wissam Mansour, 1 Marc M. Saad, 1 Boutros Karam, 1 Elias Moussaly, 1 Saqib Hussen Abbasi, 1 Elie El-Charabaty, 2 Suzanne E. Sayegh, 1 Internal Medicine Dept, Staten Island Univ Hospital, Staten Island, NY; 2Nephrology Dept, Emory Univ Hospital, Atlanta, GA; 3Nephrology Dept, Staten Island Univ Hospital, Staten Island, NY.

Background: Volume overload in End Stage Renal Disease (ESRD) patients on hemodialysis (HD) is an independent risk factor for death from cardiovascular events. B Lines detected on Lung ultrasound (BLUS) assess extravascular lung water and correlate with the physical performance of HD patients. This raises interest in its prognostic ability predicting cardiac events and mortality in this population.

Methods: 81 HD patients underwent Lung Ultrasound (US) after their dry weight and their B Line scores categorized as mild (0-14), moderate (15-29), severe (30-59) and very severe (>60). 10 were lost to follow up (6 transferred to another unit; 4 had renal transplant). 71 were followed for cardiac events (myocardial infarction; electrocardiogram(ECG)-documented angina episodes; heart failure; ECG-documented arrhythmia; cerebrovascular accident or transient ischemic attack) and death.

Results: 71 subjects were followed for a mean duration of 1.19 years. 50 were males, mean age 60.9 patients died, 20 had an incident cardiac event. A Kaplan-Meier survival analysis demonstrated an interval decrease in survival times in all-cause mortality and cardiac events with increased BLUS scores (p 0.0049). Multivariate Cox regression analysis showed the independent predictive value of BLUS for mortality and cardiac events: patients in moderate and severe classes (grouped) and very severe classes had hazard ratios of 2.98 and 7.98 respectively compared to patients in mild class (p 0.025 and 0.013). The average hospitalization rate (1.88) was not significantly different between the categories (p 0.1).

Conclusions: Lung ultrasound (US) is an independent risk factor for death and cardiovascular events in HD patients. US helps detecting lung congestion among ESRD patients on HD even at its early stage when clinically asymptomatic. The application of chest US in this population may improve patients’ clinical outcome and help refine prognosis.

TH-PO979

Extravascular Lung Water Monitoring in Low Cardiovascular Risk Hemodialysis Patients

Dimitri Cristian Siripo1, 1Luminita Voronea, 1 Ionut Nistor, 1 Mihai Onofriescu, 1 Simona Hogas, 1 Mugurel Apetri, 1 Mehmet Kanbay, 2 Adrian Covic, 1 Nephrology, “Grigore T. Popa” Univ of Medicine and Pharmacy, Iasi, Romania; 2Medicine, Koc Univ School of Medicine, Istanbul, Turkey.

Background: Fluid overload is one of the most common modifiable risk factor associated with the increased mortality risk observed in hemodialysis (HD) patients, but the precise assessment of hydration status in these patients remains a major challenge for nephrologists. Our study aimed to explore whether combining two bedside methods, lung ultrasonography (LUS) and bioimpedance, may provide complementary information to guide the treatment in specific HD patient subgroups.

Methods: In total, 250 HD patients from two dialysis units were included in this randomized clinical trial. Patients were randomized 1:1 to have a dry-weight assessment based on clinical (control) or LUS and bioimpedance (active) guided protocol. The primary endpoint was to assess the difference between the two hemodialysis modes on all-cause mortality and first cardiovascular event (CVE) - including death, stroke, and myocardial infarction.
Results: During a mean follow-up period of 21.3±5.6 months, there were 54 (21.6%) composite events in the entire population. There was a non-significant 9% increase in the risk for this outcome in the active arm (HR=1.09, 95%CI 0.64-1.86, p=0.75). Similarly, there were no differences between the two groups when analyzing separately the all-cause mortality and CVE outcomes.

Conclusions: This study shows that a LUS guided dry-weight adjustment protocol, as compared with clinical evaluation, doesn’t reduce all-cause mortality and/or CVE in HD patients. Funding: Government Support - Non-U.S.

TH-PO980
Volume Overload Hospitalization Identification among Hemodialysis Patients Using Administrative Claims

Background: There is growing interest in fluid management practices and consequently a need to identify, quantify and monitor volume-related hospitalizations among hemodialysis (HD) patients. Administrative claims databases (e.g. the U.S. Renal Data System) are often used to study such outcomes, but these data are generated for billing purposes and may not capture clinical nuance. We conducted a validation study to assess the accuracy of claims-based definitions for volume overload (VO) hospitalizations.

Methods: We examined a random sample of 315 adult maintenance HD patients admitted to a large U.S. academic medical center from 2010-13. We performed standardized chart reviews to clinically adjudicate VO admissions. Using the medical center’s administrative billing data, we built claims-based definitions for VO hospitalizations by combining various fluid-related ICD-9 discharge diagnosis codes. We computed the prevalence of claims-identified VO admissions and estimated validity metrics for each definition using adjudicated VO as the reference standard.

Results: Seventy-seven admissions (24.4%) were adjudicated as VO hospitalizations. The prevalence of claims-identified VO admissions varied across definitions (9.5-37.1%). Claims-based definitions tended to have low sensitivity and high specificity (Panel A). Definitions containing heart failure ICD-9 codes captured the most false positive events (Panel B). In sensitivity analyses, we added dialysis procedure codes to diagnosis code-based definitions and assessed validity. Small gains in definition specificity and decrements in sensitivity were observed (data not shown).

Conclusions: Claims-based VO definitions are imperfect. Investigators and regulators must carefully consider the implications of missing and misclassifying events when evaluating and monitoring HD patient VO admissions with administrative data. Funding: Pharmaceutical Company Support - Renal Research Institute (RRI), a subsidiary of Fresenius Medical Care (FMC).

TH-PO981
Management of Overhydration Using Bioelectrical Impedance Analysis in Chronic Hemodialysis Patients
Chue Kim Kim, Jung-Ho Shin, Jin Ho Hwang, Su Hyun Kim. Dept of Internal Medicine, Chung-Ang Univ Hospital, Seoul, Korea.

Background: Fluid overload is common in end-stage renal disease (ESRD) patients receiving maintenance hemodialysis, and it may be an independent risk factor for cardiovascular events and all-cause death. Recently, bioelectrical impedance analysis (BIA) has been widely used as a non-invasive method to estimate volume status. We retrospectively investigated whether management of overhydration can reduce the rate of cardiovascular events and mortality in chronic hemodialysis patients.

Methods: ESRD patients who had been treated with outpatient hemodialysis were recruited. Using BIA, the ratio of extracellular fluid to total body fluid (ECF/TBF) was obtained every 6 months. Patients were divided into two groups according to ECF/TBF: the uncontrolled group included those with all measured ECF/TBF ≥20.40; and the controlled group included those with any measured ECF/TBF <20.40.

Results: A total of 142 patients (85 [59.9%] in the controlled group and 57 [40.1%] in the uncontrolled group) were included, and were followed for 29 (12, 42) months.

Conclusions: Management of overhydration according to the ECF/TBF may be beneficial to prevent all-cause death in ESRD patients with maintenance hemodialysis.

TH-PO982
Does Fluid Balance or Rapid Fluid Removal Affect Outcome in Incident Hemodialysis Patients?
Sandrea Seidenfaden, Runolfur Palsson, 1 Olafur S. Indridason, 2 1Univ of Iceland; 2Landspitali - the National Univ Hospital of Iceland, Reykjavik, Iceland.

Background: Recent studies have shown that fluid balance affects survival in prevalent hemodialysis (HD) patients and that end-dialysis overweight (EDOW) of ≥0.3 kg and ultrafiltration rate (UFR) of more than 10-13 ml/kg/hr have been associated with decreased survival. In this study we examined if factors related to fluid balance are associated with survival in incident HD patients.

Methods: This was a retrospective study of all patients initiating HD at a University Hospital’s Dialysis Unit and surviving for at least 3 months during 2003-2014. Data were obtained from medical records, including estimated dry weight, weight before and after dialysis, dialysis duration, blood pressure during dialysis and vascular access. The mean of values for each patient during the fourth month of HD (8-12 consecutive HD sessions) were used. Volume removed and fluid removal rate was calculated and EDO was defined as the difference between attained post-dialysis body weight and dry weight. Kaplan-Meier method and Cox regression analysis were used to assess survival.

Results: A total of 197 patients began hemodialysis treatment during the study period. 153 patients survived for at least 3 months and had a full set of data available; 98 (64.0%) were men. EDO =0.3 kg was observed in 36 (23.5%) of the HD patients , 63 (41.1%) spent <3.5 hours in each dialysis session. Sixty-five (42.3%) had UFR >10 ml/kg/hr and 20 (13.0%) >13 ml/kg/hr. The type of vascular access was a native fistula in 98 patients (64.0%), a HD catheter in 37 (24.2%) and a synthetic graft in 18 patients (11.8%). Cox regression analysis, adjusting for age, sex, access type, albumin and UFR did not show association between survival and EDO ≥0.3 kg (HR 0.7, 95% CI, 0.34-1.41), UFR >10 ml/kg/hr (HR 1.0, 95% CI, 0.60-1.69) or UFR >13 ml/kg/hr (HR 1.18, 95% CI, 0.44-3.12).

Conclusions: The previously described association between UFR and EDO does not appear to affect survival of incident HD patients. Residual kidney function could not be accounted for in our model but may be of importance in incident patients.

TH-PO983
A Higher Ultrafiltration Rate Is Associated with Worsening of the Echocardiographic Left Atrial Volume Index in Incident Hemodialysis Patients
Jung-Won Lee, Kyung-Sin Jung, Joon Sung Young Choi, Jae-Won Lee, Hyun-Young Chae, Kyung Hun Kim, 1 Internal Medicine, Kidney Research Inst, Hallym Univ Sacred Heart Hospital, Anyang, Korea; 2 Internal Medicine, Sahmyook Medical Center, Seoul, Korea; 3 Internal Medicine, G Sam Heart Hospital, Anyang, Korea.

Background: Optimal fluid management is essential in caring hemodialysis patient. However, too rapid fluid removal and the resultant higher ultrafiltration rate (UFR) disadvantageously promote hemodynamic instability and cardiac injury. We evaluated the effects of the rapid UFR on the changes of echocardiographic left atrial volume index (LAVI) over period.

Methods: A prospective observational study was conducted with 124 patients who newly started hemodialysis. Echocardiography was performed at baseline and repeated 19.7 (11.3-23.1) months apart. Changes in LAVI per year (ΔLAVI/yr, mL/m²/year) were arithmetically calculated, and the 75th percentile of the ΔLAVI/yr distribution was regarded as a “significant” increment. UFR was expressed in terms of ml/hr/kg, and we employed a mean UFR over 30 days (approximately 12-13 treatment).

Results: The mean diuretic weight gain was 1.88±0.94 kg, and the UFR were 8.01±3.87 ml/kg/hr. The significant pathological increment point in ΔLAVI/yr was 4.87 mL/1.73m²/yr. Correlation analysis showed that ΔLAVI/yr was closely related to the baseline blood pressure (BP), hemoglobin level, residual renal function, and UFR. According to the ROC curve, the best cut-off of value of UFR for the predicting the pathological increment was 10 mL/kg/hr, with the area under the curve of 0.712. In multivariate analysis, systolic BP, hemoglobin level, residual renal function, and UFR were used. V olume removed and fluid removal rate was calculated and EDOW was defined as the difference between attained post-dialysis body weight and dry weight. Kaplan-Meier method and Cox regression analysis were used to assess survival.

Conclusions: The previously described association between UFR and EDO does not appear to affect survival of incident HD patients. Residual kidney function could not be accounted for in our model but may be of importance in incident patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Association of Ultrafiltration Rate with Mortality in Incident Hemodialysis Patients

**Background:** High ultrafiltration rate (UF rate; ml/h/kg BW) may have a deleterious effect on survival in maintenance hemodialysis (MHD) patients. The main determinants of UF rate are ultrafiltration and dialysis treatment time. Several studies have reported higher UF rate was associated with increased all-cause and cardiovascular (CV) mortality in prevalent hemodialysis (HD) patients. However, the association of UF rate with mortality in incident HD patients is not well known.

**Methods:** We examined a 5-year cohort of 110,880 patients who initiated MHD in the US from January 2007 to December 2011. UF rate levels were divided into 5 ordinal categories (<4, 4 to <6, 6 to <8, 8 to <10, ≥10 ml/h/kg BW). We examined the association of UF rate and all-cause mortality using Cox proportional hazard models with hierarchical adjustments for demographics, comorbidities and markers of malnutrition-inflammation-cachexia syndrome (MICS).

**Results:** The mean age of patients was 63±15 years, and included 43% females, 32% African Americans, 58% diabetics. In the case-mix and MICS adjusted model, higher baseline UF rate was linearly associated with higher all-cause mortality risk. In addition, there were consistent and, incrementally higher associations of UF rate with mortality irrespective of different urine volume, dialysis treatment time and post-dialysis systolic blood pressure categories.

**Conclusions:** Higher UF rate is independently associated with increased all-cause mortality in incident HD patients. These results suggest that longer or more frequent dialysis therapy is needed to improve outcome for patients with high UF rate.

**Funding:** NIDDK Support

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Weight Gain following Ultrafiltration (UF) Rate Threshold Implementation

**Background:** Good fluid management is critical for optimal hemodialysis (HD) care. In 2015 the National Quality Forum endorsed an UF rate threshold quality measure but did not endorse a proposed companion target weight achievement measure. Lowering UF rate requires treatment time (TT) extension or interdialytic weight gain (IDWG) reduction. Often, patients are opposed to longer TTs and have difficulty with diet restrictions. In a national cohort we 1) examined target weight achievement, and 2) simulated weight gain over a 30-day period in the setting of UF rate threshold implementation without concurrent TT extension or IDWG reduction.

**Methods:** Using large dialysis organization data from 112,373 patients (1,754 facilities) in 2015, we analyzed facility-level target weight achievement according to the Kidney Care Quality Alliance-proposed target weight achievement (post-HD weight ≥1 kg above or below target weight). Among 61,796 patients with complete pre- and post-HD weight and TT data, we simulated cumulative 30-day weight gains if UF rates were capped at 13 ml/h/kg without concurrent TT extension or IDWG reduction (Panel A).

**Results:** Facilities had, on average, 27.6±10.1% of patients with post-HD weights ≥1 kg above or below target weights per KCQA measure specifications. Facilities in the highest target weight quartile ≥33.5% of patients with missed target weight tended to be larger, located in the western US, and had more black patients and patients with shorter TTs (vs. lower quartile facilities). Overall, at the patient-level, implementation of an UF rate cap of 13 ml/h/kg with unchanged TTs and IDWGs resulted in a mean 30-day cumulative weight gain of 3±4 kg. Panel B displays facility-level simulation results.

**Conclusions:** Failure to balance UF rate thresholds with target weight achievement policies may lead to substantial weight gain if TTs are not extended and/or IDWG is not reduced.
Methods: We conducted a retrospective study between 1/2012 and 8/2015 in 232 HD patients with central venous catheters as HD access. A 6-month baseline period with at least 10 HD treatments with ScvO2 recordings preceded a 36-month follow-up. The ScvO2 values during the last 10 minutes of treatments were averaged to obtain an end-HD ScvO2. A slope was then obtained per patient between end-HD ScvO2 and cUFV across all treatments. Survival was assessed with Kaplan-Meier and spline analysis.

Results: 70% of the patients showed an inverse relationship between end-HD ScvO2 and cUFV. During follow-up, there were 54 deaths. On spline analysis, there was no association between slope and mortality. Patients were then divided into groups of negative and positive slopes. Kaplan-Meier analysis indicated no survival difference between groups.

Figure 1: Kaplan-Meier estimates for survival probabilities between negative slope (red) and positive slope (green) patients, respectively. The number of patients at risk is indicated in the table below the graph.

Conclusions: As ScvO2 is reflective of cardiac output at rest, the negative correlation of ScvO2 with cUFV suggests that a majority of HD patients respond with a drop in cardiac output in the face of ultrafiltration. Patients with a negative slope did not have increased mortality. Further research is necessary to clarify the complex relationship between ScvO2, UFV and cardiac output, in hopes of identifying a modifiable intradialytic target to improve outcomes in HD patients.

TH-PO989

Joint Effect of Pre-Dialysis Systolic Blood Pressure and Peridialytic Systolic Blood Pressure Change on Survival in Chronic Hemodialysis Patients

Anna Meyring-Wosten,1 Hanjie Zhang,1 Yu Luo,1 Alice Topping,1 Jochen G. Raimann,1 Yuedong Wang,2 Franklin W. Maddux,2 Peter Kotanko.1,3
1 Renal Research Inst, New York; 2 Univ of California at Santa Barbara, CA; 3 Fresenius Medical Care North America, Boston, MA; 4 Icahn School of Medicine at Mount Sinai, New York.

Background: Previous studies in chronic hemodialysis (HD) patients indicate an association between pre-HD systolic blood pressure (preSBP) and peridialytic SBP change (ASBP) on mortality. Yet, analyzing these two variables separately may not fully explore the nature of the interaction.

Methods: PreSBP and ASBP (post- minus pre SBP) were analyzed between 1/2001 and 2/2010. Baseline was defined as months 4-12 in the first year of HD, follow-up terminated at death, loss to follow-up, or the end of the study. Only patients who survived the baseline and had no missing covariates were included. We fitted Cox proportional hazard model with a bivariate spline for the main predictors, preSBP and ASBP, and adjusted for age, gender, diabetes, access type, relative interdialytic weight gain, body mass index and albumin.

Results: 5866 patients remained for final analysis (56% males; 50% whites). 1649 (28.1%) patients died during follow-up. Median follow-up time was 1.74 years. While with high preSBP, a SBP increase was associated with higher hazard ratio (HR), with low preSBP, a SBP increase was associated with lower HR (Fig.1). The results indicate a “trough” region of low HR.

Conclusions: Peridialytic SBP changes and pre-HD SBP are jointly associated with all-cause mortality in HD patients. While a peridialytic SBP increase may be particularly harmful in patients with high pre-HD SBP, it may be beneficial in those with low pre-HD SBP.

TH-PO990

Association between Peridialytic Systolic Blood Pressure Changes and Arterial Oxygen Saturation: Results from a Large U.S. Hemodialysis Cohort

Anna Meyring-Wosten,1 Yu Luo,2 Hanjie Zhang,1 Stephan Thijssen,1 Yuedong Wang,2 Peter Kotanko.1,3
1 Renal Research Inst, New York; 2 Univ of California - Santa Barbara; 3 Icahn School of Medicine at Mount Sinai, New York.

Background: While the physiological basis for peridialytic systolic blood pressure (SBP) decline has been studied extensively, the factors underlying a paradoxical SBP rise are not fully understood. Recent research indicated that 10% of chronic hemodialysis (HD) patients suffer from prolonged intradialytic hypoxemia [Meyring-Wösten, CJASN 2016]. Since hypoxemia induces a sympathetic response we entertained the hypothesis that SBP changes (ASBP) and intradialytic arterial oxygen saturation (SaO2) may be associated.

Methods: We retrospectively analyzed intradialytic SaO2 and ASBP (calculated as post-HD SBP minus pre-HD SBP) in chronic HD patients with arterio-venous vascular access. SaO2 was recorded by Crit-Line® monitor (Fresenius Medical Care, Waltham, MA). Patients were followed over 6 months. Linear mixed effects models (LME) were used to explore associations between ASBP and (a) HD treatment time spent below 90% SaO2, as well as (b) mean intradialytic SaO2.

Results: We assessed 982 patients (29,869 HD treatments, 61% males; 52% whites). In patients with SaO2 < 90% during HD treatments mean ASBP was -10.24 mmHg (95% confidence interval -10.57 to -9.90). In contrast, in patients in whom SaO2 was > 90% throughout the entire treatment time mean ASBP was -6.04 mmHg (95% confidence interval -8.15 to -3.93). LME revealed that for every percent point increase of time spent below 90% SaO2, ASBP increased by 0.03 mmHg (p=0.004) and that with every percent point increase in mean SaO2, the ASBP decreased by 0.46 mmHg (p<0.001).

Conclusions: We observed an inverse relationship between intradialytic arterial oxygen saturation and the blood pressure response to HD. These findings support the notion that hypoxemia activates mechanisms that partially blunt the intradialytic blood pressure decline. We speculate that sympathetic surges resulting from intermittent hypoxemia may play a role. To further explore that hypothesis specifically designed prospective studies are required.

TH-PO991

Geographical and Seasonal Patterns of Blood Pressure in Hemodialysis Patients: A EURODOPPS Study

Flore Duranton,1 Annette Kramer,2 Brian Bieber,3 Ziad Massy,2,4 Christian Combe,5 Francesca Tentori,6 Kitty J. Jager,1 Angel Argilés,1,6 1RD-Nephrology, France; 2ERA-EDTA Registry, AMC Amsterdam, Netherlands; 3Arbor Research Collaborative for Health; 4CHU Amboise Paré et Inserm U1018, France; 5CHU Bordeaux, France; 6NDSG Sète, France.

Background: In HD patients, we found that blood pressure (BP) before dialysis sessions was associated with seasons and outdoor temperature in a single facility. We wanted to extend our study to assess the geographical influences on BP.

Methods: Clinical data were obtained from the Dialysis Outcomes and Practice Patterns Study (DOPPS) phases 3-4 (2005-2011) for patients from 7 European countries (Sweden, United Kingdom, Belgium, Germany, France, Italy, Spain). Climate records corresponding to HD facilities were obtained. BP level was analyzed using mixed models with location (country or latitude), climate (season or outdoor temperature) and interactions as fixed effects, adjusting for study design and repeated measures.

Results: The study included 9655 HD patients from 151 locations and over 50,000 observations. Across Europe, pre- and post-dialysis BP were significantly lower in Southern places (fig-left, P<0.02). Pre-dialysis BP was lower in summer and higher in winter (P<0.001) and was inversely associated with outdoor temperature (fig-right, P<0.01). Post-dialysis BP showed no clear association with seasons (P=0.09) or temperature (P=0.1). The effect of temperature on preSBP was more pronounced in southern or warmer locations (P<0.01).

Conclusions: In Europe, patients from southern locations have lower pre- and post-dialysis BP. Pre-dialysis BP is lower in summer and with warmer temperature, and this effect is more pronounced in southern/warmer locations. There is a need to consider this variability when studying BP.
Exhibited an increased IDH-mortality association. ΔiSBP of ≤15 and ≥ 50 mmHg were incrementally associated with higher mortality. Frequency of IDH had an incremental association with mortality.

Background: The object of this study is to investigate optimal blood pressure (BP) target and adequate management of BP in prevalent dialysis patients group.

Methods: The data were retrieved from End-stage Renal Disease-Clinical Research Center (ESRD-CRC) which dialysis patients were prospectively enrolled from 2009 to 2014. Total 2,939 prevalent dialysis patients were analyzed. Eligible patients were assigned to five groups according to distribution of SBP (SBP<110, 110-129, 130-149, 150-169, and ≥170 mmHg). The primary outcome was all-cause mortality.

Results: The mean SBP in each group was 99.2, 119.7, 137.1, 155.9, and 179.2 mmHg, respectively (P<0.001). Baseline characteristics among the groups did not show significant differences except no number of AHAs (1.3±1.1, 1.7±1.5, 1.9±1.4, 2.2±1.1, and 2.4±1.3 pills in each group, P=0.001). During a median follow up of 4.5 years, all-cause mortality was significantly higher in SBP <110 and ≥170 mmHg group [Hazard ratio (HR) 1.96, 95% confidence interval (CI) 1.05-2.11, P=0.026], compared to reference group. Multivariate Cox analysis revealed that SBP <110 and ≥170 mmHg had significantly higher risk of all-cause mortality after adjustment for age, sex, history of diabetes and cardiovascular events, duration of dialysis, serum albumin (HR 2.06, 95% CI 1.44-2.93, P=0.001; HR 1.53, CI 1.07-2.19, P=0.02) and DBP (HR 1.96, 95% CI 1.05-2.21, P=0.001) while on dialysis. In adjusted analyses, those who were frail had a 1.95-fold (95%CI:1.01-3.76; P=0.047) increased odds of a 15mmHg decline in SBP and 5mmHg of DBP by frailty. In a separate cohort, frailty was measured on 15 hemodialysis older patients who had 10 intradialytic BP measures and we used an adjusted linear growth curve model to test the association between frailty and iSBP/iDBP.

Results: Frail dialysis patients also had a greater change in their SBP (4mmHg; p=0.001) and DBP (<7mmHg, p=0.001) while on dialysis. In adjusted analyses, those who were frail were had a 1.95-fold (95%CI:1.01-3.76; P=0.047) increased odds of a 15mmHg decline in SBP and 5mmHg of DBP by frailty. In a separate cohort, frailty was measured on 15 hemodialysis older patients who had 10 intradialytic BP measures and we used an adjusted linear growth curve model to test the association between frailty and iSBP/iDBP.

Conclusions: Under longer hemodialysis TT, the IDH events and/or lower niSBP have a greater mortality risk. Further studies are needed to identify optimal niSBP goals and corresponding treatment times.

Funding: NIDDK Support

TH-P0993

Frailty and the Blood Pressure Response to the Stressor of Hemodialysis among Older Patients


Background: Frailty is described as a multi-system dysregulation resulting in a vulnerability to stressors; yet evidence for this hypothesis is lacking. Hemodialysis represents a great stressor for older adults with ESRD. Sympathetic nervous system (SNS) activation is an essential compensatory mechanism for intradialytic blood pressure (SBP/iDBP) maintenance. We hypothesized that frail dialysis patients have worse changes in BP while undergoing hemodialysis.

Methods: Frailty was measured on 163 older hemodialysis patients and pre- and post-dialysis BP measures were collected. We used adjusted linear regression to test for a difference in the pre- and post-dialysis change in SBP and DBP and adjusted logistic regression to test for a pre- and post-dialysis change of 15mmHg of SBP and 5mmHg of DBP by frailty. In a separate cohort, frailty was measured on 15 hemodialysis older patients who had 10 intradialytic BP measures and we used an adjusted linear growth curve model to test the association between frailty and iSBP/iDBP.

Results: Frail dialysis patients also had a greater change in their SBP (4mmHg; p=0.024) and DBP (<7mmHg; p<0.001) while on dialysis. In adjusted analyses, those who were frail were had a 1.95-fold (95%CI:1.01-3.76; P=0.047) increased odds of a 15mmHg decline in SBP and 5mmHg of DBP by frailty. In a separate cohort, frailty was measured on 15 hemodialysis older patients who had 10 intradialytic BP measures and we used an adjusted linear growth curve model to test the association between frailty and iSBP/iDBP.

Conclusions: Frailty represents a state of SNS dysregulation for patients in which adults undergoing the stressor of hemodialysis have a poor BP and DBP response. This is the first evidence of SNS dysregulation among frail patients with ESRD.

Funding: Other NIH Support - NIA, Private Foundation Support

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

326A
Mannitol for the Prevention of Intra-Dialytic Hypotension - A Pilot Randomized Double-Blind Placebo-Controlled Trial

**Background:** Intra-dialytic hypotension (IDH) is a common complication of hemodialysis (HD) and may be related to relatively rapid shifts in plasma osmolality. Interventions to minimize intra-dialytic changes in osmolality may prevent IDH.

**Methods:** In this double-blind single center RCT, patients requiring initiation of RRT for acute or chronic kidney disease were randomized to receive mannitol 0.25g/kg/hr or a similar volume of 0.9% saline during their first three HD sessions. Blood pressure was measured in a standardized fashion pre-, post- and every 30 minutes during HD. The primary endpoints were: 1) the average decline in systolic blood pressure (SBP); and 2) the proportion of total sessions complicated by IDH (SBP drop of ≥20 mmHg).

**Results:** A total of 52 patients were randomized, contributing to 156 study visits.

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Placebo (n=27)</th>
<th>Mannitol (n=25)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>14 (52)</td>
<td>12 (48)</td>
<td>0.78</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>8 (29)</td>
<td>6 (24)</td>
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<td>Black</td>
<td>8 (29)</td>
<td>6 (24)</td>
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<tr>
<td>White</td>
<td>18 (67)</td>
<td>18 (72)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td></td>
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<tr>
<td>Age, yrs</td>
<td>58 ± 15</td>
<td>53 ± 17</td>
<td>0.34</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>13 (48)</td>
<td>15 (44)</td>
<td>0.76</td>
</tr>
<tr>
<td>Heart Failure, n (%)</td>
<td>9 (33)</td>
<td>7 (28)</td>
<td>0.68</td>
</tr>
<tr>
<td>EDRD, n (%)</td>
<td>22 (82)</td>
<td>13 (92)</td>
<td>0.27</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>16 (59)</td>
<td>15 (60)</td>
<td>0.96</td>
</tr>
<tr>
<td>Pre-dialysis SBP, mmHg</td>
<td>144 ± 21</td>
<td>149 ± 26</td>
<td>0.48</td>
</tr>
</tbody>
</table>

There were no differences in the mean SBP decline between the mannitol and placebo groups (15.3±11.4 vs. 19.2±15.6 mmHg; P=0.31). This remained non-significant after adjusting for the pre-dialysis SBP (P=0.27). The proportion of total sessions complicated by IDH was lower in the mannitol group compared with placebo (25.3% vs. 43.2%), with a trend towards fewer repeated sessions complicated by IDH (OR 0.38; 95%CI 0.13-1.06; P=0.06).

Conclusions: In this pilot RCT for patients requiring the initiation of HD, we found no difference in the absolute SBP decline between those who received mannitol versus placebo. However, there were fewer overall IDH events and a trend towards lower risk of repeated sessions being complicated by IDH in the mannitol group. A larger multi-center RCT is warranted.

**Funding:** NIDDK Support

Additional Volume Reduction Will Improve IDH Only in the Patients with Higher Pre-Dialytic BP

**Background:** This study was conducted to investigate the main causes in intradialytic hypertension (IDH) patients, and whether additional volume reduction will result in improvement in either blood pressure (BP) or other benefits among IDH patients.

**Methods:** A prospective, open-label, single center study of 22 HD patients with IDH was performed in this study.IDH means an increase of blood pressure (ΔSBP>10mmHg) during dialysis session. 11 patients with normal pre-dialysis BP were entered in Group A, and 10 other patients with higher pre-dialytic BP were in Group B. Another 18 HD patients with normal BP were selected as CON. The whole study was lasted for 4 weeks. The endpoints were: 1) the average decline in systolic blood pressure (SBP); and 2) the proportion of total sessions complicated by IDH (SBP drop of ≥20 mmHg).

**Results:** A total of 14 studies (6 randomized controlled trials) with a total of 797 patients were involved in this study.IDH means an increase of blood pressure (ΔSBP>10mmHg) during dialysis session. 11 patients with normal pre-dialysis BP were entered in Group A, and 10 other patients with higher pre-dialytic BP were in Group B. Another 18 HD patients with normal BP were selected as CON. The whole study was lasted for 4 weeks. The endpoints were: 1) the average decline in systolic blood pressure (SBP); and 2) the proportion of total sessions complicated by IDH (SBP drop of ≥20 mmHg).

**Conclusions:** In this pilot RCT for patients requiring the initiation of HD, we found no difference in the absolute SBP decline between those who received mannitol versus placebo. However, there were fewer overall IDH events and a trend towards lower risk of repeated sessions being complicated by IDH in the mannitol group. A larger multi-center RCT is warranted.

**Funding:** NIDDK Support

Correlation of Weight Loss and Fluid Removal via Ultrafiltration in Patients with Acute Decompensated Heart Failure

**Background:** Changes in weight and daily fluid balance are commonly used in clinical practice to monitor decongestive therapy in patients with acute decompensated heart failure (ADHF). It has recently been proposed that there exists a significant discrepancy between fluid balance and weight loss in ADHF patients who are managed with diuretics. The performance of these metrics has not been evaluated in patients undergoing ultrafiltration (UF) therapy.

**Methods:** Available data from clinical trials of UF in ADHF performed between January 2000 and March 2016 were included in the analysis. These studies evaluated decongestion both through weight change and fluid removal. Pertinent data were extracted and using Pearson product-moment correlation, the degree of linear dependence and correlation between these two variables was determined.

**Results:** A total of 14 studies (6 randomized controlled trials) with a total of 797 patients were evaluated. The mean age was 65.4 years. There existed substantial variation across studies in the reporting of surrogates of decongestion such as net and total fluid removal. Weight loss ranged from 2.6 to 10.7 Kg (mean 6.3 ± 2 Kg) and fluid removal ranged from 2.6 to 18.7 L (mean 8.6 ± 3.8 L). There was a strong positive correlation between weight loss and fluid removal (r = 0.87, 95% CI of Correlation 0.64-0.96, P = 0.00003).

**Conclusions:** Currently available evidence suggests that there is a strong correlation between weight loss and fluid removal in patients with ADHF who undergo UF therapy. Therefore, both markers may reliably be used to determine the degree of decongestion. These findings stand in contrast to patients who receive diuretics in ADHF. Future studies are needed to clarify whether this discrepancy is related to the inherent differences in sodium content of the ultrafiltrate versus urine sodium concentration or other less well explored factors such as local practice patterns and data collection.

Renal Perfusion Falls during Hemodialysis: An Explanation for the Loss of Residual Renal Function in Dialysis Patients

**Background:** To measure hepatic stiffness and body composition, all subjects underwent dce-MRI as well as liver stiffness measurements. To measure renal perfusion, all subjects underwent renal imaging before, during, and after a session of dialysis. Detailed study of renal perfusion was performed using a novel dynamic-contrast imaging algorithm, in conjunction with a latest generation 256-slice CT scanner (GE Revolution). Images were analyzed offline to create functional maps for perfusion across the entire kidney. Echocardiography was done at baseline and prior to the end of dialysis to detect myocardial stunning, as a reference organ system for ischemic responses to HD-induced circulatory stress (detected as regional changes in longitudinal strain using speckle tracking).

**Results:** Renal perfusion was markedly reduced (48.2±26.4 mL/min/100g), compared to normal control values, and was related to dialysis vintage (r=-0.67, P<0.01). HD resulted in significant reduction in renal perfusion to 25.9±16.1 mL/min/100g (p=0.001) at peak stress (3 hrs). 10/11 patients in whom perfusion fell also exhibited myocardial stunning (>2 segments with >20% reduction in longitudinal strain), whereas stunning was not seen in the patient whose renal perfusion did not fall.

**Conclusions:** An acute drop in renal perfusion is observed during HD and is related to demonstrable organ injury in another vulnerable vascular bed. Cumulative exposure to circulatory stress may be a key pathophysiological factor in the loss of RRF observed in HD patients. Longitudinal studies are needed to examine whether amelioration of circulatory stress during HD helps to preserve RRF.

Paradoxical Fluid Diversion into the Hepatic Circulation with Hemodialysis

**Background:** The hepatic circulation is involved in adaptive systemic responses to circulatory stress. However, it is vulnerable to both chronic hypervolemia and changes in cardiac function. The influence of hemodialysis (HD) and fluid removal upon the liver has never been specifically studied. We therefore conducted a detailed initial study to characterize the effects of HD upon liver water content and stiffness, referenced to peripheral fluid mobilization, total body water and cardiovascular stability.

**Methods:** We studied 55 established in-centre chronic HD patients without liver disease. To measure hepatic stiffness and body composition, all subjects underwent transient ultrasound-based elastography (Fibroscan) in combination with bioimpedance...
abnormalities. Heart rate was significantly increased in both BMI groups (p<0.05), with a greater increase in the BMI 3 group (p<0.05). These findings indicate that BMI 3 patients have a higher risk of experiencing cardiac arrhythmias during HD.

Conclusions: Our findings suggest that BMI 3 patients have a higher risk of cardiac arrhythmias during HD, highlighting the need for increased monitoring and intervention in this population.
Methods: ECG was performed prospectively on adult haemodialysis patients on two occasions 1 year apart, both on midweek non-dialysis days. QRS-T angle was calculated from the ECG as total cosine R-to-T expressed in degrees (TCRT) using singular value decomposition with the aid of custom software. Follow up was until a major cardiac event (MACE: acute coronary syndrome, coronary revascularization, heart failure, arrhythmia, sudden cardiac death), or censored at transplant. Univariate associations of above vs below median annualised changes in TCRT and other ECG parameters with MACE was calculated using Cox regression, except for QRS which was adjusted for ultrafiltration volume due to potential confounding.

Results: There were 74 patients, age 62±14 years. Baseline TCRT was 86 ± 36° and median (range) annualised change was 5 (-84 to +127). The values for QRS were 107±16ms and +1 (-40 to +25)ms, for QT were 440±23ms & -1 (-194 to +108)ms, and for heart rate were 72±13 bpm and -1 (-19 to +40)bpm. Follow up was 2.3±0.7 years. There were 17 MACE end points. The hazard ratio for MACE in above versus below median change in TCRT (dTCRT) was 3.67 (1.27–10.60, p=0.036, see figure), for dQRS was 2.04 (0.77–5.41, p=0.148), for dQT was 1.15 (0.44–3.06, p=0.771), for dHR was 3.44 (0.98–12.03, p=0.053).

Conclusions: Longitudinal changes in QRS-T angle (dTCRT) may improve risk prediction in haemodialysis patients.

TH-PO1004

Global Electrical Heterogeneity as a Predictor of Mortality and Major Cardiac Events in Hemodialysis Patients

Darren Green,1 Katerina Huutkova,2 Sofia Skampardoni,1 Philip A. Kalra,1 Marek Malik,2 Dimitrios J. Pouliakos,1 Salford Royal Foundation Trust, United Kingdom; Imperial College, London, United Kingdom.

Background: Wide spatial QRS-T angle calculated from digital 12 lead ECG is a marker of global cardiac repolarization heterogeneity associated with worse prognosis in high risk cardiac populations. We assessed its prognostic value in haemodialysis patients.

Methods: Echocardiography and ECG were performed on adult haemodialysis patients on midweek non-dialysis days. QRS-T angle (TCRT) was calculated from the ECG as total cosine R-to-T using singular value decomposition aided by custom software, and expressed in degrees. Abnormal TCRT was defined as ≥100°. End points were death and major cardiac events (MACE: acute coronary syndrome, coronary revascularization, heart failure, arrhythmia, sudden cardiac death). The association of TCRT ≥100° with these was calculated by Cox proportional hazard models adjusted for age, gender, time on dialysis, left ventricular ejection fraction (LVEF), and left ventricular mass indexed to height (LVMI). Follow up was censored at transplant.

Results: There were 170 patients: age 61±15 years, time on dialysis 4±7 years, 66% male, LVEF 66±12%, LVMI 50±19g/m², TCRT 88±39°. 70 patients (41%) had TCRT ≥100°. Follow up was 2.1±0.8 years with 40 deaths (24%) and 40 MACE. The adjusted hazard ratio (HR) for death if TCRT ≥100° was 0.80 (0.40–1.59), p=0.52. The HR for MACE was 2.1 (1.0–4.4), p=0.04.

Conclusions: Cox proportional hazard models adjusted for baseline characteristics showed that these ECG findings were associated with all-cause death; flattened T wave, adjusted hazard ratio (aHR) 1.32 (95% CI 1.03, 1.70); left atrial enlargement, aHR 1.25 (1.01, 1.54). Another random forest showed that the important ECG findings for the prediction of CVD-caused death were left atrial enlargement, long PQ interval, and flattened T wave.

Conclusion: In this study, we showed the importance of ECG findings for HD patients’ prognoses. If changes in ECG findings are observed, detailed cardiac examination should be carried out.

TH-PO1005

Evaluation of 15-Year Mortality Based on Electrocardiogram in Hemodialysis Patients Using Random Forest Machine Learning Algorithm

Ichiro Kanda,1 Bogdan I. Eneama II, Hiroshi Kawaguchi,3 Yoichiro Tabata,4 Noriyoshi Mirotani, Tomoko Maeda,5 Hidetaka Itoh, Haruki Itoh,6 1Tokyo Kyosai Hospital; 2Michigan Univ; 3Tokiwakai Medical Corporation; 4Japan Community Health Care Organization Chiba Hospital; 5Sakakibara Heart Inst Clinic; 6Toranomon Mutual Aid General Hospital; 7Sakakibara Heart Inst.

Background: Cardiovascular disease (CVD) is a leading cause of death in hemodialysis (HD) patients. The aim of this 15-year prospective cohort study of HD patients in Japan was to determine which resting electrocardiography (ECG) findings are associated with long-term prognosis.

Methods: We developed a random forest which was an ensemble of 500 decision trees, to predict each patient’s survival from a random subset of training data (N=304). Moreover, the ECG findings effective for identifying patients with a high risk of cause-specific death were identified from the mean decrease in the Gini index on a test dataset (N=305).

Results: Mean age and vintage were 52.5 and 5.6 years, respectively. 67.8% of the patients died. The random forest showed an estimation of sensitivity of 73.6% and specificity of 40.1%. Old age (>65 years) was the most discriminative variable for all-cause death, followed by flattened T waves, diabetic nephropathy, and left atrial enlargement.

Conclusions: Wide QRS-T angle (TCRT) appears to be a better prognostic marker of risk for cardiac events than standard echocardiography. This likely reflects its association with arrhythmia and may become a useful prognostic indicator.

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

Underline represents presenting author.

329A
Interplay between Arterial Functional and Structural Alteration and Their Contribution to Cardiac Abnormalities in Hemodialysis Patients

Jim Hee Jong,1 Annabel Birute,2 Brandon Kistler,3 Pei-Tzu Wu,1 Bo Fernhall,3 Ken Whanid.7 Kinesiology, Univ of Illinois, Urbana, IL; 7Nutrition Science, Univ of Illinois, Urbana, IL; 2Dietetics and Nutrition, Ball State Univ, Muncie, IN; 4Medicine, Univ of California, Los Angeles, CA; 1Kinesiology, Univ of Illinois, Chicago, IL.

Background: Hemodialysis (HD) patients often have altered arterial and cardiac features. The aim of this study is to examine the relationship between arterial structure and function and their contribution to left ventricular (LV) dysfunction and hypertrophy in HD patients.

Methods: 118 HD patients (55±12y, BMI 32±8 kg/m², 59% males, 46% diabetes) were tested for blood pressure (BP), arterial wave reflection (Aix75), arterial stiffness (aortic pulse wave velocity (PWV), pulse pressure (PP) and β-stiffness), carotid artery lumen diameter (D), carotid intima-media thickness (IMT), subendocardial viability ratio (SEVR), LV ejection fraction (EF), LV early diastolic flow-tissue ratio (E/E′) and LV mass (LVM) on a non-dialysis day.

Results: The presence of LV hypertrophy, systolic dysfunction (EF<40%) and diastolic dysfunction were 84% (concentric: 79.5% and eccentric: 10.7%), 17.7% and 45.6% respectively. There were positive associations between β-stiffness and IMT and between D and LVM and a negative association between Aix75 and LV EF (p<0.05 for all). With adjustments for age and diabetes status, each of brachial and aortic systolic BP and aortic PW were independently associated with E′, the severity of LV systolic dysfunction and SEVR (p<0.05 for all). The combination of aortic systolic BP and PP, but not individually, significantly predicted IMT (D=31.9; p<0.05).

Conclusions: This study confirms pathophysiological arterio-ventricular coupling in HD patients. Increased arterial wave reflection was accompanied with impaired LV systolic function. Augmented arterial stiffness was associated with arterial wall thickening, progression of LV diastolic dysfunction and LV enlargement. These findings may result in potential therapeutic interventions to prevent the progression of cardiovascular diseases in HD patients.

Funding: NIDDK Support

The Effect of Polysaturated Fatty Acids Supplementation on Cardiovascular Risk Factors in Patients with End-Stage Renal Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Patrizia 1Kinesiology, Univ of Illinois, Urbana, IL; 2Nutrition Science, Univ of Illinois, Urbana, IL; 3Department of Family Practice, University of British Columbia, Vancouver, BC; 4Department of Medicine, Queen’s University, Kingston, ON; 5Department of Medicine, University of California, Los Angeles, CA; 6Kinesiology, Univ of Illinois, Chicago, IL.

Background: Previous observational studies suggest that omega-3 fatty acids are associated with lower cardiovascular risk factors in adults; however, this association in patients with end-stage renal disease (ESRD) remains controversial. Therefore, the aim of the present study was to summarize the evidence from the investigations of randomized controlled trials (RCTs) related to omega-3 fatty acids supplementation on the major cardiovascular risk factors.

Methods: We performed electronic searches in PubMed, Embase, and the Cochrane Library to identify RCTs on major cardiovascular risk factors through June 2015. Standard mean difference (SMD) and a random-effect model were used to measure the effect of omega-3 fatty acid supplementation on the risk of triglyceride, total cholesterol, LDL, HDL, homocysteine, SBP, DBP, and glucose. The analysis was further stratified by factors that could affect the treatment effects.

Results: We included 19 prospective studies reporting data on 1,415 patients with end stage renal diseases. Overall, omega-3 fatty acid supplementation produced a reduction of 0.68 mg/dl (SMD: -0.68; 95%CI: -1.10 to -0.26; P=0.001) for triglyceride, and a reduction of 0.36 mg/dl (SMD: -0.36; 95%CI: -0.69 to -0.09; P=0.033) in HDL. However, omega-3 fatty acid had no significant effect on total cholesterol (SMD: -0.31; 95%CI: -0.72 to 0.09; P=0.127), HDL (SMD: 0.49; 95%CI: -0.03 to 1.01; P=0.066), homocysteine (SMD: -1.41; 95%CI: -3.07 to 0.24; P=0.095), SBP (SMD: -1.07; 95%CI: -3.14 to 1.01; P=0.313), DBP (SMD: -1.52; 95%CI: -4.95 to 1.90; P=0.383), and glucose (SMD: 0.20; 95%CI: -0.46 to 0.85; P=0.560). Finally, a sensitivity analysis suggested that omega-3 fatty acid might be associated with lower total cholesterol (SMD:-0.42; 95%CI: -0.81 to 0.04; P=0.030).

Conclusions: Omega-3 fatty acid supplementation was associated with lower cardiovascular risk for patients with ESRD.

Funding: NIDDK Support
prospectively on all patients. Hemodynamic measurements (cardiac index (CI), stroke volume index (SVI), total peripheral resistance index (TPRI), mean arterial pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP)) were collected using the NICOM™, immediately prior to the second HD session of the week. STS60 was measured on a non-dialysis day. Pearson’s correlation coefficient was performed to assess correlations between variables. Statistical significance was accepted at P < 0.05 level.

**Results:** STS60 significantly associated with CI (r=0.633, P<0.001), SVI (r=0.669, P<0.001), TPRI (r=0.675, P<0.001) and SBP (r=0.397, P<0.001). There were no significant associations between STS60 and DBP (r=0.18, P=0.920) and MAP (r=0.250, P=0.168), STS60 was also significantly associated with QTDS (r=0.702, P<0.001).

**Conclusions:** STS60 is a clinically relevant test significantly associated with cardiovascular fitness and levels of physical activity in HD patients. This highlights the relationship between physical function, physical inactivity and cardiovascular health in HD patients. Further research should investigate whether a concurrent improvement in cardiovascular fitness is observed when lower extremity strength is ameliorated in this relationship between physical function, physical inactivity and cardiovascular health in HD patients. This highlights the importance of physical activity in HD patients.

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

**TH-PO1012**

**Intradialytic Exercise Does Not Alter the Frequency or Severity of Ventricular Arrhythmias**

**Charlotte E. Grantham,1,2 Darren R. Churchward,1,2 Daniel Scott March,1,2 Matthew P.M. Graham-Brown,1,2,3 Hannah M.L. Young,1,2 Patrick J. Highton,1,2 Alice C. Smith,1,2 Anna-Marie Marsh,3 James Burton,1,2,4 Dept of Infection, Immunity & Inflammation, Univ of Leicester; 2John Wallis Renal Unit, Leicester General Hospital; 3National Centre for Sport and Exercise Medicine, Loughborough Univ; 4Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital.

**Background:** Haemodialysis (HD) patients are prone to ventricular arrhythmias, a leading cause of sudden cardiac death. Given that HD and exercise are known to be pro-arrhythmogenic, the safety of intradialytic exercise (IDE) warrants further attention. We aimed to assess whether IDE altered the characteristics of ventricular arrhythmias.

**Methods:** Twelve HD patients underwent two 48-hour Holter recordings starting immediately before a resting dialysis session and before a dialysis session including 45 minutes of moderate intensity intradialytic cycling. Recordings were analysed for frequency of premature ventricular complexes (PVC; % overall beats). Complex Ventricular Arrhythmias (CVA) were classified as Lown class 3 and above. Ultralfiltration volume (UF) was recorded for all studied sessions. Data were analysed using Wilcoxon sign rank, Fisher’s exact test or Spearman correlation as appropriate.

**Results:** The average recording was 36±15 hours. PVCs were detected in 75% (9) patients with 56% (5) classified as having CVAs during the baseline recording. Similarly, 66% (8) patients had PVCs present with 75% (6) having CVAs during the exercise recording. During the baseline recordings, frequency of PVCs was higher during dialysis than the post-dialysis phase (0.04% vs. 0.008%, P=0.02). Exercise on dialysis did not significantly alter frequency of PVCs (0.05% vs. 0.002%, P=0.21) or CVAs (P=0.67). UF was not associated with frequency or severity of ventricular arrhythmias (P=0.649).

**Conclusions:** Our results confirm previous findings that HD is potentially arrhythmogenic however the addition of moderate intensity exercise during dialysis did not significantly alter frequency of PVCs or CVAs. Similarly, increasing UF was not associated with either PVCs or CVAs. These data also highlight the hypothesis that IDE is a safe strategy to improve cardiovascular health in HD patients.

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

**TH-PO1013**

**10-Year Trends in Kidney Dialysis and Transplantation Treatment for Patients with End-Stage Kidney Disease in Canada**

**Juliana Wu,1 Michael Terner,1 Kevin Quach,2 Kelvin Lam,3 Joseph Kim,3 Scott Klarenbach.3 1Canadian Inst for Health Information, Toronto, ON, Canada; 2Univ of Toronto, Toronto, ON, Canada; 3Univ of Alberta, Edmonton, AB, Canada.

**Background:** The Canadian Organ Replacement Register (CORR) — a pan-Canadian information system for organ failure — is an important resource for examining trends in end-stage kidney disease (ESKD) and renal replacement therapies in Canada.

**Methods:** CORR data was used to calculate incidence and prevalence rates for ESKD patients who received dialysis or kidney transplants. Data from 2005 to 2014 for all provinces and territories in Canada, except Quebec, was included. Rates were calculated using Statistics Canada population estimates.

**Results:** The number of patients starting dialysis in Canada has been increasing steadily over the past 10 years, rising from 4,244 (172 RMPD) in 2005 to 5,269 (193 RMPD) in 2014; prevalent number of patients has also similarly increased. Since 2005, patient survival for those on dialysis has increased marginally, with the most notable increase being 5-year survival for peritoneal dialysis patients (47.0% in 2005 and 52.5% in 2009). The number of deceased-donor kidney transplants has increased steadily over the past 10 years; whereas the increase in the number of living-donor kidney transplants has been much smaller. Both the number on the waiting list and the number of transplants performed steadily increased over the past 10 years, with a persistent 2.5 times differential gap between the two.

**Conclusions:** The need for renal replacement therapy is steadily rising in Canada, and increases in kidney transplantation have not kept pace with demand. This puts pressure on the health care systems to improve the efficiency of kidney transplantation and the organ donation process while ensuring all dialysis modalities are accessible for ESKD patients.
TH-PO1014
End Stage Renal Disease Patients in Asia-Pacific from 2005 to 2015: A Trend Towards Concern
Xiaoqi Xu, Yun Shi. Medical Affairs, Fresenius Medical Care Asia Pacific, Hong Kong, China.

Background: The number of end-stage renal disease patients (ESRD) has continuously grown worldwide although multiple prevention strategies were implemented over the decades. There are many international registries that have provided valuable demographic and epidemiological information for ESRD. But there were very few information for entire Asia Pacific (AP) region.

Methods: ESRD patient information was collected and covers 25 AP countries in 2015 (AUS, BGD, BTN, BRN, KHM, CHN, HKG, IND, IDN, JPN, LAO, MAC, MYS, MDV, MTH, MUL, NPL, NZL, PAK, PHL, KOR, SGP, LKA, TWN, THA and VNM). The country surveys performed at the end of each calendar year focus on the total number of ESRD patients, treatment modality, products, patient care structure and funding. This report is the summary of 2005-2015.

Results: The total population in the survey comprised 3,916 million people which are more than 50% of world population in 2015. During the period numbers of ESRD and dialysis patients have been doubled to about 1.35 million and 1.25 million, respectively, with similar annual growth rate (AGR) around 10%. The ESRD prevalence increased from 153 per million population (ppm, 2005) to 345 (ppm) and dialysis prevalence reached 319 from 136 (ppm). While the transplantation (Tx) rate is rather low about 26 ppm in 2015 (17 ppm, 2005) and AGR is 6%. The individual dialysis prevalence ranged from 307 to 3,210 ppm (versus 40.1-807 ppm in 2005). TNN has the highest rate followed by JPN, KOR, MYS and SGP (over 1100 ppm). 83% patients have received hemodialysis, 9% peritoneal dialysis and 8% Tx in 2015. PD has grown fast and steadily in this region with AGR about 12%, THA, CHN and MYS have higher AGR (38%, 25%, 13%) driven by favored policy or professional advocacy. CAPD is the dominant regimen but APD has been gradually adopted (mainly in Japan and SGP) with proportion of 12% PD patients in 2015.

Conclusions: The dialysis prevalence has been growing with the economic development and inclusion of dialysis into healthcare plans in AP over the last decade. The impact on healthcare burden will be significant given the large number of population in this region.

TH-PO1015
Association of Community Health Indicators with Late Nephrology Referral, Health Status and Subsequent Outcomes in Patients Reaching End-Stage Renal Disease
Jung-Im Shin, Mari Palta, Brad C. Astor. Univ of Wisconsin School of Medicine and Public Health.

Background: Previous studies have focused on individual-level factors to identify patients reaching end-stage renal disease (ESRD) at higher risk of late nephrology referral. The relationship of environmental and socioeconomic conditions of communities in which patients live with late nephrology referral and subsequent clinical outcomes remains unclear. Such data are necessary to develop effective interventions.

Methods: We assessed the association of community health indicators with late nephrology referral (n=596,710), health status at the start of renal replacement therapy (i.e. hypoalbuminemia [n=455,603], inadequate management of anemia [n=539,712], and arteriovenous fistula [AVF]/catheter use [n=553,307]), and mortality after dialysis (n=393,251) using data from the United States Renal Data System in 2005-2012 merged with County Health Rankings database. Multivariable multilevel logistic and Cox proportional hazard regression models were used to assess the independent association of community risk factors with outcomes of interest, accounting for the clustering of individual patients within communities.

Results: A significant dose-response relationship between community risk score with late nephrology referral (n=596,710), health status at the start of renal replacement therapy (i.e. hypoalbuminemia [n=455,603], inadequate management of anemia [n=539,712], and arteriovenous fistula [AVF]/catheter use [n=553,307]), and mortality after dialysis (n=393,251) was found, with an adjusted odds ratio (OR) of 1.28 (95% confidence interval [CI]: 1.08-1.53) for the highest (90th percentile) vs. lowest-risk (10th percentile) communities. Higher community risk score also was associated with hypoalbuminemia (adjusted OR=1.38, 95% CI: 1.20-1.58), inadequate management of anemia (1.23; 1.13-1.33), AVF use (OR=0.76; 0.67-0.88), and catheter use (1.24; 1.09-1.41). Higher community risk also was associated with mortality following initiation of dialysis (adjusted hazard ratio=1.23; 95% CI: 1.17-1.28).

Conclusions: Higher community risk is significantly associated with greater risk of late nephrology referral, poorer health status and vascular access preparation at initiation of dialysis, and subsequent mortality, independent of individual-level factors. Community risk may be an important consideration for developing interventions to improve access to ESRD nephrology care and subsequent clinical outcomes.

TH-PO1016
Improved Access to Pre-End Stage Renal Disease Nephrology Care Among Beneficiaries of the Military Health System
Evan I. Fisher, Christina M. Yuan, Lawrence Agodua, Kevin C. Abbott, Robert Nee.
Nephrology, Walter Reed National Military Medical Center, Bethesda, MD, NIDDK, National Insts of Health, Bethesda, MD.

Background: Pre-end stage renal disease (ESRD) nephrology care is associated with lower mortality, morbidity, readmission and costs. The care that patients in the Department of Defense’s Military Health System (MHS), a model of an integrated universal healthcare enterprise in the US, would have better access to pre-ESRD nephrology care.

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 2,073,543 patients initiated on maintenance dialysis from January 1, 1995 through December 31, 2014, of whom 2,096 (0.1%) were MHS incident dialysis patients. We assessed care by a nephrologist and dietitian, erythropoietin use and type of vascular access upon dialysis initiation, based on the Centers for Medicare and Medicaid Services Form 2728. We also conducted multivariable logistic regression, adjusted for demographics and comorbid factors, using the individual pre-ESRD care components as the outcome variable.

Results: The proportions of MHS and non-MHS patients who were under the care of a nephrologist were 82.2% and 64.4%, respectively (p<0.001). 62.3% of MHS patients were under the care of a kidney dietitian versus 11.6% of non-MHS patients (p<0.001). 52.3% of MHS patients received erythropoietin pre-ESRD versus 29.4% of non-MHS patients (p<0.001). 29.0% of MHS patients used an arteriovenous fistula (AVF) on dialysis initiation versus 14.8% of non-MHS patients (p<0.001). On logistic regression analysis, MHS patients were significantly more likely to have had pre-ESRD nephrology care (adjusted odds ratio [aOR] 2.5; 95% confidence interval [CI] 2.0-3.0); pre-ESRD dietary care (aOR 13.9; 95% CI 11.8-16.3); pre-ESRD erythropoietin use (aOR 2.5; 95% CI 2.3-2.8); and AVF on dialysis initiation (aOR 2.2; 95% CI 1.8-2.6).

Conclusions: Compared to the broader ESRD population, MHS patients have greater access to pre-ESRD nephrology care which may improve morbidity and mortality.

TH-PO1017
Decisions about and Use of Renal Replacement Therapy in the U.S. Department of Veterans Affairs, 2000-2011
Susan P.Y. Wong, Paul L. Hebert, Chuan-Fen Liu, Nilka Rios Burrows, Ann M. O’Hare. 1Univ of Washington; 2VA Puget Sound Health System; 3Centers for Disease Control and Prevention.

Background: It is not known what proportion of US patients with advanced chronic kidney disease (CKD) do not receive renal replacement therapy (RRT). In other developed countries, receipt of RRT is highly age-dependent and is the exception rather than the rule at older ages.

Methods: We conducted a retrospective study of a national cohort of 28,568 adults who had a sustained estimated glomerular filtration rate <15 ml/min/1.73m² between January 1, 2000 and December 31, 2009 and were receiving care within the Department of Veterans Affairs (VA). We used linked administrative data from the US Renal Data System, VA and Medicare to identify cohort members who received RRT (n=19,165). For a random 25% sample of the remaining 9,403 patients, we performed an in-depth review of clinical progress notes in the VA-wide electronic medical record to understand their clinical course.

Results: Two-thirds (67.1%) of cohort members received RRT based on administrative records. Based on the results of chart review, we estimate that an additional 7.5% (95% CI 7.2-7.8) of cohort members had in fact received dialysis, 10.9% (95% CI 10.6-11.3) were preparing for or discussing dialysis but had not started dialysis at most recent follow-up and, in 14.5% (95% CI 14.1-14.9), a decision had been made not to pursue dialysis. The percentage of cohort members who received or were preparing to receive RRT ranged from 96.2% (95% CI 94.4-94.7) for those <45 years to 53.3% (95% CI 50.7-55.9) for those aged ≥85 years. Results were similar after stratification by level of comorbid burden.

Conclusions: In this large US cohort of patients with advanced CKD, the majority received or were preparing to receive RRT. These findings suggest more liberal use of RRT among older members of this cohort as compared with other developed countries.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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**Methods:** In an online Delphi survey, participants rated the importance of outcomes using a 9-point Likert scale. In Round 2 and 3, participants reviewed the scores and comments of other respondents and re-rated the outcomes. For each outcome, we calculated the median, mean, and proportion rating 7-9 (critically important).

**Results:** 1,181 participants (202 [17%] patients/caregivers, 979 health professionals) from 73 countries completed Round 1 and 838 (150 [18%] patients/caregivers) completed Round 3 (71% response rate). Outcomes achieving consensus as high priorities across both groups were: vascular access complications, cardiovascular disease (CVD), mortality, dialysis adequacy and fatigue. Patients/caregivers rated four outcomes higher than health professionals: ability to travel (mean difference 0.9), dialysis-free time (0.5), dialysis adequacy (0.3), and washed out after dialysis (0.2). Health professionals rated 11 outcomes higher: mortality (1.0), hospitalisation (1.0), drop in blood pressure (1.0), vascular access complications (0.9), depression (0.9), CVD (0.8), target weight (0.7), infection (0.4), potassium (0.4), ability to work (0.3), and pain (0.3).

**Conclusions:** The top stakeholder prioritized outcomes were vascular access complications, CVD, mortality, dialysis adequacy and fatigue. Patients/caregivers gave higher priority to lifestyle-related outcomes than health professionals. This prioritized set of outcomes can inform the establishment of a core outcome set, to improve the value of trial evidence to support decision-making for people on HD.

Funding: Government Support - Non-U.S.

**TH-PO1019**

**Pre-ESRD (Prelude) eGFR and the Relationship to Post-ESRD Mortality Outcomes among the Kaiser Permanente Southern California (KPS) CKD Cohort**

**John J. Sim,1 Hui Zhou,1 Jiaxiao Shi,1 David K. Yi,1 Shanya L. Henry,1 Sally F. Shaw,1 Csaba P. Kovesdy,2 Kamyar Kalantar-Zadeh,3 Steven J. Jacobsen,1 1Nephrology & HTN / Research and Evaluations, Kaiser Permanente Southern California; 2Univ of Tennessee Health Science; 3Univ of California Irvine Medical Center.**

**Background:** The eGFR values prior to transition to ESRD may provide insights on indications for starting renal replacement and also prognosticate early mortality after ESRD transition. We sought to describe the post-ESRD mortality outcomes among a large diverse CKD population based on prelude eGFR values.

**Methods:** A retrospective cohort study over 13 years (1/1/2002-12/31/2014) within the KPS CKD health system of all incident CKD patients (eGFR<45 using serial measurements) who transitioned to ESRD (hemodialysis (HD), peritoneal dialysis (PD), or kidney transplantation (TX)). Post ESRD mortality outcomes were determined relative to the first outpatient transition. We sought to evaluate the post-ESRD mortality outcomes among a large diverse CKD population based on prelude eGFR values.

**Results:** A total of 5,476 CKD patients transitioned to ESRD (486% HD, 13% PD, 1% TX). Mean age 69yrs with 59% males. DM (53%) and HTN (19%) were the most common ESRD causes. Prelude (pre-ESRD) eGFR was 15-50ml/min in 19% of the cohort at transition. This group had the highest rate of cardiac events, acute kidney injury (84%), and inpatient ESRD starts but the lowest fistula rates (16 vs 34%). This group also had the highest pre-emptive TX (1.9 vs 0.5%). Post transition mortality was highest immediately upon transition to ESRD and rates declined and stabilized around month 9 (Figure 1). The prelude eGFR groups >20 and 16-20 had the highest rate of mortality up to 1 yr compared to prelude eGFR <15 ml/min.

**Conclusions:** Among a CKD cohort who transitioned to ESRD, patients with a prelude eGFR >15 experienced the highest short term mortality. This subgroup is a potential area for improving access to predialysis care. Mortality was highest at week 4 to 8 for both cohorts but attenuated among MHS patients.

Funding: NIDDK Support

**TH-PO1020**

**Improved Early Survival Rates among Patients Initiated on Maintenance Dialysis in the Military Health System**

**Robert Neu,1 Evan I. Fisher,2 Christina M. Yuan,1 Lawrence Agodou,2 Kevin C. Abbott.1 Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; 2NIDDK, National Insts of Health, Bethesda, MD.**

**Background:** Previous reports have indicated increased mortality in the early period after initiation of maintenance dialysis in the general end stage renal disease (ESRD) population. We hypothesized that ESRD patients in the Department of Defense’s Military Health System (MHS), a model of an integrated universal healthcare enterprise in the US, would have better survival rates during this early high-risk period.

**Methods:** In this retrospective cohort study using the United States Renal Data System database, we identified 2,073,543 patients initiated on maintenance dialysis from January 2, 1995 through December 31, 2014, of whom 2,096 (0.1%) were MHS incident dialysis patients. We conducted Cox regression analyses by sequential multivariable adjustment with addition of potential confounders as the outcome variable. Covariates include demographic and clinical characteristics and other co-morbid conditions from the Medical Evidence Form 2728.

**Results:** MHS patients had significantly lower mortality rate compared to non-MHS patients during the first 12 months of dialysis initiation (17 vs. 26 per 100 patient-years [PY], respectively; p<0.001). Mortality rates peaked from the 4th to 6th week for both MHS and non-MHS patients (25 vs. 40 per 100 PY, respectively). The basic Cox model showed significantly lower death rates among MHS vs. non-MHS patients at 3 months (adjusted hazard ratio [AHR] 0.64; 95% confidence interval [CI] 0.52-0.79) and at 6 months (AHR 0.62; 95% CI 0.53-0.73). However, this difference was no longer significant after further adjustment for pre-ESRD nephrology care and type of dialysis vascular access, becoming significant only at 12 months (AHR 0.79; 95% CI 0.64-0.98).

**Conclusions:** Compared to the broader ESRD population, MHS patients had better survival rates during the first 12 months after starting maintenance dialysis, likely due to improved access to predialysis care. Mortality was highest at week 4 to 8 for both cohorts but attenuated among MHS patients.

**TH-PO1021**

**Co-Morbid Conditions of Incident Dialysis Patients**

**Rita L. McGill, Eduardo K. Lacson, Robin Ruthazer, Klemens B. Meyer, D. Miskulin, Daniel E. Weiner. Nephrology, Tufts Medical Center, Boston, MA.**

**Background:** US dialysis patient survival has improved. From 2004-2013, adjusted USRDS patient mortality fell by 22% for hemodialysis (HD) and 34% for peritoneal dialysis (PD). We examined trends in the comorbid diagnoses for incident patients, 2005-2011.

**Methods:** Cohorts of incident HD and PD patients with 2 years of prior Medicare were followed for each 1-year period, so claims could be used to determine if comorbidity diagnoses present before dialysis initiation. Time trends in the proportions of each co-morbid condition were evaluated using logistic regression, with odds ratio (OR) >1 representing an increased frequency over the seven year period. Overall proportions of each diagnosis were compared between HD and PD patients using chi-square.

**Results:** 265,900 HD patients and 12,268 PD patients were assessed in 7 HD and 7 PD cohorts. Median age was 74 (IQR: 67,80) for HD and 72 (IQR: 67, 78) for PD. For each diagnosis, the percentage of affected patients was greater for HD than PD patients (P<0.001 for all).

**Conclusions:** The large improvements in dialysis patient survival cannot be explained by the observed trends in the case-mix variables of incident patients. PD patients may have less pre-existing comorbid disease at dialysis initiation.

**TH-PO1022**

**A Novel Comorbidity Score for Predicting Early Mortality upon Transition to ESRD among Incident Dialysis Patients**

**Yoshitsugu Obj,1 Elani Streja,1 Connie Rhee,1 Melissa Sooho,1 John J. Sim,1 Csaba P. Kovesdy,2 Kamyar Kalantar-Zadeh,1 1UC Irvine; 2Kaiser Permanente SC; 3Univ of Tenn.**

**Background:** Mortality is exceptionally high during the first 6 months after transition to dialysis therapy. Development of a new comorbidity score for predicting early mortality by using pre-ESRD conditions may have important clinical and epidemiological implications.

**Methods:** In a nationwide cohort of 32,800 US veterans who transitioned to dialysis therapy between Oct 2007–Sep 2010, we derived a new comorbidity score comprised of primary ESRD causes and 16 comorbid conditions prior to ESRD by using a Cox model with adjustment for demographic (e.g. age, sex, race) and ESRD centers. We evaluated the model developed before and after the transition, and calibration using 5 groups of the new comorbidity score (Score model), and then validated the model among the those 7,912 who transitioned to dialysis Oct 2010–Sep 2011.

**Results:** The median comorbidity score was 9 (IQR, 6–12), ranging from 0 to 30. Compared to the middle risk group, adjusted HR(95%CI) for 6-month mortality in the lowest and highest risk groups were 0.37 (0.30–0.44) and 1.96 (1.81–2.12), respectively. C-index and adjusted R² were 0.69 and 0.20 in the Full model and 0.68 and 0.19 in the Score model, respectively. The difference in Akaake’s information criterion was <0.01% between models. In the validation cohort, we observed consistent findings and also confirmed a good calibration by comparing predicted survival probability versus observed Kaplan-Meier estimates. Compared to Charlson comorbidity index, the new score appeared to have higher C-index (0.70 vs. 0.68) and adjusted R² (0.21 vs. 0.19).

**Conclusions:** The time trends in HD revealed small decreases in cardiac disease and GI bleeding, and increase in diabetes, liver disease and stroke; PD patients had increased stroke.

**Time trends in HD revealed small decreases in cardiac disease and GI bleeding, and increase in diabetes, liver disease and stroke; PD patients had increased stroke.**
Conclusions: The new pre-ESRD comorbidity score would provide important clinical information for patients transitioning to dialysis given its significant predictive ability of early mortality among incident dialysis patients. It may also be useful for decision algorithms and comparisons in future early mortality analyses.

Funding: NIDDK Support

TH-PO1023
Long Term Survival in End Stage Renal Disease Patients Compared to General Population on a General Intensive Care Unit

Ingi Elsayed, Renal Dept. Sheffield Teaching Hospitals, United Kingdom.

Background: Prevalence of chronic kidney disease (CKD) worldwide is increasing. UK Renal Registry reported an incidence rate of 109 per million population (mpm) of end stage renal disease (ESRD) in 2013. Mortality is higher in ESRD patients compared to general population. 1.3% of admissions to adult ICUs in UK between 1995 & 2004 were ESRD patients. Knowledge of long term mortality rates in this group of patients remains deficient. We sought to quantify long term outcomes of ESRD patients admitted to ICU.

Methods: We retrospectively analysed prospectively collected data from all adult (>18 years) patients admitted to our 44-bed general ICU between Oct 2008-Oct 2013. ESRD patients were identified from renal database, as requiring long term renal replacement therapy prior to ICU admission. Patients were followed up for maximum of 6.25 years from admission to ICU. We used cox-regression analysis to examine survival and adjust for possible confounders.

Results: Study population comprised 132 ESRD & 3534 general patients admitted to ICU. 58% were male, median age 62 years (IQR 50-74), median APACHE II score 17 (IQR 12-22). 116 (82%) of ESRD patients survived to ICU discharge. Unadjusted Kaplan-Meier survival showed that long term mortality was significantly higher among patients with ESRD compared to general ICU patients (p<0.0). There was no statistically significant difference in long term mortality between ESRD & general ICU patients (p=0.590, 95%CI 0.753-1.175) when adjusting for age & APACHE II scores, using Cox-regression analysis. Age and APACHE II scores were independently associated with worse long term mortality (HR: 1.01, 95%CI 1.01-1.02, p=0.00 and HR: 1.07, 95% CI 1.06-1.08, p=0.00, respectively).

Conclusions: Our cohort suggests that significant proportion of ESRD patients admitted to ICU were discharged to unit discharge. In our cohort long term mortality was not different among ESRD compared to general ICU patients. This reflects improved mortality among ESRD patients over the years including those requiring higher intensity level of care. T

TH-PO1024
Prognosis and Related Risk Factors of ANCA-Associated Vasculitis Patients on Maintaining Dialysis

Fei Han, Xishao Xie, Ying Xu, Jianghua Chen. Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.

Background: We retrospectively analyzed the prognosis and related risk factors for ANCA-associated vasculitis (AAV) patients on maintaining hemodialysis or peritoneal dialysis.

Methods: AAV patients on maintaining peritoneal dialysis (PD) or hemodialysis (HD) treated in our center from June 2007 to June 2015 were included, and their data were retrospectively compared and analyzed by Kaplan-Meier analysis and Cox regression model to model their survival rate and the risk factors.

Results: A total of 123 cases were included, with an average duration of dialysis for 1005 ± 739 days, and with 88 cases (71.5%) on HD and 35 cases (28.5%) on PD. Seventy-one patients (57.7%) were under the age of 65 years old and 52 patients (42.3%) were more than 65 years old. At the median follow-up time of 36 months, 39 patients (31.7%) were died. The main causes of death were cardiovascular events (30.8%) and infection (23.1%). COX regression analysis showed that patients older than 65 years old, with cardiovascular disease or interstitial pneumonia at the disease onset were independent risk factors affecting survival.

Conclusions: The factors including age older than 65 years, pre-dialysis cardiovascular disease and interstitial pneumonia were independent risk factors affecting survival of AAV patients on maintaining dialysis, and infections and cardiovascular events were the main causes of death.

Funding: Government Support - Non-U.S.

TH-PO1025
Epidemiology and Outcome of Acute Pancreatitis in End Stage Renal Disease

Patients: A 10-Year National Cohort Study

Chih-Chiang Chien, Dept. of Nephrology, Chi-Mei Medical Center, Tainan, Taiwan.

Background: To determine the incidence and severity of acute pancreatitis (AP) in end-stage renal disease (ESRD) patient on dialysis and whether the dialysis modality (hemodialysis (HD) vs. peritoneal dialysis (PD)) confers a higher risk for AP as well as unadjusted or mortality related to AP.

Methods: We analyzed data from the Taiwan National Health Insurance Research Database and included 67,078 ESRD patients who initiated dialysis between 1999 and 2007. The follow-up period was from the start of dialysis to death, end of dialysis, or December 31, 2008. Cox proportional hazards models were used to identify the related risk factors.

Results: The cumulative incidence rates of AP were 0.6%, 1.7%, 2.6%, 3.4%, and 4% at 1-, 3-, 5-, 7- and 9-year, respectively. The incidence of AP was 5.11 per 1000-person years for those on HD and 5.86 per 1000-person years for those on PD. Independent risk factors for AP on ESRD patient were elderly, being female, biliary stone, liver disease and on PD. Severe AP occurred in 44.9% of HD patients and in 36% of PD patients. Patients with AP on HD had a higher incidence of upper gastrointestinal (UGI) bleeding than did those on PD (p=0.002). In contrast, patients with AP on PD had a higher incidence of total parenteral nutrition (TPN) use than did those on HD (p=0.072). The overall in-hospital mortality was 8.1%. Furthermore, mortality after AP was associated with male gender, increasing age, severity of AP, and the presence of DM or liver disease.

Conclusions: Patients on PD had a higher risk than patient on HD for AP attack. UGI bleeding more commonly occurred in HD patients and TPN use was more common in PD patients.

TH-PO1026
Survival Outcomes of Children Starting Renal Replacement Therapy in the Second Year of Life

Akira Ashida, Mayumiko Sako, Eiisu Inoue, Daishi Hirano, Masataka Honda, Shori Takashashi, Mototshi Hattori. Osaka Medical College, Osaka, Japan; National Center for Child Health and Development, Tokyo, Japan; The Jikei Univ School of Medicine, Tokyo, Japan; Tokyo Metropolitan Children’s Medical Center, Tokyo, Japan; Nihon Univ School of Medicine, Tokyo, Japan; Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Renal replacement therapy (RRT) for children with end-stage renal disease (ESRD) has been used for several decades; however, survival data for small children who start RRT are limited.

Methods: The Japanese Society for Pediatric Nephrology (JSPN) performed a cross-sectional, nationwide survey of Japanese patients aged less than 20 years who were newly diagnosed as having ESRD. This survey started in 2012 (Clin Exp Nephrol 19:933, 2015) and collected information every 3 years. The present study was performed using data from the JSPN survey database from January 1 2006 to December 31 2013, and examined survival outcomes of children starting RRT in the second year of life.

Results: A total of 152 patients who were younger than 2 years of age at the start of RRT were identified. Among them, 112 patients had started RRT at 0 to 1 years of age; 52% were boys, and 88.8% had started with peritoneal dialysis. ESRD was mostly caused by congenital abnormalities of the kidney and urinary tract (42.7%), followed by congenital nephrotic syndrome (12.5%) and cystic kidney disease (9.2%). A total of 21 deaths occurred during 520.7 patient-years (py), equivalent to a mortality rate of 40.3 deaths per 1000 py. The main known cause of death was infection (33.3%). The overall survival rate at 5 years was 81.0% (95% confidence interval (CI) 73.2-89.2%). The 5-year survival rates in the 0-1 year, and 1-2 year age groups were 76.8% (95%CI 67.7-80.7%) and 94.9% (95%CI 88.3-100%), respectively. Mortality was higher in children aged 0-1 year (49.1 deaths per 1000 py) than in children aged 1-2 years (14.9 deaths per 1000 py).

Conclusions: The present study indicates that the survival rate in children aged less than 1 year was poor. Specific therapeutic challenges continue to exist for children with ESRD aged less than 1 year who undergo RRT.

TH-PO1027
Racial/Ethnic Variations in Mortality Rates for End Stage Renal Disease (ESRD) Patients Treated in U.S. Territories Compared to U.S. 50 States

Keith Norris, Guofen Yan, Wei Yu, Lawrence Agodoa. UCLA; NIDDK, Bethesda, MD.

Background: Health outcomes for racial/ethnic minorities with ESRD treated in US territories may differ from patients treated in the US 50 states.

Methods: Using USRDS we examined 1,547,438 patients ≥18 years, with no prior transplant, and comparisons in future early mortality analyses.

Results: The factors including age older than 65 years, pre-dialysis cardiovascular disease and interstitial pneumonia were independent risk factors affecting survival of AAV patients on maintaining dialysis, and infections and cardiovascular events were the main causes of death.

Funding: Government Support - Non-U.S.
Results: Of 22,828 dialysis patients treated in territories (American Samoa, Guam, Puerto Rico, Virgin Islands), 321 were white, 666 black, 20,299 Hispanic, and 1,542 Asian. Of 1,524,610 US 50 states patients, 838,736 were white, 444,066 black, 182,994 Hispanic, and 58,814 Asian. After adjustments, the risk for death for white dialysis patients in the territories was 25% lower than US 50 states, but did not differ for black patients. Hispanics and Asian patients in the territories had 61% and 95% greater risk for death (Table). Using matched subcohorts significantly affected only whites, likely due to large differences in age; final HR 0.96 (p=0.72).

Conclusions: Mortality rates for ESRD patients in the US territories differ substantially by race/ethnicity compared to 50 US States. After matching, mortality risk did not differ for whites or blacks, but remained greater for Hispanics and Asians. A better understanding of these differences could lead to important health policy recommendations.

Funding: NIDDK Support

TH-PO1028
Ethnicity and Survival of Patients with End-Stage Renal Disease on Dialysis Abdulkareem Agubaniade, Abhijit Dasgupta, Mohammed R. Chowdhury, Michael M. Ward. NAIMS, NIH, Bethesda, MD.

Background: End-stage renal disease disproportionately affects ethnic minorities, particularly blacks and Hispanics. Minorities have longer survival on dialysis than whites, but the reasons are unclear. Differences in rates of renal transplantation partially account for the survival difference, but differences in the rate of discontinuation of dialysis have not been explored as a contributor. We examined if ethnic differences in the rate of elective discontinuation from dialysis and in transplantation account for the survival advantage of ethnic minorities on dialysis.

Methods: We conducted a retrospective cohort study of the United States Renal Data System from 2003 and 2014, which included 1,131,409 adults with incident ESRD. We performed a multivariate survival analysis with two competing risks. Our primary independent variable was ethnicity (white, black, Hispanic, Asian, and American Indian/Alaska Native). The outcome was survival on dialysis.

Results: Both transplantation and discontinuation of dialysis were more common among whites than blacks and Hispanics. In multivariate survival models with two competing risks, mortality risks were higher for blacks compared to whites in those age 18-29 years (subdistribution hazard ratio 1.49, 95% CI [1.38, 1.60], 30-39 years (1.20 [1.15, 1.25]), and 70 years and older (1.18 [1.16, 1.19]), while risks were similar in middle-age. American Indians/Alaska Natives also had higher mortality risks than whites among patients age 18-29 and 30-39 years. Hispanics and Asians had lower mortality risks than whites in all but those age 70 years and older.

Conclusions: Blacks with ESRD have no survival advantage on dialysis compared to whites after accounting for ethnic differences in renal transplantation and elective discontinuation of dialysis. Hispanics and Asians have lower risk of mortality on dialysis than whites among patients younger than 70 years.

Funding: Other NIH Support - NIH Medical Research Scholars Program

TH-PO1029

Background: Historically HIV+ dialysis patient survival has been inferior to HIV- patients. The effect of antiretroviral therapy on dialysis survival in the modern era is unknown. Since the removal of HIV as a comorbidity from the CMS 2728 form in 2005 it has been impossible to study outcomes for HIV+ dialysis patients using national registry data.

Methods: We obtained data from a national dialysis provider (Davita). Using home medications and laboratory data we identified 5356 HIV+ and 1664 HIV+/HCV+ patients who were compared to 411,363 HIV- HCV- patients dialyzed from 2004-2014. Survival on dialysis was modeled using cox regression.

Results: HIV+ patients were younger (median age 46), more often male (67%) and black (74%). We found effect modification by race (p=0.001). In a model stratified by race accounting for age, sex, diabetes, dialysis exposure and modality, white HIV+ patient survival was similar to HIV-/HCV- (HR 1.05, 0.93-1.19) but non-white HIV patients had increased risk of death (HR 1.50, 1.42-1.58). HIV+HCV+ patients had an increased risk of death regardless of race (white HR 1.59, 1.26-2.00; non-white HR 1.72, 1.62-1.87).

Conclusions: Race is an important modifier of survival on dialysis for HIV+ patients, but co-infection with HCV also contributes to increased mortality for that group.

Funding: DaVita

TH-PO1030
The Impact of Gender on Prescription and Use of Vascular Access in Elderly Patients on Hemodialysis: A European Hemodialysis Multicenter Analysis Andrei L. Weigert, Stefan H. Jacobson, Werner Kleophas, Mahesh Krishnan, Abdelkareem Alsawiuda, Fatima Ferreira Silva, Maciej B. Drozdz. 1 DaVita, Portugal; 2Karolinska Inst, Stockholm, Sweden; 3DaVita, Europe; 4DaVita, Germany; 5DaVita Inc; 6DaVita, Saudi Arabia; 7DaVita, Poland.

Background: The elderly constitute a substantial and growing fraction of the end stage renal disease population. Elderly patients on hemodialysis are a heterogeneous group with a high prevalence of comorbidities that reduce life expectancy. Although women have a survival advantage in the general population, women on hemodialysis do not survive longer than men.

Methods: In this analysis we included 1,247 patients on maintenance hemodialysis from Portugal (n=730) and Poland (n=517) and focused on treatment prescription, use of vascular access and achievement of KDIGO targets in women and men ≥80 years of age respectively.

Results: Elderly patients ≥80 years on hemodialysis were prescribed lower Qb and A VF's lower in the elderly. Women ≥80 years had lower prevalence of A VF than men, but there were no differences in the prescription of hemodialysis in relation to gender in the elderly. Elderly women had a higher Kt/V and lower body weight than corresponding men. Mean arterial BP pre HD, Charlson comorbidity index and ESA doses were similar in relation to both age and gender.

Conclusions: This indicates that there are no or small differences in clinical practice in relation to gender among patients on hemodialysis in Portugal and Poland.

Funding: Pharmaceutical Company Support - DaVita

TH-PO1031

Background: Studies of healthy black adolescents show higher parathyroid hormone (PTH) and lower alkaline phosphatase (AP) levels when compared to white adolescents. Similarly, studies of adult dialysis patients have shown higher PTH in Black patients when compared to White patients. Little is known about racial-ethnic differences in markers of mineral bone metabolism (MBM) in the pediatric dialysis population.

Methods: In a pediatric dialysis population of 661 patients from a large dialysis organization, we explored racial-ethnic differences in MBM markers within the first 90 days after dialysis initiation. All lab values were provided from samples processed in a central laboratory. Using logistic regression, we explored the odds of reaching a PTH level between 200pg/ml to 600pg/ml by 6 months.

Conclusions: This table indicates that there are no or small differences in clinical practice in relation to gender among patients on hemodialysis in Portugal and Poland.
Results: Mean age of the cohort was 17±4 years of which 34% were White, 31% Black and 35% Hispanic. 68% of patients were treated with HD and 32% with PD. Black and Hispanic patients had significantly higher median PTH values than white patients. AP levels were lower in Black patients, while higher in Hispanic patients.

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/ml)</td>
<td>368[203,584]</td>
<td>411[236,737]</td>
<td>471[277,779]</td>
</tr>
<tr>
<td>S-Ca (mg/dl)</td>
<td>9.3±0.7</td>
<td>9.2±0.7</td>
<td>9.1±0.7</td>
</tr>
<tr>
<td>S-P (mg/dl)</td>
<td>5.9±1.5</td>
<td>5.6±1.5</td>
<td>5.7±1.3</td>
</tr>
<tr>
<td>AP (IU/L)</td>
<td>90.0[66.0,145.0]</td>
<td>82.0[64.7,115.3]</td>
<td>104.8[75.3,169.7]</td>
</tr>
</tbody>
</table>

In a model adjusted for baseline PTH, calcium, phosphorous, AP, binder type, 1,25(OH)D, use, Cinacalcet use, modality, spKt/V and cause of ESRD, Hispanic ethnicity was associated with higher odds of meeting the PTH goal at 6 months (OR 1.85 [1.16, 2.95]).

Conclusions: Racial-ethnic differences in MBM exist in the pediatric dialysis population. Further studies are needed to evaluate how these differences affect the management of MBM in pediatric dialysis patients.

Funding: Other NIH Support - Ruth L. Kirschstein National Research Service Award

TH-PO1032

Thyroid Functional Disease, Quality of Life, and Mental Health in a Prospective Hemodialysis Cohort

Connie Rhee, Yanjun Chen, Amy Seung You, Csaba P. Kovessy, Steven M. Brunelli, Gregory Brent, Kamyr Kalantar-Zadeh, Danh V. Nguyen, UIC Irvine; Univ of Tennessee Health Science Center; DaVita Inc; UCLA.

Background: In the general population there is increasing recognition of the impact of hypothyroidism on patient-centered outcomes such as health-related quality of life (HRQOL) and depression. While hypothyroidism is highly prevalent in hemodialysis (HD) patients, there has not been a prior study to determine if thyroid dysfunction is a risk factor for impaired HRQOL or mental health in this population.

Methods: Among 450 HD patients from the prospective Malnutrition, Diet, and Racial Disparities in Kidney Disease study, we examined the association of thyroid status defined by TSH with HRQOL and depressive symptoms over time. Patients were recruited from 17 HD facilities and underwent protocolized TSH testing and administration of Short-Form 36 (SF-36) surveys and Beck Depression Inventory-II (BDI-II) every 6 months over 2013-15. We examined the association of baseline and time-varying TSH with the SF-36 domains as longitudinal outcomes using case-mix laboratory adjusted linear mixed effects models. Analogous methods were used to examine baseline and time-varying TSH with BDI-II score.

Results: Higher baseline TSH levels (+Δ1mIU/L) were associated with lower (worse) scores across the SF-36 domains of role limitations due to physical health (β=1.33, p=0.04), energy/fatigue (β=-0.80, p=0.03), and pain (β=-1.42, p<0.002). Higher time-varying TSH (+Δ1mIU/L) was associated with lower role limitations due to physical health scores (β=-0.96, p=0.03). Baseline and longitudinal TSH levels were not associated with BDI-II score.

Conclusions: In HD patients higher TSH levels are associated with impaired HRQOL across domains of physical health, energy/fatigue, and pain. Future studies are needed to determine if thyroid-modulating therapy improves the HRQOL of hypothyroid HD patients.

Funding: NIDDK Support

TH-PO1033

Use of a Symptom-Reporting Survey in Renal Clinic

Jeremy T. Moskovitch, Peter F. Mount, Matthew R.P. Davies, Austin Health Nephrology Dept, Melbourne, Victoria, Australia; ‘Univ of Melbourne, Victoria, Australia.

Background: Previous studies have reported a high prevalence of symptoms in dialysis patients. The POS-renal survey identifies the presence and severity of 17 symptoms in ESKD patients. Whether identification of symptoms with a survey leads to an improvement in symptoms has not been studied. Thus, the aims of this study are: To determine the prevalence and change in symptoms experienced by dialysis patients following introduction of a symptom-reporting survey in renal clinic, and to evaluate nephrologists’ satisfaction with this survey.

Methods: This is a prospective observational study of 110 prevalent dialysis patients (HD and PD). POS renal surveys were collected at baseline and follow-up (median 3 months). Surveys were completed by patients and results were available to nephrologists at clinic appointments. An anonymous survey was distributed to nephrologists to determine satisfaction.

Results: Baseline prevalence of individual symptoms ranged from 17-66% (95%CI 11-26% and 57-75%). Most common symptoms were fatigue (66%) and trouble sleeping (55%). Median number of symptoms was 7/17 (IQR 4-10). 49% of patients rated at least one symptom as severe or overwhelming. On multivariate analysis PD was associated with an increased risk of vomiting and drowsiness. Restless leg syndrome was associated with diabetic nephropathy primary renal disease (OR 9, p<0.05). On average, an improvement in severity of individual symptoms identified at baseline was seen in 55% of patients (range 30-89%, 95%CI 18-46% and 67-98%). The symptoms which improved most commonly were GI symptoms (62-89%) and itch (60%). The percentage of patients rating at least one symptom as severe or overwhelming was reduced (p<0.05), but remained high at 39%. The median number of symptoms was unchanged at 7/17 (IQR 3-10). Overall, nephrologists found that the survey was useful for symptom identification, but were unsure if its use helped improve symptom management.

Conclusions: Use of the POS-renal survey in renal clinic identified a high symptom burden in dialysis patients, and may be associated with an improvement in symptom severity. However, overall symptom burden at follow-up remained high.

TH-PO1034

Subjective Symptoms and Feelings for Daily Lives Are Not so Deteriorated in Maintenance Dialysis Patients Compared with Non-Dialyzed General Population

Ikuto Masakane, Minoru Ito. Nephrology, Yabuki Hospital, Yanagata, Japan.

Background: Quality of life of chronic dialysis patients are generally recognized to be severely deteriorated because of inevitable and endless dialysis sessions and uremia itself. However, there are fewer reports which directly compared QOL and subjective symptoms between dialysis patients (HD) and non-dialyzed general population (ND). We have evaluated the dialysis related subjective symptoms and QOL of chronic dialysis patients twice a year since 2005. We compared the subjective symptoms and feelings for daily lives between HD and ND.

Methods: 213 HD and 157 ND were enrolled into the study. The average age were 65 years old in HD and 66 years old in ND. The original assessment sheet for subjective symptoms and QOL for dialysis patients which is called “Patient-oriented Dialysis (POD) sheet” were used for the current study. POD sheet contains 19 questions about dialysis related symptoms and feelings for daily lives. The 7 questions indicated low HD such as “pain at cannulation”, “intradialytic hypotension” and so on were not provided to ND.

Conclusions: In HD patients higher TSH levels are associated with impaired HRQOL or mental health in this population. AP levels were lower in Black patients, while higher in Hispanic patients.

Funding: Other NIH Support - Ruth L. Kirschstein National Research Service Award
TH-PO1035

Patients on Dialysis following a Failed Renal Transplant Have Significantly Higher Levels of Depression as Identified by the Beck Depression Inventory and the Patient Health Questionnaire PHQ-9: The ASSEERT Study Michael K. Almond,1 Karin Friedli,2 Joseph Chilcot,3 Andrew Davenport,3 Ayman Guirguis,1 Benjamin Spencer,1 Ken Farrington.2 1Renal Unit, Southend Hospital, Essex, United Kingdom; 2Centre for Life Sciences, Univ of Hertfordshire, Hatfield, Hertfordshire, United Kingdom; 3Psychology Dept, King’s College London, United Kingdom; 4Centre for Nephrology and Mineral Metabolism, National Medical Science and Nutrition Inst Salvador Zubiran, Mexico City, Mexico.

Background: The diagnosis of depression in the presence of End Stage Renal Failure, is difficult. There is evidence that depression affects the outcome (survival) of patients on haemodialysis. The impact of a previous failed renal transplant in this group is poorly documented.

Methods: 1110 haemodialysis patients from five UK centres were invited to take part in a screening programme for depression using the Beck Depression Inventory (BDI) and the Patient Health Questionnaire (PHQ-9). The original questionnaire had 30 symptoms out of which 18 commonly complained symptoms were used. 123 patients answered the questionnaire before the doctor’s consultation in the clinic. Parameters including age, co-morbidities and urea clearances were recorded.

Results: The mean age (Mean±SD) was 62±14 years. 73% of the study group were patients on HD and remaining 27% were on PD. The top 5 symptoms among all patients were post dialysis tiredness (77.7%), joint and muscle pains (66.9%), feeling tired all the time (66.1%), itching (63.6%), breathlessness (61%). Among HD patients post dialysis tiredness (84.9%), joint and muscle pains (72.1%), feeling tired all the time (68.6%), muscle cramps (67.7%), itching (65.1%) were more common. In patients on PD, feeling tired all the time (59.4%), joint and muscle pains (59.4%), feeling low (59.4%) itching (59.4%), low appetite and breathlessness (55.4%) were more common. We did not find any correlation between the comorbid index, age or urea clearances and the number of symptoms complained. About 5 patients on PD and 12 on HD complained of at least 8 symptoms defined as a combination of nausea, itching and low appetite, but had adequate urea clearances.

Conclusions: Dialysis patients complain of multitude of symptoms which may be unrelated to urea clearances, age or comorbid index. Thorough consultations and appropriate investigations should be conducted to identify different pathological processes which may be causing symptoms and possible solutions provided.

TH-PO1036

Impact of Fluid Overload on Quality of Life in Haemodialysis Patients Carlos Adrian Chavez-Mendoza, Jose Luis Ortega Vargas, Olyinka Vega, Ricardo Corea-Rotter. Nephrology and Mineral Metabolism, National Medical Science and Nutrition Inst Salvador Zubiran, Mexico City, Mexico.

Background: The overhydration (OH) in patients with end stage renal disease (ESRD) is associated with multiple outcomes. The aim of this study was to evaluate the effect of OH in quality of life (QoL) in Mexican prevalent chronic haemodialysis (HD) patients.

Methods: Observational comparative study that included 133 prevalent HD patients from 3 centers from Mexico City. Hydration status and body composition was assessed by bioimpedance spectroscopy employing BCM, Fresenius®. The degree of OH was defined by estimating the fluid overload/extracellular water (OH/EW) index dividing the population into tertiles, being Group 1 with no OH and Group 3 with highest degree of OH. The cut off threshold for the definition of OH was set to 15% (OH/EW index >0.15, Group 3). QoL was measured using KDQOL-36 instrument. Data analysis was carried out through descriptive and inferential statistics.

Results: General characteristics are shown in Table 1. No differences between groups were present in: age, Charlson index, time on dialysis, type of vascular access, and hospitalization days in the last year. Overhydrated HD patients had a higher prevalence of DM (p=0.02). The KDQOL-36 specific kidney disease composite summary was lower in Group 3 (p=0.01). The score of the group with the mayor overhydration was lower for all KDQOL-36 generic dimensions (Figure 1). The SF-12 physical and mental composite was lower in the subgroup with OH (Physical: 38.5, 38.1 , and 33.7 (p=0.07), and: Mental: 52.4, 49.4, and 48.9 (p=0.3) in groups 1, 2 and 3 respectively.

Conclusions: Antidepressant use is common among young adult HD patients and is associated with a higher hospitalization rate during the 1st year compared to patients not on an antidepressant at initiation. Further studies may clarify the direct impact of depressed mood on healthcare use versus antidepressants as a marker of medical comorbidities.

TH-PO1037

Young Adult Hemodialysis (HD) Patients: Antidepressant Use and Healthcare Utilization in the First Year Diana L. Vork,1 Ziad El-Zoghby,2 Robert C. Albright,3 Sandra Herrmann,2 Maria Lapid,3 Terry D. Schneckloth,4 LaTonya J. Hickson.2 1Mayo Medical School, Mayo Clinic; 2Nephrology, Mayo Clinic; 3Psychiatry, Mayo Clinic, Rochester, MN.

Background: Despite having less comorbidity than older patients, young adult HD patients have high healthcare utilization. Depression and other psychosocial factors may contribute to this observation, and the relationship between antidepressant medication use and healthcare use in young adults has not been well described.

Methods: Retrospective cohort study of patients aged 18-44 years who initiated HD (01/2001-12/2013) and remained on dialysis ≥30 days at a single institution. Primary outcomes were hospitalization and ED visit rates within the 1st year of HD based on antidepressant use at baseline.

Results: Among 131 young adult HD patients, 31 (24%) were receiving ≥1 antidepressant for a mood indication at the time of HD initiation. The antidepressant group was more likely to have diabetes (61% vs. 32%), coronary artery disease (29% vs. 11%), heart failure (32% vs. 14%), and illegal drug use history (32% vs. 14%; all p<0.05).

Time to 1st hospitalization was not different (Figure), but hospitalization rate was higher in the antidepressant group (0.0085 vs. 0.0035 per person days, p<0.005). This difference remained even when controlling for diabetes (p=0.01), coronary artery disease (p=0.01), heart failure (p<0.01), and illegal drug use history (p<0.03). Psychiatric hospitalizations were uncommon (1 event). ED visit rate was similar between groups (0.0022 vs. 0.0016 per person days, p=0.46).

Conclusions: Antidepressant use is common among young adult HD patients and is associated with a higher hospitalization rate during the 1st year compared to patients not on an antidepressant at initiation. Further studies may clarify the direct impact of depressed mood on healthcare use versus antidepressants as a marker of medical comorbidities.
Conclusions: Quality of life is lower in patients with overhydration compared with euvolemic patients in HD. All dimensions that assess the components of SF-36 (generic) had lower scores in the subgroup patients with OH; not, in those specific dimensions of kidney disease.

TH-PO1039

The Association between Perceived Social and Family Support with Comorbidity and Clinical Outcome in Incident Hemodialysis Patients

Background: The aim of this study was to investigate the association between the social and family support with Charlson comorbidity index (MCCI) and mortality in dialysis patients.

Methods: A total 1,155 incident HD patients were prospectively enrolled in Clinical Research Center for End-Stage Renal Disease cohort from August 2008 to April 2013. The social support was assessed using perceived support and family scale that are expressed as a range of scores from 1 to 4. The patients were categorized into three groups according to the summation of perceived social and family support; group 1, fully independent; group 2, partially dependent; group 3, fully dependent, respectively. The primary outcome was defined as all-cause mortality.

Results: The mean age was 58.5±14.4 years. Group 3 showed significantly higher MCCI (4.59±2.03 vs. 5.44±2.25 vs. 5.62±2.3, P=0.001) and lower mean arterial pressure (MAP, 103.82±16.4 vs. 99.66±14.7 vs. 97.59±14.80, P=0.007) compared to group 1 and MCCI (1.54-7.00; P=0.002) compared to group 1 even after adjustment for age, sex, education status, MCCI, serum albumin, Hb, and PTH levels.

Conclusion: The incident dialysis patients need social support and family support are significantly associated with high MCCI and low MAP, and associated with higher all-cause mortality.

TH-PO1040

Improvement of Quality of Life in Hemodialysis Patients with Uremic Pruritus as Measured by the SkinIndex-10 Questionnaire: Effect of a Novel κ Opioid Receptor Agonist CR845

Background: Uremic pruritus (UP) is a chronic systemic itching disorder frequently reported in hemodialysis (HD) patients, which causes suffering that negatively impacts quality of life (QOL). CR845 is a selective kappa opioid receptor agonist with combined anti-pruritic and anti-inflammatory effects. We aimed to examine the effects of itch reduction on QOL as measured by the SkinIndex-10 Questionnaire and its sensitivity to discriminate to the summation of perceived social and family support; group 1, fully independent; group 2, partially dependent; group 3, fully dependent, respectively. The primary outcome was defined as all-cause mortality.

Methods: A total 1,155 incident HD patients were prospectively enrolled in Clinical Research Center for End-Stage Renal Disease cohort from August 2008 to April 2013. The social support was assessed using perceived support and family scale that are expressed as a range of scores from 1 to 4. The patients were categorized into three groups according to the summation of perceived social and family support; group 1, fully independent; group 2, partially dependent; group 3, fully dependent, respectively. The primary outcome was defined as all-cause mortality.

Results: The mean age was 58.5±14.4 years. Group 3 showed significantly higher MCCI (4.59±2.03 vs. 5.44±2.25 vs. 5.62±2.3, P=0.001) and lower mean arterial pressure (MAP, 103.82±16.4 vs. 99.66±14.7 vs. 97.59±14.80, P=0.007) compared to group 1 and MCCI (1.54-7.00; P=0.002) compared to group 1 even after adjustment for age, sex, education status, MCCI, serum albumin, Hb, and PTH levels.

Conclusion: The incident dialysis patients need social support and family support are significantly associated with high MCCI and low MAP, and associated with higher all-cause mortality.

TH-PO1041

Antipruritic Effect of the Long-Acting Peripheral κ Opioid Receptor Agonist CR845: A Novel Approach for the Treatment of Uremic Pruritus in Hemodialysis Patients


Background: Despite the availability of off-label treatments, patients with uremic pruritus (UP) continue to be afflicted by this debilitating condition with no treatment approved in the US. Although the etiology of UP is unknown, it is likely multi-factorial, including systemic inflammation and deficiency in the kappa endogenous opioid system.

Methods: Non-clinical and clinical studies were conducted to demonstrate that the novel potent and selective kappa opioid receptor (KOR) agonist CR845 may be effective for the symptomatic treatment of UP in hemodialysis (HD) patients.

Results: CR845 is a small, synthetic peptide with full agonist activity at rodent and human KORs (EC50 = 0.16 nM) with no other detectable off-target activities. A sustained anti-itch activity (>24 hours) was demonstrated for CR845 using mouse models of itch. Additionally, CR845 demonstrated anti-inflammatory properties in rodents and human macrophages. CR845 was not detectable in the central nervous system, therefore CR845 is likely to activate KORs expressed in peripheral nerves and on immune cells. CR845 is primarily excreted unchanged in urine, resulting in prolonged exposure in patients with reduced glomerular filtration rate. CR845 has been compared in healthy subjects (up to ~10-fold increase in half-life). In HD patients, CR845 was well tolerated at doses ranging from 0.5 to 2.5 mcg/kg with plasma levels remaining constant after a single injection post-HD until cleared at the following dialysis. HD patients with moderate to severe UP treated with intravenous CR845 (1 mcg/kg) post-HD for 2 weeks had a 50% decrease in itch intensity as measured by a visual analog scale of 0 to 100 (n=33) with a significant difference compared to placebo-treated patients (n=31; p=0.016).

Conclusions: These results suggest that peripheral kappa opioid receptors play an important role in the modulation of itch signals and represent a target for the development of novel antipruritic agents. The profile of CR845 makes this compound a suitable and promising candidate for the treatment of UP.

Funding: Pharmaceutical Company Support - Cara Therapeutics, Inc.

TH-PO1042

Efficacy and Safety of Pregabalin for the Treatment of Neuropathic Pain in Patients Undergoing Hemodialysis

Tomooyasu Osuki, Masanori Abe, Seishiro Baba, Noriaki Maruyama, Kazuyoshi Okada, Divs of Nephrology, Hypertension and Endocrinology, Dept of Internal Medicine, Nihon Univ School of Medicine, Tokyo, Japan.

Background: Pregabalin is a gamma aminobutyric acid derivative administered for neuropathic pain. It binds to α2Δ subunits of voltage-dependent calcium channels, and inhibits calcium inflow of synapses and the release of excitatory neurotransmitters.

This study investigated the safety and efficacy of pregabalin in patients with peripheral neuropathic pain undergoing maintenance hemodialysis.

Methods: This prospective, open-label, single-arm, multi-center trial screened 257 patients. A total of 45 patients with peripheral neuropathic pain were included, of whom 35 patients (men, 23; women, 12; age, 71.5 ± 6.1 years; duration of dialysis, 64 ± 35 months) were analyzed. Patients were treated with an initial dose of pregabalin at 25 mg; this was then increased up to a maximum of 150 mg depending on the patient during a 12-week study period. Visual analogue scale (VAS), Short Form Health Survey (SF-8), and laboratory data were collected at baseline and the end of the study.

Results: The final mean dose of pregabalin was 50.7 mg daily. Mean VAS scores significantly decreased from 52.4 mm at baseline to 34.1 mm at the end of the study (P<0.001). Scores for all eight categories of the SF-8 significantly increased compared with baseline. Both physical and mental component summary scores of the SF-8 also significantly increased. There were no significant differences in serum urea nitrogen, albumin, creatinine, lipids profile, or C-reactive protein levels during the study period.

Ten patients were withdrawn from the study due to drowsiness, dizziness, and invalidity; however, no serious adverse drug reactions were recorded.

Conclusions: If adverse effects are carefully monitored and administered dosage prudently determined, pregabalin can be an effective treatment for peripheral neuropathic pain, even in patients undergoing hemodialysis.

Funding: Pharmaceutical Company Support - Cara Therapeutics, Inc.

TH-PO1043

Association of Neuropathy and Physical Parameters in People on Maintenance Haemodialysis: A Prospective Study

Katja Jardine, Ying Wang, Cathie Sherrington, Arun V. Krishnan, Martin P. Gallagher, Alan Cass, Meg J. Jardine, The George Institute for Global Health, Camperdown, NSW, Australia; Prince of Wales Clinical School, Univ of New South Wales, Randwick, NSW, Australia; Menzies School of Health Research, Darwin, NT, Australia.

Background: Physical parameters are associated with physical quality of life (QOL) among people with end stage kidney disease (ESKD) on dialysis. While clinical or subclinical neuropathy affects 70-100% of dialysis patients, its effects upon physical parameters (muscle strength and mobility) remain poorly understood.

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

338A
Opioid Use, Morbidity and Mortality in U.S. Dialysis Patients

Paul L. Kimmer,1 Kevin C. Abbott,1 Chyng-Wen Fwu,2 Paul W. Eggers,1,2 1DOKUH, NIDDK, NIH, Bethesda, MD; 2Social & Scientific Systems, Silver Spring, MD.

Background: Pain is important for ESRD patients (pts), linked to depression and diminished quality of life. Aggressive ESRD PT pain treatment has been advocated. Medicare prescription drug benefits allow tracking ESRD prescriptions and linkage to outcomes, but few data exist regarding outcomes associated with pain and opioid medication prescription (OMP). We assessed maintenance dialysis ESRD PT OMP prevalence, and determined associations between OMP and mortality, dialysis discontinuation and hospitalization, using 2006–2010 USRDS data.

Methods: We defined the study sample to continuously treated (≥365 d) dialysis pts with full Medicare Part A, B, and D coverage in each study year to ensure complete PT claims. OMP was confirmed from Part D prescription claims. Cox proportional hazard models were used to determine hazard ratios (HR) and 95% confidence intervals (CI) comparing OMP categories to the no OMP category. All 9 opioid categories were examined, with 3 main categories: non-opioid medication (NOM), opioid prescription (OMP), and opioid prescription with non-opioid medication (OMP + NOM).

Results: Approximately 20% of pts had a prescription for 90 d opioids yearly. The most common OMP in 2010 contained hydrocodone (11.7%), oxycodone (5.4%) and tramadol (3.9%). Compared with NOM, OMP users had higher median (IQR) serum creatinine (1.89 [1.79–2.09] vs 2.10 [1.87–2.47] mg/dL), higher baseline total cholesterol (210 [190–230] vs 187 [165–218] mg/dL), and lower median (IQR) HD vintage (42 [36–50] vs 53 [47–60] months). OMP users had higher all-cause mortality (10.0 [9.6–10.5] vs 6.3 [5.9–6.7]%, p < 0.001) and dialysis discontinuation (4.7 [4.2–5.2] vs 3.2 [2.7–3.7]%, p < 0.001) than NOM users. OMP prevalence was 10.0% in 2006, 10.3% in 2007, 10.6% in 2008, 11.0% in 2009, and 11.3% in 2010.

Conclusions: Opioid prescription is associated with increased dialysis PT risk of death, discontinuation and hospitalization. While causal relationships cannot be inferred, opioid prescription may be an illness marker, efforts to treat pain effectively in dialysis PTs with less toxic techniques deserve consideration.

Funding: NIDDK Support

TH-PO1045

Executive Dysfunction among HD and PD Patients: A Comprehensive Long-Term Prospective Study

Valentina Corradini,1,2 Ornella Gambero,3 Lucia Meligrana,1 Sara Samoni,1 Mariangela Mettifogo,1,2 Alessandra Ferrari,1 Massimo de Cal,1 Elisa Scalfotto,1 Alessandra Brendolan,1 Carlo Crepaldi,1 Francesco Perini,1 Fiorenza Ferrari,2 Claudia Ronco,1,2 1Nephrology, San Bortolo Hospital; 2IRRI, San Bortolo Hospital; 3Neurology, San Bortolo Hospital.

Background: Cognitive impairment (CI) can range from a mild cognitive impairment to dementia. CI may be most prominent in pts with concurrent vascular disease, particularly among chronic kidney disease pts undergoing to dialysis. Mild CI may affect as many as 64% of dialysis pts and is displayed by worse performances on tests of processing speed and executive function. Trials that examine long-term effects of chronic dialysis are needed. The aim of this study is to evaluate the 1-year progression of executive dysfunction in HD and PD pts.

Methods: We enrolled 89 pts in chronic dialysis (HD or PD) from at least 3 months. Executive dysfunction was assessed by a Montreal Cognitive Assessment (MoCA) Equivalent Score (ES) <18.29. Statistical analysis was performed with SPSS20 software.

Results: We screened 207 dialysis pts, 73 were excluded and 133 were enrolled (mean age 64.09±13.65 yrs; 71% M) at T0. We performed MoCA test in 58 HD pts [mean age 64.90±14.27 yrs, 71% M, median dialysis time 5.66(2.70–9.07) yrs] and 75 in PD pts (63.46±13.22yrs, 71% M, 1.94(1.53–5.56)]. Median values of MoCA (ES) are shown in table 1.

TH-PO1046

Dementia as a Risk Factor for Mortality and Ischemic Stroke in Elderly Korean Patients on Hemodialysis

Sung Min Jung, Seung-Jung Kim, Duk-Hee Kang, Kyu Bok Choi, Dong-Ryeol Ryu. Dept of Internal Medicine, College of Medicine, Ewha Womans Univ, Seoul, Korea.

Background: Cognitive dysfunction and dementia is common in ESRD patients on hemodialysis (HD). It is associated with worse quality of life and higher risk for mortality. This study aimed to investigate the incidence of major adverse cardiac and cerebrovascular events (CE) in elderly Korean patients initiating HD with dementia.

Methods: Using the database from the Health Insurance Review & Assessment Service, we analyzed 10,171 patients aged 65 years or older who had initiated dialysis from 2005 to 2008 and had followed up until 2009. MACCE was defined as a composite outcome including all-cause mortality, nonfatal acute myocardial infarction, target vessel revascularization, and nonfatal stroke. Kaplan-Meier method was used to compare the incidence of MACCE among elderly ESRD patients with and without dementia. The risk factors for all-cause mortality were identified by Cox proportional hazards model.

Results: A total of 303 elderly patients (3.0%) starting HD had dementia. In all elderly incident HD patients, dementia was a significant predictor for MACCE (HR, 1.289; 95% CI, 1.08–1.54; P = 0.002) after adjustment of all eligible confounding variables. Dementia was also a risk factor for all-cause mortality (HR, 1.334; 95% CI, 1.140–1.562; P < 0.001), whereas it was not a risk factor for other endpoint of MACCE. However, when we perform analyses in propensity-score matched groups, dementia was an independent predictor for nonfatal ischemic stroke (HR, 1.982; 95% CI, 1.027–2.268; P = 0.036) as well as all-cause mortality (HR, 1.301; 95% CI, 1.053–1.607; P = 0.015).

Conclusions: Dementia is an independent risk factor for mortality and ischemic stroke in elderly ESRD patients initiating HD. Dialysis providers should pay more attention to patients with dementia to reduce the risk for mortality and ischemic stroke.

TH-PO1047

Frailty Is Correlated with Increased Length of Hospitalization and Death in Hemodialysis Patients

Garyfalia Perysiniak1, Panagiota Papadaki,1 Stavroula Doua1, Spiros Paparidis,1 Maria Psoma,2 Kournouli Evangelia,1 Gavriana Vlachopoulos,1,2 Evdoxia Vymbras,1 Sofia Kourou,1 Eirini Ntaountaki,1 Rethymno Hospital,1 Heraklion Univ Hospital Greece.

Background: Research on prognostic indices in hemodialysis (HD) patients is of great importance. Frailty, a geriatric syndrome not adequately studied in HD patients is characterized by reduced physical and cognitive reserve under stress. It is correlated with increased health services utilization and death. We investigated the association of frailty with mortality and hospitalization in HD patients.

Methods: Forty nine (67.3% males) single unit HD patients were enrolled for this observational prospective (12 months) study. Patients were classified as nonfrail, prefrail, and frail according to the SHARE-FI instrument. Demographic, social, physical, and HD related data, medication, comorbidities and functional and nutritional status were recorded.

The end points were death and days of hospitalization.

Results: At study beginning the mean (95% confidence interval: CI) age, Charlson Index, Barthel Index, Karnofsky scale, KiV, nPCR, serum albumin and CaXP were 76.7 (63.1–77.3) years, 3.2 (2.8–3.7), 18 (16.8–19.3), 73.6 (67.9–79.4), 2.1 (1.81–0.30), 0.98 (0.88–1.08), 3.8 (3.7–3.9) and 46.2(42.8–49.6) respectively. Sixteen patients (36.6%) were nonfrail, 16 (32.7%), prefrail and 17 (34.7%) frail. Older age was associated with higher frailty rates (P = 0.004). Subcapacilar skin fold thickness was larger in fraills and prefrails (P = 0.04). Frailty was not associated with the gender, the lean body weight, the serum albumin, the KiV, the nPCR and the CaXP. One nonfrail, three prefrails (18.8%) and six frails (35.3%) died during the follow-up period. Lower serum albumin (P = 0.02) and frailty (P = 0.04) was associated with mortality. Mortality was not associated with the KiV, the nPCR and the CaXP. The mean (95% CI) length of hospitalization was significantly longer in the frails vs in the nonfrail and prefrails (15.8±7.24 vs 9.3±2.0–18.3±3 days, p < 0.05).

Conclusions: Frailty was correlated with age among HD patients. Mortality and length of hospitalization within 12 months were significantly correlated with frailty.
TH-PO1048
Frail Elderly Patient Outcomes on Dialysis: An Update on the Longitudinal Study

Oasha Kovera,1 Edwina A. Brown,1* Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, United Kingdom;2 Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, United Kingdom.

Background: Assisted peritoneal dialysis (aPD) enables home dialysis for older patients. The Frail Elderly Patient Outcomes on Dialysis (FEPOD) study is a prospective 2 year longitudinal study comparing quality of life (QoL) between HD and aPD. Baseline analysis showed no differences between dialysis modality and that frailty was predominant predictor of poor outcomes.

Methods: 206 (106 aPD; 100 HD) patients > 60 years, on dialysis for > 3 months and hospitalisation free for 30 days were recruited from 20 UK centres. HD patients (requiring hospital transport) were matched to aPD recruits by age, sex, diabetes status, dialysis vintage, ethnicity and postcode Index of Deprivation. Frailty was assessed using the Clinical Frailty Scale. QoL was assessed using Hospital Anxiety and Depression Scale (HADS), SF-12, Palliative Outcomes Symptom scale (renal) and Illness Intrusiveness Rating Scale (IBRS).

Physical function was assessed using Barthel’s score. Assessments were performed for 2 years, at 3 monthly intervals.

Results: There were 121 dropouts (death: 59, study withdrawal: 61, transplant: 5). After linear mixed model analysis, dialysis modality was not associated with any QoL measured in patients completing 2 year follow-up except SF12 MCS. In the aPD cohort, SF12 MCS decreased with increasing frailty scores (P<0.002). In the cox regression survival model, survival was poorer in female HD patients compared to female aPD patients (Female Gender * PD vs HD, Exp B = 0.28, p<0.012). The interaction between HD and male gender was not significant. The principal predictor for survival, though, was frailty (hazard increased by factor of 1.38 for unit increase in frailty score, p<0.008).

Conclusions: There was no significant difference in QoL over time between matched older patients on aPD and HD. Survival is associated with frailty but may also be poorer in older female patients on aPD. These findings suggest that assisted PD should be considered as a valid alternative to HD in older patients, at least from a QoL viewpoint. This would allow for true patient choice.

Funding: Pharmaceutical Company Support - Baxter Healthcare, Private Foundation Support

TH-PO1049
Comparing the Effect of Electric Bicycle Training and Conventional Exercise on Physical Function of End-Stage Renal Disease Patients Undergoing Hemodialysis

Misaki Mura,1 Ryo Yoshizawa,1 Aki Hirayama,1 Osamu Ito,1 Masahiro Kohoku,1 Shiho Egawa,1 Teruhiko Maeba,1 Health, Tsukuba Univ of Technology, Tsukuba, Ibaraki, Japan;2 Asoo Clinic, Kawasaki, Kanagawa, Japan;3 Tokoh University Graduate School of Medicine, Sendai, Japan.

Background: While chronic kidney disease (CKD) is common in older adults, approaches to treat geriatric patients with CKD remain undefined. However, exercise training for hemodialysis patients has been shown to improve fitness, physical function, quality of life, and cardiovascular disease markers such as arterial stiffness. This study aimed to determine whether aerobic training or electrical bike exercise for 12 weeks could improve physical function and/or relevant biochemical results in geriatric patients with end-stage renal disease (ESRD).

Methods: This controlled clinical trial consisted of 71 ESRD patients (38 males, 33 females; 71.0 ± 7.3 years), randomized to receive 12 weeks of hemodialysis and concurrent aerobic training (ER-gp: n = 22), electrical bike training (EA-gp: n = 10), or no specific training (Con-gp: n = 39). The Borg scale was employed to control training intensity. At baseline and study completion, primary outcome measures included exercise tolerance, grip strength, quad muscle torque, balance, 10-mm maximum walking and various biochemical outcomes.

Results: In the ER-gp, lower muscle endurance and exercise tolerance increased significantly (200±37 vs 174±36, P<0.016) and CE (180±45 vs 152±46, P=0.003) at 12-week compared with baseline. When comparing between-group changes to MET there was a significant increase in CE (0.03±0.03 vs 0.01±0.04, P=0.014) compared with CG. The total number of sedentary bouts (per week) decreased significantly in AE (200±37 vs 174±36, P=0.016) and CE (180±45 vs 152±46, P=0.031) at 12-week compared with baseline. The average sleep fragmentation index indicating poor sleep quality decreased significantly at 12-week compared with baseline in AE (51.4±8.0 vs 44.5±9.6, P=0.041) and RE (52.3±7.3 vs 40.0±15.4, P=0.017).

Conclusions: These findings suggest that IDE may play a significant role in the improvement of QoL and sleep quality in MHD patients, although future studies with more study subjects and longer intervention duration are needed to confirm our findings and if this would also lead to improvement of clinical outcomes, such as QoL, hospitalization, and mortality.

TH-PO1051
Pattern of Dermatoses in Chronic Hemodialysis Patients

Maria Soledad Ferrari,1 Rodrigo Sarantes,1 Paula Gauiron,1 Andrea Nicola,2 Silvana Mazzolini,2 Lidice Dufrechou,1 Patricia Larre Borges,2 Alejandro Larre Borges,2 Miguel Martinez,2 Oscar A. Noboa.1 1Centro de Neurologia; 2Catedra de Dermatologia, Hospital de Clinicas, Univ de la Republica, Uruguay.

Background: Skin diseases are highly prevalent in dialysis patients but are frequently overlooked. The aim of this study was to diagnose dermatoses in renal replacement therapy patients receiving hemodialysis (HD-RRT) and analyze the association with background, laboratory data, and treatment.

Methods: A descriptive cross-sectional multicenter study was performed in a convenience cohort of patients over 18 years old in HD-RRT for more than 6 months. The study committee approved the study. Patients with previous renal transplant were excluded. Dermatologist performed systematic evaluation of skin.

Results: We evaluated 195 patients, 98 females (50.2%), mean age 64.4±9.0 years (31-94). The average time on HD-RRT was 3.9±0.3 years (0.7-25). At least one skin disease was diagnosed in 98.5% (n=192) of patients. Xerosis 79% (n=154), pruritus (n=65, 33.7%), yellowish tint was related with diffuse alopecia (p=0.034) and acquired perforating dermatitis (p=0.029), yellowish tint was related with hyperpigmentation (p=0.038) and loss of hair shine with amenia (p=0.01).

Conclusions: Skin diseases were present in 98.5% of the patients. Most prevalent dermatoses were xerosis and pruritus. Of note is the high prevalence of skin cancers with 7.6% with non melanoma skin cancer and 2 cases of melanoma. This data indicates the relevance of periodic skin assessment in patients treated with HD-RRT.

TH-PO1052
Higher Risk of Malignant Neoplasms in Young Adults with End-Stage Renal Disease under Hemodialysis: A Nationwide Population-Based Study

Heng-Chih Pan,1 Nephrology, Chang Gung Memorial Hospital, Keelung, Taiwan.

Background: Malignant neoplasm is prevalent in elderly and negatively impacts patient outcomes. Previous investigations have shown that end-stage renal disease (ESRD) is associated with an increased risk of malignancies. Our study was designed to explore the contribution of ESRD for incidence of malignancy in patients with different ages.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: We analyzed a nationwide cohort, retrieved from Taiwan’s National Health Insurance Research Database (NHIRD), to study the incidence of malignancy in patients with and without receiving hemodialysis (HD). We obtained 1,000,000 random subjects and followed them from 2005 to 2013. 3086 of them developed ESRD and received regular HD during this period. For each HD patient, four age- and gender-matched controls, a total of 12341 patients, were selected from the NHIRD. We further stratified the patients according to different ages. The study endpoint was the occurrence of malignancy.

Results: The incidence of malignancy was 6.71% and 4.42% for HD, and control patients, respectively. Among HD patients aged younger than 40 years, 40 to 49 years, 50 to 59 years, and 60 to 69 years, the incidence rate of malignancy was 4.15%, 4.72%, 6.22%, and 8.12%, which were significantly higher than that of control group. After adjustments for known risk factors, HD had the highest odds ratio of developing malignancy.

Conclusions: ESFRD patients with HD had a significantly higher risk of malignancy, especially in a relative young age. Based on the results of our study, we believe that the development of ESFRD signifies higher risk of malignancy in young adults.

<table>
<thead>
<tr>
<th>Incidence of Cancer</th>
<th>HD, n (%)</th>
<th>non HD or PD, n (%)</th>
<th>P OR</th>
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<tr>
<td>HN organs</td>
<td>3,086 (100)</td>
<td>12,344 (100)</td>
<td></td>
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<tr>
<td>GI organs</td>
<td>16 (0.52%)</td>
<td>46 (0.37%)</td>
<td>0.252 1.3993</td>
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<tr>
<td>Respiratory organs</td>
<td>90 (2.92%)</td>
<td>251 (2.03%)</td>
<td>0.028 1.4479</td>
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<td>Bone, connective tissue, skin, and breast</td>
<td>17 (0.55%)</td>
<td>100 (0.81%)</td>
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<tr>
<td>GU organs</td>
<td>12 (0.39%)</td>
<td>46 (0.37%)</td>
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<tr>
<td>Other sites</td>
<td>251 (2.03%)</td>
<td>725 (5.84%)</td>
<td>&lt;0.0001 2.2005</td>
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<td>Symptomatic and hematopoietic tissues</td>
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<td>88 (0.71%)</td>
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<td>Liver</td>
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<td>133 (1.08%)</td>
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<td>Total</td>
<td>207 (6.71%)</td>
<td>545 (4.42%)</td>
<td>&lt;0.0001 1.5566</td>
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</table>

TH-PO1053

Risk of Skin Cancer in Chronic Haemodialysis Patients: A Nationwide, Population-Based Study in Taiwan

Background: Chronic haemodialysis (HD) patients have a higher incidence of cancer. However, the risk of skin cancer in this population has rarely been investigated. The purpose of this study is to investigate the risk of non-melanoma skin cancer (NMSC) and cutaneous melanoma in chronic HD patients and explore the associated risk factors.

Methods: We performed retrospective cohort and nested case-control studies using records in the Taiwanese National Health Insurance Research Database from 1999 and 2013. The HD cohort included 79,668 incident HD patients, of which the standardized incidence ratio (SIR) for NMSC and cutaneous melanoma were determined. In the nested case-control study, HD patients with NMSC were matched to those without skin cancers. The impact of various factors on the development of NMSC was determined by conditional logistic regression analysis.

Results: Of the 79,668 HD patients, 248 cases of NMSC and 22 of cutaneous melanoma occurred after a mean 4.95 years of follow-up. The SIRs for NMSC and cutaneous melanoma in HD patients were 1.58 (95% confidence interval [CI], 1.39–1.79) and 1.44 (95% CI, 0.91–2.19), respectively. Of the patients with HD, a higher risk of NMSC was found in men (1.5-fold), South Taiwan residents (2-fold), and patients with uremic pruritus after long-term dialysis and immunosuppressive treatment (1.53-fold). However, the incidence of NMSC was not increased in patients with uremic pruritus receiving ultraviolet-B (UVB) phototherapy.

Conclusions: Chronic HD patients are at higher risk of NMSC. Uremic pruritus further increases the risk of NMSC, which might be prevented by UVB phototherapy.

TH-PO1054

Cancer Diagnosis and Treatment for Patients under Hemodialysis; Multicenter Surveillance Takeshi Matsubara, Tatsu Tsukamoto, Motoko Yanagita. Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, NA, Japan.

Background: Cancer is the third leading cause of death among end-stage renal disease (ESRD) patients in Japan. However, little is known about the diagnosis and treatment of them. Therefore, the aim of this study is to clarify the clinical practice of cancer patients under hemodialysis (HD).

Methods: This retrospective case series study enrolled HD patients who subsequently developed cancer from 2010 to 2012 in 20 institutions. The clinical courses were reviewed under hemodialysis (HD).

Results: From 686 patients enrolled at baseline, 509 patients registered. The main primary cancer sites were kidney (32%), followed by colorectum (17%), and stomach (14%). In all patients, the median time for cancer diagnosis after the beginning of HD was 74 months. Notably, median time was significantly longer in kidney cancer than others (142 vs 54 months, respectively). 391 (77%) cancers were assessed to be surgically resectable, and 366 (72%) cases underwent operation. On the other hands, 44 (8.6%) and 39 (7.7%) patients were successfully supported by chemotherapy and radiation therapy. After a median follow-up of 25 months, there were 130 deaths, including 66 patients (51%) died of causes other than cancer. 2-year survival in all cancer was 75% of patients showed better survival than other cancers (HR 0.43: 0.27-0.65, p<0.01). After multivariate adjustment for sex, cause of ESRD, cancer primary site, disease status, and hypoalbuminemia, anemia was independently associated with mortality (HR: 1.64: 1.10 to 2.41, p<0.01).

Conclusions: This is the first and largest study about cancer patients under HD in Japan. Kidney cancer had longer interval between HD initiation and diagnosis of cancer, but 2-year survival was not different from others. Anemia could be a good predictor of the cancer mortality in HD patients.

Funding: Government Support - Non-U.S.

TH-PO1055

Pregnancies in Patients on Dialysis: A Multi-Center Retrospective Study on Outcomes and Prognosis Factors


Background: Pregnancies in hemodialysis (HD) patients are rare and often associated with maternal and fetal complications. We aimed to determine pregnancy outcomes in HD patient and to identify maternal and fetal prognosis risk factors.

Methods: This is a descriptive, retrospective, multi-center study. Pregnant women on HD from 1985 to 2015 in France were included. A favorable fetal outcome was defined as a living infant discharged from hospital.

Results: We identified 90 pregnancies in 84 women on HD, from 41 centers, with a mean age of 30 years (± 5). Mean delay between initiation of dialysis and onset of pregnancy was 44.7 ± 9.7 months. Fourteen patients (14.9%) began chronic HD during their pregnancy explaining a high rate of catheter (19.8%) and a preserved residual diuresis for 43 patients (50%). Mean weekly dialysis time was 14.6 ± 4.6 hours, 19 ± 4.1 hours and 20.4 ± 3.9 hours for the first, second and third trimester respectively. Seventy-six (89.4%) women performed daily dialysis during the third trimester. Fetal survival was 78% with a mean gestational age of 33.3 ± 3.9 weeks and a mean birth weight of 1719 ± 729 g. Fetal outcome worsened after 2010 with a fetal loss of 16% for pregnancies between 2010 et 2015, compared to 9% before 2010. No significant correlation was found between a low maternal hematocrit or a high fetal outcome. The worsening of fetal outcome after 2010 could be explained by an increase in pregnancies number due to a better acceptance of these pregnancies by the medical community. Nevertheless, these pregnancies remain at high risk, reinforcing the need for an early nephrologist-obstetrician dialogue.

Conclusions: Our study is one of the largest series of pregnancies in HD patients. Its long observation period, multi center and retrospective design could explain the lack of correlation between classical prognosis factors and fetal outcome. The worsening of fetal outcome after 2010 could be explained by an increase in pregnancies number due to a better acceptance of these pregnancies by the medical community. Nevertheless, these pregnancies remain at high risk, reinforcing the need for an early nephrologist-obstetrician dialogue.

TH-PO1056

Dialysis Facility Variation in Primary Care Physician (PCP) Involvement in the Care of Chronic Dialysis Patients in the U.S. Vahakn B. Shahinian, Patrick Albertus, Sai Hurrish Dharmarajan, John Z. Ayanian, R. Hirth, William H. Herman, Rajiv Saran. Univ of Michigan, Ann Arbor, MI.

Background: We previously demonstrated increasing involvement of PCPs in the care of dialysis patients, and that PCP involvement is associated with greater delivery of preventive care compared to a nephrologist alone. In this study, we examined dialysis facility variation in PCP involvement.

Methods: Using the United States Renal Data System (USRDS), prevalent dialysis patients in 2013 with Medicare as primary insurance were identified. PCP involvement was based on ≥1 claim for an outpatient (non-dialysis) visit with a family practice, general medicine or geriatrics physician. The % of patients with ≥1 PCP visit for each facility was plotted in a rank order. A multilevel logistic regression model was performed to examine facility-level predictors (size, profit status, free-standing/hospital-based, % below poverty line in county of facility) of PCP involvement, adjusted for patient age, sex, race, and comorbidities. An intra-class correlation (ICC) was calculated to assess clustering by facility, unexplained by observed patient and facility level predictors.

Results: Of a total of 219,266 dialysis facilities, there was wide facility variation in PCP involvement (Figure). The median facility had 65% of its patients with PCP involvement, with interquartile range from 53 to 76%. The only significant facility level predictor was county poverty (Odds ratio 0.89 [95%CI 0.85-0.93] for ≥20% of residents below poverty line vs above). The ICC was 0.09, suggesting a moderate degree of clustering at the facility level.

Conclusions: Facilities in areas with greater poverty were less likely to have patients with PCP involvement. Substantial unexplained variation at the facility level may reflect differences in attitudes of nephrologists regarding who should be responsible for primary care of dialysis patients.

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

Underline represents presenting author.
TH-PO1057

The Challenges of Achieving Universal Health Coverage for Chronic Conditions in Low Income Settings: A Case Study of Dialysis Outcomes in India

**Background:** India has set itself the target of achieving universal health coverage by 2022. The provision of financial protection from the costs of treating high cost chronic conditions such as kidney disease is one of many challenges. Little is known about the economic impacts of maintenance dialysis in India. We conducted a prospective observational cohort study of incident dialysis patients to understand the household economic impact of dialysis, barriers to treatment continuation and the extent to which existing insurance programs provide financial protection.

**Methods:** Incident patients commencing hemodialysis at two North Indian centers were followed prospectively for 12 months. Baseline demographic and clinical outcome data were collected as well as data on direct, indirect costs and economic impact on the patient and family.

**Results:** We present the results of the 6 month interim analysis. A total of 119 patients (82 male, 37 female) have been enrolled thus far, 70 at a public hospital (Chandigarh) and 49 at a private hospital (Delhi). Median age at enrollment was lower at the public hospital compared to the private (37.5 yrs vs 60 yrs). Baseline Median monthly income was USD$980 at the public hospital and USD$377 in the private hospital. Of the 94 patients at the 6 month interim analysis, 18(19%) have died, 19(20%) have been transplanted, 47 (50%) remain on dialysis and 10 (11%) patients have discontinued dialysis. Median total monthly expenditure for dialysis was USD$231 in the public hospital and USD$1526 in the private hospital.

**Conclusions:** These relatively young Indian dialysis patients have high mortality and dialysis discontinuation rates but also a high rate of transplantation. Costs were high relative to income and are likely to impact upon ongoing treatment decisions and survival. The high and ongoing nature of such costs pose particular challenges to how risk protection programs are designed, particularly given the limited capacity to pay of its beneficiaries.

TH-PO1058

Undocumented with End Stage Renal Disease: Characteristics and Outcomes Associated with Delayed Initiation

**Background:** Most undocumented patients with ESRD in Houston, TX rely on emergent dialysis treatments. Each day, 50% of the patients who present to the hospital for dialysis are either admitted due to critical illness or are turned away without treatment. For this reason, physicians delay initiation of dialysis until absolutely necessary. This abstract characterizes the undocumented population at initiation and compares them to a representative cohort of patients in the United States Renal Data System (USRDS).

**Methods:** There were 155 undocumented patients who initiated dialysis at the county hospital system in Houston, TX between July 2009 and July 2014. Data was obtained from chart review. A standard mortality rate (SMR) was calculated for the 92 patients who received emergent dialysis for one year (2013) and this was compared to a representative USRDS cohort (Hispanics in Texas). Six of the 18 patients 'lost to follow-up' were presumed dead.

**Results:** The average Charlson Comorbidity Index (CCI) for the undocumented patients at initiation is 4.36 (±2.26). Data is presented in Table 1. The p-value was <0.05 for all comparisons except female gender and Hispanic race.

**Conclusion:** Effect of Citizenship Status on Hemodialysis Adherence

**Background:** Previous studies have shown that undocumented ESRD patients (UPs) tend to be younger and continue working once on hemodialysis (HD). We explored whether UPs have difficulty with adherence to HD treatments by reviewing various clinical markers of adherence.

**Methods:** Records of all our adult HD patients were reviewed for one full year beginning 4/1/15. Yearly Kidney Disease Quality of Life (KDQOL) questionnaire was reviewed. Documentation status was determined by presence or absence of a social security number. Variables analyzed included sex, age, ethnicity, phosphorous (P), parathyroid hormone (PTH), potassium (K), interdialytic fluid gains, hospitalizations, missed and shortened treatments.

**Results:** 158 patients were analyzed: 44% of all patients were UPs (n=70). Hispanics made up majority of UPs (74%). PTH, P levels were higher in the UPs. UPs were more likely to be on shorter treatments. KDQOL was similar in both groups except for a higher score on physical health assessment in UPs.

**Conclusions:** The undocumented patients who begin dialysis in Houston, TX have a high CCI score, which is correlated with increased mortality in the established ESRD population. These patients have significantly reduced hemoglobin and albumin levels at initiation; these biomarkers have an established correlation with increased mortality. Critical illness at initiation, along with inconsistent access to dialysis, places this population at a high risk of mortality despite younger age.

**Table 1: Demographics and KDQOL Scores for Hemodialysis Patients

<table>
<thead>
<tr>
<th><strong>Demographics</strong></th>
<th><strong>Undocumented (n=155)</strong></th>
<th><strong>USRDS Cohort (n=18,411)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>44.7</td>
<td>60.2</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>26.7</td>
<td>29.8</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>40.6%</td>
<td>46.0%</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td>96.8%</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Ethiology of ESRD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>48.4%</td>
<td>68.9%</td>
</tr>
<tr>
<td>Unknown</td>
<td>20.0%</td>
<td>1.8%</td>
</tr>
<tr>
<td><strong>Labs at Dialysis Initiation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.86</td>
<td>3.08</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>7.81</td>
<td>9.26</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>13.94</td>
<td>6.93</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Mortality Ratio (SMR)</td>
<td>1.72</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Conclusions:** The undocumented patients who begin dialysis in Houston, TX have a high CCI score, which is correlated with increased mortality in the established ESRD population. These patients have significantly reduced hemoglobin and albumin levels at initiation; these biomarkers have an established correlation with increased mortality. Critical illness at initiation, along with inconsistent access to dialysis, places this population at a high risk of mortality despite younger age.
In-Center Hemodialysis Absenteeism: Prevalence and Association with Outcomes

Steven M. Brunelli, Kathryn S. Gray, Dena E. Cohen. DaVita Clinical Research, Minneapolis, MN.

Background: Patients with end-stage renal disease often miss in-center hemodialysis (ICHD) treatments. Here, we estimated the percentage of missed treatments that were attributable to hospitalization, emergency department (ED) visit, or out-patient procedure, versus no identifiable cause (‘no-show’), and estimated the impact of a single no-show on the short-term risk of hospitalization and mortality.

Methods: In one analysis, we retrospectively aligned treatment attendance records for calendar year 2012 with claims data for adult Medicare Parts A and B enrollees who received ICHD on a Monday-Wednesday-Friday (MWF) schedule at a large US dialysis organization (LDO). In a second analysis, we considered prevalent adult Medicare beneficiaries receiving MWF ICHD at the LDO who had not missed dialysis or been hospitalized between 21 Apr and 20 May 2012. We identified patients who had a no-show on 21 May 2012 and propensity matched them (1:5) to patients who attended treatment on that date. We compared hospitalization and death over the subsequent 30 days. The process was repeated for 23 and 25 May 2012, and data were pooled for all three dates.

Results: Of 462,028 missed treatments observed in 2012 (15.31 per patient-year at risk), 45.1% coincided with a hospitalization; 1.9% with an ED visit, and 0.1% with a procedure. The remaining 52.8% were no-shows. A single no-show (vs. attending the treatment) was associated with a significantly increased risk of hospitalization (adjusted odds ratio [aOR] 1.41, 95% confidence interval [CI] 1.18-1.69) and death (aOR 2.18, 95% CI 1.13-4.20).

Conclusions: In conclusion, over half of missed hemodialysis treatments are no-shows; i.e., not resulting from hospitalization, ED visit, or procedure. Dialysis no-shows are potently and significantly associated with greater short-term risk of hospitalization and death. Reducing no-show rates may improve patient outcomes.

Funding: Clinical Revenue Support

Processes of Care and Outcomes of End Stage Renal Disease Hemodialysis Patients during a Man Made Disaster

Maid Isreb,1,7 Lina Murad,2 Akram Almakki,2 Mohamad Alhosaini,3 Kamel Hatateh,6 Mohamed A. Sekkark,4,5 PeaceHealth Medical Group, Vancouver, WA; Nephrology & Hypertension Associates, Bluefield, WV; Metropolitan Access Center, Washington, DC; Indiana Univ Health System, West Lafayette, IN; Loyola Univ, Springfield, IL; Temple Univ Hospital, Philadelphia, PA; Syrian National Kidney Foundation, Panama City, FL.

Background: The health of dialysis patients is negatively impacted by natural disasters. The degree of this impact in the setting of war is not well known. Herein we compare processes of care and outcomes, including survival, in two ESRD hemodialysis facilities in Syria. Both units are charitable but one is located in a besieged area (B) where getting supplies and medications is very difficult, and the other has a fairly free access to these items (NB).

Methods: Baseline characteristic of all the patients dialyzing in the facilities on 1/1/2015, including demographics, etiology of ESRD, type of vascular access, smoking history, and history of major cardiovascular disorders were collected retrospectively. Follow up was for a maximum of one year and included data collection on availability of medications, dialysis duration and frequency, and survival.

Results: There were no statistically significant differences in patients’ demographics, smoking history, and dialysis vascular access type. The average patient age was 47 years. Less than 5% of the patients dialyzed 3 times a week. Data on medications availability, dialysis duration and frequency, and duration of hospitalizations are shown in the table.

Conclusions: War has a strong negative impact on the health of ESRD hemodialysis patients especially when access to medications and supplies is restricted by beseigeing. The renal community should be more involved in guaranteeing access of care to the vulnerable population of ESRD patients.

Funding: Private Foundation Support

Tele-Nephrology: Delivering Acute Dialysis in Rural Hospitals via Telehealth

Charuldas V. Thakar,1,2 Mahmoud T. El-Khatib,3 Amit Govil,4 Doug Johnson,5 Robert Parker,2 Pam Kimmel,5 Anya Sanchez.1,2 Nephrology/Medicine, Univ of Cincinnati/UC Health, Cincinnati, OH; 2Dialysis Clinics Incorporated, Nashville, TN; 3Meadowview Regional Medical Center, Maysville, KY; 4Cincinnati VA Medical Center, Cincinnati, OH.

Background: 38% of the 4,926 community hospitals in the U.S.A. are designated as rural hospitals. Although dialysis use is similar across rural and urban areas (3.9 /1000 residents); 77% of remote rural counties lack an in-county dialysis facility. Only a third of rural hospitals offer acute dialysis due to lack of dialysis and/or renal providers.

Methods: We describe the development of a tele-nephrology program, partnering with a national dialysis provider (Dialysis Clinics Inc.), and Meadowview Regional (rural hospital) in Maysville, KY. Lack of dialysis providers had forced transferring of patients requiring acute dialysis to larger hospitals, resulting in transportation costs and real/ intangible costs to patients.

Results: Key elements of implementation included: 1. Planning (needs assessment; technology; dialysis provider; contracting); 2. Stakeholders (business, nursing, informatics, hospitalist, pharmacy, renal). Metrics of success include: A. Clinical performance; B. Patient satisfaction; C. Provider satisfaction; D. Opportunity cost savings. After careful planning, the program went live in January 2016. Clinical pathway is shown in Fig 1. To date, we have treated 12 patients (32 bed-days; 20 dialysis treatments) via tele-health for conditions requiring medical/surgical/critical care. 67% of patients were successfully treated and discharged from the rural hospital.

Conclusions: By applying innovative technology, we demonstrate surmounting traditional barriers to deliver specialty renal care at rural/critical access hospitals. This patient-centered program plans to build a hub-and-spoke model for specialty care, and can be emulated nationally.

Funding: Clinical Revenue Support

Increased Hospitalizations and Costs Associated with Suboptimal Initiation of Chronic Dialysis

Edwin J. Anand,1 Kabir Jalal,2 Brian M. Murray,3 Pradeep Arora,4 Rocco C. Venuta,5 Nephrology, Univ at Buffalo. Buffalo, NY; 2Diastatistics, Univ at Buffalo, Buffalo, NY; 3Nephrology, VA Medical Center, Richmond, VA.

Background: Initiation of maintenance dialysis with a cather is associated with increased mortality. Nearly 80% of patients start dialysis with a cather, despite concerted efforts to increase fistula use. Using data from a large 3rd party payer, we studied the comorbidities leading to increased hospitalizations and costs in the first 12 months after starting chronic dialysis.

Methods: We used data (costs, hospitalizations, labs, billing codes) from a large 3rd party payer. We studied the comorbidities leading to increased hospitalizations and costs in the first 12 months after starting chronic dialysis.

Results: Of the 1.3 million patients in the database, 38,857 had CKD. Of these, 1298 developed ESRD. There was a significantly higher rate of hospitalization (2.3 vs 1.9 P=0.008), as well as total medical costs in the first year ($104,674 vs $81,575) in patients who crashed vs those who did not. Presence of a fistula (mature or maturing) was associated with reduced hospitalizations (1.5 vs 2.1 P<0.001).

Conclusions: War has a strong negative impact on the health of ESRD hemodialysis patients especially when access to medications and supplies is restricted by beseigeing. The renal community should be more involved in guaranteeing access of care to the vulnerable population of ESRD patients.

Funding: Private Foundation Support

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

Underline represents presenting author.

343A
Conclusion: Dialysis initiation with a catheter is associated with increased hospitalizations and costs. More effective interventions following to increase fistula rates would reduce avoidable hospitalizations. 3. Care coordination of ESRD patients with experts in respiratory diseases and mental illness should reduce hospitalizations and costs for this population.

TH-PO1064

Impact of Dialysis Access Modality on Emergency Department Utilization

Brendan P. Lovvasik, Rebecca H. Zhang, Justin D. Schragar, Stephen O. Pastan, Rachel E. Patzer. Emory Univ, Atlanta, GA.

Background: Initiation of dialysis with an arteriovenous fistula (AVF) is associated with lower costs and improved patient survival. However, the impact of dialysis access modality on ED utilization among a national ESRD patient population has not been examined.

Methods: We examined a cohort of 103,155 incident adult ESRD patients in the United States Renal Data System data from 2005-2011. ED utilization, hospital admission, and diagnoses were obtained from the USRDS and Medicare Physician/Supplier and Inpatient databases for Medicare beneficiaries. Multivariable regression was conducted to assess the association of relevant patient variables with ED utilization.

Results:

<table>
<thead>
<tr>
<th>Variable</th>
<th>ED Visits</th>
<th>ED Visits/Patient-Year</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AVG</td>
<td>Catheter</td>
<td>Rate Ratio</td>
</tr>
<tr>
<td>All ESRD</td>
<td>1,782,441</td>
<td>2.89</td>
<td>REF</td>
</tr>
<tr>
<td>AV Fistula</td>
<td>146,327</td>
<td>1.83</td>
<td>REF</td>
</tr>
<tr>
<td>Graft</td>
<td>53,078</td>
<td>2.63</td>
<td>1.229</td>
</tr>
<tr>
<td>Catheter</td>
<td>1,394,263</td>
<td>3.22</td>
<td>1.12</td>
</tr>
<tr>
<td>Peritoneal &amp; Other</td>
<td>188,573</td>
<td>2.25</td>
<td>1.235</td>
</tr>
</tbody>
</table>

For each first year of ESRD, 55% of patients presented to the ED, with a total of 1,782,441 ED visits among 422,738 unique ESRD patients. The median Medicare claim for an ED visit by an ESRD patient was $466 (IQR: $274-$745). Extrapolating this cost yields an annual ED cost of $668 million for first-year ESRD patients. Only 13% of ESRD patients initiated dialysis with a mature AVF; AVF patients had the lowest rate of ED utilization (1.83 visits per patient-year [PY]). Catheter-based patients had the highest rate of ED utilization (3.22 PY). In multivariable analysis controlling for sociodemographic and clinical factors, patients with a graft (RR: 1.22; 95% CI: 1.21-1.23) or catheter (RR: 1.12; 95% CI: 1.11-1.13) for dialysis access had higher rates of ED utilization compared to those with an AVF.

Conclusion: Despite Fistula-First guidelines, AVFs remain an underutilized dialysis access modality, with significant deleterious patient outcome and healthcare resource utilization implications. Initiatives to increase pre-ESRD nephrology referrals may improve AVF rates.

TH-PO1065

Vascular Access and Mortality in Elderly Incident ESRD Patients

Tarek H. Saleh, 1 Miklos Zsolt Molnar, 1 Keichi Sumida, 1 Jun Ling Lu, 1 Praveen Kumar Potukuchi, 1 Elami Streja, 1 Kamyar Kalantar-Zadeh, 1 Csaba P. Kovessy. 1, 2

1 Univ of Tennessee Health Science Center, Memphis, TN; 2 Univ of California, Irvine, CA; 1 VA Medical Center, Memphis, TN.

Background: Creating a mature AV fistula (AVF) can be challenging in elderly individuals. It is unclear if elderly incident HD patients derive a survival benefit from an AVF fistula (AVF) over an AV graft (AVG) or a tunneled catheter (TC).

Methods: We examined 46,748 US veterans who transitioned to dialysis between 2007 and 2011 using an AVF, AVG or TC. We examined the association of AVG and TC (vs. AVF) with all-cause and cause-specific mortality in Cox and competing risk regression models adjusted for age, race, comorbidities and pre-dialysis nephrology care in patients aged <60, 60–<70, 70–<80, and ≥80 years old. Effect modification by age was examined with interaction terms.

Results: Upon dialysis transition, patients were 70±12 years old, 94% male, 25% African-American, and 58% diabetic. 8,936 (19%) started HD with an AVF, 1,232 (3%) with AVG, and 36,580 (78%) with a TC. 31,354 patients died (mortality rate 290/1000 patient-years, 95%CI: 287-293) over a median follow-up of 2.1 years. Use of a TC was associated with significantly higher all-cause mortality in all age groups (Figure), with no significant age interaction (p=0.6). TC use was also associated with both higher infectious mortality (HR 1.76, 95% CI 1.33 - 2.32) and CV mortality (HR 1.34, 95% CI 1.37 - 1.74) in patients ≥80 years old. Use of an AVG was not associated with higher risk of all-cause, infectious or CV mortality in patients ≥80 years old.

Conclusion: Staring HD with a TC is associated with higher mortality in all age groups, the risk being highest for infectious mortality. Use of an AVG appears to be associated with similar outcomes as an AVF in patients ≥80 years old. A catheter-last approach should be advocated in elderly incident HD patients.

Funding: NIDDK Support, VA Support

TH-PO1066

Predictors of Adverse Outcomes of Permanent Vascular Access (PVA) in Pediatric Hemodialysis (HD) Patients: A MWPNCC Study


Background: Few data exist on what factors contribute to success or failure of PVA in pediatric HD. We investigated predictors of adverse outcomes of PVA in a large cohort of pediatric HD patients.

Methods: Retrospective chart reviews were performed in 20 participating centers. Variables collected included duration and number of non-permanent vascular access (NPVA), type of PVA, complications, interventions, and final outcome.

Results: 146,527 PVA were created in 117 children during the study period: 103 (88%) were AV fistulas and 14 (12%) were AVG grafts. AVF demonstrated better primary patency rates compared to AVG (p=0.0391, Wilcoxon signed rank test). Primary failure occurred in 16 PVA (13.6%). AVG was about twice as likely to have primary failure compared to AVG (Odds ratio=2.1). Secondary failure occurred in 14 PVA (12.2%). AVG’s had about 3 times increased risk for secondary failure compared to AVF’s (Odds ratio=3.34). As the number of NPVA increased, the probability of secondary failure decreased (p=0.0343, inverse correlation). Longer NPVA duration directly correlated with increased risk for secondary failure (p=0.0501). As Kt/V at the time of permanent vascular access creation increased, the probability of secondary failure increased (p=0.0263). There were 196 interventions in total. PVA’s were more likely to be intervention-free (p=0.0456, Odds ratio=0.84). Twenty-seven interventions resulted in non-functional PVA. Both Intervention-free survival (p=0.0252, Odds ratio=0.093) and the total number of interventions were able to predict secondary failure (p=0.0006). For each additional intervention, the odds of having secondary failure increase by 1.535. Finally, intervention-free survival directly correlated with overall survival of PVA (p=0.0197, Spearman correlation coefficient = 0.28028).

Conclusion: We found that both the number and duration of NPVA, and baseline Kt/V may affect the outcomes of AVF and AVG. While most interventions were able to salvage the function of PVA, both the intervention-free survival and total number of interventions were predictive of secondary failure.

TH-PO1067

Predictors of Maturation Time for Permanent Vascular Access (PVA) in Pediatric Hemodialysis (HD) Patients: A MWPNCC Study


Background: Maturation time is one of the limiting factors in using PVA for children on HD. Our objective was to investigate the predictors of maturation time of AVF’s and AVG’s in a large cohort of pediatric HD patients.

Methods: Retrospective chart reviews were performed in 20 participating centers. Variables collected included duration and number of non-permanent vascular access (NPVA), type of PVA, patient demographics, baseline laboratory findings at time of placement and final outcome.

Results: PVA were created in 117 children during the study period: 103 (88%) were AV fistulas and 14 (12%) were AVG grafts. The average maturation time was 3.7±3.9 months. AVG’s had significantly shorter maturation times when compared to AVF’s after exclusion of the 2 outlier centers (p=0.0028). In the logistic regression model for the predictors of maturation time, there were 4 predictors; Study site (p=0.0165), duration of NPVA (p=0.0001), number of previous NPVA (p=0.0061, inverse correlation), and age at placement (p=0.0001). When AVF and AVG were separately analyzed, these predictors were only significant for AVG’s. The overall PVA survival was 23.9±13.9 months, with AVG’s being statistically indifferent from AVF’s (p=0.8270). Maturation time could not predict secondary failure of either access type (p=0.8817). There was no difference in maturation time between PVA with secondary failure and those that were still functional at the end of the observation period (p=0.3675).

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

Underline represents presenting author.

344A
Conclusions: We demonstrated that the study site, both the duration and number of years from ESRD to age at placement may affect the maturation times for AVF’s. AVG’s had significantly shorter maturation times and none of the variables could predict their maturation times. Time to maturation was not a predictor of secondary failure of PDA in this cohort.

TH-PO1068

The Role of Vascular Access on Medicare Reimbursement among Patients with Incident End-Stage Renal Disease Receiving Hemodialysis

Background: Studies suggest better outcomes among patients with end-stage renal disease (ESRD) initiating hemodialysis (HD) with arteriovenous fistulas (AVFs), versus central venous catheters (CVCs). We sought to compare Medicare reimbursements during the first year of HD by vascular access at initiation.

Methods: A retrospective cohort of patients with incident ESRD in 2011 or 2012 was selected from a 5% sample of all Medicare beneficiaries. We included patients aged ≥67 years, covered by traditional fee-for-service Medicare two years before and one year after HD initiation, and alive one year after HD initiation. Initial vascular access was identified using the ICD-10 code (V7 and V7-7) on an outpatient hemodialysis claim in the initial 60 days of HD. Inpatient, outpatient, and other claims were utilized to obtain reimbursement data. Medicare reimbursement in the first year of HD was modeled as a function of vascular access, age, sex, race, healthcare setting of first HD, and reimbursement in the year prior to HD as a proxy for baseline health status and utilization using a generalized linear model.

Results: Of 1,635 included beneficiaries, 23% and 77% started hemodialysis with AVF and CVC, respectively. In the year prior to HD initiation, crude median reimbursements were $15,452 and $19,026 among those initiating via AVF and CVC. In the year after HD initiation, crude median reimbursements were $38,604 and $39,165 among those initiating via AVF and CVC. Adjusted reimbursement was 18% lower (0.82, 95% CI: 0.77-0.87, P<.0001) among beneficiaries initiating with fistula compared with CVC.

Conclusions: Among a fully covered Medicare ESRD cohort surviving the first year of HD, those with fistula had lower total Medicare reimbursements during the first year of care even after adjusting for baseline reimbursement and other characteristics. These findings suggest a missed opportunity to prevent excess healthcare costs to Medicare associated with HD initiation with CVC.

Funding: Other U.S. Government Support

TH-PO1069

Effect of Hemodialysis on Anterior Chamber Biometric Structure and Intraocular Pressure in Non-Diabetic Patients with End-Stage Renal Disease

Background: To evaluate the short-term changes in the ophthalmologic findings after low-flux hemodialysis in non-diabetic end-stage chronic renal failure (CRF) patients. Previous studies have shown that patients with CRF are at risk to have glaucoma or history of glaucoma were studied. We observed the patients on maintenance hemodialysis therapy after HD (lens’ thickness significantly increased from 4.23±0.22 mm before HD to 4.30±0.12 mm significantly after HD, from 2.46±0.38 to 2.38±0.36 mm (paired t test, p<0.01). Mean central anterior chamber depth also decreased with an A VF was 5-20ml/min/1.73m2.

Results: The mean age of the patients at the time of dialysis was 49.7±12.0 (range 33-65) years. 53.5% (23) were men. After hemodialysis treatment, the blood urea nitrogen, creatinine, patient weight decreased significantly (P<0.01). There was no significant difference in the change of serum calcium, serum phosphorus, serum albumin and hemoglobin after the treatment(P>0.05). Mean central anterior chamber depth also decreased significantly after HD, from 2.46±0.38 to 2.38±0.36 mm (paired t test, P<0.01). Mean lens’ thickness significantly increased from 4.23±0.22 mm before HD to 4.30±0.12 mm after HD (P<0.01) in group. However, Mean IOP increased from 12.32±4.31 mmHg to 14.2±2.9mmHg after HD (paired t test, P<0.01).

Conclusions: Conventional hemodialysis can affect the ophthalmologic findings. Patients with chronic renal failure should be checked of their anterior chamber structure and be given corresponding treatment before haemodialysis.

TH-PO1070

Persistent Disparities in Hemodialysis Vascular Access

Background: Despite gains over the past decade with AV fistula (AVF) creation, concerns remain about vascular access (VA) disparities. Prior studies are limited by sample size or ability to adjust for clinical risk factors that influence AVF creation. Using data on Medicare ESRD patients we analyze the impact of patient demographic factors on likelihood of different VA types after adjusting for incident and prevalent comorbidities.

Methods: We used 2014 CROWNWeb for monthly VA data for all Medicare hemodialysis patients in the US. Incident comorbidities were obtained from the CMS 2728, and prevalent comorbidities from the prior 12 months of Medicare claims. Multivariate generalized logistic regression modeled odds of AVF/AVG/catheter (CVC) use associated w/ demographic and clinical factors.

Results: Of 2,920,145 patient-months AVF and AVG were used in 65% and 21% of patient-months. After adjusting for ethnicity, BMI, nursing home status, pre-ESRD care, duration of ESRD and 12 categories of comorbidities those aged 75+ were 19% and 16% less likely to have an AVF versus (V) AVG and CVC. Black patients were 47% and 16% less likely to have AVF AVG or CVC compared to whites/other race. Hispanic ethnicity was associated with higher AVF use V CVC. Females were 52% and 46% less likely than males to have AVF V AVG or CVC.

<table>
<thead>
<tr>
<th>AVF v AVG</th>
<th>AVG v AVG</th>
<th>AVG v CVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>25-59</td>
<td>1.25</td>
<td>0.81</td>
</tr>
<tr>
<td>Age Ref: 60-75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td>0.85</td>
<td>0.81</td>
</tr>
<tr>
<td>Black race</td>
<td>0.84</td>
<td>0.53</td>
</tr>
<tr>
<td>Hispanic eth.</td>
<td>1.28</td>
<td>1.06</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.54</td>
<td>0.48</td>
</tr>
<tr>
<td>5-&lt;7y</td>
<td>1.03</td>
<td>0.77</td>
</tr>
<tr>
<td>75+</td>
<td>0.76</td>
<td>0.48</td>
</tr>
</tbody>
</table>

p<0.01

Conclusions: We observed differences in AVF use by demographic characteristics. After adjustment for patient comorbidities, patients ≥75+, of black race, and females were less likely to have an AVF compared to AVG or CVC. Absent strong biological bases for barriers to achieving optimal vascular access outcomes by race and sex, caution is required in considering these risk adjustment factors as part of public reporting to avoid masking potential care disparities.

Funding: Other U.S. Government Support
Conclusions: In VA Healthcare System, placement of AVF early (eGFR>20) or late (eGFR<5) in users with CKD stage 5 was associated with lower success in AVF use at HD start. The optimal window for AVF placement was eGFR in the 5-20 range. Geographic variation in VA AVF placement warrants further review. 

Funding: VA Support

TH-PO1072

Use of a Vascular Access Coordinator to Increase Arteriovenous Fistula (AVF) Prevalence and Decrease Tunnelle Catheter Duration and Use in an Inner City Hemodialysis Clinic

Cesar Y Cardona, Marquetta L. Faulkner. Internal Medicine and Nephropathy, Meharry Medical College, Nashville, TN.

Background: The National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (NKF, KDOQI) push for dialysis practice standards envisioned a goal of >10% catheter use and >66% AVF use for each hemodialysis (HD) unit. A major component of First Fistula Breakthrough Initiative is use of AVF within 90 days of first dialysis treatment to minimize time a tunneled catheter is present while awaiting AVF or arteriovenous graft (AVG) maturation in patients dialyzing via a tunneled catheter. Goals of study to establish, evaluate a protocol that can be replicated to minimize catheter use and maximize AVF prevalence and cannulation of AVFs or AVGs within 90 days of tunneled catheter placement.

Methods: In June, 2007 we designed a pilot program to increase prevalent AVF use from baseline of 19.9% to 60% by using a vascular access coordinator to coordinate care and monitor access creation and maturation.1,2 We enrolled 60 patients based on inclusion criteria of GFR of less than or equal to 30 ml/min (assessed by MDRD equation) who were followed in the nephrology clinic or those who were referred to our clinic and met inclusion criteria or deemed appropriate by attending nephrologist for referral for vascular access placement. Patients were enrolled beginning June, 2007 to November, 2014.

Results: We were able to increase prevalent AVF use in our hemodialysis clinic from 19.9% to 56.9% (p<0.0001) and decrease catheter use for greater than 90 days from 32.5% to 12.6% (p<0.0001) and our total patients with catheters decreased to 18.9% from 42.5% (p<0.0001).

AVF 19.9% AVF 56.9%
Total Catheter (TC) 42.5% TC 18.9%
Catheter >90 days (C>90) 32.5% C>90 12.6%

Conclusions: Use of a VAC helped increase AVF use and decrease both total tunneled catheter use and catheter use of greater than 90 days in an inner city hemodialysis clinic and results were statistically significant despite not reaching goals established by NKF and KDOQI.

Funding: Pharmaceutical Company Support - DCI helped support the funding for the position of the Vascular Access Coordinator

TH-PO1073

Why Not “Fistula First”? The Obstacles

Sijie Zheng, Andrea Remeta, Joanna Mroz, Leonid Prazovorov. The Permanente Medical Group, Oakland, CA.

Background: In the US, 80% of patients initiate maintenance HD with a central venous catheter (CVC). One reason for low incidence of AVF/AVG was attributed to late referral. Kaiser Permanente Northern California (KPNC) is an integrated health care system providing health care to approximately 400,000 members with an estimate of 40,000 CKD patients. Despite higher mortality and complications associated with central venous catheter (CVC) use, 80% of incident HD patients in US are using CVC as their dialysis access. Kaiser Permanente Northern California (KPNC) is an integrated health care system providing health care to 3.9 million members. The East Bay service area provides hemodialysis with a CVC, we analyzed the reasons for failure to have a matured AVF/AVG and maturation.

Methods: A retrospective analysis was conducted of CKD patients who initiated dialysis in the KPNC East Bay Service Area from 2013 to 2015. For patients who initiated hemodialysis with a CVC, we analyzed the reasons for not having a matured AVF/AVG upon hemodialysis initiation.

Results: A total of 199 patients initiated HD from January 1, 2013 to December 31, 2015. Among them, 127 (63.8%) patients used CVC as their dialysis access upon initiation. 57 (28.6%) patients had a matured AVF at the start of dialysis and 15 (7.5%) patients had a matured AVG. We analyzed the reasons for failure to have a matured AVF/AVG and classified them into 4 categories: (1) delays due to patient indecision (63 patients, 49.6%), (2) system related delays (19 patients, 15%), (3) patients with Acute Kidney Injury (42 patients, 33.1%) and (4) medically contraindicated (3 patients, 2.4%).

Conclusions: In our integrated health care system, incident hemodialysis patients have lower CVC rates compared with the national average. Delays due to patient indecision and unexpected AKI requiring immediate dialysis initiation represent the majority of cases when permanent access is not established prior to initiation of dialysis. Patient education and close monitoring in the pre-dialysis period will likely have the highest effect in decreasing CVC rates in the future. In our integrated organization, system related delays represent a smaller overall opportunity to increasing the use of AVF/AVG as a primary access at initiation of dialysis.

Funding: VA Support

TH-PO1074

Strategies to Increase Incident AVF/AVG in Hemodialysis Patients

Sijie Zheng, Andrea Remeta, Joanna Mroz, Leonid Prazovorov. The Permanente Medical Group, Oakland, CA.

Background: Despite higher mortality and complications associated with central venous catheter (CVC) use, 80% of incident HD patients in US are using CVC as their dialysis access. Kaiser Permanente Northern California (KPNC) is an integrated health care system providing health care to 3.9 million members. The East Bay service area provides hemodialysis with a CVC, we analyzed the reasons for failure to have a matured AVF/AVG and maturation.

Methods: We strengthened the collaboration between nephrologists and vascular surgeons by instituting a dedicated dialysis access nurse coordinator. Since June 2013, a dialysis access nurse coordinator to prospectively monitor patients approaching CKD 5. Patients with eGFR ≤ 25 ml/min/1.73 m² were referred for evaluation for AVF/AVG placement if they choose hemodialysis (HD). Protocols were developed to create consistent patient education about risks and benefits of various dialysis access types, uniform process of referral for vein mapping, pre-operative evaluation and operating room scheduling. In addition, the dialysis access nurse coordinator involved patient’s caregivers, educating them on the importance of timely preparation for dialysis, thus improving adherence to appointments. Once the AVF/AVG was placed, a vascular surgeon examined the patient at 2 weeks and 8 weeks to ensure successful maturation of the AVF/AVG. The nurse coordinator ensured patient has follow up appointments with the vascular surgeons, nephrologists, duplex studies and AVF/AVG revision surgeries as needed.

Results: The incident AVF/AVG rate increased from 25% to 44% since 2013 to 2015, and the incident CVC rate decreased from 75% to 55% during the same period of time.

Conclusions: By increasing the overall integration of the pre-existing team of providers, an access nurse coordinator is able to significantly and consistently reduce rate of CVC in patients initiating hemodialysis in our integrated health care system.

TH-PO1075

Quality Improvement Project for Permanent Dialysis Access Rates in End-Stage Renal Disease

Elliot M. Charen, Naitik Sheth, Chiara Marie Ornillo, Nikolas B. Harbord. Div of Nephrology and Hypertension, Mount SinaiBeth Israel, New York, NY.

Background: Dialysis patients with central venous catheters (CVC) are expected to have more interventions for access dysfunction at higher cost, worse patency rates, and higher morbidity and mortality. Many incident dialysis patients initiate dialysis in the hospital and do not meet the expectation from NKF-KDOQI of CVC free by 90 days of dialysis initiation; many new-start dialysis patients have not consulted with a surgeon prior to initiation of dialysis.

Methods: New start chronic dialysis patients initiated while hospitalized and followed by the renal consult service were included. The retrospective first phase of data collection (January-March, 2014) involved a study of incident End-Stage Renal Disease (ESRD) patients who ultimately were discharged to an out-patient dialysis center. The hospital record (PRISM) was checked to see if the patient had a permanent dialysis access placed, a surgical consult for access was completed, or an out-patient office visit was scheduled. The prospective second phase (5 non-contiguous months from 2014-2015) involved teaching all new start ESRD patients about options for dialysis including the benefits of a permanent access and surgical evaluation with possible access placement.

Results: In the implementation phase as compared to the study phase, a greater percentage of patients had in-patient surgical consults (56% versus 29%, p=0.08) and out-patient surgical appointments (67% versus 43%, p=0.38). The amount of permanent dialysis accesses were no different between the two groups (28% versus 29%, p=1). The most common reason for not having an access placed during hospitalization was patient choice (n=7/18). The most common medical reason for not having an access placed was cardiac risk (n=3/18).

Conclusions: Patient education can be improved during an incident ESRD patient’s hospitalization, but access planning education in the hospital may not allow patients sufficient time to make decisions about access placement.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
AV Fistula Creation by Nephrologist: An Indian Experience 
Vinati Bhargava, Ritesh Kauntia, Devinder S. Rana, Anil Bhalla, Ashwani Gupta, Manish Malik, Anurag Gupta. Nephrology, Sir Gangaram Hospital, New Delhi, India.

Background: AV fistula is the preferred vascular access for long term hemodialysis as it has higher patency rates and lower infection morbidity, mortality and morbidity. The aim of this study was to assess the outcomes and primary patency rates of radiocephalic AV fistula created and venography recommended. 18 of 44 created. The use of PV increased forearm access options. Here, we describe the use of PV is associated with identifying more forearm veins by US do in fact have forearm access options. Here, we describe the use of PV was significantly associated with identifying CV stenosis with p= 0.00.

Results: 301 patients underwent AV-fistula surgery. 260 patients underwent 270 AV-fistula creation. 10 patients underwent AV fistula revision in view of primary failure. Data regarding maturation was not available for 41 patients. Analysis of 270 AV-Fistulae was done for primary maturation. The mean age of patients was 50.6±15.3 years, 73.3% were males. 41.8% of patients had diabetes mellitus. Preexisting coronary artery disease was present in 20% and peripheral vascular disease was present in 1.85% of the patients. On follow up, 204 (75.56%) of AV fistula created had successful maturation. Primary failure was seen in 66 (24.44%) patients. Primary failure in patients with diabetes was seen in 38 out of 66 (57.57%) and 75 out of 204 (36.76%) had successful maturation (p=0.002). Correlation was used in 20 out of 66 (30.3%) patients with primary failure and 34 out of 204 (16.67%) patients with successful maturation (p=0.016). The KDOQI guidelines advocate the creation of forearm over upper arm arteriovenous fistulas (AVFs), as these typically last longer and are associated with fewer access and systemic complications. In addition, forearm AVFs increase the success of secondary accesses created more proximally. Duplex ultrasound is the preferred method for preoperative vessel mapping and has increased the success creation of AVFs when compared to physical exam alone. However, in clinical practice many patients without a suitable forearm vein by US do in fact have forearm access options. Here, we describe the use of peripheral venography (PV) with serial released tourniquets to visualize the veins of the upper extremity and compare the peripheral vein findings from PV to that of ultrasound vein mapping (UVM).

Methods: The Brigham and Women’s Interventional Nephrology Database was used for this study to identify a historical cohort of patients who received pre-operative PV and UVM between January 2008 and December 2015. The UVM and PV reports were reviewed for appropriate forearm veins to be used in AVF creation by Silva criteria. The presence of suitable veins was recorded as a dichotomous outcome. The extremities were treated as paired data-points and evaluated using McNemar’s test. The primary outcome was successful primary maturation. We also looked at predictors of successful AVF and complications. Based on author’s personal experience patients with prominent “V” at the elbow were taken for this type of fistula. (Prominent V at the elbow is formed by median basilic and median cephalic veins.)

Results: During the study period 122 patients underwent median basilic vein to brachial artery AVF. Of the study group 12 patients were lost to the follow up and 6 patients died before completing three weeks of post operative period. Of 104 patients, 96 patients (92.3%) patients had successful AVF. Male outnumbered females (66 males and 39 Females). Hypertension (78.8%) was the most frequent co-morbidity, followed by Diabetes Mellitus (39.4%). Failure of maturation was seen in 8 patients and arm edema in 4 patients. Results: During the study period 122 patients underwent median basilic vein to brachial artery AVF. Of the study group 12 patients were lost to the follow up and 6 patients died before completing three weeks of post operative period. Of 104 patients, 96 patients (92.3%) patients had successful AVF. Male outnumbered females (66 males and 39 Females). Hypertension (78.8%) was the most frequent co-morbidity, followed by Diabetes Mellitus (39.4%). Failure of maturation was seen in 8 patients and arm edema in 4 patients. Conclusions: Side to side median basilic vein to brachial artery arteriovenous fistula is promising vascular access. Prominent “V” at the elbow is a strong predictor for success of such AVF.

Conclusions: This study shows that AV fistula created by nephrologists have comparable success rates of maturation. Diabetes mellitus and coronary artery disease are significant risk factors for AV fistula primary failure.

Pre-Operative Venography and the Identification of Forearm Veins Compared to Ultrasound Vein Mapping 
Patrick McGlynn, Dirk M. Hentschel. Nephrology, Brigham and Women’s Hospital, Boston, MA.

Background: The KDOQI guidelines advocate the creation of forearm over upper arm arteriovenous fistulas (AVFs), as these typically last longer and are associated with fewer access and systemic complications. In addition, forearm AVFs increase the success of secondary accesses created more proximally. Duplex ultrasound is the preferred method for preoperative vessel mapping and has increased the success creation of AVFs when compared to physical exam alone. However, in clinical practice many patients without a suitable forearm vein by US do in fact have forearm access options. Here, we describe the use of peripheral venography (PV) with serial released tourniquets to visualize the veins of the upper extremity and compare the peripheral vein findings from PV to that of ultrasound vein mapping (UVM).

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anastomosis size by side to side was limited to just 3 mm. Primary VA patency was defined as the time from first VA intervention, and secondary patency as the time to creation of a new VA. Kaplan-Meier curves of primary and secondary VA patency were generated. Also, comparisons between the two groups were performed using a log-rank test. Results were considered significant at P<0.05. Results: The primary patency rates were 88.0% and 77.9% for GroupA and GroupB at 12 months, also 71.2% and 37.2% (p=0.03) at 36 months, respectively. The secondary patency rates for each were 92.2 % and 85.4 % at 12 months, also 78.6% and 59.8% at 36 months. Secondary VA patency did not show any significant difference (p=0.34).

Conclusion: Our results disclosed lower secondary patency rate of smaller AVFs in elderly patients. Although excessive blood flow must be unfavorable for any dialysis patient, our attempts to make small AVFs to not achieve a new additional value for the elderly from the viewpoint of lives of VA.

TH-PO1081

Procedural Burden during Arteriovenous Fistula Maturation following Operative Placement: An Analysis of the United States Renal Data System

Background: Over the last decade, the number of arteriovenous fistula (AVF) in the population is increasing. The problems on AVF were increasing. We sought to determine the procedural burden required for successful AVF maturation in the incident United States HD population.

Methods: Using the United States Renal Data System (USRDS) Medicare claims and CROWNWeb data, we analyzed patients incident to HD from 7/1/12 to 6/30/13 with first-time AVF placements (after HD start) from 7/1/12 to 6/30/14. Successful maturation was defined as documentation of first AVF use in CROWNWeb by 12/31/2014.

Results: Among the 102,703 incident HD patients, there were 24,416 first-time AVF placements. A total of 70.7% were successfully utilized, 25.5% failed to mature, and 3.9% were lost to follow-up. Of those that successfully matured, 44.2% required interventions during the maturation phase, with half of these interventions requiring angioplasty. Interventions were performed on 58.8% of AVFs that failed to mature. Not surprisingly, thrombectomy were carried out much more often in those with AVF maturation failure. Rates of interventions per patient (pp) are summarized in the Table.

Table: Interventions during AVF maturation.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Successful Maturity (n=21,672)</th>
<th>Failed Maturity (n=6,725)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>17,370</td>
<td>6,238</td>
</tr>
<tr>
<td>Procedural Interventions</td>
<td>7,682</td>
<td>3,271</td>
</tr>
<tr>
<td>Intervention Procedures</td>
<td>11,049 (0.60 pp)</td>
<td>9,681 (1.56 pp)</td>
</tr>
<tr>
<td>Diagnostic Fistulogram Only</td>
<td>2,659 (0.12 pp)</td>
<td>1,691 (0.27 pp)</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>9,892 (0.46 pp)</td>
<td>5,134 (0.83 pp)</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>897 (0.05 pp)</td>
<td>5,600 (0.98 pp)</td>
</tr>
<tr>
<td>Revision</td>
<td>2,124 (0.12 pp)</td>
<td>846 (0.14 pp)</td>
</tr>
<tr>
<td>Other</td>
<td>446 (0.03 pp)</td>
<td>390 (0.06 pp)</td>
</tr>
</tbody>
</table>

Conclusion: While there have been improvements in AVF utilization in the prevalent HD population, mortality on AVF were increasing. We sought to determine the procedural burden required for successful AVF maturation in the incident United States HD population.

TH-PO1082

Risk Factors for Arteriovenous Fistula Nonmaturation in a European Cohort

Background: Nonmaturation of permanent vascular access (VA) conduits is a significant burden for hemodialysis (HD) patients. European data about the current prevalence of nonmaturation are lacking. This study evaluated demographic and applied an existing clinical risk prediction model for AVF FTM. The main objective of this study was to identify clinical risk factors that are related to Failure to Maturate (FTM) AVF and whether such model could be applied to non HD population.

Methods: Prospective cohort study of patients with CKD at the Vancouver General Hospital (Canada) vascular access clinic who had an AVF created from April 2009 - April 2012. AVF maturation was defined by an experienced vascular access nurse. The primary outcome was failure to achieve functional patency (HD with 2 needles, blood pump speed >=350 for 12 consecutive treatments). Stepwise logistic regression was used for multivariable analysis.

Results: Functional patency was assessed in 200 patients (of 247 total; 13 died, 21 remain CKD-ND) of which 123 (61.5%) were radiocephalic. At AVF creation: 54.5% were CKN-ND, mean age 63.1y, 62.5% male, 47.5% white, 62.0% diabetes. 26.5% of AVFs failed (34.1% of lower arm vs. 14.3% of upper arm AVFs. P=0.002). Univariable predictors of AVF failure included: older age (P=0.03), female sex (P=0.05), smaller arterial diameter (P=0.001), lower arterial volume flow (P=0.04), smaller vein diameter (P=0.01), previous CVC or pacemaker (P=0.07). In multivariable analysis, age (OR 1.03, 95% CI 1.004-1.057), and artery diameter (OR 0.9, 95% CI 0.27-0.65) remained significant predictors of AVF failure. Older age, female sex, diabetes, peripheral vascular disease, race, and previous AVFs were not significantly associated. Vascular access nurse assessment 6 weeks postoperatively correctly predicted outcome in 83.8% of AVFs that achieved functional patency and 65.0% of AVFs that failed (kappa 0.45, p<0.0001).

Conclusions: Older age and smaller arterial size predict a higher risk of AVF failure. Failure to achieve functional patency is common for radiocephalic AVFs despite use of preoperative ultrasound mapping. Further studies are needed to determine which patients should proceed directly to an upper arm AVF.

TH-PO1084

Maturation of Arteriovenous Fistula and Parameters That Predict Failed or Delayed Maturity - A Single Centre Study

Background: Arteriovenous fistula (AVF) is the best vascular access for long-term haemodialysis. However, many fistulae (28-53%) never mature to support dialysis. The majority of these were salvageable with interventions. In our center, all fistulae have maturity assessment conducted by vascular access nurse between week 6 and 8. Those with maturation failure were investigated and/or discussed with primary vascular surgeon for appropriate early salvaging interventions.

Methods: We conducted a single center study to evaluate AVF maturation. Prospective data collected by vascular access nurse on all AVF created between January 2010 and December 2015 was reviewed. Patients who died before AVF maturity assessment were excluded. Clinically matured AVF was defined using the Kidney Disease Improving Global Outcomes (KDIGO) rule of 6’s. Secondary outcomes evaluated include: causes of maturity failure; numbers of salvage interventions performed and their success rate; and clinical predictors (e.g., age, gender, site of AVF, body mass index (BMI), venous and arterial diameter) for delayed maturity.

Results: 159 patients (71 females; mean age of 65) had primary AVF created and 42% (67/159) failed to mature. Significantly more female patients had failing to mature fistulae (p=0.05). There was no difference in mean age, diabetes, AVF site, arterial diameter and venous diameter. 78% of failed to mature fistulae (52/67) underwent salvage interventions with 60% success rate subsequently. Causes of maturity failure include: stenosis (44%), thrombosis (33%) steal syndrome (9%), accessory veins (4%) and deep AVF (13%). Factors associated with delayed maturity (>12 weeks, with or without salvage interventions) were female gender, site of AVF, body mass index (BMI), venous and arterial diameter for delayed maturity.

Conclusions: Failure to mature is a common issue with AVF but the majority is salvageable. Clinical assessment to detect early AVF failure is critical to improve rate of eventual maturation. Female gender, obesity and distal AVF were associated with delay maturation of AVF.

TH-PO1085

Correlation of AV Fistula Maturation with Scoring System - A Prospective Study from Developing Nation with Non White Population

Background: Choosing the most appropriate vascular access site is guided by many factors. A validated scoring system for the creation of AV Fistula (AVF) Failure to mature (FTM) and applied an existing clinical risk prediction model for AVF FTM. The main objective of this study was to identify clinical risk factors that are related to Failure to Maturate (FTM) AVF and whether such model could be applied to non HD population.
Methods: A prospective study was designed that included all patients undergoing AVF creation between February 2014 and February 2016 in a single centre of a city from developing nation, whose functional AVF outcome was observed 6 weeks after creation of fistula. The preoperatively determined FTM predicted risk model (Lok et al) was applied to our cohort.

Results: Out of 113 AVF, 72 (63.7%) matured and 41 (36.3%) failed to mature at 6 weeks. The FTM scoring was applied to our cohort. The variables that were considered were age ≥65 years, Coronary Artery Disease and Peripheral Vascular Disease. In our study all patients were non white race, the scores ranged between 3-10.5 There were no patients in the low risk category because all patients start with a score of 3. In the moderate risk category (score 3; 44/59 fistulas matured and 15 did not. In the high risk category (score 3.1-6.9), 25/47 fistulas matured and 22 did not. In the very high risk category (score ≥7), 3/7 matured and 4 did not. Thus, no maturation rates in the moderate, high, and very high risk categories were 25.4%, 46.8%, and 57.1% respectively, which was statistically significant (p<0.037).

Conclusions: Factors associated with AVF FTM are likely to vary from population to population. It is important to investigate local rates of AVF FTM and associated predictors of AVF patency in order to guide appropriate vascular access decision making. Clinical predictors of AVF FTM may not be sufficient on their own to improve vascular access functional patency rates. We suggest that the FTM score be revised as per population, and the categories be changed as follows for non white population: Low to moderate, moderate to high and very high risk categories.

TH-PO1086

Prediction of AVF Clinical Maturation from Postoperative Ultrasound (US) Michelle L. Robbin, Tom Greene, The HFM Study Group. NIDDK, NIH.

Background: The utility of early US measurements to predict AVF clinical maturation is uncertain. Primary unassisted and overall (assisted+ unassisted) clinical AVF maturation were related to centrally measured US parameters.

Methods: We explored the prognostic accuracies of clinical maturation prediction from US parameters at 1 day, 2 and 6 weeks after AVF creation in 602 study participants of the 7-center Hemodialysis Fistula Maturation Study. A backward selection algorithm chose independent US predictors of unassisted and overall maturation among AVF blood flow, mean vein diameter, vein depth, arterial diameter, presence of stenosis, and presence of accessory veins, accounting for AVF location (upper arm vs. forearm), 5 case mix factors (age, sex, AVF location, diabetes, dialysis status) and clinical center. Missing US measures were multiply-imputed.

Results: At each time point, AVF flow, diameter, and depth were predictive of both unassisted and overall maturation (Figure). Accounting for AVF flow, diameter and depth, none of the remaining US parameters, AVF location, or case mix factors improved prediction, but maturation probabilities differed significantly among clinical sites after accounting for all these parameters. Cross-validated areas under ROC curves for prognostic models based on only the three US parameters increased from 0.69 at 1 day to 0.74 and 0.79 at 2 and 6 weeks for primary unassisted clinical maturation, and 0.69, 0.71, and 0.76 respectively for overall maturation. The US-prognostic models classified 6%, 11%, and 19% of subjects at 1 day, 2 and 6 weeks for primary unassisted clinical maturation, and 0.69, 0.71, and 0.76 respectively for overall maturation. None of the remaining US parameters, AVF location, or case mix factors improved prediction.

Conclusions: Factors associated with AVF FTM are likely to vary from population to population. It is important to investigate local rates of AVF FTM and associated predictors of AVF patency in order to guide appropriate vascular access decision making. Clinical predictors of AVF FTM may not be sufficient on their own to improve vascular access functional maturation rates. We suggest that the FTM score be revised as per population, and the categories be changed as follows for non white population: Low to moderate, moderate to high and very high risk categories.

TH-PO1087

Ultrasound-Guided Evaluation of Fistulas Safely Decreases Time to Cannulation and Catheter Removal Orlando Nicholas Machado, 1,2 Farzin Farpour,1,2 Tina Adjei-Bosompem,1 George N. Cortisidis,1,2 1Div of Nephrology, Elmhurst Hospital, Icahn School of Medicine at Mt Sinai, Queens, NY; 2Broadway Dialysis Center, Queens, NY.

Background: Use of bedside ultrasonography (USG) has dramatically increased in Medicine. Our dialysis center has used USG to evaluate arterio-venous fistula (AVF) maturation. Retrospective data from our center show significant improvement in time to cannulation without increased complications. We now present prospective data using USG as an aid to cannulation.

Methods: AVF cannulation based on physical exam alone from 2012-2014 was compared to USG cannulation using USG 2014-2016. AVF maturation criteria were Diameter ≥6mm, Depth ≤6mm, Length ≥6cm. If by 4 weeks these criteria were not met the AVF was classified as failure of maturation (FOM). Examinations were done by fellows after completing the Emory renal-ultrasound course. Need for interventional radiology was considered a complication (early, 0-3 months; late, 4-12 months).

Results: 8/13 patients had USG for AVF cannulation compared to 12/29 as control. The remainder were FOM. Age and ethnic makeup were similar. USG examined AVFs had the shortest time to cannulation (17 days earlier, p<0.05) and dialysis catheter (DC) removal (<100 days earlier, p<0.005). FOM results using USG were similar, except for fewer complications (0 vs. 10, p<0.05). Bloodstream infection rates were similar.

Conclusions: USG resulted in early and safe AVF cannulation and earlier removal of DCs. USG also helped identify FOM allowing for earlier cannulation in this group (p<0.07).

TH-PO1088

Central Venous Oxygen Saturation as a Novel Means to Monitor Arterio-Venous Fistula Maturation Israel Campos,1 Hanjie Zhang,1 Schantel Williams,1 Stephan Thijssen,1 Peter Kotanko,1,2 1Renal Research Inst, New York, NY; 2Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Most patients start hemodialysis (HD) with a central-venous catheter (CVC) as vascular access. Whenever possible, an arterio-venous fistula (AVF) is created, which will serve as a permanent vascular access after an appropriate maturation time. Progress of fistula maturation is primarily evaluated clinically. Central venous oxygen saturation (ScvO2) can be measured using Crit-Line® monitor in HD patients with a CVC. The main objective of this study was to assess the change in ScvO2 after AVF creation.

Methods: We analyzed ScvO2 measurements before and after AVF creation using Crit-Line® monitor (Fresenius Medical Care, Waltham, MA). We compared the four closest values of ScvO2 before AVF creation, the first three ScvO2 measurements after AVF creation and the last three ScvO2 measurements before AVF cannulation; finally we compared these values with the first two ScvO2 measurements after AVF cannulation day.

Results: We studied 6 patients. Mean ScvO2 before AVF creation was 63.2 ± 0.3% and increased to 74.1 ± 0.8% after AVF creation. The average ScvO2 of the final 3 HD sessions immediately preceding the first AVF cannulation was 76.1 ± 0.8%. After AVF cannulation arterial and no longer central venous blood circulated in the extracorporeal system with a mean oxygen saturation of 92.9 ± 0.2% (Figure 1).
not associated with A VF maturation in a large prospective cohort study of ESRD patients.

Central venous backflow to the right heart. This increase in ScvO\textsubscript{2} is recorded by the monitor to objectively track the A VF maturing process.

Jonathan Kubiak,1 Bryan R. Kestenbaum,1 Leila R. Zelnick,1 Jonathan Himmelfarb,2 Gerald J. Beck,3 The HFM Study Group,1 2NIDDK, NIH; 3Cleveland Clinic Foundation.

Background: The arteriovenous fistula (A VF) is central for providing life sustaining hemodialysis treatments. However, half of all A VFs fail to mature within the toxic environment of end stage renal disease (ESRD). Disturbances in mineral metabolism affect most ESRD patients and may impair AVF maturation by disrupting endothelial function and promoting vascular calcification. We hypothesized that lower serum concentrations of vitamin D metabolites and higher concentrations of FGF-23 and phosphate would be associated with AVF maturation failure.

Methods: We evaluated 562 participants from the Hemodialysis Fistula Maturation study, a multicenter study of ESRD patients undergoing planned A VF creation. At the pre-surgical study visit, we measured serum concentrations of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and 24,25-dihydroxyvitamin D using liquid chromatography-mass spectrometry, fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH) using immunoassays, and phosphate and calcium. We used Poisson regression with robust errors to estimate associations of mineral metabolism markers with unassisted A VF maturation – or the failure thereof – using ScvO\textsubscript{2}. We observed a ScvO\textsubscript{2} rise after A VF creation. If successful, ScvO\textsubscript{2} values could be used as a novel means to objectively track the AVF maturing process.

Funding: NIDDK Support

TH-PO1090

Postoperative Medial Fibrosis Predicts Maturation Failure in Two-Stage Arteriovenous Fistulas

Laisel Martinez,1 Juan Camilo Duque Ballesteros,2 Marwan Tabbara,1 Angela Paez,1 Guillermo Selman,1 Loay H. Salman,3 Roberto I. Vazquez-Padron.1 1DeWitt Daughtry Family Dept of Surgery, Leonard M. Miller School of Medicine, Univ of Miami, Miami, FL; 2Dept of Medicine, Miller School of Medicine, Univ of Miami, Miami, FL; 3Section of Interventional Nephrology, Miller School of Medicine, Univ of Miami, Miami, FL

Background: The purpose of this study is to evaluate the impact of vascular fibrosis on arteriovenous fistula (AVF) outcomes.

Methods: Native vein and justa-anastomotic AVF biopsies were obtained from patients undergoing two-stage AVF creation. Pre-existing, postoperative and change in intimal and medial fibrosis (% area of collagen) were quantified in Masson’s trichrome stained cross-sections using color thresholding methods. Associations between vascular fibrosis and clinical outcomes (maturation failure and unassisted primary patency) were assessed using logistic regressions and Cox proportional hazards models adjusted for sex.

Results: Intimal and medial fibrosis in native veins (n=63) ranged from 10.1 to 71.7% and 16.2 to 64.8%, respectively. Nonetheless, neither measure of pre-existing fibrosis was associated with AVF outcomes. Postoperative intimal and medial fibrosis in AVF (n=78) ranged from 16.5 to 66.7% and 25.7 to 74.3%, respectively. Increased postoperative medial fibrosis, but not intimal fibrosis, predicted maturation failure (odds ratio [OR] 1.078, p<0.022), and this effect was more pronounced using the collagen/cell area ratio (OR 1.368, p<0.038). None of the measures of postoperative fibrosis were associated with primary patency. Change in fibrosis over time was assessed in 54 patients from whom both vein and AVF biopsies were available. Supporting the postoperative fibrosis association, a higher increment in medial fibrosis, but not intimal fibrosis, predicted maturation failure (OR 1.106, p<0.032) but not primary patency.

Conclusions: Our results suggest that elevated fibrosis and loss of medial smooth muscle cells are signatures of adverse AVF remodeling and predispose for early access failure. In contrast, increased fibrosis does not appear to determine the long-term potency of working fistulas.

Funding: NIDDK Support

TH-PO1091

Association between Preoperative Venous Medial Collagen Fiber Configuration and Arteriovenous Fistula Development

Yan-Ting E. Shiu,1 Silvio H. Litovsky,1 Alfred K. Cheung,1,2 Daniel Piek,1 C.S. Jason Tey,1 Y. Zhang,1 Carlson J. Young,2 Michael Allon,2 1U of Utah; 2U of Alabama; 1VASLCHCS.

Background: Arteriovenous fistula (AVF) maturation requires an increase in the diameter and blood flow of the fistula vein following its creation. The native vein wall’s microstructure may affect the magnitude of these changes. We hypothesized that the orientation of collagen fibers in the venous media modulates the vein’s capacity to dilate and mature.

Methods: Veins used for anastomosis were sampled during AVF creation surgery. The second harmonic generation (SHG) signals of collagen fiber bundles in vein samples were analyzed for anisotropy index (AI) and orientation angle (OA). AI ranged from 0 (random fiber network) to 1 (completely aligned fiber network). OA ranged from 0° (parallel to lumen) to 90° (perpendicular to lumen). The fiber configuration index (FCI) was defined as the product of AI and sin(OA). Unadjusted gamma regressions with natural cubic splines were used to model the association of the FCI in 84 patients and their 6-week AVF blood flow assessed using ultrasound.

Results: Venous medial collagen fiber patterns varied among patients with end-stage renal disease (Fig. 1A). The 6-week AVF blood flow was positively associated with the collagen FCI (per 0.1 unit difference in FCI: A blood flow = 131 ml/min; 95% CI, 8 to 254 ml/min; p=0.038) (Fig. 1B). The FCI of clinically matured AVFs (those successfully used for dialysis) was significantly higher than that of non-matured AVFs (0.13±0.07 vs. 0.08±0.05, p=0.02).

Conclusions: The venous medial collagen fiber orientation was associated with subsequent AVF development. Veins with collagen fibers more uniformly aligned perpendicular to the lumen were associated with higher AVF blood flow and clinical maturation by yet undefined mechanisms.

Funding: NIDDK Support

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

Underline represents presenting author.

350A
Uremic Regulation of Endothelial Krüppel-Like Factor 2 in Arteriovenous Fistula (AVF) Maturation Failure

Keith Louis Saum,1 Begoña Campos,1 Diego Celdran-Bonafonte,2 Albert Philip Owens,1 Prabir Roy-Chaudhury,2 1Univ of Cincinnati; 2Univ of Arizona.

Background: AVF maturation failure resulting in prolonged dialysis catheter exposure, is an important cause of clinical morbidity and mortality. The endothelial transcription factor Krüppel-like factor 2 (KLF2) is an important regulator of vascular homeostasis linking changes in hemodynamics to inflammation, vasodilation, and vascular remodeling. While KLF2 expression plays a critical role in arteriogenesis, little is known about its role in AVF maturation failure. Our objective was to determine how endothelial KLF2 is regulated in vitro by uremic metabolites and translate these findings into a uremic mouse model of AVF maturation failure.

Methods: Human umbilical vein endothelial cells (HUVECs) were cultured with uremic toxins, including carbonyl myoglobin lysine (CML), an advanced glycation end product (AGE), and analyzed for KLF2 expression by qPCR and western blotting. In addition, C57BL/6J mice underwent 5/6 nephrectomy to produce renal insufficiency followed by AVF creation (after 14 days). The venous segment of the AVF was harvested 14 days post-AVF creation and KLF2 expression assessed by immunohistochemistry (IHC) and qPCR.

Results: CML treatment of HUVECs decreased KLF2 mRNA and protein expression, which was rescued by siRNA-RAGE ablation. Similarly, KLF2 decreased in the endothelium of uremic versus non-uremic mice (IHC). Interestingly, KLF2 was upregulated in the neointima of uremic mice, which corresponded to a three-fold increase in KLF2 venous segment mRNA expression in uremic versus non-uremic mice.

Conclusions: Our results suggest that uremia can suppress endothelial KLF2 in-vitro and in-vivo. However, uremia increases KLF2 expression within the neointima (smooth muscle cells) of the AVF. Ongoing studies utilizing endothelial and myeloid-specific KLF2 knockout mice will further delineate these mechanisms and also identify the specific roles of KLF2 in AVF stenosis. This data could then be used to develop novel therapies that target the KLF2 pathway in order to enhance AVF maturation rates.

Quantification of Venous Adaptation in Patients with Brachiocephalic Fistula Access

Mary S. Hannes,1 Kevin Cassel,2 Michael Boghosian,2 S.M. Javid Mahmoudzadeh A.2 1Univ of Chicago; 2Illinois Inst of Technology.

Background: While angiography provides two-dimensional lumenography, the intraluminal surface of an arteriovenous fistula (AVF) is often a complex three-dimensional structure. Intravascular ultrasound (IVUS) is a technique using a high frequency ultrasound transducer on the tip of a catheter inserted directly into a blood vessel to obtain a series of high-resolution three-dimensional images. The aim of the current study was to reconstruct three-dimensional images of the cephalic arch in patients with brachiocephalic fistula access as the basis for computational modeling of the hemodynamics.

Methods: 13 IVUS procedures were performed in 8 subjects. A Doppler for blood flow velocity, venogram and blood sample were collected for whole blood viscosity. An IVUS catheter was then inserted into the cephalic arch to the axillary vein and pull back measurements were made. Image analysis and reconstruction with computational modeling were performed to determine the hemodynamics, including wall shear stress (WSS), velocity and pressure profiles.

Results: An example of a three-dimensional reconstruction is shown. The graphic on the top shows velocity magnitude contours highlighting regions of interest such as abnormally low and high velocities and locations of recirculation and swirl.

Conclusions: The ability to assess vessel wall morphology and luminal characteristics of diseased veins in an AVF is a novel application of IVUS and may ultimately improve the understanding of hemodynamic determinates of AVF function.

Funding: NIDDK Support, Other NIH Support - National Institute of Diabetes and Digestive Diseases (NIDDK) and the National Institutes of Health (NIH) under award number R01DK090769

TH-PO1094

In Vitro Analysis of Vascular Access Flow by Laser Doppler Vibrometry

Camille Johnson,1 Israel Campos,1 Schantel Williams,1 Jie Ma,1 Laura Rosales,1 FANSAN Zhu,1 Peter Kotanko,1,2 1Renal Research Inst, New York, NY; 2Cahn School of Medicine at the Mount Sinai Hospital, New York, NY.

Background: A contact-free assessment of arterio-venous access (AVA) flow is currently elusive. Laser Doppler vibrometry provides a novel means to quantify flow-induced AVA vibrations (“thrill”) and may thus assist in diagnosing AVA malfunction.

Methods: We engineered an AVA bench model (Fig. 1) to systematically study the effects of lumen stenosis on radial velocities of an artificial AVA conduit. Flow (Qa) was provided by a pump delivering pulsatile patterns resembling arterial flow (Model 1423, Harvard Apparatus. Holliston, MA, USA). We kept Qa constant at 1500 mL/min (stroke volume 30 mL; stroke rate 50/min). AVA conduit inflow and outflow stenoses were applied by graduated lumen constrictions (Fig. 1). Stenoses were either partial (50% stenosis), or complete (100% stenosis). AVA conduit radial velocities were measured by laser Doppler vibrometry (PDV-100, Polytec, Waldbronn, Germany). Radial velocity data are presented in mm/s and as mean±SD.

Conclusions: The ability to assess vessel wall morphology and luminal characteristics of diseased veins in an AVF is a novel application of IVUS and may ultimately improve the understanding of hemodynamic determinates of AVF function.

Funding: NIDDK Support, Other NIH Support - National Institute of Diabetes and Digestive Diseases (NIDDK) and the National Institutes of Health (NIH) under award number R01DK090769
Results: The highest radial velocities were observed with complete outflow stenosis and concurrent absent or partial inflow stenosis. Irrespective of the degree of outflow stenosis, any inflow stenosis drastically reduced radial conduit velocities (Table 1; Fig. 2).

Conclusions: This bench research shows that both inflow and outflow stenosis affects the radial velocities of AVA conduits to an extent that can be quantified by laser Doppler vibrometry. Moreover, this study indicates that laser Doppler vibrometry can potentially distinguish between inflow and outflow stenosis. While these results are encouraging, in vivo studies are warranted to determine if these experimental findings can be replicated in a clinical setting. To that end, analysis of access flow pressures and thrill frequency spectra may add to our understanding of the system dynamics.

TH-PO1096
A Novel Mathematical Model to Non-Invasively and Contact-Free Assess Arterio-Venous Access Characteristics
Ahaii Chen1, Doris H. Fuertinger1, Valtibav Maheshwari1, Israel Campos1, Camille Johnson1, Schantel Williams1, Jie1, Laura Rosales1, Fannsin Zhu1, Peter Kottke2,1 Renal Research Inst, New York, NY; 1Icahn School of Medicine, Mount Sinai Hospital, New York, NY.

Background: While clinically desirable, a non-invasive and contact-free assessment of arterio-venous (AV) access characteristics is elusive. The aim of the current work is to assess the applicability of a novel theoretical model with laser Doppler vibrometer (LDV) data to analyze AV access characteristics.

Methods: We engineered a bench model where a pump (Model 1423, Harvard Apparatus, MA) produced pulsatile flow with arterial characteristics in a tube that resembled an AV access. The vibrations (“thrum”) the AV access model were then quantified with LDV (PVD-100, Polytec, DEU). Using dimensional analysis informed by a 1D Navier-Stokes equation describing the relationship between flow and cross-sectional area of a compliant vessel, we derive an expression (Fig. 1) relating the radial velocity of the vessel wall (VR) and the flow rate (Q) with characteristic parameters a=1/(2*pi*R0*L) and b=mu/(E*h), where R0, L, E, h and μ are reference radius, vessel length, Young’s modulus, wall thickness, and fluid viscosity, respectively.

Results: Using LDV signals, we fit the model to the data and estimated the characteristic parameters with goodness of fit coefficients R2=0.968 and adjusted R2=0.964 (Fig. 1). The results show the relationship between the VR and Q exhibits a functional shape where the velocity increases linearly until the vessel compliance (viscoelasticity) dominates.

Conclusions: The preliminary results illustrate the use of LDV and modeling to evaluate AV access characteristics with a good model-data fit. Further studies and modeling efforts are needed to explore the robustness of the modeling framework to identify the characteristics of AV access both in bench and clinical studies.

TH-PO1097
De Novo Induction of Mineralocorticoid Receptors in Vascular Tissue Mediates Hemodialysis Fistula Dysfunction
Pei Wang1,2, Andrew S. Brem1, Xianhui Liang1, Minglei Lu1, Zhengguo Liu1, Rujun Gong1, Nephrology, Brown Univ; 1The First Affiliated Hospital of Zhengzhou Univ, China.

Background: Fistula stenosis is a major cause of vascular access failure in patients undergoing maintenance hemodialysis (HD). Since mineralocorticoids can induce inflammation and fibrosis in vascular tissues, we hypothesized that these sterols may play a role in fistula failure.

Methods: Mineralocorticoid receptor (MR) expression was examined in normal human veins and in the dysfunctioning fistulae by immunohistochemistry. The effects of aldosterone were also measured in cultured vascular smooth muscle cells (VSMC) programmed to over express MR. Lastly, as a clinical correlate, we measured MR expression on sphenoid bone because of cardiac disease were compared to age matched controls on HD and fistula patency was evaluated.

Results: Dysfunctioning stenotic fistulae exhibited a marked thickening of the intima and media. Overexpression of aldosterone demonstrated proliferation [staining for proliferating cell nuclear antigen (PCNA)] and hypertrophy [large cellular size plus staining for phosphorylated p70S6K, a transducer of the mTOR pathway associated with cellular hypertrophy]. While normal veins express minimal MR, a marked increase in MR expression was observed in affected VSMC with a pattern of distribution across all tunicae layers of the fistula, and this positively correlated with the intima-media thickness. Cultured VSMC over expressing MR (GFPI-MR=147) showed excessive cellular proliferation [measured by the tetrazolium assay and PCNA expression] and hypertrophy [measured by protein to DNA ratio], compared to control cells (P<0.05). Moreover, aldosterone induced p70S6K phosphorylation (10 nM). These effects were largely abolished by the MR antagonist spironolactone (1 μM). Lastly, patients on HD who received spironolactone exhibited an improved rate of fistula patency compared to control HD patients.

Conclusions: MR is induced in fistula VSMC probably from baro-trauma associated injury. Excess expression of MR in the presence of physiologic concentrations of aldosterone promotes cell proliferation and hypertrophy leading to fistula stenosis. MR antagonism may be a promising therapy for retarding the progression of fistula stenosis in patients on HD.

Funding: NIHDK Support, Government Support - Non-U.S.

TH-PO1098
Association of Genetic Polymorphisms of Renin–Angiotensin– Aldosterone System-Related Genes with Arterio-Venous Fistula Malfunction in Hemodialysis Patients
Chih-Ching Lin1, Yaeni Kim2
1Div of Nephrology, Dept of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; 2School of Medicine, National Yang Ming Univ, Taipei, Taiwan.

Background: Hemodialysis (HD) is the most commonly-used renal replacement therapy for patients with end-stage renal disease worldwide. Arterio-venous fistula (AVF) is the vascular access of choice for HD patients with lowest risk of infection and thrombosis. In addition to environmental factors, genetic factors may also contribute to malfunction of AVF. Previous studies have demonstrated the effect of genotype polymorphisms of angiotensin-converting enzyme access malfunctions and relationships to HD outcomes.

Methods: We conducted a multicenter, cross-sectional study to evaluate the association between genetic polymorphisms of renin-angiotensin-aldestosterone system and AVF dysfunction.

Results: Totally, 577 patients were enrolled. Their mean age was 60 years old and 53% were male. HD patients with AVF malfunction had longer duration of HD (92.5 ± 68.1 vs. 61.2 ± 51.9 months, p < 0.001), lower prevalence of hypertension (44.8% vs. 55.3%, p = 0.025), right-sided (31.8% vs. 18.4%, p=0.002) and upper arm AV (28.6% vs. 7.9%, p < 0.001). Moreover, mean dynamic venous pressure (DVP) (147.8 ± 28.3 vs. 139 < 30.0, p = 0.021). In subgroup analysis of different genders, location of AVF and DVP remained significant clinical risk factors of AVF malfunction in univariate and multivariate binary logistic regression in female HD patients. Among male HD patients, right-side AVF and upper arm location are two important clinical risk factors. In addition, two single nucleotide polymorphisms (SNPs), rs275653 (Odds ratio 1.90, p < 0.038) and rs1492099 (Odds ratio 2.29, p = 0.017) of angiotensin II receptor 1 (AGTR1), were associated with increased risk of AVF malfunction. After adjustment for age and other clinical factors, minor allele-containing genotype polymorphisms (AA and CA) of rs1492099 still remained to be a significant risk factor of AVF malfunction (Odds ratio 3.63, p < 0.005).

Conclusions: In conclusion, we demonstrated that rs1492099, a SNP of AGTR1 gene, could be a potential genetic risk factor of AVF malfunction in male HD patients.

Funding: Government Support - Non-U.S.

TH-PO1099
Oxidative Stress-Induced High Mobility Group Box 1 (HMGB1) Stimulates Monocyte Chemoattractant Protein-1 (MCP-1) Expression in the Human Umbilical Vein Endothelial Cells (HUVECs)
Jeong-Sun Han, Yaein Kim, Yong-Soo Kim
Division of Nephrology, Dept of Internal Medicine, Catholic Univ of Korea College of Medicine, Seoul, Korea.

Background: Oxidative stress and inflammation are the main causes of vascular intimal hyperplasia and subsequent stenosis of hemodialysis arteriovenous fistula. In our previous study, oxidative stress directly stimulated the MCP-1 expression. In this study, we studied whether HMGB1 was involved in the process of oxidative stress-induced MCP-1 expression.

Methods: HMGB1 mRNA and MCP-1 mRNA were measured by quantitative real-time PCR. MCP-1 protein expression was measured by ELISA. HMGB1, MAPK, NF-kB and AP-1 activities were measured by western blot. Glycyrrhizin or a monoclonal antibody to TL4 was used to inhibit HMGB1.

Results: After treating HUVECs with H2O2, MCP-1 mRNA and protein expression was significantly increased in a time- and dose-dependent manner. When the cells were pre-treated with inhibitors of p38 (SB203580), JNK (SP60012), AGTR1 (Losartan), H2O2-induced HMGB1 mRNA expression was significantly decreased. When the cells were treated with HMGB1, the MCP-1 mRNA and protein expression was significantly increased in a time- and dose-dependent manner. When the cells were pre-treated with glycyrrhizin or a monoclonal antibody to TL4, the HMGB1-induced MCP-1 expression was blocked in a time- and dose-dependent manner. HMGB1 treated cells stimulated phosphorylation of p38, JNK, c-Jun and p65 together with a decrease in IκBα.

Conclusions: Oxidative stress-induced MCP-1 expression in HUVECs is partially mediated by HMGB1 via the TLR4/p38/JNK/AP-1 pathway. This study suggests that HMGB1 inhibition in vein endothelial cells might be a challenge to prevent venous neointimal hyperplasia in hemodialysis arteriovenous fistula.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
352A
High-Mobility Group Box Protein 1 (HMGB1) Induces Endothelial-to-
Mesenchymal Transition (EndMT) in Human Umbilical Vein Endothelial Cells (HUEVCs) Jeong-Sun Han, Yaeni Kim, Yong-Soo Kim. Div of Nephrology, Dept of Internal Medicine, The Catholic Univ of Korea College of Medicine.

Background: Myofibroblasts are the major cells within the venous neointima in stented hemodialysis vascular access. However, the origin of the myofibroblasts has not been clearly determined. In our previous study, oxidative stress stimulated HMGB1 expression in HUEVCs. In this study, we investigated whether HMGB1 induced EndMT in HUEVCs.

Methods: After stimulating the HUEVCs with HMGB1, the key biomarkers for endothelial and mesenchymal cells were evaluated by fluorescent immunocytochemistry and western blot. EndMT transcription factors (snail1, snail2, and twist1) were measured by RT-qPCR in a dose dependent and in a time dependent manner up to 48 hours. In addition, HMGB1 stimulated the expression of TGF-β1, and the phosphorylation of smad2/3 and NF-κB p65. When the cells were pre-incubated with antibodies to HMGB1 receptors, TLR4 or RAGE, the changes in HMGB1-induced EndMT were studied.

Results: HUEVCs were normal round shape with cobble stone appearance with strong labeling of CD31, VE-cad, and vWF, but a-SMA was not expressed in the cells. When the cells were exposed to HMGB1, cells changed into the spindle shape with decreased expression of CD31, VE-cad, vWF and high expression of a-SMA. Western blot revealed same changes in biomarkers before and after HMGB1 treatment. When the cells were pre-incubated with antibodies to HMGB1 receptors, TLR4 or RAGE, the changes in HMGB1-induced endothelial and mesenchymal biomarkers were reversed in a dose dependent manner. HMGB1 stimulated the expression of EndMT transcription factors (snail1, snail2, and twist1) in a dose dependent and in a time dependent manner up to 48 hours. In addition, HMGB1 stimulated the expression of TGF-β1, and the phosphorylation of smad2/3 and NF-κB p65. When the cells were pre-treated with anti-RAGE antibody or Glycyrrhizin, the expression of TGF-β1 by HMGB1 were reduced. When the cells were pre-incubated with SB431542, the changes in the HMGB1-induced endothelial and mesenchymal biomarkers were reversed in a dose dependent manner.

Conclusions: To our knowledge, this is the first report showing that HMGB1 induces EndMT via the RAGE/TGF-β1 signaling in the venous endothelial cells. These data might provide a new mechanism of myofibroblasts accumulation within the venous neointima in stented hemodialysis vascular access.

Funding: Government Support - Non-U.S.

TH-PO1101

Selecting End Points for Pivotal Hemodialysis AV Fistula Clinical Trials - Anatomical Surrogates versus Functional Suitability Maria V. De Vita, Eric S. Chemla, Konstantine B. Kipiani, Srimat Iyer. 1 Div of Nephrology, Lenox Hill Hospital, New York, NY; 2Vascular Surgery, St. George’s NHS Trust, London, United Kingdom; 3Vascular Surgery, Georgian Center of Angiology and Surgery, Tbilisi, Georgia; 4Vascular Therapies Inc, Cresskill, NJ.

Background: Although an ultrasound (US) vein diameter (VD) of 4mm and AVF blood flows >500mL/min are often proposed/used as surrogates to support fistula functionality, these parameters have never been validated in large clinical trials. Anatomical AVF patency, a “successful metric” in pre-dialysis patients, correlates poorly with functional use; in the DAC flows >500mL/min are often proposed/used as surrogates to support fistula functionality.

Methods: 30 pts undergoing AVF surgery [22 Radiocephalic (RCF), 8 Brachiocephalic (BCF)] received a Sirolimus eluting collagen implant around the anastomosis. Serial US was performed. Cannulation decisions were based on clinical exam.

Results: Pre op mean: VD for RCF and BCF were 2.71±0.5 and 3.91±0.6mm. 4. RCF thrombosed within 2 weeks(8), 26 AVF (87%) were successfully cannulated for D (Mean 7w). Relative to cannulation, VD in 22/26 AVF (85%) was ≥6 mm (Range: 5.1-10 mm), there were no infiltrations. At 12mos 74% of AVF maintained functional patency.

Funding: National Heart, Lung, and Blood Institute (5R01HL096130-02 & K07HL096130-01). The views expressed herein are those of the authors and do not reflect the official policy of the Department of VA, Department of Defense or the US government.

TH-PO1102

The Effect of Beraprost Sodium to Treat Primary Hemodialysis Vascular Access Failure Hyun Woo Kim, Miyeon Kim, Tae Hee Kim. 1 Dept of Internal Medicine, Jeju National Univ, School of Medicine, Jeju National Univ Hospital, Jeju-si, Jeju-do, Korea; 2Dept of Internal Medicine, Inje Univ College of Medicine, Busan, Korea.

Background: Hemodialysis vascular access dysfunction is a major cause of morbidity and hospitalization in the hemodialysis patients. The major cause of hemodialysis vascular access failure has been reported to be venous stenosis as a result of neointimal hyperplasia. Although several studies suggest a role for antiplatelet agents in the prevention of hemodialysis vascular access failure, it has not been complete. It has been reported that prostaglandin I1 has pleiotropic effects including antiplatelet, vasodilating, anti-inflammatory and anti-thrombogenic properties. In addition, several studies have shown that prostaglandin I1 can inhibit the neointimal formation generated after vascular injury.

Methods: The purpose of this study was to research the effects of beraprost sodium, an oral synthetic analog of prostaglandin I1, on vascular access patency in hemodialysis patients with primary hemodialysis vascular access failure. The primary outcome was secondary vascular access failure. Between April 2013 and February 2014, forty-nine patients with end stage renal disease on hemodialysis were prospectively chosen for this study. Twenty-three patients were assigned to be treated with 120 μg/day of beraprost sodium and the other patients (n=26) were assigned to a control group.

Results: After a median follow-up of 3.0 years (interquartile range 1.8-3.1 years), the secondary vascular access failure was detected in twelve patients (46%) in control group and fourteen patients (17%) inberaprost sodium group, respectively (P = 0.032). Analysis of covariables indicated that this effect occurred principally as a result of beraprost sodium administration. No life-threatening adverse event or severe bleeding was recorded in both groups.

Conclusions: Our data indicated that oral prostaglandin I1 is effective and safe for the prevention of secondary vascular access failure in hemodialysis patients with primary vascular access failure.

Funding: National Health Insurance Service (Health Insurance Fund)

TH-PO1103

Palliative and End of Life Care for End Stage Renal Failure Patients Managed without Dialysis in Denmark. A National Survey Jens Kristian Madsen, Fliss E. Murtagh. 1Dept of Renal Medicine, Aarhus Univ Hospital, Aarhus, Denmark; 2King’s College London, Cicely Saunders Inst, London, United Kingdom.

Background: In Denmark, there is a growing focus on conservative kidney management (CKM) for older frail patients with end stage renal failure (ESRF). This survey aimed to assess the current provision of palliative and end of life (EOL) care to Danish patients with ESRF following a non-dialytic pathway or discontinuing dialysis. Methods: An electronic questionnaire was sent to all Danish hospital-employed nephrologists and department nurses (15 centres). Data were handled anonymously. Descriptive statistics were used for analyses.

Results: 140 senior renal staff were invited. The response rate was 83%, including 93% (14/15) of medical directors/head physicians. All units had CKM patients, but numbers were mostly unknown. When asked whether nephrologists had same practice regarding choice of CKM for ESRF patients, 24% of respondents answered ‘yes’, 58% answered ‘no’, and 18% answered ‘don’t know’. Criteria of patients’ suitability for CKM were similar. Criteria for timing discussion of CKM with patients differed (at a certain level of renal function, 33%; at low-clearance clinic referral, 17%; not known, 15%; when symptoms, 11%; other, 24%). One renal centre had a dedicated clinic, one centre had treatment guidelines, and 12% staff had training in CKM. Follow-up mostly occurred in general renal outpatient clinics (75%). Advance care planning (ACP) was formally practiced in two units. One third of respondents reported involvement of specialist palliative care (SPC) with CKM patients at EOL and when stopping dialysis. Only 7% did not see a future role for SPC for ESRF patients. Suggestions for improvement were more education (87%), better collaboration (67%), and implementation of ACP (64%).

Conclusions: Great variation exists in practices patterns of delivery of palliative and EOL care for Danish ESRF patients managed without dialysis or discontinuing dialysis. Formal CKM pathways are not yet developed. Nephrologists report that SPC is under-utilized among Danish ESRF patients at the end of life. Education and better collaboration between specialties are key elements in further development.

TH-PO1104

The Practice of Withholding of and Withdrawing from Dialysis Treatment to Patients with Persistent Vegetative State in Affluent Arabic Countries: Renal Physician Survey Ow man Bachou, Ahmed Chaaban, Mona Alrukhaimi, Bassam Bernheim. 1Nephrology Dept, Tsawwam Hospital, Al Ain, AbuDhabi, United Arab Emirates; 2Internal Medicine, Dubai Medical College, Dubai, United Arab Emirates; 3College of Medicine and Health Sciences, United Arab Emirates Univ, Al Ain, AbuDhabi, United Arab Emirates.

Background: Persistent vegetative state (PVS) is severe disability which requires full care. Potential non-therapeutic benefits of PVS is associated in patients with persistent vegetative state. The number of dialysis patients with persistent vegetative state (PVS) is increasing worldwide. In United Arab Emirates, 29 patients out of 650 patients on regular dialysis treatment were in PVS. This study aimed to explore the practice patterns of withhold and withdrawal of dialysis in patients with PVS in affluent Gulf Arabic countries.

The survey was completed by 29 nephrologists taking care of patients with ESKD. 83% of respondents will continue dialysis if a dialysis patient went into persistent vegetative state, furthermore dialysis will be initiated by 55% of respondents if a PVS patient developed severe renal failure. Institutional haemodialysis is most common modality (81%) offered to PVS. The respondents identify the cultural background (76%), the local policy (72%), and the religious background (65%) to be the major impacts on the decision making process for ongoing dialysis treatment for patients with PVS.

Conclusions: The contextual sociocultural factors and the preferences of the patient’s proxy strongly influence the physician decisions for initiation and continuation of dialysis treatment for patients in PVS. Early integration of quality palliative care within the healthcare system for such severely ill patients is required to face the increasing burden of PVS in such developing affluent countries.

TH-PO1105

‘La Familia es lo mas Importante’: Palliative Care Perspectives of Latinos on Dialysis

Lilia Cervantes,1,2 Claudia Camacho,1 Maria Francisca Zabalaga Palma,1 Stacy M. Fischer.1 1Univ of Colorado; 2Denver Health.

Background: Patients with end-stage renal disease (ESKD) have a high symptom burden and mortality yet palliative care is often overlooked. Hispanics have a nearly 2-fold higher incidence of ESRD and suffer disproportionately at end-of-life (EOL) compared to nonHispanic white. The purpose of our study was to understand the palliative care experiences and preferences of Hispanics on dialysis.

Methods: We conducted qualitative, semi-structured interviews with Hispanic ESRD patients. We used an interview guide with open-ended questions to elicit the patient’s palliative care experiences and preferences with advance care planning. Interviews were audio-recorded, transcribed, and then analyzed by four members using a deductive approach.

Results: We interviewed 20 Hispanic ESRD patients between October 2015 and January 2016. Our qualitative theme analysis yielded five main themes: Family, advance care planning (ACP), patient preferences and experiences with advance care planning, interviews were audio-recorded, transcribed, and then analyzed by four members using a deductive approach.

Conclusions: The survey results suggest that decreased QOL is the most common reason for patients and/or families to initiate supportive care discussions. The study also reveals tools that clinic staff and patients/families may find helpful to facilitate discussions on supportive care options. Overall, these survey findings reinforce the need for strategies that support patient’s values and wishes in regards to supportive care.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO1106

Improving Comfort with Comfort Care Discussions

Julia Henmert,1 Elke Quint2,1 Faisal Rehman,1 Valerie Schulz,1 Norman Murieha,2 1Nephrology, London Health Sciences Centre, London, ON, Canada; 2Schulich School of Medicine & Dentistry, London, ON, Canada; 1Perioperative Medicine & Anesthesia, London Health Sciences Centre, London, ON, Canada.

Background: Previous studies have demonstrated a gap in nephrology training on end-of-life discussions. We addressed this deficiency in the curriculum by creating a goals of care (GOC) discussions workshop using role plays and didactic teaching.

Methods: We designed and implemented a 3 hour workshop consisting of a didactic session on an evidence based approach to GOC discussions in chronic kidney disease patients, followed by small group simulations to practice this approach. Participants included nephrologists, a palliative care physician, nurses, social workers, Standardized Patients (SP) and nephrology fellows. Small group participants were divided into four teams led by a pre-selected staff nephrologist. Nephrology fellows led two, and observed one, of two simulated family meetings discussing: 1) withdrawing from dialysis in a frail patient and 2) conservative management in end-stage renal disease. At the end of each scenario the fellows received constructive feedback from the other participants. Participants evaluated their experience using anonymous surveys containing 7 questions evaluating the appropriateness of the workshop using a 5 point Likert scale and additional space for comments.

Results: 14 out of 16 participants completed the anonymous surveys. The workshop was ranked “very useful,” “important,” and “relevant” to their practice. In particular, the use of SPs was highly rated.

Conclusions: Our workshop is the first in Canada to teach GOC discussions using didactic teaching and dynamic simulations involving the main stakeholders in nephrology. This educational intervention proved to be effective in improving current knowledge and comfort levels of care providers.

TH-PO1107

Factors Influencing Supportive Care Discussions in Hemodialysis Patients

Billie Axley, Michael R. O’Connell, Dugan Maddux, Marta Reviriego-Mendoza, John W. Larkin, Stephanie Johnstone, Michelle L. Gilliland, Rebecca L. Wingard, Tammy C. Green, Franklin W. Maddux. Fresenius Medical Care North America.

Background: Advanced care planning has been reported to be rarely discussed, despite that most hemodialysis (HD) patients desire better communication for supportive care needs (Goff SL, et al. 2015). We explored what factors are considered influential to initiating these discussions by surveying a group of HD nurses (RNs).

Methods: In March of 2016, a voluntary, electronic survey was offered to RNs at a Fresenius Medical Care nursing focused meeting. Survey questions and responses are as outlined in Figure 1. Questions 1 & 2 had 116 responses, and questions 3 & 4 had 68 responses.

Results: Based on this survey of dialysis clinic RNs, decreased quality of life (QOL) and multiple comorbidities were the most common reasons for care providers to have initiated conversations about supportive care (88% & 52%, respectively) (Figure 1A). Similarly, the patients/family members reported to have initiated conversations due to decreased QOL, followed by symptom burden from HD (89% & 49%, respectively) (Figure 1B). Responses from questions 3 & 4 found that 70% of RNs believe a private talking area could better enable clinic staff to initiate supportive care discussions, followed by educational courses and materials for staff (Figure 1C). It was identified that the staff also believe patients would benefit from more educational materials (Figure 1D).

Funding: Private Foundation Support

TH-PO1108

International Variation in Dialysis Discontinuation: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Sarbhit Vanita Jassal,1 Maria Larkina,2 Kitty J. Jager,3 Fliss E. Murtagh,4 Ann M. O’Hare,5 Manjula Kurella Tamura,6 Norio Hanafusa,7 Richard D. Swartz,8 Hal Morgenstern,9 Friedrich K. Port,10 Keith McCullough,11 Francesca Tenori,12 1Univ Health Network, Toronto; 2Arbor Research, MI; 3Academic Medical Center, Amsterdam; 4King’s College London; 5VA, Seattle; 6Stanford Univ; 7Univ of Tokyo Hospital; 8Univ of MI, Ann Arbor.

Background: Dialysis is a burdensome and difficult treatment. In some cases, patients, their families, or their healthcare team may consider discontinuation of dialysis therapy (DIT). DIT provides an opportunity to assess international variability in DIT across 12 countries and associated clinical characteristics.

Methods: Staff identified the reason each patient left a DOPPS facility, with DIT (n=5412) as an option (i.e. death, transfer, etc.) from 1996 to 2015. Adjusted Cox regression was used to test associations of DIT with country, age, sex, dialysis vintage, DOPPS phases, and diabetes status.

Results: Adjusted DIT HRs varied greatly, with 30-fold variation across countries (fig 1A) and 15-fold variation across age groups (fig 1B). DIT rates were highest within 4 months of dialysis initiation (HR[95% CI]=1[1.3, 1.5] x 1-year), and those with diabetes (1.2[1.1, 1.2]). No consistent era effect over DOPPS phases was seen.

Conclusions: The wide variation of DIT amongst 12 countries suggests sociocultural determinants are important contributor to DIT, and over how DIT is designated and accepted. The strong association of DIT with age and vintage may imply different considerations and practices with respect to DIT for different patient populations. Enhancing our understanding of DIT, particularly during the first few months of dialysis therapy, may help align practices when considering dialysis initiation and help us better understand the need for palliative renal care services.

Funding: Fresenius Medical Care North America.
**TH-PO1109**

**Dialysis Nurses’ Perspectives on Advance Care Planning**

Katharine L. Cheung,1 Bette J. Gilmartin,2 Ann S. Lamarre,1 Prema R. Menon,1 Robert Macauley,3 Allison Tong,4 Medicine-Nephrology, Univ of Vermont College of Medicine, Burlington, VT; 1Dialysis & Apheresis, Univ of Vermont Medical Center, Burlington, VT; 2Dialysis and Palliative Care, Univ of Vermont Medical Center, Burlington, VT; 3Medicine/Cardiology and Palliative Care, Univ of Vermont Medical Center, Burlington, VT; 4Pediatrics, Univ of Vermont Medical Center, Burlington, VT; 5School of Public Health, The Univ of Sydney, Sydney, New South Wales, Australia.

**Background:** Advance care planning (ACP) is recommended for dialysis patients and yet there has been no systematic implementation. Dialysis nurses often spend more time with patients than other providers, and have the potential to contribute to ACP. We aimed to describe nurses’ perspectives on their role and challenges of ACP in the dialysis setting.

**Methods:** Nurses with experience in dialysis from a university hospital network participated in face-to-face semi-structured interviews. Transcripts were coded using investigator triangulation. Results were based on grounded theory and thematic analysis.

**Results:** We interviewed 26 dialysis nurses, median age 55 (range 32-72), with 18 (±45) years of dialysis experience. We identified five themes: advocating for patients (witnessing suffering, coaching healthy behaviors, facilitating communication); dispersed knowledge (operating in clinical silos, sense of helplessness, managing prognostic uncertainty); navigating family-like relationships (respecting patient’s struggles, maintaining independence, and desire to lessen caregiving burden. Religious faith and support of the healthcare team and loved ones aided decision-making. All interviewees felt they had enough information and support during the decision-making process to opt for conservative care.

**Limitations:** Small sample size, self-reported rather than objective skills assessment, lack of control group.

**Conclusions:** A novel curriculum to enhance communication skills for nephrology fellows improved self-reported scores in communication.

**Funding:** Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsa, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain

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**TH-PO1112**

**Racial Disparities in the Utilization of Palliative Care in Dialysis Patients from the United States Renal Data System**

Haytham Alkhaimh,1 Jennifer L. Weller,2 Murfaddal F. Kheda,3 Jake Everett Torrentine,3 Rhonda E. Colombo,1 N. Stanley Nahman,1 Lu Y. Huber.3 1Augusta Univ, Augusta, GA; 2Charlie Norwood VAMC, Augusta, GA.

**Background:** CMS has approved payment for voluntary end-of-life counseling as part of its 2016 Medicare physician fee schedule. We queried the USRDS to investigate how palliative care (PC) has been utilized in the USRDS population.

**Methods:** All deaths of incident dialysis patients from 2004-2011, age 18-100, were queried. Those with an ICD-9 code V66.7, received hospice care or dialysis discontinued after dialysis withdrawal, and as having received PC were included. Basic descriptive statistics were calculated. Kaplan-Meier analysis was used to estimate survival. Generalized linear models were used to estimate the relative risk (RR) of PC.

**Results:** Among the 874,777 incident dialysis patients, 459,679 (52%) died by the end of 2012. 30% (136,917) of deaths had PC, with increasing usage from 2004 to 2011 (2%, 6%, 9%, 11%, 13%, 15%, 17%, 20%, respectively). Compared to those who did not undergo PC (NPC), the PC group was significantly older at initiation of dialysis (72±12 vs. 67±14 years) and at time of death (74±12 vs 69±15 years), more likely to be female (47% vs. 44%), and be on HD when died (92% vs 78%). There were only 17% Blacks in PC comparing with 28% in NPC. The final multivariable model found that older age (RR=1.02), female (RR=1.09), death in more recent years (RR=1.05 for 2005-2012), and more hospitalizations (RR=1.04) were associated with use of PC, while being black (RR=0.65) or “other” race (RR=0.62) were less likely to have PC. Cause of death for PC was less likely to be coded as cardiac (RR=0.39), GI (RR=0.42), infection (RR=0.52), metabolic (RR=0.83) or vascular causes (RR=0.62). There was no difference in time to death by PC status.

**Conclusions:** Age, gender, race and underlying chronic conditions all appear to influence the use of PC. Despite increasing utilization of PC since 2004, there has been a racial disparity in the employment of PC, with less frequent use in non-white patients. The reasons for this difference cannot be determined from this study; however, cultural and/or socioeconomic variables may play a role.

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**TH-PO1113**

**Patient Perspectives on Choosing Conservative Management of End-Stage Renal Disease**

Katherine Rozia,1 L. Ebony Boulware,2 Ion D. Bucaloiu,3 Frank Daniel Davis,1 Patti Ephraim,1 Christina Yule,2 Jamie Alton Green,1 1Dept of Medicine, Geisinger Medical Center, Danville, PA; 2Dept of Medicine, Duke Univ School of Medicine, Durham, NC; 3Dept of Nephrology, Geisinger Medical Center, Danville, PA; 4Bioethics, Geisinger Medical Center, Danville, PA; 5Dept of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology and Clinical Research, Baltimore, MD.

**Background:** Little is known about what factors are important in patients’ decisions about conservative management of end-stage renal disease (ESRD).

**Methods:** We conducted semi-structured, telephonic interviews of patients with advanced chronic kidney disease (stages 4-5) who have opted not to pursue dialysis or have a renal transplant. We recruited patients from nine nephrology clinics in a large integrated health system in rural Pennsylvania. We asked patients to discuss 1) important factors in their decision about conservative management, 2) educational needs and resources, 3) support from family, friends, and providers, 4) decision-making ambivalence, and 5) advance care planning. We audio-recorded interviews for analysis.

**Results:** Of 13 eligible individuals, six (46%) patients completed interviews. Mean age was 81 years (range 74-88), and four (67%) were male. Factors reported as important in patients’ decision to choose conservative management included: advanced-stage impact of dialysis on health and quality of life, inconvenience of dialysis, desire to maintain independence, and desire to lessen caregiving burden. Religious faith and support of the healthcare team and loved ones aided decision-making. All interviewees felt they had enough information and support during the decision-making process to opt for conservative management and expressed satisfaction with their decision. Most (83%) had engaged in advanced care planning discussions.

**Conclusions:** Patients identified key factors in their decision to pursue conservative management. Our findings can inform interventions to improve shared decision-making and communication between patients and providers about conservative management of ESRD.

**Funding:** Private Foundation Support

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

**Poster Thursday**

**Adjustment of association of country and age with dialysis discontinuation**

![Figure 1 A: By Country Hazard Ratio](image1)

![Figure 1 B: By Age Hazard Ratio](image2)

**Funding:** Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsa, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain

![Cox model adjusted for country, phase, age, vintage, sex, diabetes, DOPPS phase 1-5, NH=4214, EOT=NH72](image3)
Symptom Burden in Veterans on Chronic Hemodialysis

Matthew Tyler,1 Joshua Hauser,1 Shubhada N. Ahya,2 1Medicine - Palliative Care, Northwestern Memorial Hospital, Chicago, IL; 2Medicine - Nephrology, Northwestern Memorial Hospital, Chicago, IL.

Background: The Coalition for Supportive Care of Kidney Patients (CSCPK), a national organization of renal and palliative care health professionals, patients, and families, suggests “meticulous pain and symptom management” for ESRD patients. However, there is no consensus on what symptom assessment instrument to use or how to implement it at the point of care. This quality improvement project sought to assess the feasibility of administering the Edmonton Symptom Assessment Scale (ESAS) during a veteran’s regularly scheduled outpatient hemodialysis (HD) session. We also sought to catalogue the physical symptom burden of our veterans receiving routine HD.

Methods: A palliative care physician administered the ESAS to each patient during their routine HD session at a VA hospital-affiliated dialysis center in a major metropolitan area. The physician also documented the time to complete each ESAS and the patient’s self-perceived difficulty with completing the ESAS.

Results: Fifty-two patients completed an ESAS during their routine dialysis session. Of these, 36 (69%) patients reported at least 1 moderate to severe symptom, with 40% of patients endorsing at least 3 moderate to severe symptoms. Tiredness was the most commonly reported symptom, endorsed by 56% of patients. Thirty-eight (73%) patients were able to complete an ESAS in less than 5 minutes. Most patients (85%) did not find the ESAS challenging to complete, with the rest (15%) only finding it somewhat challenging.

Conclusions: Symptom burden in patients on chronic hemodialysis is high. The ESAS is an easy to use symptom inventory that most patients can complete in less than 5 minutes during their routine dialysis session. Implementation of routine symptom screening should be a high priority for dialysis centers but does not need to be resource-intensive.

Improving Palliative Care Communication Skills in Nephrology Training:

Description and Outcomes of the NephroTalk Communication Program

Jane O. Schell,1 Jamie Alton Green,2 Robert A. Cohen.3 1Nephrology, Univ of Pittsburgh Medical Center, Pittsburgh, PA; 2Nephrology, Geisinger Health System, Danville, PA; 3Nephrology, Beth Isreal Deaconess, Boston, PA.

Background: Effective communication is essential to being a competent nephrologist. We describe NephroTalk communication curriculum for nephrology fellows and report educational outcomes utilizing two years of data. The three-day course includes didactics and small group practice with simulated patients addressing palliative care communication tasks in nephrology. The primary objective was to evaluate skill acquisition using a validated communication checklist analyzing pre- and post-training standardized patient encounters. Secondary objectives included fellow satisfaction with the course and changes in self-reported preparedness.

Methods: Nineteen first and second year fellows from six academic nephrology programs participated in NephroTalk in 2014 and 2016. Audio-recorded pre- and post-training encounters with standardized patients giving bad news were evaluated using a modified communication checklist. Skill acquisition was measured using paired T-tests.

Results: Over half of participants were male and in the second year of fellowship. Sixty-five percent reported no formal education in either how to discuss conservative treatment options for end-stage kidney disease (ESKD). Five patients (23%) of participants were male and in the second year of fellowship. Sixty-five percent reported no formal education in either how to discuss conservative treatment options for end-stage kidney disease (ESKD). Fifty-two patients completed an ESAS during their routine dialysis session. Of these, 36 (69%) patients reported at least 1 moderate to severe symptom, with 40% of patients endorsing at least 3 moderate to severe symptoms. Tiredness was the most commonly reported symptom, endorsed by 56% of patients. Thirty-eight (73%) patients were able to complete an ESAS in less than 5 minutes. Most patients (85%) did not find the ESAS challenging to complete, with the rest (15%) only finding it somewhat challenging.

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Using Storify as a Learning Tool in Nephrology: The NephJC Experience

Hector M. Madariaga,1 Swapnil Hiremath,2 Nikhil A. Shah,3 Matthew A. Sparks,4 Joel Topf.5 1Div of Nephrology, Univ of Maryland Medical Center, Baltimore, MD; 2Div of Nephrology, Univ of Ottawa, Ottawa, ON, Canada; 3Dept of Nephrology and Immunology, Univ of Alberta, Edmonton, AB, Canada; 4Nephrology Div, Duke Univ, Durham, NC; 5Nephrology Div, St. John’s Providence Hospital, Detroit, MI.

Background: Social media (SoMe) is increasingly being used in medical education and information is scattered across SoMe. It is difficult to bring information together, hence the importance of using hashtags (#). Storify is a tool that enables users to curate information from Social Networks, creating a digital narrative of events, media and tweets. We use it in our twice-a-month Twitter-based nephrology journal club, NephJC, to curate discussions and generate a narrative for readers to review.

Methods: We performed an analysis to determine the utilization of Storify in the dissemination of tweetchats by examining the number of times people viewed each NephJC Storify and by performing a survey asking participants how they review NephJC information. We have hosted 50 chats since April 2014. Pageviews were quantified on www.storify.com through May 2016. Each tweetchat has two Storify versions: American and European chat.

Results: We have had a total of 2744 participants during the 50 discussions, with a total of 26521 tweets and average of 530 tweets per discussion. Storify narratives condense this down to a mean of 115 tweets per discussion. The total number of NephJC Storify page views was 6212, average of 124 page views per Storify and median 95 (interquartile range 60,145). 13% of respondents said they interact with NephJC primarily through Storify.

Conclusions: Storify is an online tool to help users to gather information across SoMe by using hashtags and share. At NephJC we use it to preserve critical elements of chat discussions and make them easier to review. Without the curated Storify version, most of the individual conversational threads would be hard to retrieve and follow. Storify is a compelling tool for organizing and archiving real-time tweets for enriching the online continuing medical education experience.

Queen’s Nephrology E-Learning: WhatsApp - Q-NEW Study

Muhammad A. Bukhari, M. Khaled Shamseddin. Nephrology, Queen’s Univ, Kingston, ON, Canada.

Background: Competency based medical education (CBME) is gaining more attention. E-learning is becoming a central modality of medical education. Social media applications are now a regular source of e-learning. WhatsApp Messenger allows exchange of messages and media, and holds promise as a CBME teaching tool.

Methods: We performed a pilot study of Nephrology Clinical Case problems sent to volunteers (Internal medicine trainees) via WhatsApp in an effort to assess and improve Nephrology competency. Responses were requested at 5 days. Answers and explanations were then sent out. Pre- and post-study surveys reported Trainees self-assessed competency in managing Nephrology topics.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: 29 (46%) out of 63 trainees enrolled (48% Females; 14, 10, & 5 PGY-1, 2, & 3, respectively). On a scale of 5; 1; very unconfident, 5; very confident, Trainees self-reported competency managing the problems. Scores improved significantly post-study, in specialized fields of Nephrology (e.g. Transplantation, Nephritis and Dialysis). There was no significant improvement in scores in more common areas like acute kidney injury.

Management

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<th>Post-Study Mean ± SD</th>
<th>Pre-Study Mean ± SD</th>
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<th>95% CI Upper</th>
<th>P Value</th>
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</tr>
<tr>
<td>Hypertension</td>
<td>3.33(0.62)</td>
<td>3.13(0.52)</td>
<td>0.23 (0.63)</td>
<td>(0.33)</td>
</tr>
<tr>
<td>Overdoses</td>
<td>3.20±0.68</td>
<td>2.80±0.86</td>
<td>-0.15 ±0.95</td>
<td>(0.14)</td>
</tr>
</tbody>
</table>

Conclusions: Trainees’ competency improved using WhatsApp as a tool to enhance critical thinking. Most Trainees reported interest in e-learning and WhatsApp to learn nephrology, however, the Trainee response rate diminished with time questioning the durability of using such a teaching method.

TH-POI119
Enhancing Renal Physiology and Pathophysiology Education Using a Novel Mobile Learning Platform R. Lance Miller, Medical Education, Inquiiza LLC, Penn Valley, PA.

Background: Optimal learning occurs when content is given in small, digestible chunks, which are followed up with regularly spaced formative assessments to promote retention. Our innovation leverages technology to make it easy for students to engage in the best educational practices, anywhere, anytime, and on any device and it makes it easy for medical educators to supplement in class lectures and track student progress in real-time to optimize content to maximize learning and promote a flipped classroom.

Methods: Using smartphone technology we automatically “feed” students content via text-messages containing links to 5 minute learning modules, i.e., videos or assessments. The student or educator can choose from the content library and enter associated exam dates, grades, mid-terms, and finals. Our platform allowed educators or students to automatically “feed” the student content, in spaced out intervals. Results are reported by question and quiz and logged to the user’s and/or educator’s dashboard. If the student scores below a certain percentage, the system sends a text message with a link for remediation.

Results: We tested our platform on first year medical students (n=20) and undergraduates (n=15). After completing the mobile learning modules on first-year renal physiology (i.e., acid-base physiology, renal hemodynamics, and urine concentration mechanisms), medical students and undergraduate students scored 92 ± 3% and 83 ± 4% on the 25 question multiple choice quiz.

Conclusions: Greater than 90% of students found this approach highly favorable and thought it would be a helpful supplement to in class lectures. This novel mobile learning platform represents a viable approach to supplementing in class lectures and improving retention of difficult material, like renal physiology and pathophysiology.

TH-POI1120
The Acute Dialysis Orders Objective Structured Clinical Examination (OSCE): A Formative Assessment for Nephrology Fellows Lisa K. Prince,1 Sam W. Gao,2 Christopher J. LeBrun,1 Dustin J. Little,1 David L. Mahoney,1 Robert Nee,1 Mark C. Saddler,2 Maura A. Watson,1 Christina M. Yuan,3 Walter Reed National Military Medical Center, Bethesda, MD; 2Naval Medical Center, Portsmouth, VA; 3Baptist Memorial Hospital Golden Triangle, Columbus, MS; 1Private Practice, Fairfax, VA; 4Mercy Regional Medical Center, Durango, CO.

Background: Few quantitative, validated, Nephrology-specific simulations assess fellow competency. We developed and validated a formative OSCE to assess medical knowledge, patient care, and systems-based practice in acute dialysis.

Methods: There are 3 scenarios: acute CRT in a septic, hypotensive oncology patient; chronic dialysis initiation in a volume-overloaded, moderately uremic patient; and acute dialysis in an ESRD patient with hyperkalemia and volume overload. Fellows use mock institutional protocols and order sets. The test was developed by 5 academic military nephrologists.

Results: The test was validated by 10 external volunteers who were not on the test committee. All trained in the WRNMMC program; 7/10 were in the military. All were board certified in nephrology; a median 3.5 years (1-11) from graduation. Median time to take the test was 75 minutes. Score was determined by Ebel’s method applied to each item. Passing threshold was 46/58 points. No item had median relevance less than “important”, and 42/58 (72%) were of easy or medium difficulty.

Results: The test was validated by 10 external volunteers who were not on the test committee. All trained in the WRNMMC program; 7/10 were in the military. All were board certified in nephrology; a median 3.5 years (1-11) from graduation. Median time to take the test was 75 minutes. Score was determined by Ebel’s method applied to each item. Passing threshold was 46/58 points. No item had median relevance less than “important”, and 42/58 (72%) were of easy or medium difficulty.

Conclusions: We will administer the test to first and second year fellows at the end of the 2016 training year. We hypothesize that performance will be significantly better in second vs. first year fellows, and associate with ITE score. We will also analyze performance on evidence-based questions. The views expressed are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, the Department of the Army, the Department of Defense, nor the US Government.

TH-POI1121
Best Practices to Increase Medical Student Interest in Nephrology: A Qualitative Study Stephen M. Sozio,1 Kurtis Pivert,2 Hitesh H. Shah,3 Harini A. Chakker,4 Katlyn Leigh,1 Mark G. Parker,3 Johns Hopkins U; 2American Society of Nephrology; 3Hofstra Northwell School of Medicine; 4Mayo Clinic; 5Maine Medical Center.

Background: Interest in nephrology as a career has been declining. Understanding practices of medical schools that successfully generate nephrology interest is sorely needed.

Methods: This “Best Practices” project was an initiative designed to use ASNE Workforce Committee to increase nephrology interest. Medical school graduates from 2002-2009 who became board certified in nephrology were identified through the AMA Masterfile. From the top 10 producing medical schools, renal educators were asked to participate in 1 of 4 directed interviews about key factors in each school’s success. Transcripts were analyzed using thematized content analysis with inductive reasoning.

Results: Of the 10 schools, 3 were in the Northeast, 3 Midwest, and 4 South. Medical school class size was 185 students; 26% of graduates chose Internal Medicine. 18 educators from 9 institutions were interviewed. Programs identified aspects in their renal course, rotations, research, and faculty that made them successful.

Conclusions: Early and consistent clinical experience and faculty contact with medical students is important to help generate interest in nephrology.

TH-POI1122
Outcomes of Tunneled Hemodialysis Catheters Insertion by Nephrology Fellows in Singapore Alicia Ong,1 Ru Yu Tan,2 Kian Guan Lee,3 Suh Chien Pang,4 Pei Loo Tok,5 Chieh-Suai Tan.6 Duke-NUS Medical School, Singapore; 2Renal Medicine, Singapore General Hospital, Singapore.

Background: Increasingly, nephrology fellows (NF) in Singapore are beginning to insert tunneled hemodialysis catheters (THC) under fluoroscopic guidance. This is done with the supervision of interventional nephrologists as part of fellowship training. Data on THC insertion outcomes are however lacking. This study aims to report their outcomes and complications rates.

Methods: In a single-center retrospective study of THC insertion performed from March 2015 to February 2016, outcomes of catheter insertion by NF and accredited proceduralists (AP) comprised of Interventional Radiologists, Vascular Surgeons, and Interventional Nephrologists were compared. Data were collected from electronic medical records and procedural reports. Patients were followed up from the time of insertion until hospital discharge. Primary outcomes evaluated included bleeding and infection. Secondary outcomes included procedural fluoroscopy time and patient radiation exposure.

Results: THCs were successfully inserted under fluoroscopic guidance in combination with real-time ultrasound cannulation in 140 patients (mean age of 61 ± 13 years old, 51.4% male, 88% Asian Chinese). The majority of the insertions (n=91; 65%) were performed by AP although NF placed more catheters in newly diagnosed end stage renal failure patients compared to AP (65.3% vs. 46.2%, p=<0.02). The right internal jugular was the preferred site of insertion in both groups (89.8% vs 83.5%, p=0.37). There were no differences in post-procedural bleeding (6.1% vs 4.4%, p=0.47) and infection within 24 hours of placement (4.1% vs 2.2%, p=0.44). In insertions done by NF, median fluoroscopy time [1.1mins (0.3, 17.9) vs. 1.1mins (0.1, 3.8), p=0.42] was higher whereas the median radiation exposure (4.1% vs 2.2%, p=0.17) was lower although these differences did not reach statistical significance.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Conclusions: In carefully selected patients, tunneled hemodialysis catheter can be safely inserted by nephrology fellows with minimal complications rates and radiation exposure. Larger studies are necessary to validate our findings.

TH-PO1123


Background: CKD is a serious public health issue. Appropriate nutritional care may help to prevent CKD onset in patients at risk, and slow progression in those at early stage. To improve care of patients with early CKD, it is mandatory to know the dietitian’s clinical competence; however, no adequate tool to measure this issue has been published. Aim: to develop and validate a test to evaluate dietitian’s clinical competence about nutritional care in patients with early CKD.

Methods: Development and evaluation of the test was performed as follows: 1) A group of experts in psychometrics and nutrition of early CKD was integrated; 2) Clinical competence and its dimensions were defined; 3) Four real clinical cases and questions (based on the latter) were elaborated; 4) content validity was established; 5) Test was applied to dietitians with or without previous CKD training; 6) Reliability assessment by question exclusion, based on internal consistency and discrimination index, was established. A Cronbach’s alpha ≥ 0.70 and discrimination index ≥ 0.30 were considered adequate.

Results: Dietitians with previous training obtained higher scores than those with no training (123 vs 92, respectively, p<0.0001), confirming test validity criterion. As a first step to increase reliability, questions were dropped according a correlation coefficient cutoff value < 0.15 (item-total correlation); from the latter, discrimination capacity of remaining questions was controlled by elimination of those with discrimination index < 0.15. Final test contained 92 from the original 239 questions, increasing Cronbach’s alpha value from 0.83 to 0.91, and discrimination index from 0.15 to 0.34.

Conclusions: The clinical competence test developed for dietitians is a consistent and suitable instrument to identify dietitians with or without adequate competence in nutritional care of early CKD patients. The availability of a reliable test to measure dietitian’s clinical competence may help to improve care of early CKD patients.

TH-PO1124

Awareness and Knowledge among House-Staff for Dose Adjustment of Analgesic Medications in Chronic Kidney Disease Chadi Y. Saad, 1 Joshua Fogel, 1 Sofia Rubinstein, 1 1Nephrology and Hypertension, Nassau Univ Medical Center, East Meadow, NY; 2Business Management, Brooklyn College, Brooklyn, NY.

Background: Drug dosing errors result in adverse patient outcomes and are more common in patients with chronic kidney disease (CKD). As internists treat the majority of patients with CKD and pain is common in those with CKD, we study if Internal Medicine (IM) house-staff have awareness and knowledge about the correct dosage of commonly used analgesic medications for those with CKD.

Methods: We performed a cross-sectional survey of 353 IM house-staff. Our outcomes are the awareness of whether a medication needs dose adjustment in patients with CKD and whether there was knowledge at what level of glomerular filtration rate (GFR) a medication needs to be adjusted.

Results: There were high percentages for lack of awareness and knowledge. Lack of awareness and knowledge was highest for acetaminophen at 83.0% and 90.9%, respectively.

Conclusions: There is a poor awareness and knowledge among IM house-staff for dose adjustment of analgesic medications in CKD patients. Internal medicine house-staff should receive more Nephrology exposure and formal didactic training during residency to better manage complex treatment regimens and prevent medication dosing errors.

TH-PO1125

Health Literacy of Nephrology Patients and Their Family Caregivers Jamie Alton Green, 1 Deserec N. Clarke, 2 Amanda Young, 2 Jennifer L. Wolff, 4 Rebecca A. Stamey, 2 1Nephrology, Geisinger Medical Center, Danville, PA; 2Center for Clinical Innovation, Geisinger Medical Center, Danville, PA; 4Bostatistics, Geisinger Medical Center, Danville, PA; 1Health Policy and Management, Johns Hopkins Univ, Baltimore, MD.

Background: Many patients with kidney disease rely on assistance from a family or informal caregiver to help manage their care. The presence of a caregiver may compensate for patient difficulties related to limited health literacy; however, little is known about what proportion of nephrology patients receive help from a caregiver, the health literacy of their caregivers, or how caregiver health literacy corresponds to that of the patient.

Methods: Patient-caregiver dyads were identified and surveyed utilizing a health information technology enabled process embedded into clinical nephrology care at a large integrated health system in Pennsylvania. Health literacy was assessed using a single item screening question, “How confident are you filling out medical forms by yourself?” with response options of extremely, quite a bit, somewhat, a little bit, or not at all. A response of “somewhat” or less was used to define limited health literacy.

Results: Of 790 patients surveyed, 466 (59%) reported they receive help from a family caregiver with at least one health related activity. Caregivers were most often a spouse (61%) or an adult child (12%). Among 316 complete dyads, patients were overall more likely to have limited health literacy than caregivers (45% vs. 19%, p<0.01). Patient-caregiver dyad health literacy varied with 103 (33%) consisting of a patient with limited health literacy and a caregiver with adequate health literacy, 22 (7%) consisting of a patient with adequate health literacy and a caregiver with limited health literacy, 39 (12%) where both had limited health literacy, and 152 (48%) where both had adequate health literacy.

Conclusions: More than half of nephrology patients receive help from a family caregiver. Both patients and caregivers are at risk for limited health literacy which should be considered when providing patient instructions or education. Future studies should examine how patient and care giver health literacy affect patient outcomes.

Funding: Private Foundation Support

TH-PO1126

Primary Care Provider Education in Nephrology - Improving Chronic Kidney Disease Care on the Front Lines Rob Rope, 1 Nhat M. Pham, 1 Internal Medicine/Nephrology, Stanford Univ; Palo Alto, CA; 2Internal Medicine/Nephrology, Santa Clara Valley Medical Center, San Jose, CA.

Background: The majority of CKD care takes place in the primary care setting. Effective treatment can reduce disease progression and cardiovascular complications but is underutilized. This project demonstrates cost-effective educational outreach to PCPs designed to increase provider knowledge in CKD care.

Methods: The intervention consisted of five small-group lectures covering topics in CKD care: diagnosis/referral; preventing progression; cardiovascular disease; managing complications; and dialysis/post-transplant care. Lectures were given at 3 primary care sites within a county health system. Fifteen providers attended 4-5 talks. A control group of 9 providers received a review article only. 80% of participants were IM physicians with the remainder FM or NPs. The intervention was evaluated in 3 ways: a survey evaluating provider confidence in, and knowledge of, CKD management; chart reviews of all patients referred from the physicians in the intervention and control groups; and chart reviews of patients with CKD from the intervention and control clinics.

Results: 13 providers (intervention) and 7 (control) took the knowledge survey before and after the intervention. McNemar (paired Chi-square) testing indicated that knowledge improved in the intervention group (17% improvement, p<0.05) but not in the control group (2% improvement, p=0.38). Analysis of the confidence data is pending. Chart review of referrals for the year prior showed that 30% of referrals in both groups met KDIGO indications for referral. Chart review of care for patients with CKD revealed that < 75% of all patients were prescribed RAASi or statins and < 66% of patients were controlled to an LDL< 140.

Conclusions: This project demonstrates that specialist led education can be effective in improving knowledge in CKD care. We also identified significant need for improvement in referrals to nephrology and CKD care. Follow-up data one year after the intervention will assess for improvements in the appropriateness of referrals as well as markers of CKD care (use of RAASi, use of statins, and BP control to <140/90 mmHg).

Funding: Other NIH Support - Stanford University Division of Nephrology, T32 Training Grant provided funding for Rob Rope’s salary.
TH-PO1127
Replacement Modality Choice Knowledge in the Non-Renal Multidisciplinary Team - Experience from a Single UK Centre
Fatima Abdelaal, Hatem Ali, Jyoti B. Baharani. Renal Medicine, Birmingham Heartlands Hospital - Heart of England NHS Foundation Trust, Birmingham, United Kingdom.

Background: Chronic Kidney Disease (CKD) is a common health problem which is on an upward trend. Dialysis treatment remains the mainstay for patients with End Stage Renal disease (ESRD). In the UK there has been a significant decline in home dialysis despite its benefits and convenience. There are many reasons for this including lack of awareness about availability and effectiveness of home dialysis by both patients and healthcare professionals. Patients with CKD often have multiple co-morbidities and are known to other medical specialties who they may continue to consult when approaching the need for dialysis. We wished to assess home dialysis awareness among the non renal Multi-Disciplinary Team (MDT).

Methods: Home dialysis awareness was assessed by an on-line survey sent to the choosing specialties likely to deal with CKD patients at our centre. The questionnaire aimed to assess knowledge of these individuals regarding home dialysis and establish whether further targeted education was warranted.

Results: 364 questionnaires were sent out with a 26.4% response rate. 69.32% of respondents were working in common specialties dealing with CKD patients (geriatrics 15.9%, cardiology 14.8%, haematology 10.2%, endocrinology 10.2%, urology 10.2% and vascular surgery 8%). 81.5% of non-renal MDT did not feel confident in discussing home dialysis options with patients despite seeing a large number of CKD patients. 70% felt that their knowledge about Home Haemodialysis (HHD) was poor and 74.5% felt that they need further education about home dialysis.

Conclusions: Knowledge of home dialysis among the non-renal MDT is poor and they lack the confidence to discuss this with CKD patients. In our sample, respondents felt they would benefit from further education. This may increase the uptake of home dialysis by the multi-morbid CKD patient who has a complex care package delivered to them by all relevant healthcare teams about the benefits of home dialysis.

TH-PO1128
Early Validation of a Low-Literacy Smartphone and Web-Based Application on Chronic Kidney Disease Knowledge and Self-Management
Maria E. Ferris,1 Nina Jain,2 Meaghan Nazareth,1 Stephen James,2 Melanie Livet,2 Jordan Richards,1 Alex Phillips,3 Stephen R. Hooper,1 Janey Sturz McMillen.2 1UNC Chapel Hill, Chapel Hill, NC; 2UC Inst, Durham, NC.

Background: Effective disease self-management requires knowledge about chronic kidney disease (CKD). The effectiveness of patient education delivered via smartphone applications remains to be determined.

Methods: English-speaking adolescents and young adults (AYA) who attended the UNC Kidney Center utilized Planet K, a low-literacy smartphone and web-based application designed to teach about kidney function, chronic kidney disease (CKD) stages and self-management skills via interactive games. Pre-post performance on the Self-management activity in a video format, significant improvement in knowledge of nephrologists and PCPs, 44%.

Results: 364 questionnaires were sent out with a 26.4% response rate. 69.32% of respondents were working in common specialties dealing with CKD patients (geriatrics 15.9%, cardiology 14.8%, haematology 10.2%, endocrinology 10.2%, urology 10.2% and vascular surgery 8%). 81.5% of non-renal MDT did not feel confident in discussing home dialysis options with patients despite seeing a large number of CKD patients. 70% felt that their knowledge about Home Haemodialysis (HHD) was poor and 74.5% felt that they need further education about home dialysis.

Conclusions: Knowledge of home dialysis among the non-renal MDT is poor and they lack the confidence to discuss this with CKD patients. In our sample, respondents felt they would benefit from further education. This may increase the uptake of home dialysis by the multi-morbid CKD patient who has a complex care package delivered to them by all relevant healthcare teams about the benefits of home dialysis.

TH-PO1129
Assessment of Clinical Practices in the Management of Hyperkalemia
Edward L. Jackson, Don Blatherwick, Karen Badal. Medscape Education, LLC.

Background: Concerns regarding hyperkalemia may contribute to the underuse of renin-angiotensin aldosterone system (RAAS) inhibitor therapies. The current study was developed to assess gaps in knowledge and competence of nephrologists regarding assessment and management of hyperkalemia.

Methods: A continuing medical education (CME)-certified clinical practice assessment survey consisted of 25 multiple-choice questions that assessed knowledge, confidence and barriers with regard to hyperkalemia management. Hosted on the Medscape Education website, participant responses were collected between September 22, 2015 and November 22, 2015. Responses were de-identified and aggregated prior to analysis to maintain confidentiality. Questions were based on clinical trials, guidelines, and expert faculty recommendations.

Results: Data were collected from 394 nephrologists who participated during the study period. 88% correctly identified that impaired potassium excretion was the primary cause of chronic hyperkalemia, only 55% correctly identified physiologic details of normal potassium regulation •Although 89% recognized that the presence of all stages of CKD was the strongest associated risk factor for hyperkalemia, only 47% were able to correctly identify key predictors of risk •In a scenario of a patient with stage 3 CKD and type 2 diabetes, without effective treatments 40% opted for discontinuation of RAAS therapy in the event of an elevation in potassium, with a lower percent (35%) instead opting for dose-reduction •Less than one-half (46%–49%) recognized the mechanisms of action for novel potassium binders •Only 57% of respondents were familiar with clinical trial data for a novel potassium binder •Among confidence and barrier questions, 93% of respondents indicated a likelihood to maximize RAAS therapy provided there were better treatment options for hyperkalemia, and 55% selected knowledge of new agents for hyperkalemia as the area of greatest educational need.

Conclusions: While general knowledge and confidence among nephrologists are high in several areas of hyperkalemia, gaps in the detailed understanding of clinical aspects relevant to treatment, educational efforts in management, tailored to nephrologists, are warranted to address these gaps.

Funding: Pharmaceutical Company Support - Relypsa

TH-PO1130
Iron Deficiency Anemia in Chronic Kidney Disease: Educational Effects from a Case-Based Online Intervention
Edward L. Jackson, Don Blatherwick, Anne Le. Medscape Education, LLC.

Background: A study was conducted to determine whether an online educational intervention could address an underlying care gap in the area of evaluation and management of iron deficiency anemia in patients with chronic kidney disease (CKD).

Methods: The educational intervention consisted of a video panel discussion activity for nephrologists and primary care physicians (PCPs). The video involved a case-based discussion and interactive panel discussion. Educational impact was assessed by comparing each participant’s responses to the same 4 questions asked both pre- and post-education. A paired 2-tailed t-test was used to assess whether the mean post-assessment score was different from the mean pre-assessment score for each question. McNemar’s χ² statistic was used to measure changes in responses to individual questions. Probability values (P values) were also calculated for both t-test and χ² statistics to determine significance, with a P < .05 as meeting statistical significance. Cramer’s V was used to calculate the effect size of the intervention, with large effect sizes defined as V > .30.

Results: For nephrologists (n = 113) and PCPs (n = 214) who participated in the online activity and completed all pre- and post-education assessment questions, comparison of responses to pre- and post-education assessment questions demonstrated statistically significant improvements (P < .05) and a large effect (nephrologists, V = 0.32; PCPs, V = 0.319). Significant absolute increases in correct responses were observed in several specific areas of managing iron-deficiency anemia in CKD (all P < .05), including: •Contributors to iron-deficiency anemia in CKD (Nephrologists, 37%; PCPs, 41%) •Appropriateness of oral iron compounds for treatment (Nephrologists, 18%; PCPs, 27%) •Risks from intravenous iron replacement in CKD patients who are also being treated for comorbidities (Nephrologists, 27%; PCPs, 15%) •Options for iron replacement therapy (Nephrologists, 42%; PCPs, 44%).

Conclusions: As a result of participation in this case discussion-based educational activity in a video format, significant improvement in knowledge of nephrologists and PCPs was demonstrated in several important aspects of managing iron-deficiency anemia in patients with CKD.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals, Inc.

TH-PO1131
Assessment of Current Clinical Practices in the Diagnosis and Management of Hepatorenal Syndrome
Edward L. Jackson, Don Blatherwick, Susan Smith. Medscape Education, LLC.

Background: Hepatorenal syndrome (HRS) is a potentially devastating form of acute renal injury seen in clinical practice. The current study was conducted to assess gaps in knowledge and competence of nephrologists regarding diagnosis and management of patients with HRS.

Methods: A continuing medical education (CME)-certified clinical practice assessment survey was developed comprising 20 multiple-choice questions that assessed knowledge, attitudes, and confidence with regard to the diagnosis, clinical course, treatment, and management of patients with HRS. The survey questions were based on clinical trials, guidelines, and expert faculty recommendations. The survey was launched on August 14, 2015 and collected on the Medscape Education website, and participant responses were collected through October 11, 2015. Confidentiality was maintained and responses were de-identified and aggregated prior to analysis.

Results: Data were collected from 198 nephrologists who participated in the survey during the study period. When asked about diagnosing HRS, 85% correctly recognized HRS as a diagnosis of exclusion, yet only 38% reported being fully confident in making the diagnosis. With respect to evaluation and staging, only 37% of nephrologists correctly recognized the most appropriate tests for evaluating kidney function in patients with chronic kidney disease (CKD). When presented with a case scenario and laboratory test result, only 40% were able to properly stage the HRS presentation. In the area of HRS management, a majority of nephrologists (79%) correctly recognized that HRS is potentially reversible and 75% correctly stated that liver transplantation is the definitive treatment. However, only about one-half (54%) were able to identify the most appropriate pre-transplantation management strategy, and less than one-quarter (24%) were able to correctly answer a question related to effectiveness of therapeutic options.

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

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Conclusions: Low self-reported confidence among nephrologists in establishing a diagnosis of IBS was substantiated by responses to specific questions on diagnosis and staging. Further gaps were identified in the area of pre-转plant management options. Educational efforts tailored to nephrologists are warranted to address these gaps. Funding: Pharmaceutical Company Support - Mallinckrodt Pharmaceuticals

TH-PO1132

Identifying Utility and Challenges for an Established Online Journal Club: The NepHJC Experience

Background: Online journal clubs have become widespread as a method for dissemination and discussion of new research. Since its inception in April 2014, the online twitter based journal club @NephJC has conducted more than 50 tweet-chats. We developed a survey to characterize participants and better understand the perceived benefits and potential barriers to participation.

Methods: The online survey was conducted using the Google forms platform. We invited individuals to participate by a direct message to @NephJC Twitter followers, including a link in the weekly NepHJC email digest for 2 weeks and displaying a link prominently on nephrology blogs. Institutional review board approval was obtained.

Results: 328 individuals responded to the survey; 221 men (68%), from North America (49%), Europe (25%), and rest of world (26%). 178 (54%) were practicing physicians, 81 trainees (25%) and the remaining other healthcare professionals (44, 14%) or interested citizens (24, 7%). The responding physicians were mostly nephrologists (147, 82%). The overwhelming majority of the respondents (>90%) compared it favorably to traditional journal clubs. There was considerable interest in discussing non-traditional articles, such as guidelines (220, 67%) and interesting case reports/series (131, 40%). Despite only 10 respondents working in basic science, there was enthusiasm for discussing basic science articles (120, 37%). The major barrier was active chat participation was lack of time in general (50%). Hence, 64 respondents (20%) actively participate in the live tweetchat, and most others follow the feed passively (34%) or review individual tweets (40%) or curated versions (13%). Others noted issues regarding the specific time of the chat (31%).

Conclusions: NepHJC, the online journal club, has near-unanimous positive feedback. We identify lack of time as the most important barrier to participation. Online journal clubs are a promising tool which interest MDs and non-MDs alike from different specialties and training levels. Funding: Clinical Revenue Support

TH-PO1133

The Renal Interactive Learning Module (ILM): A Novel Nephrology Curriculum for Interns

Background: Interest in nephrology among US medical graduates is in decline, and this may be due to inadequate exposure to the more appealing aspects of this field during residency. It has been suggested that more exposure to ambulatory nephrology may stimulate interest in nephrology as a career among residents. A dedicated nephrology ambulatory experience followed by two weeks of ambulatory time. The “+2” ambulatory time has been organized into six themed blocks called interactive learning modules (ILMs). As nephrology is followed by two weeks of ambulatory time. The “+2” ambulatory time has been organized into six themed blocks called interactive learning modules (ILMs). As nephrology is a promising tool which interest MDs and non-MDs alike from different specialties and training levels.

Conclusions: NepHJC, the online journal club, has near-unanimous positive feedback. We identify lack of time as the most important barrier to participation. Online journal clubs are a promising tool which interest MDs and non-MDs alike from different specialties and training levels. Funding: Clinical Revenue Support

TH-PO1134

Applying the Flipped Classroom Model in the Outpatient Renal Clinic: A Pilot Study
Amir Kazory, Abhilash Koratala, Maryam Sattari. Univ of Florida College of Medicine.

Background: Suboptimal exposure to outpatient nephrology has been proposed as an important driving force for the fading interest in this subspecialty. We hypothesized that development of a focused educational activity for medical residents can increase their knowledge and interest. This pilot project was designed to evaluate the impact of a flipped classroom model and “Snapshot Exposure” in the outpatient nephrology setting on the knowledge of internal medicine residents about chronic kidney disease (CKD).

Methods: As part of the ambulatory rotation at the University of Florida, internal medicine residents attended a half-day CKD clinic between May 2013 and December 2015. A curriculum was developed focusing on evidence-based management of CKD. The flipped classroom model consisted of e-mailing the developed pre-clinic reading material to the residents prior to the clinic. The “Snapshot Exposure” consisted of a structured clinic session with the faculty nephrologist and a fellow. The baseline knowledge of residents was assessed at the beginning of the clinic through a multiple-choice pre-test. A post-test was administered at the end of the activity to assess the benefit of the clinic exposure. Student’s t-test was used to compare the scores.

Results: Thirty-seven medical residents participated in this pilot study, attended the CKD clinic, and completed both the pre- and post-tests. The mean pre-clinic score was 3.87 ± 0.38 out of 6 (range = 2-6) and the mean post-clinic score was 5.6 ± 0.18 (range = 4-6). A statistically significant increase was seen in participants’ knowledge as evaluated by the difference between the post-clinic versus pre-clinic scores (t = 4.17, P < 0.001). Conclusions: The main finding of this pilot study is that a snapshot exposure to CKD clinic can have a positive impact on the learners’ knowledge. Moreover, the low pre-activity score implies that the conventional hand-out teaching might have limited impact on the knowledge of the learners. The next step would be to validate these findings in a larger population, and to evaluate the impact of this educational method on the interest and attitude of the learners regarding career choices.

TH-PO1135

Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD) Are amongst the Most Common Clinical Renal Questions Asked by Primary Care Providers (PCPs).
Raimund H. Pichler, Nancy M. Harris,1 Maureen Gernerni,1 Elizabeth A. Mattox,1 Lauren Beste,1 Michael F. Chang,1 Bessie A. Young,1
1Dept of Veterans Affairs, Puget Sound Healthcare System, Seattle, WA; 2Dept of Veterans Affairs, Portland Healthcare System, Portland, OR.

Background: The Department of Veterans Affairs (VA) has used various forms of Telemedicine to improve care for Veterans. In 2010, the VA launched a form of electronic consultations (or non-visit consults (NVCs)) involving electronic medical record review of patients by specialists. To date there is little data on what renal clinical questions are most commonly asked by PCPs in referrals.

Methods: We conducted a qualitative chart assessment of NVCs (n=402) submitted to a Nephrology service. Using chart review, we determined clinical characteristics of the referred patients and qualitatively extracted the primary clinical question for referral.

Results: Of the 402 NVC referrals, 53% were for urban, 43% rural, 3% highly rural and 1% unknown patients. The most commonly asked clinical questions in descending order were: renal imaging (30%); AKI (25.7%); followed by AKI-on-chronic kidney disease (18.7%), CKD (14.1%), request for medication review (13.4%), hypertension (10.5%), abnormal renal imaging (7%), and electrolyte imbalances (3.9%). Of all patients with AKI alone, 17% had a low blood pressure as defined by a systolic blood pressure of less than 120mm Hg, while 11% were taking non-steroidal anti-inflammatory drugs (NSAIDS). Consults for “renal imaging” referred to renal ultrasound reports that commented on “medical renal disease” and/or “renal cysts”.

Conclusions: NVCs serve a relatively rural patient population. AKI and CKD are the most common clinical questions posed by PCPs in NVCs. Interestingly, low blood pressure and NSAID use appear to be overlooked causes of AKI amongst PCPs. Frequently reported and clinically insignificant abnormalities on renal imaging reports also prompt specialty consultation. The above results will help refine ongoing renal education outreach programs to address common knowledge gaps amongst PCPs.

Funding: VA Support

TH-PO1136

A Re-Evaluation of Pain Assessment in Hemodialysis Patients
Tatiana Tanasivchuk, Muhammad Ab Elhalim, Daniel Kushnir, Victor Frajewick. Dept of Nephrology and Hypertension, Carmel Medical Center, Haifa, Israel.

Background: Patients suffering from Chronic Kidney Disease treated by hemodialysis often complain about pain. The presence of chronic pain greatly impacts on patients quality of life (QOL) and may have effects on morbidity and mortality. The prevalence and severity of pain (acute or chronic) in this population and its influence on QOL is not well recognized. Although most patients use the Visual Analogue Scale (VAS) which includes just one question about the presence of current pain and its intensity, the best method for pain assessment has not been established.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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360A
Method:VAS is routinely performed every treatment by our dialysis nurses. A modified Brief Pain Inventory (BPI) questionnaire includes 18 questions about localization, intensity and response to pain. BPI was given to our chronic hemodialysis patients. VAS results were obtained from the patients electronic files for the same session.

Results:67 patients completed the questionnaire during the first week of 2016. Mean age was 73.5 years, 58% were diabetics, 68% were male. Average vintage on dialysis was 37.3 months. Only 1.5% of patients reported pain in VAS. In contrary, the BPI showed that 25% of patients had pain at that dialysis session and 61% suffered from pain for the previous 24 hours. Intensity of pain was significantly higher (*P < 0.001) with the BPI than with VAS. No significant difference were detected between genders or diabetics/non-diabetics. In 52% of cases musculoskeletal pain was reported. Half of patients noted pain related reduced QOL defined by walk capability (54%), sleep disorders (57%), bad mood (64%), work disability (51%) or interference in familiar relationships (49%). Almost half of patients use any kind of analgesics and 10% use narcotics. Only 13% of patients reported to be pain free under analgesics treatment.

Conclusions: Pain is a frequent and debilitating condition in chronic hemodialysis patients, affecting all aspects of life, including not only the dialysis session. Standard short VAS may underestimate this problem leading to undertreatment and impairment of QOL.

The use of a comprehensive pain tool may improve the outcomes.

TH-PO1137
Restless Legs Syndrome in Chronic Kidney Disease: Association with Objective Measures of Sleep/Wake Behaviors

Maria Elena Roulometto, Mark L. Unruh, Orrin Myers. Internal Medicine, Div of Nephrology, UNM, Albuquerque, NM.

Background: Restless legs syndrome (RLS) is a common sleep disturbance among patients with kidney failure and leads to severe initiation insomnia, daytime sleepiness and increased mortality risk. In this cross-sectional study we examined the prevalence of RLS and its effect on objective measures of sleep/wake behavior among patients with CKD (stages 4-5) and chronic dialysis patients.

Methods: Objective measures of sleep/wake behavior included one in-home polysomnography and wrist actigraphy for two weeks. Presence of RLS was estimated with the Hopkins RLS Questionnaire.

Results: We studied 96 patients with stages 4b-5 CKD, 159 hemodialysis (HD) and 29 peritoneal dialysis (PD) patients. Average age was 54.7±60.2% were men, 64.4% were white. RLS was found in 36.8% of CKD, 28.7% of HD, and 44.4% of PD patients. Increased risk of RLS was associated with higher BMI, presence of DM and hyperglycemia.

<table>
<thead>
<tr>
<th>Age</th>
<th>No RLS</th>
<th>RLS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.7(15.1)</td>
<td>56(16)</td>
<td>54(13)</td>
<td>0.2</td>
</tr>
<tr>
<td>Male(%)</td>
<td>50.2</td>
<td>62</td>
<td>57</td>
</tr>
<tr>
<td>White(%)</td>
<td>64.1</td>
<td>61</td>
<td>69</td>
</tr>
<tr>
<td>BMI</td>
<td>27(8.5)</td>
<td>27(8)</td>
<td>29(6)</td>
</tr>
<tr>
<td>Smoking</td>
<td>50.3</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td>Caffeine(%)</td>
<td>70.4</td>
<td>69.5</td>
<td>72</td>
</tr>
<tr>
<td>Ferritin</td>
<td>464(422)</td>
<td>455(358)</td>
<td>476(506)</td>
</tr>
<tr>
<td>Cr</td>
<td>121(50)</td>
<td>117(22)</td>
<td>131(59)</td>
</tr>
<tr>
<td>Ph</td>
<td>7.4(5.2)</td>
<td>7.4(6.7)</td>
<td>7.2(3.4)</td>
</tr>
<tr>
<td>Dm(%)</td>
<td>34.2</td>
<td>31</td>
<td>38</td>
</tr>
</tbody>
</table>

PSG data

| TSAT(min) | 334(111) | 344(106) | 325(117) | 0.3 |
| AHI | 21.2(23.3) | 20.2(24.6) | 23.4(26.8) | 0.4 |
| PLMI | 4.4(4.9) | 3.9(4.5) | 5.3(4.4) | 0.1 |
| Actimetry data | AvgOfACSLPTOT | 337(93) | 340(102) | 327(76) | 0.2 |
| AvgVOGAFACWSO | 81(14) | 76(29) | 80(39.5) | 0.06 |
| AvgOfACMASE | 69(11) | 70(14) | 67(14) | 0.04 |
| AvgOfACMDSL | 43(46) | 41(50) | 46(42) | 0.06 |

RLS was associated with decreased average of actigraphy scored sleep efficiency (SE), and with a trend towards increased actigraphy-scored wake after sleep onset and sleep latency.

Conclusions: RLS is common across the whole spectrum of CKD and is associated with decreased actigraphy-measured SE. Assessing appropriately and treating RLS in obese patients with CKD, especially due to DM, may improve their sleep and long-term outcomes.

TH-PO1138
Predicting 1-Year Mortality in Peritoneal Dialysis Patients by the Surprise Question, Palliative Care Screening Tool, and Clinical Risk Score

Cheng Chieh L1, Chun-Fu Lai2. 1Dept of Nursing, National Taiwan Univ Hospital and National Taiwan Univ College of Medicine, National Taiwan Univ Hospital, Taipei, Taiwan; 2Renal Div, Dept of Internal Medicine, National Taiwan Univ Hospital and National Taiwan Univ College of Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.

Background: Identifying potential candidates is an important issue to facilitate palliative care into the dialysis population. This study aimed to develop risk models to predict the 1-year mortality risks of patient under peritoneal dialysis (PD).

Methods: A total of 422 adult patients under PD for ≥3 months were recruited in March 2015. In addition to obtaining clinical characteristics and parameters, each patient was evaluated by the "surprise question" and the "palliative care screen tool" by the primary care nurse in the PD unit. Subjects were followed up from April 1, 2015 until March 31, 2016 for the outcome of all-cause mortality. The developed using Cox proportional hazards regression.

Results: During the 1-year follow-up, 34 (8.06%) patients died. Kaplan-Meier analysis showed significantly worse survival in patients of the "no, not surprised" group or those with a score ≥ 4 of the palliative care screening tool (both log-rank P < 0.0001). The area under the receiver operating characteristic curve (AUROC) to predict 1-year mortality by the two methods were comparable (0.743 vs. 0.763, P = 0.59). We also defined a clinical risk model that included gender, malignancy, Karnofsky Performance Status score, hemoglobin, white blood cell count, fasting serum glucose, serum creatinine, and intact parathyroid hormone level with good discrimination to predict 1-year mortality. Combining the above clinical model with the surprise question and the palliative care screen tool increased the AUROC to 0.938.

Conclusions: These results underscored the values of the surprise question and the palliative care screen tool to identify vulnerable patients undergoing PD.

Funding: Government Support - Non-U.S.

TH-PO1139
Medication Related Hospitalizations in Hemodialysis Patients

Harold J. Manley, Jessica L. Baugh, Margaret Mcnamara, Doug Johnson. Dialysis Clinic Inc; Albany, NY.

Background: Hemodialysis (HD) patients’ medication regimens are complex with 10-12 medications daily and medication related problems (MRPs) are common. The frequency and preventability of medication-related hospital (MED-HOSP) admissions in HD patients is unknown.

Methods: An observational study was conducted Sept. 2014-Sept 2015. MED-HOSP frequency, preventability (definite, possible, not-preventable), associated MRPs, length of stay (LOS) and potential risk factors were determined via ≥ 75% consensus within a group (3 pharmacists and 1-2 pharmacy students, 1-2 nurses). Reviews included information from discharge summaries and corresponding electronic medical record information (e.g., lab results, medical diagnoses, medications, progress notes). Patient age, number of medications prescribed, hospitalization type (index or readmit) and LOS for each event was recorded.

Results: A total of 343 (194 index; 149 readmit) hospitalizations in 218 unique patients (55.4% female; 59.7±15.1 yr) were included. Overall 35.3% (n=121) hospitalizations were MED-HOSP. Index admissions were less likely to be MED-HOSP events compared to readmits: 29.4% versus 42.9%, respectively (*P = 0.012). MED-HOSP were considered definitely (35.4%), possibly (61.2%), or not-preventable (3.3%) of time. MRPs contributing to a MED-HOSP were dosing errors (27.3%; high) (19%) or low (8.3%), adverse drug event (24.8%), failure to receive drug (24.8%), indicated drug not prescribed (16.5%), different drug needed (3.3%), drug interaction (1.7%), and drug without indication (1.7%). MED-HOSP events were not predicted by gender (p=0.50) or number of medications (p=0.21). However, MED-HOSP events was associated with younger age (57.3±18 v. 63.4±26, p=0.037) and had shorter LOS (5.6±4.7 v 7.3±7.8 days, p=0.026) compared to non-MED-HOSP events.

Conclusions: MED-HOSP events occur frequently and are preventable in HD patients. Dosing errors, adverse drug events, and failure to receive prescribed therapy (e.g., adherence) are the most common causes of MED-HOSP events. The impact of structured medication reviews to reduce MED-HOSP warrants investigation.

TH-PO1140
Fixing the Gap in Vancomycin Use among Patients on Hemodialysis at a Dialysis Center

Nishkarsh Saxena, Laura J. Maursetter. Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: Vancomycin is the first line antibiotic for resistant gram positive infections, particularly MRSA. Its dosing should be guided by serum trough level with therapeutic goal of 15 to 20 mcg/mL. 30 to 40% of the drug is removed during 3 to 4 hour session of hemodialysis (HD). Pre-HD drug level can be used to guide vancomycin dose after accounting for extracorporeal elimination of the drug.

Methods: We first determined if there is a gap in dosing and monitor of vancomycin in patients on HD at a dialysis center (Wisconsin Dialysis, Inc, (WDI) WDI East (WDE)- and WDI, Fitchburg (WDI-F)). Among patients on HD at WDI who received vancomycin within a three month period (10/1/15 - 12/31/15), we calculated: a) Percentage of serum vancomycin level drawn to the total number of dose given. b) Percentage of serum vancomycin level within therapeutic range (15 to 20 mcg/mL).

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Results: Among patients on HD at WDI who received vancomycin within a three month period (10/1/15 - 12/31/15), serum vancomycin level was drawn only 23% of the time and only 36% of the serum drug levels were within therapeutic range (15 - 20 mcg/mL).

<table>
<thead>
<tr>
<th>Serum vancomycin level drawn (%)</th>
<th>Therapeutic range (15 - 20 mcg/mL, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WDI-F 23.5% (n=21; N=89)</td>
<td>38.09% (n=8; N=21)</td>
</tr>
<tr>
<td>WDI-E 25% (n=4; N=16)</td>
<td>25% (n=1; N=4)</td>
</tr>
<tr>
<td>WDI-EL 23.8% (n=25; N=105)</td>
<td>36% (n=9; N=25)</td>
</tr>
</tbody>
</table>

Conclusions: Of the small percentage of serum vancomycin levels drawn, only 36% fell in the therapeutic range with a potentially much larger group that were not monitored falling outside the target range as well. The gap in care can lead to sub-optimal treatments and complications including multidrug resistant organisms, recurrent infections and increased mortality. To overcome this gap, we plan to implement a protocol and train the dialysis staff to use the protocol for vancomycin dosing for patients on HD at WDI.

TH-PO1141

Targeted Deprescribing in an Outpatient Hemodialysis Unit: A Study to Decrease Polypharmacy

Marisa Battistella,1,2 Caitlin McIntyre,1,2 Chaim Bell,3 Rory F. McQuillan.3 1Nephrology, Univ Health Newwork, Toronto, ON, Canada; 2Pharmacy, Massachusetts General Hospital, Boston, MA; 3Medicine/Gastroenterology, Massachusetts General Hospital, Boston, MA.

Background: Polypharmacy in hemodialysis patients can result in a higher risk of non-adherence, adverse drug events, hospitalizations, and mortality. Deprescribing tools can reduce polypharmacy yet no method exists for an outpatient hemodialysis population. We aimed to (1) develop a deprescribing tool for target medications with poor evidence for efficacy and safety; (2) determine its effectiveness in decreasing polypharmacy; and (3) monitor patient safety and satisfaction.

Methods: In a single-center prospective observational study, a deprescribing tool for specific medications was developed, validated, implemented and evaluated in a tertiary care center - outpatient hemodialysis unit. All 240 patients in the unit were screened using the deprescribing tool. The primary outcome was the proportion of target medications completely deprescribed at 6 months. Patient safety and satisfaction were monitored during the trial using drug-specific monitoring parameters outlined in the tool.

Results: Five medication classes were selected: quinine, diuretics, alpha-1 blockers, proton pump inhibitors, and HMGR Co-reductase inhibitors (statins). There were 171/240 (71%) patients prescribed at least one of the five target medications and 71 patients (80 medications) underwent a deprescribing trial. After applying the tool, 55/40 (88%) eligible patients initiated a deprescribing trial. There were 31 of 40 (78%) target medications prescribed at least one of the five target medications and 71 patients (80%) of the 240 patients in the unit were screened using the deprescribing tool. The primary outcome was the proportion of target medications completely deprescribed at 6 months. Patient safety and satisfaction were monitored during the trial using drug-specific monitoring parameters outlined in the tool.

Conclusions: Deprescribing tools can be applied successfully in an outpatient hemodialysis unit to reduce polypharmacy while maintaining patient safety and satisfaction.

Funding: Government Support - Non-U.S.

TH-PO1142

Prolonged Intravenous Antibiotic Use in Hemodialysis Patients

Evamaria Anvari, Laura Ferreira Provenzano. Nephrology and Hypertension, Cleveland Clinic.

Background: Infection is common in hemodialysis patients. The presence of a hemodialysis catheter and a weak immune system are recognized risk factors. Infections could be bacterial or non-bacterial, and bacterial infections include blood stream infections, pneumonia, urinary tract infections and others. Recognizing which patients to treat with antibiotics is essential, as bacterial infections are the second most common cause of death in hemodialysis patients, but treating patients with antibiotics when not needed, might lead to many adverse events. Despite this, many hemodialysis providers prescribe empiric antibiotics when patients are found to be febrile on hemodialysis, assuming a bacterial blood stream infection, sometimes without a clinical evaluation. In addition, many times blood cultures are not checked and prolonged antibiotic courses are given.

Methods: We analyzed blood culture and antibiotic use data from 10 hemodialysis units from a single dialysis provider in the Cleveland area, from January to November 2015. Patients were under the care of both private and academic practice physicians.

Results: During this period, 279 patients had blood cultures sent. Of these patients, only 49 had positive cultures. (17.6%) and 230 were negative (84.4%). A total of 124 patients received antibiotics during hemodialysis, 75 of which ended having negative blood cultures. 37/5 of culture negative patients received more than 3 doses of antibiotics (range: 1-24 doses). Of the 49 patients with positive blood cultures, 33 had catheters.

Conclusions: Our data shows that there is significant variability in antibiotic use and duration in patients in hemodialysis. We found significant number of patients that received antibiotics without a clear indication. Protocols to help providers could help identify patients that require antibiotics in hemodialysis are needed, to avoid improper or prolonged use of antibiotics in the dialysis units.

TH-PO1143

Safety and Efficacy of Novel Direct-Acting Antiviral Therapies in Patients with Chronic Kidney Disease

Meghan E. Sise,1 Gregory L. Hunderman,1 Guillermo Ortiz,1 Elke Backman,2 Donald Chute,3 Joseph Brancale,3 Ravi I. Thadhani,1 Raymond T. Chung.1 1Medicine/Nephrology, Massachusetts General Hospital, Boston, MA; 2Pharmacy, Massachusetts General Hospital, Boston, MA; 3Medicine/Gastroenterology, Massachusetts General Hospital, Boston, MA.

Background: Sofosbuvir-based therapy has revolutionized the management of Hepatitis C Virus infection; however, little is known about the safety of this medication in patients with chronic kidney disease (CKD). The active metabolite of sofosbuvir, GS-33107, is renally eliminated. Recent studies suggest that patients with baseline CKD may experience adverse events including nephrotoxicity when treated with sofosbuvir.

Methods: Retrospective study of patients with CKD who began DAA treatment (tx) between 11/01/2013 - 12/31/15. CKD defined by mean eGFR < 60mL/min or albuminuria > 30mg/g in the 6months prior to tx. Safety, tolerability and laboratory results were assessed by chart review. Mean and standard deviation (SD) are presented.

Results: 107 subjects were included. Mean age 62 years (SD 8), 77% male, 46% White, 19% Black. 45% had diabetes, 86% hypertensive, 12% HIV co-infected, 37% were cirrhotic, 33% prior liver or kidney transplant recipients. 50% were HCV tx naïve. Regimens used were SOF/simeprevir 42%, SOF/ledipasvir 24%, and SOF/ribavirin 34%. 6% had a transient creatinine rise of >= 0.5mg/dL during tx.

Despite transient rises on therapy, average creatinine 12 weeks after therapy was 1.24mg/dL (SD 0.8) compared to baseline 1.26mg/dL (SD 0.37). SVR was 81%. Causes of renal and other serious adverse effects are presented, with discussion of relationship to DAAs.

Conclusions: SOF-containing DAA regimens are effective and appear relatively safe in patients with CKD, although adverse effects were common; significant nephrotoxicity was noted in 6% percentage of cases.

Funding: NIDDK Support
TH-PO1144
The Drugs That Most Frequently Induce Acute Kidney Injury: A Case-Non-Case Study of a Pharmacovigilance Database
Sophie Liebetob,1,2 Marion Pierson Marchandise,1 Julien Moragany,1 Kamel Masmoudi,1 Valérie Gras,1 1Royal Pharmacovigilance Centre, Div of Clinical Pharmacology, Amiens Univ Hospital, Amiens, France; 2Inserm U1088, UPJF, Amiens, France.

Background: Acute kidney injury (AKI) is associated with a high hospitalization rate, accelerated and long-term decline in kidney function and a high mortality rate. Adverse drug reactions (ADRs) constitute one of the most important modifiable factors in the context of AKI. Most studies of drug-induced AKI have focused on a sole drug class. The objective of the present survey was to establish a comprehensive overview of drug-induced AKI on the basis of ADRs spontaneously reported in the French national pharmacovigilance database (FPVD).

Methods: We performed a case/non-case study of drug-induced AKI. Cases of AKI were reported in the FPVD between January 1, 2015, and December 31, 2015. The non-cases corresponded to all other reports during the same period. Data were expressed as a reporting odds ratio (ROR) with its 95% confidence interval.

Results: Of the 38782 ADRs recorded in the FPVD during the study period, 3.2% were classified as cases of AKI. A total of 1254 patients experienced AKI (males: 55%; mean ± standard deviation age: 68.7 ± 15.0; median age: 70). Two or more concomitantly administered drugs were involved in 60% of the cases of AKI. The most frequently implicated drug classes were antibacterials for systemic use (29.5%), diuretics (18.5%) agents acting on the renin-angiotensin system (16.3%), antiplatelet agents (10.2%) and anti-inflammatory agents (5.4%). Gentamicin, enalapril, spironolactone, candesartan, cisplatin and aciclovir had the highest RORS (>10).

Conclusions: Drug-induced AKI is a preventable event. A comprehensive study of a national pharmacovigilance database enabled us to identify the drug classes that most frequently induced AKI. Even though most of the identified drugs were already known to induce AKI, the present work should raise pharmacovigilance awareness of the compounds responsible for triggering this potentially life-threatening condition.

TH-PO1145
Incidence of Hyperphosphatemia and Hypocalcemia Secondary to Phosphate Enema Administration

Background: The use of sodium phosphate solutions as a purgative implies an exposure to phosphate administration 8 times the normal daily intake. This overload of phosphorus can lead to a significant increase in phosphatemia within the first 24 hours, which is usually accompanied by a decrease in serum calcium levels. This has been demonstrated in patients undergoing bowel preparation with oral phosphate solutions, but few studies have analyzed electrolyte abnormalities after the use of phosphate enemas.

Methods: This study aims to analyze changes in serum phosphorus and calcium levels following the administration of sodium phosphate enemas in a cohort of hospitalized patients. During a follow-up period of three months, all patients admitted to the Foundation Hospital Alcorcon who received sodium phosphate enemas were studied prospectively. Serum phosphorus and calcium determinations were performed 48 hours before and 24 hours after sodium phosphate enema exposure.

Results: Changes in serum calcium and phosphorus levels were studied after 22 exposures to phosphate enemas in fourteen patients. In most cases a single enema (dosage of 8 g of sodium phosphate; Casen Fleet Enema 250 cc) was administered. The average serum concentration of phosphorus and calcium before enema administration was 2.94 ± 0.46 mg/dl and 8.31 ± 0.65 mg/dl, respectively. The average concentration of phosphorus and calcium after sodium phosphate exposure was 3.2 ± 0.67 and 6.78 ± 0.70 mg/dl, respectively. In fourteen patients (63.5%) the sodium phosphate enema led to positive phosphatemia balance and negative calcium balance. The mean increase in serum phosphorus was 0.34 mg/dl after administration of the enema, and the mean decrease in plasma calcium was - 0.2 mg/dl. Two patients (9%) developed mild hyperphosphatemia and 5 patients (22.7%) with previous normal calcium levels developed relevant hypocalcemia.

Conclusions: The use of sodium phosphate enemas led to an increase in serum phosphorus levels and decrease in serum calcium levels in a high percentage of patients. These electrolyte changes are mild and transient in most cases, but may determine the onset of significant hyperphosphatemia or hypocalcemia in a significant number of patients.

TH-PO1146
Monitoring Urinary Protein Excretion in Patients with Heart Transplant Receiving Torinhibitors-Need for Raising Awareness
Negin Pourrafshar,1 Ashkan Karimi,2 Jon A. Gregg,1 Amir Kazory.1 1Div of Nephrology, Univ of Florida, Gainesville, FL; 2Div of Cardiovascular Medicine, Univ of Florida, Gainesville, FL.

Background: The inhibitors of the mammalian target of rapamycin (mTOR) are used in the setting of orthotopic heart transplantation (OHT) mainly to avoid the nephroprotection of calcineurin inhibitors (CNI) or to slow the progression of allograft vasculopathy. Proteinuria is a well-recognized complication of mTOR inhibitors use in the renal transplant recipients but its extent is limited data in the OHT population. We studied the monitoring of patients with OHT who received mTOR-based regimens with respect to development of proteinuria.

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

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Conclusions: Our review showed that appropriate pre-pharma exchange labs were not completely performed when TTP was present, including STEC test, haptoglobin and most importantly ADAMTS13 level. The relapse at one month, although not unexpected, should raise the question of the accuracy of initial TTP diagnosis and the provision of ADAMTS13 level testing is crucial. Further studies should help define the recommended testing algorithms for TMA.

TH-PO1149
Effectiveness of UV Light in the Disinfection of Peritoneal Dialysis Catheter Connections

Julia Rasooly, John Ashley, Ian Tran, Glenn Matthew Chertow, PuraCath Medical, Inc., Fremont, CA.

Background: The purpose of the current study was to evaluate the microbiological performance (log reduction) of a modified ultraviolet (UV) light-based peritoneal dialysis catheter connection system. The system included an enhanced UV light generating device which provides greater coverage for the UV transparent connector incorporated into the transfer set and a modified UV transmissive connector which improves patient ease of use.

Methods: Prior to being coupled to the non-UV transmissive Y-set connector with a membrane sealing the distal lumen which is attached to a PD solution bag, each UV transparent transfer set was inoculated with 10^6 to 10^7 cfu of cultured microbes. After being exposed to the UV light, the membrane seal was broken, the plunger valve on the UV transmissive transfer catheter was pushed to the open position, and 10 mL of dialysate was flushed through the connection over 7 seconds. The flushed solution was collected, diluted, and plated on agar medium matched to the organism. All plates were incubated for a 24-48 hour period (48 for C. albicans). Sample results were compared to positive controls which were collected in an identical manner but without exposure to the UV light.

Results: Twenty-nine (29) separate test samples, 3 positive controls, and 1 negative control of the connection set, were collected for each organism. All positive control samples had significant bacterial growth and negative controls had no growth following the 24 hour incubation period. All test samples exposed to UV light had complete kill of bacteria. Log reduction ranged from 4.93 in the C. albicans group, to 5.56 in the S. aureus group, to 6.24 in the E. coli.

Conclusions: The application of 400 mJ/cm² UV light (254nm) combined with an easy-to-use UV transmissive transfer catheter connector produces a germicidal effect upon microorganisms which have been found to be associated with peritonitis in patients receiving peritoneal dialysis.

Funding: Other U.S. Government Support

TH-PO1150
Application of Comfeel Hydrocolloid Transparent Dressing Combined Specified Electromagnetic Wave in the Patients with Arteriovenous Fistula Complicated with Subcutaneous Hematoma

Hui-Qun Li, Wenbo Zhao, Geng-Xi Sun, Hui Peng, Tan-Qi Lou.1 'The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong; 'Affiliated Hexian Memorial Hospital, Southern Medical Univ, Guangzhou, Guangdong.

Background: Comfeel transparent dressing is a hydrocolloid dressing which can promote local blood circulation, relieve pain and Reduce inflammatory reaction. And Teding Dianci Pu (TDP) specific electromagnetic wave irradiation instrument can diminish inflammation and promote the growth of the local epithelial tissue. The purpose of this study is to explore the effect of Comfeel transparent dressing combined TDP irradiation treatment in the chronic kidney disease patients with arteriovenous fistula (AVF) complicated with subcutaneous hematoma.

Methods: 30 patients (14 male, 16 female) were involved in this study. All the patients were randomly divided into observation group (n=15) and control group (n=15).

There was no significant difference in gender, age, primary disease, use time of AVF and the size subcutaneous hemATOMA between the two groups. The methods of control group included clean the local skin and use the Hirudoid ointment to massage, 3 times a day, but not to use within 6 hours after hemodialysis. The methods of observation group clean the skin, paste the Comfeel transparent dressing (No.3533), and use TDP irradiation for 15 minutes, twice a day, but not to use TDP within 24 hours after hemodialysis. The effect of treatment was observed by 3 days after the treatment and the skin ecchymosis, swelling, local pain (NRS Pain Assessment Scale), AVF tremor and patient satisfaction were assessed after 1 week.

Results: The subsidence of the skin ecchymosis and swelling was faster (P < 0.05) in the observation group. Any adverse event was not seen in our study.

Conclusions: The research results show that use of Comfeel transparent paste combined TDP irradiation can effectively relieve the local pain, and promote the subsidence of the skin ecchymosis and swelling. It is worthy to be popularized in clinic practice.
due to continuous bleeding. Macrophatemia occurred in 5 patients (1.0 %), and perirenal hematoma at sonography in 36 patients (8.5 %). The median decrease in Hb was 0.33 g/dl. Anemia (defined above) was observed in 54 patients (11.7 %). The risk of anemia was higher in women, older patients, and patients with lower serum albumin, lower CCRF and lower diastolic blood pressure after biopsy. A multivariate analysis revealed that anemia was associated with female gender, lower serum albumin, and lower diastolic blood pressure after biopsy. Next, we performed a further analysis in 187 patients for whom baPWV data was available. A higher baPWV value was found to be a risk factor of anemia. The ROC analysis for predicting anemia revealed baPWV 1839 m/s to be the best performance (AUC 0.689, p < 0.005).

Conclusions: An increase in the baPWV, which is non-invasive parameter of arterial stiffness, was the factor significantly associated with anemia after biopsy, and thus may be a more valuable predictor of bleeding complications than any of the other reported risk factors.

TH-PO1154

Outpatient Percutaneous Native Renal Biopsy: Safety Profile in a Large Monocentric Single Operator Cohort

Dario Roccatello, Savino Sciaccia, Nephrology Dept, San Giovanni Bosco Hospital, Torino, Italy.

Background: Debate exists on the appropriate observation period after percutaneous native renal biopsy. We evaluated the safety of performing renal biopsy as an outpatient procedure compared to the traditional inpatient policy.

Methods: We retrospectively studied native kidney biopsies performed in our Institution (Jan 2000-Nov 2015). Since Jan 2012, we began performing renal biopsies as outpatient procedures. Two groups of patients were considered; Group I: biopsy was performed and followed by at least 1-day hospital admission; Group II: biopsy was performed as outpatient and discharged within 6 hours observation period and with outpatient visits. All biopsies were performed by a single nephrologist with the use of real-time ultrasound and automated biopsy needle (18 gauge), following a structured protocol.

Results: 462 biopsies were reviewed, 210 (45.5%) of patients were female and the mean age was 54.7±17.9 years. 129 (27.9%) of these biopsies were performed in outpatients. A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arteriovenous fistula (6 cases,1.2%), ischaemic stroke (2, 0.4%), thromboembolic pulmonary embolism (1, 0.2%) and 27 (5.8%) for minor [macroscopic haematuria (12 cases, 2.6%), haematoma on sonography not requiring intervention (15 cases, 3.2%)]. When comparing the complication rate between group I and II, no statically difference were observed (overall 24/333 (7.2%) complications in group I and 12/129 (9,3%) in group II; 5/333 (1,5%) and 4/129 (3,1%) major, 19/333 (5,9) and 8/129 (6,2%) minor complications, respectively in group I and II). When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95%CI 1.18-6.81) and known hypertension (OR 2.01 95%CI 1.24-3.17) were found to be independent risk factors for minor and major complications, respectively. We found no association of risk with the biopsy passes, gender, age, diagnosis, presence of haematuria before the kidney biopsy and the nor degree of proteinuria.

Conclusions: Outpatient kidney biopsy could be a valuable, safe, and perhaps cost-effective method of obtaining diagnostic renal tissue in the majority of patients.

TH-PO1155

Complications of Percutaneous Renal Biopsy Performed by Nephrology Fellows: Analysis of 1071 Procedures

Manuel Alejandro Marquez,1 Monica Chap'a, Ricardo Correa-Rotter,2 Juan M. Mejia-Vilet.1 1Nephrology, Inst Nacional de Ciencias Medicas y Nutricion, Mexico; 2Radiology, INCMNSZ, Mexico.

Background: The performance of percutaneous renal biopsies (PRB) is a key element for renal diagnosis and nephrology training. The aim of this study was to evaluate safety and performance of PRB performed by nephrology fellows(NF) in an academic training program and to determine risk factors for major complications(MC).

Methods: All PRB performed by NF between 2008-2015 were analyzed.PRB procedures were ultrasound-guided and supervised by staff.In all patients, a doppler ultrasound was performed 10min after the procedure. MC were defined as those requiring medical intervention(blood transfusion, renal angiography, surgery or death).

Results: A total of 1071 PRB were analyzed,≥10 glomeruli were obtained in 989(92%) patients (85.9 %). The predicting AUC was 0.89. There were no differences in MC in 28 patients who had total anticoagulation(suspended prior to PRB). The absence of a renal hematoma in the immediate postprocedure US had a NPV for MC of 99%. The addition of postprocedure PRB to this model improved the AUC to 0.92.

Conclusions: The predicting AUC was 0.89. There were no differences in MC in 28 patients who had total anticoagulation(suspended prior to PRB). The absence of a renal hematoma in the immediate postprocedure US had a high NPV for MC. RBP is a safe procedure when performed by NF, as MC presented in a similar pattern and percentage as compared to large published series.

TH-PO1156

Background: Outpatient Kidney Biopsies

Bojana Gardijan, Mihaela Gunjaca, Branislav Cingel, Miladen Knotek. Renal Div, Dept of Medicine, Univ Hospital Maribor, Zagreb, Croatia.

Results: There were 71 female and 184 male patients. Average age was 42.6±16.1 yrs. Indications for native kidney bx included nephrotic syndrome (51%), subnephrotic proteinuria with hematuria (29%), follow-up bx (15%), and other (5%). From 216 transplant bx 31% were indication and 69% were protocol bx. The glomerular yield in 96.9% of bx was reduced for one or more of the following reasons: vWF was positive in 82% of bx, in 72% of bx was a Hb rise after biopsy. Average postbx Hb decline in the other 82% was 5% (1-16%). In 13.3% pts there was >10% reduction in Hb level, with no evident bleeding, including by US. In 2% of the patients postbx macrohematruia was present, without requirement for intervention or blood transfusion. In univariate analysis age, gender, serum creatinine, prebx Hb and indication for bx were not predictive for postbx Hb decline. There were no therapeutic interventions required for bx complications.

Conclusions: We found that kidney biopsy performed in an outpatient setting in select patients is only rarely associated with adverse events and is a safe procedure.

TH-PO1157

Self-Monitoring Creatinine after Kidney Transplantation: Reliability of Patient Reported Data

Céline Lianne van Lindt,1 Wexrin Wang,2 Sandra Van Dijk,3 Ton Rovekamp,1 Ton J. Rabelink,1 Willen-Paul Brinkman,1 Paul J. Van der Bosch.2 Nephrology, Leiden Univ Medical Center, Leiden, Netherlands; 3Technology in Healthcare, Prevention and Health (TNO), Leiden, Netherlands; 4Health, Medical and Neuropsychology & Behavioural Sciences, Leiden Univ, Leiden, Netherlands.

Background: Our previous study shows that self-monitoring creatinine can significantly decrease the high number of outpatient visits in the first year post-transplantation without compromising on quality of care. In the current study we analyzed data from this same self-monitoring RCT to investigate the reliability of reported creatinine values.

Methods: During the first year post-transplantation 54 patients registered their self-measured creatinine values in an online Self-Management Support System (SMSS) which provided automatic feedback (e.g. contact hospital). Values registered in the SMSS were compared to those logged in the creatinine device to study reliability of registered values. Adherence to measurement frequency was determined by comparing number of requested with number of performed measurements. To study adherence to provided feedback, SMSS logged feedback and information from the electronic hospital files were analysed.

Results: Level of adherence was highest during month 2-4 post-transplantation with over 90% of patients performing at least 75% of the requested measurements. Ninety percent of all registered creatinine values was entered correctly, although values were often registered several days later. In case more measurements were performed than registered on a single day (10%), registered values were significantly lower than unregistered values (p <0.5) suggesting selection of lower creatinine values. Adherence to SMSS feedback ranged from 53-85% depending on the specific feedback.

Conclusions: Self-monitoring creatinine enables the high number of outpatient visits to be reduced. However, patients’ tendency to postpone measurements is in line to select lower creatinine value for registration and the suboptimal adherence to the SMSS provided feedback might challenge safety. These issues can mostly be overcome by transferring measured data automatically.

TH-PO1158

Eradication of Chronic Helicobacter pylori Infections in Inflammatory Patients with Chronic Renal Insufficiency

Alexander M. Swan, Kay Thwe Kyaw. NHRT RT, LLC, Avenel, NJ.

Background: Based on some epidemiological studies, there are more frequent infection rate of Helicobacter pylori (H. pylori) in children of developing nations. Surprisingly, more than 50 % of second-generation immigrants are infected with H. pylori. Some studies showed that the factor differences are somewhat related to socio-economic status. Most route of transmission of H pylori is either oral-to-oral or fecal-to-oral contacts. Some patients with
H pylori do not present symptoms. When comes to treatment, triple therapy regimen is the first line. It is critical to be aware of known complications of H. pylori such as gastric adenocarcinoma, gastric MALToma, and squamous cell esophageal cancer.  

Methods: This study is a non-randomized parallel clinical trials study design. The study population was selected from renal failure patients who were H. Pylori Ig G Ab positive after treated with standard triple regimen, consisting of 88 participants of renal failure ranging from CKD Stage one to five, with age between 20 to 65, 80 participants finished and 8 drop out from the study. There are 16 participants contributed in each chronic kidney disease stage from one to five. The participants were given the new treatment, which included 24 mg of amoxicillin, 40 mg of omeprazole, and 500 mg of levofloxacin daily; Levaquin 500 mg tab daily; and Doxycycline 100 mg twice daily, and the renal dose adjustments were done according to creatinine clearance. The duration of new treatment was 4 weeks. H. pylori Ig G Ab levels were measured before and after new treatment. 

Results: At the end of the study, H. Pylori Ig G Ab of all patients in the study population was reduced to “0”. The outcome measure is a complete resolution of symptoms of H. Pylori and the disappearance of H. pylori Ig G antibody. 

Conclusions: There is evidence that the new treatment regimen reduced H. pylori Ig G level to 0, and clearly showed that more effective in eradication of H pylori infection in patients who have chronic renal failure. The drawback of the new treatment is expensive. However, more researches with larger populations are needed for developing a new guideline for eradication of H pylori in all patients to prevent complications of H. pylori infections.

# TH-POI1159

**Improving Post-Kidney Transplant Immunization: A Clinical Practice Improvement Project**

*Sanela Redzepagic,1,2 Angus G. Ritchie,1,2 Martin P. Gallagher,1,2 1Concord Hospital, Sydney, Australia; 2University of Sydney, Australia; 3Kolling Inst of Medical Research, Sydney, Australia; 4The George Inst, Australia.*

**Background:** Kidney transplant recipients (KTR) are at increased risk of influenza and invasive pneumococcal disease. Audit after 2 cases of pneumococcal infection in KTR at our institution identified low prevalence of pneumococcus (35%) and influenza (30%) vaccination. We devised a quality improvement program in partnership with primary care, who manage vaccination in Australia, to improve up-to-date vaccination to>90% in this population.  

**Methods:** We conducted a single centre prospective clinical practice improvement study on a KTR cohort over 3 years (2013-15). The diagnostic phase indicated low awareness of vaccination importance, non-adherence to local immunisation guidelines and suboptimal communication with primary care doctors. Two interventions of annual reminders to primary care doctors with local immunisation guidelines were devised. The primary outcome was up-to-date vaccination reported in annual surveys. A logistic regression model using Generalized Estimating Equations was used in analysis. The study was approved by our ethics board.  

**Results:** Surveys were conducted to the primary care doctors of 59 KTR. Responses were received to 48/59(81%) and 37/59(53%) surveys to interventions 1(2014) and 2(2015) respectively. For pneumococcus 34% of eligible patients were reported to have received vaccination in the period prior to baseline survey, increased to 69% by the second survey; while up-to-date influenza vaccination increased from 45% to 59% in the same period. KTR were significantly more likely to have up to date vaccination by the second survey for pneumococcus, OR 3.4 (95% CI:1.8–6.4; p<0.001) but not influenza, OR 1.8 (95% CI:0.9–3.5; p=0.09). No reported cases of IPD during the study.  

**Conclusions:** Most smartphone digital images of U-Sed are of acceptable quality. Muddy brown casts, crystals, and red cells can be recognized, but candida is less obvious. Sampling error may occur based on the experience of photographer. Keeping faculty in the loop by sharing U-Sed images may be of educational and clinical utility.

# TH-POI1160

**Emergency Preparedness in the Kidney Transplant Community**

*Shimie Sharief, Daniel J. Freitas, Nicole Rich, Deborah B. Adey, James A. Wiley, UCSF.*

**Background:** In the ten years since Hurricane Katrina, the Centers for Medicare and Medicaid Services and KCER (Kidney Community Emergency Response) Coalition have taken several steps to regulate and mandate emergency preparedness planning in dialysis units. Similar steps have not been taken to ensure the safety of kidney transplant patients who rely on specialized pharmaceuticals to maintain the function of their allografts. The diagnostic phase indicated low awareness of preparedness information. The objective of this study was to develop and pretest a self-administered questionnaire to assess the disaster preparedness of a cohort of kidney transplant recipients in an earthquake-prone region of the United States.  

**Methods:** Based on information obtained from the National Kidney Foundation Planning for Emergencies handbook, we designed a preliminary questionnaire. We recruited 10 Bay Area patients and 5 kidney transplant providers from the transplant clinic at the University of California San Francisco and the general nephrology clinic at San Francisco General Hospital. Our two-step protocol included a self-administered questionnaire followed by an interview regarding attitudes and barriers around preparedness and feedback on the survey. Three researchers coded and analyzed the data and categorized the responses into themes.  

**Results:** The questionnaire was easily readable but subjects had difficulty in understanding the context of the questions. Most defined disasters as man-made terrorism instead of the intended meaning of natural disasters. Patients reported lack of salience and relevance of the issue and lack of access to information as major barriers to disaster preparation. Providers cited their patients’ education and engagement as key determinants of their level of preparedness. We modified the questionnaire to include a hypothetical scenario to frame the questions, and organized the questions into sections. Providers’ deficiencies in understanding and recognizing transplant patients as a vulnerable population contributed to their complacency in providing them with preparedness information.  

**Conclusions:** We noted serious deficiencies in disaster awareness and planning in the kidney transplant community. Ongoing research and collaboration between medical and city services are necessary to ensure safety in disaster-prone regions.  

_Funding: NIDDK Support_
**FR-PO001**

**Infectious Endocarditis Mimicking ANCA Associated Pulmonary-Renal Syndrome with Crescentic Necrotizing Glomerulonephritis**

Samer Mohandes,1 Anjali A. Satoskar,2 Tibor Nadasy,3 Lee A. Hebert,1 Isabelle Ayoub.1 1Medicine, The Ohio State Univ, Columbus, OH; 2Pathology, The Ohio State Univ, Columbus, OH.

**Introduction:** Pulmonary renal syndrome (PRS) is a life threatening disease requiring early diagnosis and prompt treatment. Its most common cause is ANCA- associated pauci immune crescentic Glomerulonephritis (Granulomatosis with polyangitis, GPA). Treatment usually involves high dose steroids, an immunosuppressant, and plasmapheresis. However, ANCA- associated pauci immune crescentic GN can also be the result of infection.

This case illustrates the dilemma of medical management until these forms of PRS can be clearly differentiated.

**Case Description:** A 57-year old white man with bioprosthetic aortic valve placement 5 years earlier transferred to our medical center with altered mental status and PRS. Diagnostic work up was significant for oliguria with Scr 3.5mg/dl, anemia, thrombocytopenia, positive PR3-ANCA, low complement and diffuse alveolar hemorrhage by bronchoscopy. He received hemodialysis, plasmapheresis and intravenous methylprednisolone. Kidney biopsy showed severe crescentic and necrotizing glomerulonephritis with C3 and IgM mesangial staining on immunofluorescence and rare paramesangial electron dense deposits. While on steroids, he develops fever. Blood cultures from the referring hospital showed MRSE. A transesophageal echocardiogram showed vegetations on the aortic and mitral valve along with a perivalvular aortic abscess. Appropriate antibiotic coverage was begun. Plasmapheresis and immunosuppression were stopped. He was too unstable for surgical intervention. The family decided to withdraw care. He died seven days later.

**Discussion:** PRS due to infection can be difficult to distinguish from GPA. In this case, clues to the presence of infection included low complement (C3, C4 <8) and fever after starting immunosuppression.

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**FR-PO002**

**Proteinuria, Edema, and Hypertension: A Case of Lupus Podocytopathy**

Farah Daccuel1, Kathleen Leger,1 Nobuyuki (Bill) Miyawaki,1 Joseph Mattana,1 Vivette D. D’Agati,2 James Drakakis.1 1Medicine, Winthrop Univ Hospital, Mineola, NY; 2Pathology and Cell Biology, Columbia Univ Medical Center, New York, NY.

**Introduction:** Lupus podocytopathy is an emerging subgroup classification of lupus nephritis with proteinuria but there is no immune deposition or endocapillary proliferation on renal biopsy. A diagnosis of lupus podocytopathy can be made when a patient is identified as having minimal change disease (MCD) or FSGS. We report a case of lupus podocytopathy as per American College of Rheumatology proposed diagnostic criteria, with coexisting focal glomerular tip lesion on biopsy.

**Case Description:** 39 year old male with hypertension for 12 years presented with abdominal pain, facial edema, and hyperpigmented lesions. He was noted to have blood pressure consistently over 160/80 despite two blood pressure medications. Blood work showed a creatinine of 1.08mg/dl, cholesterol of 392, triglyceride of 530, serum albumin of 2.2g/dl with normal HgA1C. Two days after our office visit he was hospitalized with flank pain and found in acute kidney injury with a creatinine of 2.5mg/dl. Hospital work up showed normal anti-DNA, complement level, HIV, hepatitis profile, immunofixation and ANCA. Laboratory result showed proteinuria of 2.9 gram/gram of creatinine, positive anti-Smith antibody and ANA=1280. He admitted to NSaid use in the last month. With his worsening kidney function 1mg/kg/d, a kidney biopsy was performed. Biopsy showed podocytopathy, focal glomerular tip lesion approximating minimal change disease. There was accompanying speckled nuclear positivity for IgG, suggesting characterization as a lupus podocytopathy. A formal diagnosis of lupus based on systemic and serologic findings is being strongly considered by rheumatology. High dose steroid was initiated and thus far creatinine has improved to 1.2mg/dl. Repeat proteinuria quantification is pending.

**Discussion:** Lupus podocytopathy is an emerging subgroup classification of lupus nephritis, where there is no immune deposition or endocapillary proliferation on biopsy, but significant proteinuria and MCD or FSGS is noted. Ongoing literary work and case reports have aimed at defining lupus podocytopathy as its own entity in order to better categorize the disease and provide directed treatment plan.

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**FR-PO003**

**A 61 Year Old Male with Dense Deposit Disease and Monoclonal Gamopathy of Undetermined Significance**

Farah Daccuel1, Nobuyuki (Bill) Miyawaki,1 Vivette D. D’Agati,2 Naveed N. Masani.1 1Medicine, Winthrop Univ Hospital, Mineola, NY; 2Pathology and Cell Biology, Columbia Univ Medical Center, New York, NY.

**Introduction:** Dense deposit disease (DDD) is a rare cause of glomerulonephritis (GN), predominantly seen in children and young adults. Dysregulation of the alternative complement pathway is implicated in the development of DDD. D-Dominant gamopathy of undetermined significance (MGUS) has been linked to AP activation. Here we report a case of biopsy proven DDD in an adult male with MGUS.

**Case Description:** A 61 year old Caucasian male presented with newly diagnosed hypertensive urgency and acute kidney injury with an increase in serum creatinine to 2.7 mg/dl from baseline of 0.8 mg/dl after a recent URI. Examination was significant for a BP of 160/80 and lower extremity edema. Urinalysis was significant for 2+ protein, 3+ blood, 3-10 RBC/hpf, no red cell casts. Spot quantification revealed approximately 3.2 grams of protein per gram of creatinine. Serum immunofixation was remarkable for Igkappa with a normal kappa lambda ratio. Further work up done at the time, showed normal negative ANA, anti-dsDNA, anti-CCP, C4, C150, HBAg, HCV, ANCA and anti-neutrophil cytoplasmic antibodies. Renal biopsy findings included membranoproliferative and exudative pattern of glomerulonephritis, with isolated C3 deposits, and highly electron dense deposits, consistent with DDD. Subsequent bone marrow biopsy demonstrated a 3% clonal population Patient was treated with high-dose prednisone and rituximab induction. Seven months post treatment, patient appears to be in remission with a negative urinalysis, no significant proteinuria on spot sample, and a serum creatinine of 1.96 mg/dl. Patient is due for maintenance rituximab. Disease is attributed to dysregulation in the alternative pathway of the complement system. MGUS has been linked to AP dysregulation. This case report demonstrates a patient with DDD & MGUS successfully treated with prednisone and B-cell depleting therapy (rituximab) leading to short term remission of GN.

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**FR-PO004**

**Concomitant Diagnosis of Fibrillary Glomerulonephritis Secondary to Multiple Myeloma and Mycosis Fungoides: Simultaneous Diagnosis of B and T Cell Malignancies**

Farah Piracha, Neeraj Sharma, Michael Yudd, Jennie Michnaid. Nephrology, East Orange Veterans Affairs, East Orange, NJ.

**Introduction:** Fibrillary glomerulonephritis (FGN) is a rare proliferative glomerulonephritis associated with malignancies including Multiple Myeloma (MM). B cell disorders including MM and T cell lymphomas including Mycosis fungoides (MF) occur concomitantly at a higher rate than expected by chance.

**Case Description:** 71 year old African American male underwent a kidney biopsy for nephrotic syndrome and hematuria. His creatinine was 1.2 mg/dl, serum M spike of 0.5g/dl, bone marrow was hypercellular, and had a serum free light chain of 0.5g/dl. Renal biopsy revealed C3 and monoclonal IgG deposits on immunofluorescence with randomly arranged, Congo Red negative, fibrils 15-25nm in diameter in a mesangiproliferative pattern. Bone marrow biopsy revealed 4% plasma cells; flow cytometry showed 0.4% Igk restricted plasma cells. Serum k free light chains were 7730 mg/ml with a serum free light chain ratio (SFLC) ratio of 228, establishing the diagnosis of MM. Several large hyperpligmented lesions were noted on his trunk; biopsy proven to be MF. MM was treated with cyclophosphamide, bortezomib and dexamethasone; topical steroids for MF. After 4 cycles, serum free k decreased to 3100 mg/dL, SFLC ratio to 142; proteinuria decreased to 1.2 grams.

**Discussion:** FGN is seen in 0.5-1% of biopsy samples with 10% having monoclonal deposits; an M spike can be seen in up to 17% of patients. A contemporaneous cutaneous T cell lymphoma was found in this the patient. A 2009 review from the Mayo Clinic found a higher than expected incidence of concomitant B and T cell disorders which can present simultaneously or sequentially. Proposed theories for this includes immunosuppressive medication for one malignancy stimulating another, direct immune suppression of one malignancy leading to a second malignancy, genetic predisposition or release of stimulatory cytokines. Ours is the first case of MM and MF identified with C3 and FGN. Several large hyperpligmented lesions were noted on his trunk; biopsy proven to be MF. MM was treated with cyclophosphamide, bortezomib and dexamethasone; topical steroids for MF. After 4 cycles, serum free k decreased to 3100 mg/dL, SFLC ratio to 142; proteinuria decreased to 1.2 grams. **Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.**
FR-PO006

Fibrillar Glomerulonephritis in a Patient with Systemic Lupus Erythematosus

Mohit Gupta, Rupesh Raina, Karla Detoya. Internal Medicine, Akron General Medical Center, Akron, OH.

Introduction: Fibrillar Glomerulonephritis (FGN) is a rare disorder that is characterized by nephritic range proteinuria, hematuria and reduced renal function. It has a reported incidence of 0.6 – 1.5% in adults and carries a poor prognosis. It is rarely associated with systemic lupus erythematosus (SLE) and is not considered a lupus nephritis (SN). Herein, we report a case of a patient who presented with worsening kidney function and was found to have fibrillar glomerulonephritis associated with SLE.

Case Description: A 70 year old Female with a known history of CKD III initially presented with a complaint of progressive diarrhea. Upon presentation she was found to have a Creatinine of 5.3 mg/dl significantly above her baseline of 1.5 mg/dl. She was started on IV Fluids for a suspected pre-renal injury. Creatinine improved initially but not to baseline. During the next 2 days, she worsened clinically and developed bilateral pleural effusions. She was started on Oxygen therapy for worsening oxygen requirements. Urinalysis showed proteinuria in excess of 3 g/day. ANA pattern was positive with nucleolar pattern and a titre of 1:80. She remained oliguric despite diuretics and was transitioned to renal replacement therapy. Renal biopsy was planned for suspected Lupus nephritis and she was placed on pulse dose steroid therapy. Biopsy revealed the presence of extensive Congo Red Positive electron dense deposits arranged in fibrils measuring 20 to 25 nm along the mesangium and glomerular walls. This was consistent with a diagnosis of fibrillar glomerulonephritis associated with SLE. She was discharged with renal replacement therapy, but offered for comfort care only.

Discussion: SLE associated fibrillar glomerulonephritis is a rare disorder and only a handful of cases have been reported till date. It differs from other forms of fibrillar glomerulonephritis in that fibrils are generally arranged in a fingerprint pattern of concentrically curved lines. Immunosuppressive therapy with cyclophosphamide, steroids and recently Rituximab have been used in the treatment of this disorder. However, given its rare incidence and lack of studies, the treatment of the same still remains a therapeutic challenge.

FR-PO007

Thin Basement Membrane Disease or Alport Syndrome: Albarya Said, Cybele Ghossein. Nephrology, Northwestern Univ Feinberg School of Medicine, Chicago, IL.

Introduction: Thin basement membrane disease (TBMD) is characterized by diffuse thinning of the glomerular basement membrane (GBM). It is a common disorder that is frequently familial in nature and is caused by genetic defects in COL4A3 or COL4A4, genes that encode type IV collagen. These same alleles are affected in patients with Alport. In fact biopsies done early in patients with Alports frequently reveal diffusely thin GBMs as seen in TBMD. Clinically, however, TBMD has a much more benign course. GBM disease patients typically present with hematuria and mild proteinuria while Alports frequently progress to end stage renal disease (ESRD). We present a patient with presumed familial TBMD and no family history or ESRD whose biopsy revealed Alports.

Case Description: A 29 year-old male with a history of TBMD presented to our clinic for evaluation. The patient had been followed yearly from early childhood for hematuria and proteinuria. He states his mother, brother, and sister have the same disease and they all were given the presumptive diagnosis of TBMD. There was no family history of kidney dysfunction or hearing loss. None of his family members had ever undergone a kidney biopsy. Labs revealed a creatinine of 0.84 mg/dl and a 24 hour urine protein of 2400mg. A renal biopsy was performed and this revealed variably thickened basement membranes from 130nm to 780nm consistent with Alports. Genetic testing was performed and an in-frame deletion of three amino acids in the triple helix repeat domain of the COL4A5 protein was found. This variant has been reported to cause Alports.

Discussion: TBMD is an often familial GBM disease that causes hematuria. Patients with this disease tend to follow a benign course, have minimal proteinuria, and almost never have kidney disease progression. For this reason biopsies are rarely performed and the diagnosis is frequently a clinical one. However it is important to consider alternative diagnoses if the clinical picture isn’t clear. Our patient exhibited a higher than expected level of proteinuria and thus a biopsy was performed revealing Alports. This diagnoses will help with genetic counseling in our patient and may affect future management.

FR-PO008

Leukocyte Cell-Derived Chemotaxin 2 (ALect2) Associated Renal Amyloidosis: A Case Report

Benjamin Kwei Sarsarh, Amy Nicole Sussman, Erika R. Bracamonte, Bijin Thajudeen. 1 Nephrology, Banner Univ of Arizona Medical Center, Tucson, AZ; 2 Pathology, Banner Univ of Arizona Medical Center, Tucson, AZ.

Introduction: ALect2-associated renal amyloidosis (RA) is a recently recognized and distinct clinicopathologic type of amyloid manifested in adults by varying degrees of impaired kidney function and proteinuria. There are limited number of cases reported in the literature.

Case Description: We present a 64-year-old Hispanic female with a history of hypertension who was referred for CKD management. Review of her laboratory tests revealed a serum Cr of 1.5-1.8 mg/dl and microalbuminuria (in the presence of a bland urine sediment). She denied any history of diabetes, rheumatologic disorders or exposure to intravenous contrast, NSAIDS, herbs and heavy metals. Serological work up was negative. A renal biopsy was performed. Light microscopy showed diffuse infiltration of glomeruli with pale ALECT2 amyloid deposits. Congo red stain was negative. Electron microscopy showed marked infiltration of mesangium, capillary loops and interstitium with haphazardly arranged fibrillar deposits. Liquid chromatography tandem mass spectrometry was performed on peptides extracted from Congo red positive, microdissected areas of the paraffin- embedded kidney specimens and showed ALect2 as the amyloid protein.

Discussion: ALect2-amyloidosis should be suspected in renal biopsy specimens exhibiting extensive and strong mesangial as well as interstitial congophilia. Individuals with ALect2 RA have varying prognosis depending on the extent and rate of deposition. Therapeutic options include supportive measures (including dialysis when necessary) and consideration of kidney transplant from a histocompatible donor for those with ESRD.

FR-PO009

A Case of Waldenstrom’s Macroglobulinemia Presenting as Acute Renal Failure and Nephrotic Syndrome


Introduction: Waldenstrom’s macroglobulinemia (WM) is a rare B-cell disorder characterized by bone marrow (BM) infiltration of B lymphocytes and plasma cells along with a serum monoclonal immunoglobulin M (IgM) component. Renal involvement is uncommon compared to other dysproteinemias. We report a case of WM presenting with severe acute kidney injury (AKI) and Minimal change disease (MCD).

Case Description: A 56 year old WF with no history of renal disease developed shortness of breath and anasarca of 4 weeks duration. Clinical exam showed signs of volume overload and labs showed severe AKI (below). She was admitted and diuresed. CXR showed a large left pleural effusion and ECHO showed a normal EF. Admission creatinine was 7.5 mg/dl. Hemoglobin 9 gm/dl and 24hr urine protein was 18.4 gms. ANCA and ANA were negative. SPEP and UPEP showed monoclonal spike and IFE labeled it as IgM kappa. Serum IgM levels was elevated at 1940 mg/dl and free kappa level was 667. Kappa to lambda ratio was 56. Bone marrow biopsy confirmed a lymphoplasmacytic lymphoma consistent with WM. Renal biopsy showed minimal glomerular changes (MCD), immunofluorescence showed dominant IgM deposition with kappa light chain restriction in the subendothelial space and no amyloid. Our patient did not have neurological symptoms and serum cryoglobulins were negative ruling out hyperviscosity. She was started on plasmapheresis with a rapid reduction in serum IgM to 204. She received bortezomib, rituximab and steroids without improvement in renal function and needed dialysis. Chemotherapy for B-cell lymphoma (cyclophosphamide, rituximab, steroids) was given for 6 cycles. She achieved full remission of lymphoma, and was weaned off dialysis.

Discussion: Renal involvement in WM is rare and is usually due to amyloidosis. We report this case of WM with AKI requiring dialysis and MCD caused by IgM kappa in the glomeruli and no amyloidosis. There are only a few cases in the literature with a similar presentation. We also show that the renal injury could be permanent despite full remission of the WM with aggressive chemotherapy and plasmapheresis.

FR-PO010

ANCA-Negative Paucl-Immune Necrotizing Glomerulonephritis in a Patient with Multicentric Castleman’s Disease

Div of Hematology and Oncology, Emory Univ.

Introduction: Castleman’s Disease is a rare lymphoproliferative disorders first described by Dr. Benjamin Castleman in 1956 in patients with lymphadenopathy having atypical follicles and interfollicular vascular proliferation. It is classified as unicentric (UCD) or multicentric disease (MCD) where MCD presents with lymphadenopathy, hepatosplenomegaly and fever and is associated with Human Herpes 8 (HH8) in HIV infection. Kidney involvement in MCD is unusual and case reports have noted various lesions, mostly amyloidosis, membranoproliferative glomerulonephritis (GN) and thrombotic microangiopathy. Other lesions were rarely seen less including 3 cases of crescentic GN. We describe a case of MCD disease with HH8 presenting with hematuria, proteinuria, and near normal renal function whose kidney biopsy showed Pauci-immune necrotizing GN with cellular crescents.

Case Description: A 55-year-old African American male patient with HIV and wasting came to Grady Memorial Hospital with fevers, and weight loss. CT chest and abdomen was performed and he was found to have a large left upper quadrant mass. He was started on IV Fluids for a suspected pre-renal injury. Achieved full remission of lymphoma, and was weaned off dialysis.
A BPI-ANCA Associated Rapidly Progressive Glomerulonephritis with Immunocomplexes: A Case Report
Boiana Gardjian,1 Danica Galesic Ljubanovic,2 Zeljka Jurkovic,1 Branislav Cingel,1 Mladen Knotek,1 Renal Div, Dept of Medicine, Medical University of Graz, Graz, Austria; 2Dept of Pathology, Univ Hospital Dubrava, Zagreb, Croatia.

Introduction: Antineutrophil cytoplasmic antibodies are a major cause of rapidly progressive glomerulonephritis (RPGN). Routinely tested ANCA are MPO and PR3. A number of atypical ANCA is also known, such as anti-bacterial/permability-increasing protein (BPI) ANCA, which is a well-described cause of vasculitis. Overlap syndromes of pauci-immune ANCA, GN and immune complexes (IC)-mediated GN have been reported. A review of literature, this is the first reported case of BPI-ANCA associated RPGN with IC.

Case Description: A 35-year-old Caucasian man with malignant liver cirrhosis was referred to our hospital with the diagnosis of hepatoportal syndrome. At admission, the pt was dialysis-dependent and oliguric, with ascites and atelectasis. Edema was noted with P2 C.6 (g/dL). Kidney biopsy was performed. The finding was diffuse endocapillary proliferative glomerulonephritis, active, without signs of chronicity. Immunofluorescence (IF) was positive for IgG, IgM, C3, and C4 chains. ANA, ENA, dsDNA, RF, anti-CCP, LA Abs and biotinylated IgG, L3 IgM and 12 g/2-glycoprotein were negative. Serum C3 was 0.52 g/L (0.90-1.80) and C4 0.15 g/L (0.10-0.40). Testing for HCV, HBV and HIV was negative, as well as bacterial respiratory and urine cultures. ANCA was positive by IF (1:640), with negative ELISA for PR3- and MPO-ANCA. ANCA was specified as BPI-ANCA. The pt was treated with combination of PXR, steroid pulses and IV cyclophosphamide (CYC). After 4 PEX, ANCA declined to 1.160. After 10 days the pt was no longer dialysis-dependent. He received in total 6 CYC pulses. After a follow-up of 6 months, his eGFR is 115 ml/min.

Discussion: This is to our knowledge the first described case of BPI-ANCA-associated RPGN with IC. Pathohistology corresponded to lupus grade IVa nephritis (lupus-like GN). Cytoscopy and bladder cytology were negative. Kidney biopsy showed pauci-immune, focal, necrotizing GN with cellular crescent formation. Tubules and interstitial scarring was mild (14%) with little interstitial fibrosis or tubular atrophy. Treatment was begun with prednisone and Rituximab. Urinalysis demonstrates resolution of proteinuria and hematuria. 5 months later Cr remained stable at 0.9mg/dL.

Discussion: Kidney involvement in MCD is unusual, and we report a case of ANCA-negative crescentic pauci immune GN in a HHV-8 positive HIV patient.

A BPI-ANCA Associated Rapidly Progressive Glomerulonephritis with Immunocomplexes: A Case Report
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Genetic testing for complement factors revealed a mutation in CFH gene. She was started on Eculizumab. Unfortunately, 12 months later she is still requiring intermittent hemodialysis.

Discussion: In Eculizumab trials in aHUS, younger age, higher baseline LDL and lower baseline hemoglobin were associated with greater eGFR improvements. Early Eculizumab initiation led to improved renal recovery. Mean eGFR change from baseline at 1 year was significantly higher in patients treated in >7 days than ≤7 days (57 vs. 23 mL/min/1.73 m², p = 0.0098). After 1 year, 17/21 and 36/76 patients in the >7 and ≤7 day groups, respectively, achieved a sustained increase in eGFR. Retrospectively, in this patient, he delay in initiation of Eculizumab may have impaired our patient, leading to non-recovery. Also, Eculizumab is a terminal (C5) complement blocker that may not work better in higher complement disorders.

FR-PO016
Membranous Nephropathy and Autoimmune Hemolytic Anemia in a Patient with a History of Hodgkin Lymphoma and Immune Thrombocytopenic Purpura
Molly Fisher, Yelena Rekhtman, Drexler. Nephrology, Montefiore Medical Center, Bronx, NY.

Introduction: We report the first known case of a patient with a history of Hodgkin lymphoma and immune thrombocytopenic purpura (ITP), both in remission, who developed membranous nephropathy (MN) and autoimmune hemolytic anemia (AIHA) in the absence of any overt clinical signs of a lymphoma recurrence.

Case Description: 41 year-old female with a history of Hodgkin lymphoma and ITP who presented with nephrotic syndrome. In 2010, she was diagnosed with Stage II Hodgkin lymphoma and was treated with rituximab and radiation therapy, resulting in a complete remission. In 2014, she was diagnosed with ITP, which remitted with IVIG and steroids. In June 2015, she presented with two months of gradual onset lower extremity edema, 40-lb weight gain, and foamy urine. Labs showed serum albumin 1.8 g/dL, total cholesterol 586 mg/dL, 16g of protein on a 24hr urine collection, and serum creatinine 1.3 mg/dL. Serologic evaluation, including SPEP, ANA, and testing for HIV and hepatitis B and C, was negative. Renal biopsy showed MN with extensive subepithelial and a few mesangial deposits and negative glomerular staining for PLA2R. She had no evidence of severe foot process effacement on Electron Microscopy, in the absence of subendothelial or subepithelial immune deposits. She was treated with prednisone and edaravone and radiation therapy, resulting in a complete remission of AIHA and a partial remission of membranous nephropathy.

FR-PO017
De Novo Collapsing Glomerulopathy in Renal Allograft: A New Potential Culprit?
Yorg Al Azzi, Oluarem Williams, David J. Cohen. Medicine, Columbia Univ, New York, NY.

Introduction: Collapsing glomerulopathy(CG) is a disease than can recur post-transplantation however its occurrence de novo is very rare. Case reports described de novo CG in renal allografts and in most of them no etiology was identified. We report a case of de novo CG in a renal allograft recipient with CMV being the potential culprit.

Case Description: 34yo AAF with ESRD 2/2 HTN on HD for 7 years s/p DDRT 07/14 from 20yo AAM (COD:GSW,KDPI 33%,multiple HLA-I and II DSA,EBV and CMV IgG D+/R+). She was induced with alemtuzumab, Rituximab and IVIG and maintained on tacrolimus and mycophenolic acid with rapid steroid withdrawal. Post-reperfusion bx showed ATN and diffuse glomerular fibrin thrombi. On 7/23/14, 1-wk protocol bx showed AMR and features of acute TMA(SCr 10.4). Started plasmapheresis 3 times/ week with IVIG repletion and tacrolimus was switched to belatacept. She was re-biopsied after 6 sessions of PPO(no rejection,no TMA,no more DSA). She was maintained on belatacept,mycophenolic acid,prednisone 5mg daily. Scr reached 0.92. On 7/14/15, 1-yr protocol bx revealed CG (CMV stain neg). Urine PCR ratio 5.3 and SCr 0.9. No events of renal ischemia, no new medications including no OTC medications. Viral serologies including HIV, parvoB19,adenovirus.BK,CMV and EBV PCRs were sent. CMV PCR resulted 5033 IU/mL, she was started on valganciclovir 900mg BID and followed with weekly labs. By the following week, CMV PCR levels were decreased to 353 IU/mL, and on the 3rd week CMV PCR was negative and remains negative to date.

Urine protein/creatinine ratio | Serum creatinine (mg/dL)
--- | ---
August 2014 | 0.4 | 1.4
October 2014 | 0.3 | 0.89
November 2014 | 0.2 | 0.88
January 2015 | 0.3 | 0.83
July 2015 | 5.3 | 0.9
September 2015 | 0.7 | 0.88
December 2015 | 0.6 | 0.94
January 2016 | 0.5 | 0.89

Discussion: To our knowledge, this is the first case report of de novo CG occurring in a renal allograft in the setting of CMV viremia. The timing of CMV viremia and development of proteinuria as well as resolution of the viremia with improvement of the proteinuria, in the absence of history of FSGS, addition of new medications and episodes of hypotension and renal ischemia, suggest that CMV might be the potential etiology of this de novo CG.

FR-PO018
Idiopathic Collapsing FSGS Presenting as “Forme Fruste” Lupus

Introduction: Patients with SLE commonly develop lupus nephritis during their disease course. Only a subset of patients have been described to have lupus podocytopathy, a form characterized by a full nephrotic syndrome in the setting of overt SLE with diffuse and severe foot process effacement on Electron Microscopy, in the absence of subendothelial or subepithelial immune deposits.

Case Description: A 45-year-old African American man on hemodialysis presented for shortness of breath and was found to have a large pericardial effusion with a tamponade physiology. He underwent pericardiocentesis with drainage of 700 cc of exudative fluid. His laboratory studies and his clinical presentation allowed a diagnosis of active SLE. Six years prior he presented with nephrotic syndrome and kidney failure requiring hemodialysis. His biopsy revealed collapsing FSGS presumed to be idiopathic at which time he did not meet clinical or serologic criteria for lupus.

<table>
<thead>
<tr>
<th>Test</th>
<th>Admission year 0 (Renal Failure)</th>
<th>Admission year 6 (Lupus Flair)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>1:640</td>
<td>1:160</td>
</tr>
<tr>
<td>anti-dsDNA (0-29 IU/mL)</td>
<td>26.0</td>
<td>&gt;300</td>
</tr>
<tr>
<td>C3 (90-180 mg/dL)</td>
<td>101</td>
<td>55</td>
</tr>
<tr>
<td>C4 (10-40 mg/dL)</td>
<td>34.7</td>
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<tr>
<td>Platelets (150-450 K/uL)</td>
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<td>87</td>
</tr>
<tr>
<td>HIV</td>
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<tr>
<td>Hepatitis C antibody</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Hepatitis B surface Antigen</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Serum Albumin (3.4-5.4 g/dL)</td>
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<td>3.1</td>
</tr>
<tr>
<td>Urine protein to creatinine ratio</td>
<td>3.34 gm</td>
<td>--</td>
</tr>
<tr>
<td>TB quantiferon gold</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Figure 1. (a) Light microscopy showing collapsing focal segmental glomerulosclerosis (FSGS). (b) Electron Microscopy showing podocytes displayed >95% foot process effacement and, no immune type electron dense deposits or endothelial tubulocapillary inclusions. The patient’s immunofluorescence was negative.

Discussion: This case illustrates that idiopathic collapsing FSGS could represent a lupus podocytopathy in the absence of overt lupus on initial presentation. We suggest following patients with idiopathic collapsing FSGS closely for possible subsequent development of SLE and perhaps treating them similarly to LN classes 3 and 4.

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

Underline represents presenting author.
FR-PO019

Recurrent Atypical Anti-Glomerular Basement Membrane Disease after Successful Kidney Transplantation: A Rare Case

Masaki Yamada,1 Andrey G. Chiesa-Votto,2 Lead C. Herlitz,2 Richard A. Fatica.3 1Nephrology, Cleveland Clinic, Cleveland, OH; 2Pathology, Cleveland Clinic, Cleveland, OH.

Introduction: Renal anti-glomerular basement membrane (GBM) disease typically presents with rapid renal dysfunction and crescentic glomerulonephritis. Several published reports describe an indolent variant of anti-GBM disease with atypical clinical and pathological features compared to classic anti-GBM disease. Patients with atypical anti-GBM disease manifest a smoldering disease course with hematuria, proteinuria, and more gradual decline in GFR.

Case Description: The patient was a 53-year-old never-smoker Caucasian female with a history of microscopic hematuria whose serum creatinine rose from 0.7 to 1.3 mg/dL over 5 years. She developed proteinuria (1.4 g/day) and hypertension around the onset of renal dysfunction. All serological evaluations were negative including RF, ANA, ANCA, complements, hepatitis B and C, HIV, anti-GBM antibody. Kidney biopsy revealed a small-vessel vasculopathy without crescent formation. Immunofluorescence showed strong linear GBM staining for IgG and lambda with negative kappa. Electron microscopy showed no electron-dense deposits but was notable for lucent subendothelial expansion and mesangial interpositioning suggestive of glomerular microangiopathy. Further tests; Sci-70, SS-A, SS-B, antiphospholipid, and M protein, were negative and no clinical evidence of a systemic thrombocytopenia. Her renal function was steady for the first 5 years, but started to decline over the next 3 years despite a trial of oral prednisone. Repeat kidney biopsy showed findings similar to the initial biopsy and no crescents were seen. She was preemptively transplanted from a three antigen HLA mismatched living-related donor. She had an excellent graft function but microscopic hematuria persisted. A 2-year post-transplant biopsy revealed focal segmental mesangial and endocapillary proliferation and linear IgG and lambda staining again in the GBMs. Atypical anti-GBM disease was diagnosed and retrospectively considered her original disease.

Discussion: This is the second reported case of recurrent atypical anti-GBM disease antibody disease after renal transplant.

FR-PO020

Collapsing Glomerulopathy due to Lupus Podocytopathy: Successfully Treated - A Case Report

Arani D. Nanavati,1 Lead C. Herlitz,2 Juan C. Calle.1 1Nephrology, Cleveland Clinic Foundation; 2Pathology, Cleveland Clinic Foundation.

Introduction: Collapsing glomerulopathy (CG) is described in SLE patients and represents a severe form of lupus podocytopathy (LP). The diagnosis of LP requires podocyte effacement without peripheral capillary wall immune deposits. We report a case of CG superimposed on lupus membranous glomerulonephritis (class V) lupus nephritis (LN V) who was successfully treated and became dialysis free.

Case Description: A 49 year old African American male, recently diagnosed with SLE, presented initially with proteinuria of 2 gm/day and serum creatinine (SCr) of 0.9 mg/dL. Renal biopsy at that time revealed LN V. Therapy with mycophenolate mofetil and prednisone was recommended; however he was lost to follow up and did not comply with treatment. He presented again one month later with confusion, weakness. Lab studies revealed SCr of 9.75 mg/dL, urine protein-to-cr ratio of 4.1. He was started on dialysis for anuria renal failure with uremia and was empirically treated with intravenous (IV) pulse methylprednisolone. Repeat renal biopsy revealed CG superimposed on the previously documented LN V. There was no evidence of endocapillary proliferation, necrosis or glomerular basement membrane rupture. Work up for HIV, EBV, parvovirus and CMV was negative. In the absence of known infectious causes of CG the diagnosis of LP was favored. The patient was treated with pulse IV cyclophosphamide. After 4 weeks of hemodialysis and within 12 days of IV cyclophosphamide dose, renal function began to recover. His SCr continued to trend down to 1.1 mg/dL. He continues to have proteinuria with recent urine protein to cr ratio of 2.7.

Discussion: The diagnosis of LP in this case is somewhat controversial given the underlying membranous changes. However, the presence of collapsing features, which are not seen in membranous lupus alone and the dramatic clinical deterioration supported the diagnosis of collapsing LP superimposed on class V lupus nephritis. While collapsing are not seen in membranous lupus alone and the dramatic clinical deterioration supported underlying membranous changes. However, the presence of collapsing features, which are not seen in membranous lupus alone and the dramatic clinical deterioration supported the diagnosis of collapsing LP superimposed on class V lupus nephritis.

FR-PO021

Metastatic Pulmonary Calcification with Progressive Respiratory Failure in the Course of Peritoneal Dialysis

Yuna Onozawa, Yosuke Nakagawa, Naoto Hamano, Masahiro Koizumi, Takehiko Wada, Masafumi Fukagawa. Dept of Nephrology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan.

Introduction: Metastatic pulmonary calcification is characterized by deposition of calcium salts in the normal alveoli and is commonly caused by end-stage renal disease (ESRD). It is often asymptomatic, but can develop respiratory failure.

Case Description: A 56-year-old male peritoneal dialysis (PD) patient was referred to our hospital due to progressive shortness of breath with pulmonary abnormal shadow on chest X-ray. He had been on PD for 10 years and had uncontrolled secondary hyperparathyroidism (SHPT). His intact PTH level stayed 500 pg/mL despite of a severe hyperparathyroidism. The renal shadow on chest X-ray had observed for a year. Initially he was asymptomatic, however, he presented with progressive dyspnea just before the referral. Chest computed tomography (CT) showed consolidation in bilateral lungs with diffuse calcification as well as cardiac enlargement and pleural effusion. Bone scintigraphy revealed intense uptakes in bilateral lungs. Taken together, he was diagnosed as metastatic pulmonary calcification and chronic heart failure. In echocardiogram anterior wall motion was decreased and coronary artery calcification score (CACS) was calculated to over 3,000 in multi-detector CT, indicating severe coronary artery stenosis due to metastatic calcification. In order to control his SHPT, he was switched to hemodialysis (HD) to improve his dialysis efficiency. In addition, percutaneous coronary angiography was performed due to his cardiac function. Renal function gradually improved although he remained on oxygen therapy. On a follow-up CT at 3 months after the conversion to HD, the calcification was obviously diminished.

Discussion: This case suggested that improved dialysis efficiency might reverse metastatic pulmonary calcification.

FR-PO022

Lupus Podocytopathy and Collapsing Glomerulopathy in a Patient without Nephrotic Syndrome

Delin Wang, Lance D. Dwarkin. Nephrology, Brown Univ; Providence, RI.

Introduction: Lupus podocytopathy is an unusual type of lupus nephritis characterized by nephrotic syndrome with podocyte foot process effacement and mesangial electron-dense deposits. We report a patient with lupus-like disease whose kidney biopsy showed pathological features of lupus podocytopathy and collapsing glomerulopathy but only exhibited microalbuminuria.

Case Description: A 39-year-old African-American female with history of hypertension, hyperlipidemia, and obesity status post gastric bypass surgery presented with an elevated serum creatinine (sCr) at 1.83 mg/dL <GFR 31 mL/min/1.73 m2, which had increased from 1.62 mg/dL 4 months prior. She was transiently on Chlorthalidone which was discontinued due to normalization of blood pressure (BP). Physical exam was remarkable for BP of 154/82 and frontal alopecia. Urine microalbumin-to-creatinine ratio (UMCR) was 265mg/gm. Serologic tests revealed high-titer antinuclear antibody (1:2560) with normal complements C3/C4 and anti-dsDNA (<1:10). Antiphospholipid antibodies were negative. Patient underwent a kidney biopsy which showed collapsing focal segmental glomerulosclerosis with podocyte foot process effacement and mesangial electron-dense deposits. Viral studies including HIV, Hepatitis B/C, Epstein-Barr virus (CT), Parvovirus B19, and Cyto megalovirus were negative. Because of progressive renal failure, she was treated with Mycophenolate Mofetil (MMF) 3 grams/day, Prednisone 60mg/day, and an angiotensin-converting enzyme inhibitor (ACEI). Bactrim was used for prophylaxis. After four months (Figure 1A) her sCr has increased to 2.27 mg/dL, although Bactrim may be contributing. In contrast, microalbuminuria has declined to 43 mg/gm per UMCR.

Discussion: To our knowledge, this is the first published case of a patient with collapsing lupus podocytopathy who lacks nephrotic range proteinuria. Although lupus podocytopathy often leads to immunosuppressive therapy, the limited number of reported patients with collapsing glomerulopathy have had a much poorer response. Additional patients and longer term follow-up are needed to determine whether the combination of MMF, steroid and ACEI helps induce remission and prevent progressive renal failure in patients with the collapsing variant.

FR-PO023

Renal Limited Polymyositis Nodosa with Positive Anti-Myleoperoxidase

Darwish Naji, Rupal Mehta. Nephrology Dept, Northwestern Medicine, Chicago, IL.

Introduction: Polymyositis Nodosa (PAN) is a systemic necrotizing vasculitis that typically affects medium-sized muscular arteries.

Case Description: M.W. is a 71-year-old Caucasian female with no past medical history who complained of fatigue, decrease urine output, lower extremity swelling, weight gain of 53 pounds over 2 months, and new elevated blood pressure. Laboratory investigation demonstrated an elevated creatinine of 4.6 mg/dL (baseline of 0.51 mg/dL one month prior). Urinalysis demonstrated non-dysmorphic red blood cells with no casts. Antinuclear antibody, complement levels, Hepatitis panel, serum and urine protein electrophoresis were unremarkable. Renal ultrasound revealed the incident microaneurysm and normal size kidneys. Renal biopsy demonstrated fibrinoid necrosis with little glomerular involvement (Figure 1A). Renal angiogram to investigate the microaneurysm demonstrated numerous microaneurysms (Figure 1B). Serology later returned with a positive anti-neutrophil cytoplasmic antibody (ANCA) titer of 1:640 and positive anti-myo-plexeroxidase (MPO) at 91 units. M.W. was started on pulse dose steroids and Cyclophosphamide for treatment of PAN.
Discussion: We describe an atypical presentation of PAN, which manifested with acute renal failure and positive serologies, without any other systemic organ involvement. As a result, the patient was treated with prednisone 60 mg/day, and he reported improvement in LoF. However, on day 20, the patient presented with acute abdominal pain and fever. Abdominal ultrasound revealed an intra-abdominal mass. He was admitted to the hospital for further work-up and management.

Introduction: Secondary membranous nephropathy may be caused by drugs, malignancy or infection. While it is known that infections can cause renal diseases little is known about the associations between parasitic infections and specific nephrotic syndromes. Here we present the first reported association between strongyloid infection and membranous nephropathy.

Case Description: This is a 65-year-old Nigerian man with history of hypertension on losinopril and hydrochlorothiazide who was referred for proteinuria and elevated creatinine. The patient reported chronic diarrhea. Physical examination showed gross leg edema. Serum creatinine was 2.2 mg/dl, and his urine protein/creatinine ratio was 7 g/g. Renal biopsy showed mesangial proliferation and thickened glomerular basement membrane. Anti-PLA2R immunofluorescence was negative, and electron microscopy showed intramembranous deposits. The patient denied NSAID use or use of other medications associated with membranous nephropathy. His age-appropriate cancer screening was up-to-date. Interestingly, his blood differential showed persistent eosinophilia of 20%. This prompted an investigation for a parasitic cause of his membranous nephropathy. Strongyloid antibody was positive, and the patient received ivermectin. His antihypertensive medications were continued. One-month follow-up showed improvement in his proteinuria to 4 g/g and creatinine to 1.4 mg/dl.

Discussion: This case demonstrates the first reported association between strongyloid infection and membranous nephropathy. While strongyloid infection is known to cause nephrotic syndrome, most of the biopsies show minimal change disease. Strongyloid parasitemia may induce type 2 T helper cells to produce eosinophils, interleukin 5 and IgE which results in a nephritogenic immune response and subsequent membranous nephropathy.

FR-PO026
Strongyloid-Associated Membranous Nephropathy
Josef Bautista, Katherine Mikovna Scovnet. Section of Kidney Diseases and Hypertension, Brown Univ - Rhode Island Hospital, Providence, RI.

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FR-PO026
Strongyloid-Associated Membranous Nephropathy
Josef Bautista, Katherine Mikovna Scovnet. Section of Kidney Diseases and Hypertension, Brown Univ - Rhode Island Hospital, Providence, RI.

Introduction: Secondary membranous nephropathy may be caused by drugs, malignancy or infection. While it is known that infections can cause renal diseases little is known about the associations between parasitic infections and specific nephrotic syndromes. Here we present the first reported association between strongyloid infection and membranous nephropathy.

Case Description: This is a 65-year-old Nigerian man with history of hypertension on losinopril and hydrochlorothiazide who was referred for proteinuria and elevated creatinine. The patient reported chronic diarrhea. Physical examination showed gross leg edema. Serum creatinine was 2.2 mg/dl, and his urine protein/creatinine ratio was 7 g/g. Renal biopsy showed mesangial proliferation and thickened glomerular basement membrane. Anti-PLA2R immunofluorescence was negative, and electron microscopy showed intramembranous deposits. The patient denied NSAID use or use of other medications associated with membranous nephropathy. His age-appropriate cancer screening was up-to-date. Interestingly, his blood differential showed persistent eosinophilia of 20%. This prompted an investigation for a parasitic cause of his membranous nephropathy. Strongyloid antibody was positive, and the patient received ivermectin. His antihypertensive medications were continued. One-month follow-up showed improvement in his proteinuria to 4 g/g and creatinine to 1.4 mg/dl.

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Discussion: This case demonstrates the first reported association between strongyloid infection and membranous nephropathy. While strongyloid infection is known to cause nephrotic syndrome, most of the biopsies show minimal change disease. Strongyloid parasitemia may induce type 2 T helper cells to produce eosinophils, interleukin 5 and IgE which results in a nephritogenic immune response and subsequent membranous nephropathy.
Electron microscopy showed dysmorphic red blood cells. Spot urine protein/creatinine ratio was 0.3 g/g and serologies were unrevealing. Kidney biopsy showed a focal and segmental necrotizing glomerulonephritis with an interstitial nephritis. Immunofluorescence (IF) was positive for IgM, IgG, C3, C1q, kappa, lambda and fibrinogen. No electron dense deposits were identified on electron microscopy. His Cr rose to 7.2 mg/dL despite receiving high dose steroids, and plasmapheresis was initiated. He received a total of 7 plasmapheresis sessions along with R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). He didn’t require dialysis and his Cr subsequently improved to and has stayed stable at 2 mg/dL. He is currently on maintenance rituximab every 3 months and his lymphoma is in remission.

Discussion: Renal involvement in lymphoma occurs through direct or indirect mechanisms. Direct mechanisms include laminopathies infiltration or obstruction. Indirect effects include GN, paraproteinemia and cryoglobulinemia. Kidney injury secondary to tumor lysis, drugs or infections may also occur. The first case of MCL associated GN was reported in 1999 and since then, only 14 cases have been reported in the literature. The most common manifestation is proliferative GN, with or without crescent formation. IF typically includes IgG, IgM and C3 staining. In most cases, chemotherapy leads to resolution or improvement of MCL associated GN. In conclusion, MCL associated GN can precede, coexist or follow the diagnosis of lymphoma. Decline of renal function and microscopic hematuria should increase the suspicion for a glomerular process in patients with MCL and prompt a renal biopsy.

FR-PO029

Focal Segmental Glomerulosclerosis in a Patient with Multiple Myeloma and Autoimmune Hematopoietic Cell Transplantation

Bogdan Obriescu, Roxana Adriana Jurbita, Marina Felicia Paraschiv, Andreana Gamala, Andreea Andronescu, Gner Ismail.

Nephrology and Internal Medicine, “Carol Davila” Univ, Bucharest, Romania.

Introduction: Glomerulopathies occur less often in recipients of autologous as compared to allogeneic hematopoietic cell transplantation (HCT) and, therefore, renal pathology in this setting is less well characterized.

Case Description: A 54 year-old man was admitted for the evaluation of a nephrotic-range proteinuria. His past medical history included a L. light chain secreting multiple myeloma (MM) diagnosed 4 years ago, treated with bortezomib and dexamethasone. Two years ago, the patient underwent autologous HCT. During the past two months, proteinuria at submit check-up was 4.3 g/day and 4.6 g/day, respectively. A relapse of MM was ruled out by bone marrow biopsy. At the time of admission, the clinical examination was unremarkable. Initial testing showed a proteinuria of 5.6 g/day, but without other signs of NS (normal serum albumin and lipid panel). Urinalysis was unremarkable, the renal function was normal, the serologic and virological studies were negative and there were no signs of active MM. The patient underwent a kidney biopsy that revealed perihilar focal and segmental glomerulosclerosis (FGS) and was started on cyclosporine 5 mg/kg/day. After 4 months of immunosuppressive therapy, the patient experienced a partial remission (proteinuria of 2 g/day).

Discussion: Glomerulopathies occurring after allogeneic HCT reveal a close temporal relationship between the onset of NS and the diagnosis of chronic graft-versus-host disease (GVHD), indicating a possible pathogenic link. Similarly, in autologous HCT, GVHD-like manifestations have been described as a result of a possible immune dysregulation. A review of the literature reveals several cases of membranous nephropathy and minimal-change disease occurring after autologous HCT, but, to our knowledge, FGS in this setting wasn’t described before. As in previous reported cases of glomerulopathies diagnosed after autologous HCT, our patient didn’t show any sign suggestive of a GVHD-like manifestation. Whether there is a pathogenic link or it is just a coincidental finding remains debatable.

FR-PO030

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin G Deposits in Pediatric Patients: A Possible Differential Diagnosis of Membranoproliferative Glomerulonephritis

Eiji Nakano,1,2 Ken-Ichi Miura,1 Shoichi Kanda,2 Yuji Tomi,1 Keichi Takizawa,1 Naoto Kaneko,1 Tomoo Yabuchi,1 Kiyonobu Ishizuka,1 Hiroko Chikamoto,1 Yuko Akioka,1 Yutaka Harita,1 Yutaka Yamauchi,1 Motoshi Hattori,1 Department of Pediatric Nephrology, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan, 2Department of Pediatrics, the Univ of Tokyo, Bunkyo-ku, Tokyo, Japan, 3Yamaguchi’s Pathology Laboratory, Moriyodo, Chiba, Japan.

Introduction: Proliferative glomerulonephritis with monoclonal IgG deposits (PNMG) is a rare described entity of glomerulopathies, which is characterized by glomerular staining for a single light chain isotype and a single heavy chain subtype. In adults, the biopsy incidence of PNMG is 0.17%, and the most frequent histologic pattern is membranoproliferative glomerulonephritis (MPGN) (56.8%). To date, reports of PNMG in pediatric patients are very limited.

Case Description: The patient was a 15-year-old boy. At the age of 9, mild hematuria and proteinuria were noted by chance during a school urine screening test. The amount of urinary protein gradually increased and a renal biopsy was performed at 15 years old. Light microscopy revealed MPGN pattern, and immunofluorescence (IF) revealed granular staining for monoclonal immunoglobulin of IgG3-kappa along the glomerular capillary loops. On electron microscopy, glomerular immune deposits were predominantly subepithelial. There was no clinical and serological evidence of cryoglobulinemia. Based on these results he was diagnosed as PNMG. Next, 14 pediatric cases diagnosed as MPGN in our hospital between 1994 and 2013 were reviewed. Two patients (14.3%) showed glomerular deposits staining for a single light chain isotype and a single heavy chain subtype (IgG3-kappa in one patient and IgG3-lambda in the other), which was suggestive of a diagnosis of PNMG.

Discussion: We experienced a pediatric case of PNMG. Furthermore, our preliminary study found two cases with PNMG pattern in pediatric MPGN patients. Further studies are clearly needed; our data indicate that pediatric patients showing MPGN may require immunosuppression for monoclonal IgG deposits for a definitive diagnosis.

FR-PO031

An Exceptional Case of Lyme Disease Associated MPGN

Shraddhha Rana, Aparu Khanna, Tiffany Nicole Caza, Sylvia L. Betcher. Nephrology Dept, Syracuse VA Medical Center, Syracuse, NY; SUNY Upstate Medical Univ, Syracuse, NY.

Introduction: Lyme disease, an endemic multisystem disorder caused by the tick-transmitted spirochete Borrelia burgdorferi, is known to cause glomerulonephritis in canine models. It has been postulated that renal injury of this infection leads to an initial IgM response with polyclonal B cell activation with possible formation of cryoglobulins with eventual IgG response against spirochete polypeptide. Injury is mediated by the classical complement pathway. In the few cases of Lyme disease related glomerulonephritis reported in humans, patients had systemic manifestations of classical Lyme disease. Case Description: A 70 year old man presented with increasing creatinine and proteinuria over 4 months. PMH included DM type II, HTN, Hyperlipidemia, chronic hematuria with negative urological work up and recent history of tooth extraction for dental infection. He denied usual symptoms of Lyme disease. Kidney biopsy revealed MPGN with circulating cryoglobulins and positive ANCA antibodies, but absence of the usual symptoms of Lyme disease. This case highlights that Lyme disease may manifest in a renal limited and should be considered when unexplained MPGN occurs where Lyme disease is endemic.

Lupus Flare Presenting as Acute Pericarditis in a Patient with Stage V CKD on Hemodialysis Secondary to Lupus Nephritis

Introduction: Development of end-stage renal disease (ESRD) does not always result in resolution of the extra-renal manifestations of Systemic Lupus Erythematosus (SLE). Lupus nephritis is the cause of pericarditis in a patient with stage V CKD on hemodialysis secondary to lupus nephritis until proven otherwise.

Case Description: A 41-year-old AA woman with a medical history of SLE, HTN, Gout, HLD and CKD stage V on hemodialysis presenting with one day duration severe chest pain. The EKG revealed a pericardial effusion. Her last lupus flare was documented more than three years ago. She had normal labs showing AAN 7.0, WBC 12.3, platelet 501,000, with CRP 2.76 mg/dL on 5/3, and 1.46 mg/dL on 6/1. Her urine P:Cr ratio however increased from 0.3 to 40. She was admitted to the hospital, started on oral prednisone 20 mg twice daily. On hospital day 2 ECG was normal, with no tamponade.

Discussion: This case underscores the importance of close follow up of SLE patients on hemodialysis for lupus activity. It also helps making decision regarding renal transplantation.

Nephrotic Syndrome with Cancer Immunotherapies

Introduction: Oncologic immunotherapy utilizes a patient’s immune response to eliminate tumour cells by disruption of immune checkpoints, including programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) pathways. Autoimmune sequelae, including cases of acute kidney injury from intestinal nephropathy, have been reported, however, less frequent in primary glomerular disease cases. Here we describe two cases of nephrotic syndrome in patients treated with these agents.

Case Description: Patient 1, a 43 year old male, received the anti PD-1 antibody pembrolizumab, after a 9 year history of Hodgkin’s lymphoma. Following his second dose he developed edema and nephrotic syndrome (proteinuria 5.6 g/dl) and acute kidney injury (creatinine 4.9 mg/dl). Renal biopsy showed diffuse foot process effacement and mild acute tubular injury. Following cessation of pembrolizumab and corticosteroid treatment he had resolution of his proteinuria and renal insufficiency. Patient 2, a 45 year old male with melanoma, received the CTLA-4 antibody ipilimumab. Following four cycles he had resolution of his proteinuria and renal insufficiency. Patient 2, a 45 year old male with melanoma, received the CTLA-4 antibody ipilimumab. Following four cycles he developed proteinuria and nephrotic syndrome with serum creatinine of 1.46 mg/dL. IgG subclass IV levels were elevated at 56. Serum albumin was low (1.8 g/dL). Scr remained elevated at 1.8 mg/dL.

Discussion: These cases provide insights into the pathogenesis of nephrotic syndrome. While affecting T cell regulation at different stages of T cell activation, both the PD-1 and CTLA-4 pathways modulate T cell activation through signals involving antigen presenting cell CD80 (B7.1). These cases may support the hypothesis of a ‘permeability factor’ causing proteinuria.

Nephrotic Syndrome in Adults: Etiology and Presentation

Introduction: Nephrotic Syndrome (NS) has been rarely associated with acute HPV B19 infection in patients with sickle cell disease (SCD). We present an interesting case of abrupt onset severe NS and AKI secondary to acute HPV B19 infection.

Case Description: A 61 year old female with past medical history of Sjogrens disease, IgG4-RD, CKD Stage III (baseline creatinine [Cr] 1.0-1.2), retroperitoneal fibrosis with history of bilateral hyperalgesia requiring stent placement and ureterolysis, presented with sore throat, shortness of breath, and productive cough. Cr was 2.4 mg/dL on admission and increased to 4.5 mg/dL within 2 days, accompanied by urine protein/Cr (P/Cr) ratio of 25.6, and an acute cellular sediment. There was no evidence of recent ureteral obstruction.

Discussion: This patient had biopsy proven MGN with mesangial and subendothelial deposits and negative anti PLA2R serologies, strongly favoring a secondary form of MGN. While PLA2R testing along with histology can help exclude primary MGN, there is no reliable way to differentiate between secondary MGN due to Sjogrens disease versus IgG4-RD. This case underscores the need for a more thorough understanding of how the many secondary causes of MGN cause this pathology so that therapy can be targeted appropriately.

Acute Parvovirus B19-Associated Nephrotic Syndrome in a Patient with Sickle Cell Disease

Introduction: Human parvovirus B19 (HPV B19) infection is a common cause of transient aplastic crisis (TAC) in patients with sickle cell disease (SCD). However, nephrotic syndrome (NS) has been rarely associated with acute HPV B19 infection in patients with SCD. We present an interesting case of abrupt onset severe NS and AKI secondary to acute HPV B19 infection.

Case Description: A 37-year-old AA female with history of SCD was hospitalized with fever and severe anemia. Both serum creatinine (Scr) and albumin were normal on admission. Pt. was found to have TAC secondary to acute HPV B19 infection. HPV B19 DNA by PCR was elevated (1.8 X 10^5 IU/mL). HPV B19 IgM was positive. Scr increased to 2.4 mg/dL during hospitalization. Pt. was treated with Prednisone 40 mg daily for 10 days, and hydroxyurea. Pt. was discharged on Hydroxyurea, aspirin, and iron replacement. Pt. received IV fluids and Scr decreased to 1.8 mg/dL on the day of discharge. Five days later, pt. presented to the clinic with worsening lower extremity (LE) edema, abdominal distention, and 35 lbs weight gain. Pt. was noted to have significant LE edema on exam. Urinalysis showed proteinuria. Spot urine total protein to creatinine ratio (TP/CR) was elevated at 56. Serum albumin was low (1.8 g/dL). Scr remained elevated at 1.8 mg/dL. Serological work up for NS including HIV infection was negative. Pt. was subsequently rehydrated and for management of generalized body swelling that was resistant to oral diuretic therapy. Pt. received IV albumin and diuretic treatment during hospitalization. Kidney biopsy performed subsequently revealed collapsing FSGS that was thought to be secondary to acute HPV B19 infection. Scr peaked to 3.4 mg/dL during that hospitalization. Three months after initial presentation, Scr was elevated at 3.7 mg/dL. Pt. also continues to have significantly elevated spot urine TP/CR (21.5) and NS despite decreasing HPV B19 DNA levels.

Discussion: Collapsing FSGS as a result of acute HPV B19 infection has been rarely described in patients with SCD. Optimal therapy and renal outcomes in such cases are unclear. Our patient continues to have significant renal failure and severe NS, 3 months after initial presentation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO038
Resolution of Hepatitis C Related Membranoproliferative Glomerulonephritis after Treatment with Combination Ledipasvir/ Sofosbuvir
Havenav Novak, Kosunarya Fa. Methodist Dallas Medical Center; Dallas, TX.

Introduction: Advent of new medications indicated for the treatment of Hepatitis C has drastically changed the landscape of end-stage liver disease. With the increased use of these new modalities their effect on other virus-related pathologies has yet to be fully established.

Case Description: K3 is a 56 year old female with end-stage liver disease secondary to chronic hepatitis C cirrhosis listed for orthotopic liver transplant. December 15, 2014 patient is noted to have apparently normal kidney function with creatinine 0.94. However by mid-January her creatinine is noted to be increased and on January 23 2015 she is admitted to hospital with a mass of breath, anasarca, and acute kidney injury, leading to a preliminary diagnosis of nephrotic syndrome (16.7 grams proteinuria). Creatinine peak was 4.1 on 30 January 2015. Renal biopsy did show membranoproliferative glomerulonephritis (MPGN) and acute tubular injury without vasculitis. She did later develop a vasculitic rash of both legs. Considered treatment with solumedrol, plasma phosphanesis, and rituximab, ledipasvir/sofosbuvir (Harvoni) therapy was initiated on 30 January 2015. In April 2015, creatinine had improved to 1.2 and vasculitic rash resolved. 24 hour collection in June 2015 showed 245 mg proteinuria. In November 2015 patient completed 24 weeks’ duration of ledipasvir/sofosbuvir treatment, and creatinine was 0.89.

Discussion: This report of biopsy proven MPGN in the setting of cryptoglobulinemia related to HCV, with recovery to baseline of renal function after ledipasvir/sofosbuvir treatment is unique in the current literature. The resolution of MPGN in this patient enabled evaluation for single organ transplant in lieu of dual organ transplant. With this association, new avenues for investigation are opened into the treatment and management of end-stage renal disease secondary to HCV-associated conditions.

FR-PO039
PLA2R-Antibody Positive Membranous Nephropathy Associated with Inflammatory Demyelinating Radiculopathy after Hepatitis B Vaccination
Rejjis Stephen, Evmamria Anvari, Laura Ferrere Provenzano. Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH.

Introduction: PLA2R is a biomarker of idiopathic membranous nephropathy (MN). However, it can be positive in some secondary cases, including hepatitis B (HBV) associated MN. MN has also been associated with inflammatory demyelinating diseases, but the nature of the association remains unclear. This case describes a case of PLA2R positive MN associated with an inflammatory demyelinating polyradiculopathy in the background of a recent HBV vaccination.

Case Description: A 56-year-old Caucasian male was referred for a second opinion regarding MN. He initially presented with joint pain and bilateral extremity paresis. He soon developed marked edema and hypertension, with over 20 lb weight gain, associated with weakness and unsteady gait. No preceding illness was reported, but he had received hepatitis B vaccination one month prior. He had taken NSAIDs for pain but no other medications. He was found to have 17 grams of proteinuria/24 hrs and was diagnosed with nephrotic syndrome. His renal function was normal. Serological workup including C3/C4, ANA, RF, ANCA, anti-GBM antibodies, hepatitis panel, SPEP, UPEP was negative. A screening colonoscopy 6 years prior and a PSA level were normal. Renal biopsy showed membranous nephropathy: PLA2R was positive (1.40). Concomitantly, he was diagnosed with inflammatory demyelinating polyradiculopathy and was started on prednisone 60 mg daily. Over the next several months he showed neurological improvement, and the steroid dose was titrated down. Proteinuria also improved (<1g/24 hrs) and the nephrotic syndrome resolved. Repeat PLA2R levels have been negative.

Discussion: To our knowledge, this is the first case of MN associated with an inflammatory demyelinating radiculopathy with PLA2R positivity. The time correlation with the hepatitis B vaccination series raises the possibility that the HBV antigen triggered the autoimmune response.

FR-PO040
Crescentic and Necrotizing Glomerulonephritis with IgA Depositions and Circulating IgG and IgA ANCA
Elsie M. Alderman McInnis, Volker Nickel, Patrick H. Nachman. UNC Kidney Center, Univ of North Carolina; Dept of Medicine, CHU Nice, Nice, France.

Introduction: Several observations of crescentic and necrotizing glomerulonephritis (CNGN) with IgA depositions and IgA ANCA have been reported in literature, suggesting an overlap between IgA nephropathy (IgAN) and ANCA-associated vasculitis (AAV). In this situation, we evaluate the presence of ANCA of IgA isotype.

A 22-year-old male with no previous medical history presented with acute kidney injury (serum creatinine went from 1.1 mg% to a stable baseline of 1.1 mg%) one month after a screening colonoscopy. The patient received a possibly contaminated single-dose oral polio vaccine when he was 18, but was not vaccinated for hepatitis B. At presentation, the patient was afebrile, his vital signs & exam were normal. Hydronephrosis was absent. Chest X rays, urine & blood cultures were negative. IgG was 96 g/L, WBC 8 k, platelet 21 k (normal bone marrow). Liver function, LDH, CPK, hepaticobiliary, troponin were normal. IV fluids yielded only mild transient drop in Sore. Initial urinalysis was normal but NS soon emerged. Anasarca was resolved by diuresis, thrombocytopenia by -plat. 3 weeks after peak Sore of 6.7, his ARF spontaneously & largely resolved.

Discussion: 1. RTK inhibitors, like sunitinb, could cause nephrotoxicities, including thrombotic microangiopathy, intestinal nephritis, proteinuria & mild-to-moderate ARF. Among the dozen reported cases, ours seemed to have the worst renal failure compounded by NS that spontaneously resolved by supportive care & stopping sunitinib. 2. Given the growing use of these agents in many cancers, we would call attention to these hitherto little described renal toxicities & urge regular monitoring of renal functions.

Funding: NIDDK Support, Private Foundation Support

FR-PO041
A Case of Isolated Renal Involvement of Polymyositis Nodosa Successfully Treated with Steroid Monotherapy
Negin Pourshafir, Eric S. Sobel, Mark S. Segal. Univ of Florida, Gainesville, FL.

Introduction: Polymyositis nodosa(PAN) is a systemic necrotizing vasculitides that typically affects medium-sized arteries, with occasional involvement of small arteries. Renal involvement would frequently result in variable degrees of renal insufficiency, proteinuria and hypertension.

Case Description: A 75-year-old man was referred for management of uncontrolled hypertension and worsening renal function. Patient recently developed uncontrolled HTN as well as renal function impairment. Further work-up of hypertension was unremarkable. A renal angiogram was then obtained due to suspicion for renal artery stenosis which revealed patent renal arteries, marked irregularity of the interlobar branches of the renal arteries with multiple areas of strictures as well as numerous microaneurysms involving interlobar branches of renal arteries (figure 1), suspicious for PAN.

Discussion: We investigated the presence of IgA-ANCA by indirect immunofluorescent (IFI) on ethanol fixed neutrophils and western blot electrophoresis on purified MPO, PR3 and Neutrophil extract. The IFI was positive for cytoplasmic staining. The western blot substantiated the presence of an circulating IgA anti-PR3.

Discussion: Only 19 cases of AAV and associated IgAN have been reported in the literature. These patients presented with systemic symptoms in 60% of cases, had a proteinuria >2g/24h and ANCA were mostly anti-MPO subtype. Moreover, studies found that proteinuria is higher in CGN-ANCA than in crescentic IgAN. A recent study comparing CNGN-ANCA to ANCA-vasculitis showed greater proteinuria in CGCN-ANCA. IgA-ANCA have the capacity to modify neutrophils degranulation and so, could play a role in CGCN-ANCA pathogenesis. Our observation suggests an overlap between IgAN and AAV, and IgA-ANCA could be involved in the pathophysiology of this entity.

FR-PO042
Severe but Reversible Acute Renal Failure (ARF) and Nephrotic Syndrome (NS) Induced by Sunitinib (Sutent), an Inhibitor of Receptor Tyrosine Kinase (RTK) Used to Treat Metastatic Renal Cell Carcinoma (m-RCC)
Sushanta K. Goswami, 1,2 Kai Lau, 1,2 Dept of Nephrology, Univ of Oklahoma, Oklahoma City, OK; 1,2 Medical Service, VA Medical Center, Oklahoma City, OK.

Introduction: Sunitinib is a multi-target RTK inhibitor including VEGFR. Used in many advanced cancers (breast, lung and colon and RCC), it has many extra-renal & renal side-effects. We here report a 51 year old man with m-RCC, prior left nephrectomy, admitted for severe ARF & NS evolved over 4-5 weeks.

Case Description: We reviewed all clinical & lab data in this man consulted for ARF & NS. His hypertension & hyperuricemia were controlled. We excluded all potential causes like NSAID, contrast dye, sepsis, obstruction, thrombodinomylitis & tumor lysis. 2 weeks into 50 mg/d of sunitinib, he developed diarrhea & steadily climbing serum creatinine (Scre) from a stable baseline of 1.1 mg%.

Afebrile, his vital signs & exam were normal. Hydrenephrosis was absent. Chest X rays, urine & blood cultures were negative. IgG was 96 g/L, WBC 8 k, platelet 21 k (normal bone marrow). Liver function, LDH, CPK, hepaticobiliary, troponin were normal. IV fluids yielded only mild transient drop in Sore. Initial urinalysis was normal but NS soon emerged. Anasarca was resolved by diuresis, thrombocytopenia by -plat. 3 weeks after peak Sore of 6.7, his ARF spontaneously & largely resolved.

Discussion: RTK inhibitors, like sunitinib, could cause nephrotoxicities, including thrombotic microangiopathy, intestinal nephritis, proteinuria & mild-to-moderate ARF. Among the dozen reported cases, ours seemed to have the worst renal failure compounded by NS that spontaneously resolved by supportive care & stopping sunitinib. 2. Given the growing use of these agents in many cancers, we would call attention to these hitherto little described renal toxicities & urge regular monitoring of renal functions.

Funding: NIDDK Support, Private Foundation Support
He was initially started on prednisone 40 mg/day which was subsequently increased to 60 mg/day. While on the increased dose of steroids, his hypertension and renal impairment improved. He did not require anti-hypertensive therapy.

Discussion: Renal failure and uncontrolled hypertension could represent renal involvement in PAN. Diagnosis of PAN is based on the recognition of a vasculitic syndrome with supportive evidence deriving from radiologic or pathologic studies or both. Biopsy involvement in PAN is also diagnostic. The diagnosis of PAN is based on the recognition of a vasculitic syndrome with supportive evidence deriving from radiologic or pathologic studies or both. Biopsy involvement in PAN is also diagnostic.

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Underline represents presenting author.
was ruled out (fractional excretion of sodium <1% repeatedly). He continued to be symptomatic despite receiving salt tablets 4 grams 3 times daily, midodrine 5 mg 3 times daily, fludrocortisone 0.1 mg twice daily, an abdominal binder, and thigh-high compression stockings. We hypothesized that systemic and renal vasodilatation, possibly paraneoplastic in origin, were playing a role in the patient’s severe orthostatic hypotension. Low systemic vascular resistance calculated from the patient’s echocardiogram further reinforced our hypothesis. We therefore started ibuprofen, after which there was a dramatic improvement in the patient’s clinical symptoms and he was able to walk after being bed bound for more than a week (Table 1).

Discussion: In appropriate clinical conditions, NSAIDs can be considered for treatment of severe refractory orthostatic hypotension.

### Table 1

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**FR-PO048**

Reversible Heart Failure and Nephrotic Syndrome Associated with Massive Protein Intake in a Bodybuilder

**Khaled Boobes, Robert M. Rosa, Cybele Ghossein, Daniel Battle.**

**Nephrology/Internal Medicine, Northwestern Univ, Chicago, IL.**

**Introduction:** High protein diet in addition to anabolic steroid ingestion is common among bodybuilders to promote muscle development/hypertrophy. Acute tubular necrosis and segmental glomerulonephrosis have been described in the setting of high protein intake and anabolic steroid use.

**Case Description:** We present a case of a previously healthy 42 year-old African American male bodybuilder, on anabolic steroid supplements, who was consuming a 150g of protein/kg/day diet-for a total intake of >1500 g of protein a day- who was hospitalized for decompensated heart failure.

On evaluation, he was found to have a decreased ejection fraction (EF) of 15% and proteinuria of 6g/day. Serum protein electrophoresis did not show any gammopathies, and Urine protein electrophoresis revealed that his urinary protein consisted primarily of albumin. His GFR based on creatinine clearance was 113ml/min. A renal biopsy to evaluate proteinuria showed mild chronic tubulo-interstitial disease without acute tubular necrosis. His myocardial biopsy showed hypertrophied myocytes, but no specific etiology for his heart failure. Five days later, while still an inpatient, his proteinuria decreased to 2g/day while on a hospital low protein diet. He was started on an ACE inhibitor and asked to modify his lifestyle. Six months later his proteinuria was reduced to 115mg/day and his EF improved to 45%.

**Discussion:** This unique case highlights a rarely recognized cause of heavy proteinuria and acute heart failure attributable to massive protein intake and possibly anabolic steroids use. In addition to the reversible heart failure associated with myocyte hypertrophy our case illustrates that chronic tubular interstitial nephropathy can develop as well. The proteinuria and tubular damage observed in this 1.2 mmol/L Cortisol-C also contains Hawthorn extract, which has been shown to interfere with the narrow therapeutic index of cardiac glycosides, similar to those found in the pharmaceutical drug Digoxin, derived from the *digitalis lanata* (foxglove) plant. These plants are responsible for a number of cases of acute poisonings yearly. We report a case of cardotoxicity, AKI, and hyperkalemia in an elderly female caused by the health supplement Cardiol-C, which contains Lily of the Valley extract.

**Case Description:** An 86-year-old Polish female with history of CAD and HTN presented to the ED with nausea, vomiting, and weakness for 5 days. While her cardiac medications were at first unknown, she admitted to a 3-month use of Cardiol-C. Her BP was as low as 64/32 and heart rate 42bpm. Initial EKG showed junctional bradycardia with old LBBB. Labs revealed potassium level of 7.2 mMol, creatinine 3.8 mg/dL (baseline unknown), bicarbonate of 17 mMol. She was given atropine and DigiFab with improvement of hemodynamics, symptoms, and EKG, and transferred to the ICU for monitoring of possible symptom recurrence secondary to xenobiotic redistribution. Her potassium normalized with temporizing measures, including intravenous fluids and diuretics; her discharge creatinine was 1.59 mg/dL.

**Discussion:** Although the degree of hyperkalemia correlates with cardotoxicity in acute ingestion, special care was made not to lower the potassium drastically as hypokalemia can enhance the effect of cardiac glycodies. Our patient’s glycoside-induced hyperkalemia was likely exacerbated by a prerenal AKI and her use of medications known to induce hyperkalemia. This case illustrates the importance of asking patients about over-the-counter (OTC) supplement use as there can be lethal consequences, most of which patients are unaware of. Cardiol-C also contains Hawthorn extract, which has been shown to interfere with digoxin immunoassay measurements and compete with Na+/K+ ATPase. Given the narrow therapeutic index of cardiac glycosides, extreme caution—if not complete avoidance—should be used with their non-standardized use as toxicity often occurs even with close monitoring.

**FR-PO051**

An Unusual Case of Hypertension and Acute Kidney Injury during Pregnancy and Postpartum Course

**Mahrkush Rivzi, Sai Subhodhini Reddy, Andrea Zynda-Weiss, Guan Wu, Wei Chen.**

**Univ of Rochester School of Medicine.**

**Introduction:** New onset hypertension (HTN) complicates 6-8% of pregnancies. Approximately 20% of women remain hypertensive beyond 3 months postpartum. We present an interesting case of new onset HTN and acute kidney injury (AKI) during pregnancy that persisted beyond 3 months postpartum.

**Case Description:** A 27 year old pregnant woman with no significant past medical history was referred to Nephrology for persistent HTN and elevated creatinine (Cr 1.1mg/dL, baseline 0.7) 3 months postpartum. During the third trimester, she developed HTN with blood pressure (BP) in 140/90’s (baseline BP 120/70’s), proteinuria (~400 mg/day) and AKI with a peak Cr of 1.4 mg/dL. She was diagnosed with pre-eclampsia and induced at 38 weeks. Despite delivery, she continued to have HTN with a mean BP of 150/90’s. This prompted work up for secondary HTN. Renal ultrasound showed bilateral renal cysts. Follow up CT scan and MRI revealed malrotated right pelvic kidney, bilateral ureteropelvic junction configurations with moderate to severe hydroureter and areas of cortical thinning.

**Discussion:** Catecholamine secreting Paragangliomas of head and neck are rare (3 percent). F-18 FDG PET scan is more sensitive than I-123 MIBG scan (85 versus 52 percent) in diagnosing Paragangliomas of the neck.

**FR-PO050**

The Mysterious Polish Supplement: A Case Report of Cardiac Glycoside Poisoning with Lily of the Valley Extract

**Payam Pourhassani, Christopher Richard Kern, Hasan Arif.**

**Internal Medicine, Drexel Univ College of Medicine, Philadelphia, PA.**

**Introduction:** The plant *convallaria majalis* (Lily of the Valley) contains multiple cardiac glycosides similar to those found in the pharmaceutical drug Digoxin, derived from the *digitalis lanata* (foxglove) plant. These plants are responsible for a number of cases of acute poisonings yearly. We report a case of cardotoxicity, AKI, and hyperkalemia in an elderly female caused by the health supplement Cardiol-C, which contains Lily of the Valley extract.

**Case Description:** An 86-year-old Polish female with history of CAD and HTN presented to the ED with nausea, vomiting, and weakness for 5 days. While her cardiac medications were at first unknown, she admitted to a 3-month use of Cardiol-C. Her BP was as low as 64/32 and heart rate 42bpm. Initial EKG showed junctional bradycardia with old LBBB. Labs revealed potassium level of 7.2 mMol, creatinine 3.8 mg/dL (baseline unknown), bicarbonate of 17 mMol. She was given atropine and DigiFab with improvement of hemodynamics, symptoms, and EKG, and transferred to the ICU for monitoring of possible symptom recurrence secondary to xenobiotic redistribution. Her potassium normalized with temporizing measures, including intravenous fluids and diuretics; her discharge creatinine was 1.59 mg/dL.

**Discussion:** Although the degree of hyperkalemia correlates with cardotoxicity in acute ingestion, special care was made not to lower the potassium drastically as hypokalemia can enhance the effect of cardiac glycodies. Our patient’s glycoside-induced hyperkalemia was likely exacerbated by a prerenal AKI and her use of medications known to induce hyperkalemia. This case illustrates the importance of asking patients about over-the-counter (OTC) supplement use as there can be lethal consequences, most of which patients are unaware of. Cardiol-C also contains Hawthorn extract, which has been shown to interfere with digoxin immunoassay measurements and compete with Na+/K+ ATPase. Given the narrow therapeutic index of cardiac glycosides, extreme caution—if not complete avoidance—should be used with their non-standardized use as toxicity often occurs even with close monitoring.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
increasing fetal size (which could exacerbate the hydronephrosis) likely all contributed to the development of preeclampsia and AKI. Interestingly, the hydronephrosis was first thought to be renal cells on ultrasound. This highlights the importance of pursuing further workup for multiple renal cysts in young individuals.

Funding: Other NIH Support - University of Rochester Clinical and Translational Science Award (CTSA) award number KL2 TR000095 from the National Center for Advancing Translational Sciences of the NIH.

FR-PO052

Canagliflozin (Invokana) Induced Ketoacidosis and Proximal Renal Tubular Acidosis in the Setting of Euglycemia following Surgery. Robert Flevishman, Christopher Richard Kern, Hasan Arifil. Hahnemann Univ Hospital, Philadelphia, PA.

Introduction: Canagliflozin, a selective sodium glucose cotransporter-2 (SGLT-2) inhibitor, works by blocking glucose reabsorption at the proximal tubule. Its most significant side effect is hypoglycemia. A rarer side effect in type 1 diabetes improperly labeled as type 2 diabetes is normoglycemic diabetic ketoacidosis. We present a case of canagliflozin-induced ketoacidosis and proximal renal tubular acidosis following surgery in the setting of euglycemia in a patient with type 2 diabetes mellitus (DM2).

Case Description: 55 year old female with past history of DM2 (diagnosed 4 years prior) and left breast cancer status post mastectomy was admitted for left breast reconstruction surgery. Her home medications included anastrozole, insulin glulisine and insulin aspart. She also reported several weeks prior and last taken one day prior to surgery. On post-operative day 2, she was noted to have pH of 7.08, serum chloride 114 mmol/L, serum bicarbonate of 6 mmol/L, anion gap, 16, serum potassium of 3.2 mmol/L, serum calcium of 7.1 mg/dl, blood sugar of 155 mg/dl and normal lactate acid. After surgery, she reported nausea along with decreased appetite and oral intake. Elevated beta-hydroxybutyric acid on day 3 confirmed likely euglycemic DKA, accounting for her significant gap acidosis. Her abnormal delta ratio, revealing a concurrent non-gap acidosis, was thought to be secondary to a canagliflozin-induced RTA2, in the setting of glucosuria and abnormal urinary electrolytes. She was treated with IV bicarbonate and sliding scale insulin until her anion gap closed on post-operative day 5. Her hypokalemia, hypophosphatemia, and hypomagnesemia were treated with aggressive electrolyte repletion; each derangement normalized by post-operative day 7.

Discussion: Canagliflozin is approved for DM2. Most common side effects include genital mycotic infections and urinary tract infections. A rare, but significant side effect, is hypoglycemia when used with other diabetic medications. Our case illustrates a rare but serious side effect of ketoacidosis and RTA2 in the setting of euglycemia following surgery and decreased oral intake.

FR-PO053

Severe Metabolic Acidosis as a Complication of an Oral SGLT-2 Inhibitor Benjamin Griffin, Charles L. Edelstein. Nephrology, Univ of Colorado, Aurora, CO.

Introduction: Sodium-Glucose Cotransporter 2 (SGLT-2) inhibitors, a novel class of anti-glycemics, work by inhibiting the SGLT-2 cotransporter in the proximal tubule, leading to significant glucosuria. There is also evidence that they increase insulin sensitivity and decrease glucagonogenesis. Canagliflozin was approved by the FDA in 2013 for Type II Diabetes Mellitus (DM), but is occasionally used as an off-label treatment for Type 1 DM as well.

Case Description: KR is a 40 year old lady with a past medical history of Diabetes Type I and hypertension who presented to the hospital with two days of nausea, vomiting, abdominal pain, and confusion. Blood glucose levels at home had not been elevated. Physical exam was remarkable for tachycardia, dry mucous membranes, and abdominal tenderness, but was otherwise unremarkable. Laboratory investigations revealed an arterial pH of 6.845, pCO2 of 25, bicarbonate of 3, anion gap of 28, glucose of 222, creatinine of 1.24 (from a baseline of 0.8), small ketones in the serum, and 3+ ketones on urinalysis. She was treated for Diabetic Ketoacidosis (DKA) with an insulin drip and fluid repletion. Creatinine peaked at 1.7, and then recovered to baseline over the course of one week. Upon further questioning, she was on an insulin pump for diabetic control, and also on Canagliflozin orally. Because her blood glucose levels were normal, she had not been receiving an adequate dose of subcutaneous insulin, which was thought to be the trigger of her DKA episode.

Discussion: DKA is the recently described phenomenon of glucosicotic DKA in the setting of Canagliflozin use. This medication is currently only approved for use in type II DM, and caution must be exercised if used off-label in type I DM. In this case, the patient was not receiving an adequate amount of insulin because serum glucose levels were within normal limits, and developed DKA. Recognition of this disorder in the euglycemic patient is important in order to avoid delays in diagnosis and treatment.

FR-PO054


Introduction: SGLT2 inhibitors have been shown to improve glycemic control in patients with diabetes mellitus type 2 (DM2). These agents have been shown to increase the risk of ketoacidosis, however lactic acidosis is not currently a known complication.

Case Description: JO is a 48 year old female referred to nephrology in April 2015 for further evaluation of metabolic acidosis. She had been taking Metformin and Invokana for DM2. She was advised to stop Metformin and sodium bicarbonate was started. Seven months later, she was noted to have worsening metabolic acidosis. She was taking the sodium bicarbonate; however she also continued Metformin and Invokana. At this point she agreed to stop taking both medications. Repeat labs showed improved serum bicarbonate and normal lactic acid. Four months later, her endocrinologist restarted her Invokana due to poor glycemic control. Two months after Invokana was restarted, she developed worsening metabolic acidosis and lactic acid was elevated (see table). Although she was asymptomatic she was referred to the ED for further evaluation. Repeat labs showed persistent lactic acidosis. Workup for DKA, sepsis, and hyperperfusion was negative. Furthermore there was no clear cause of the lactic acidosis. Invokana was stopped and repeat labs showed that her lactic acid and serum bicarbonate had normalized.

Discussion: Although lactic acidosis has been reported as a potential complication of SGLT2 inhibitors, to our knowledge this is the first reported case of lactic acidosis secondary to Invokana. Clinicians should be aware of this potential complication among patients taking SGLT2 inhibitors.

FR-PO055

Oxymorphine Hydrochloride (Opana) Related Acute Kidney Injury with Lamellated Bodies in Podocytes Yan Yatsynovich,1 Anjali A. Satoskar,1 Nataliaii Maroz,2,3 Dmitri Souzdalniksi,3 Glen R. Rech,4 Kettering Medical Center, OH; 4Weiss State Univ, RPI, OH; 2Ohio State Univ, OH; 3Western Reserve Hospital, OH.

Introduction: Opana (Oxymorphone hydrochloride) is a semi-synthetic oral opioid analgesic used for management of severe pain. While side effects of CNS, respiratory and GI depression are well known, acute kidney injury (AKI) is generally not expected.

Case Description: A 69 year old female was admitted to clinic evaluation of progressive peripheral edema and dyspnea. He had underlying CKD stage IIIA, related to prolonged use of NSAID’s. He had baseline creatinine of 1.6 mg/dl in the absence of proteinuria. He was abstinent from NSAID’s for the last 2 years. On physical examination he had weight gain of 20 lb and +2 edema of LE extending to the abdominal wall. There was an acute rise in creatinine of 2.4 mg/dl. UA showed proteinuria 0.4 mg/gm without hematuria. Serological work up, evaluation of thyroid, liver and heart function was unremarkable. Review of the medications revealed recent modification of his pain regimen with substitution of extended release oxymorphone (MS Contin) by Oxymorphone hydrochloride (Opana), occurring 4 months prior to presentation. Renal biopsy was performed. Electron microscopy showed presence of lamellated lipid containing curvilinear bodies in the cytoplasm of podocytes referred to as “myeloid or zebra bodies”. Alpha galactosidase activity in serum was normal. Therefore, drug induced podocyte injury was suspected. Opana was discontinued, with resolution of edema and creatinine improvement to prior baseline.

Discussion: Opana has been described to cause thrombocytopenia in the kidney. This case illustrates an unusual link between the use of Opana and development of AKI. Lamellated bodies in the podocytes were first described in Fabry’s disease. Similar structures with curvilinear appearance have been later described in association with drug toxicity from Chloroquine, Hydroxychloroquine and Amiodarone but never associated with Opana. Importantly, discontinuation of Opana has led to resolution of edema and AKI. While renal complications from use of opioid analgesics are uncommon, awareness of this rare nephrotoxicity is important.

FR-PO056

Cola-Colored Urine and Acute Kidney Injury after Type A Aortic Dissection. Khaleel Sheelvath, Vishwanath Sheelvant, Khaleel Sheelvath, William Luke Whittier.1 Internal Medicine, Rush Univ Medical Center, Chicago, IL; 2Nephrology, 1, Chicago, IL; 3Nephrology, 1, Chicago, IL.

Introduction: Hemolysis after mechanical heart valve replacement is caused by trauma to the cell membrane. The most common cause of hemolysis is related to the embolization of prosthetic valvular structures with curvilinear appearance have been later described in association with drug toxicity from Chloroquine, Hydroxychloroquine and Amiodarone but never associated with Opana. Importantly, discontinuation of Opana has led to resolution of edema and AKI. While renal complications from use of opioid analgesics are uncommon, awareness of this rare nephrotoxicity is important.
FR-PO057
Alirocumab (Praluent) Induced Renal Injury: A Novel Side Effect of a Novel Drug
Valerie Suzanne Barta,1 Kenan D. Jhaveri,1 James M. Pullman,2 1Nephrology and Hypertension, NorthShore/LIJ Health System, Great Neck, NY; 2Pathology, Montefiore Medical Center, Bronx, NY.

Introduction: We report the first case of biopsy-proven acute tubular injury (ATN) associated with alirocumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), shown to be a valuable treatment of hypercholesterolemia. ATN is typically associated with atheroembolic disease, iatrogenic causes, or yet to be identified cytokine or lymphokine may contribute to podocyte damage and tubular atrophy with focal chronic inflammation and eosinophils suggestive of chronic interstitial nephritis. Both agents were held after third cycle secondary to AIN and prednisone 1mg/kg was initiated. SCR decreased to 1.38 mg/dL and AEC back down to 0 KU/L. Currently, the patient’s cancer is not progressing.

Discussion: Immune checkpoint inhibitors such as nivolumab and ipilimumab are known to cause AIN. Their combined use seems to confer an increased risk. Only one prior case exists of combined therapy leading to AIN in a native kidney. AIN appears to be related to an immune response to the kidney. It is essential for nephrologists and oncologists to understand this risk. Frequent monitoring of Scr during treatment and swift referral to nephrology for AKI can aid in early diagnosis of this newly recognized side effect and early initiation of treatment to prevent continued renal damage in these patients.

FR-PO058
Combined Anti-CTLA-4 and Anti-PD1 Immunotherapy Induced AIN
Valerie Suzanne Barta,1 Nupur N. Uppal,1 Rimda Wanchao,1 James M. Pullman,2 Kenan D. Jhaveri.1 1Nephrology, Hofstra Northwell School of Medicine; 2Pathology, Montefiore Medical Center.

Introduction: Both anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-program death 1 (PD-1) have been used more frequently to combat an increasing variety of cancers. Their nephrotic side effects are only recently being discovered. We present a case of acute interstitial nephritis (AIN) caused by combined treatment of nivolumab and ipilimumab.

Case Description: A 62 year old male with metastatic melanoma was started on nivolumab 5 months prior to consultation for acute kidney injury (AKI). He experienced arthritis and dermatitis as side effect treated and resolved with course of prednisone. His baseline creatinine (Scr) was 1.2 mg/dL throughout treatment. Within 2 weeks of starting combination therapy with addition of ipilimumab, Cr rose to 1.6mg/dL and absolute eosinophils (AEC) went from 0 to 9 KU/L. There were no other new medications started in this time and no exposure to contrast or other nephrotoxins aside from occasional use of NSAIDS in the past. The urine eosinophils were positive and serological work up for AKI was negative. SCR and eosinophil increases coincided temporally post infusions of combined immunotherapy. SCR peaked at 1.8 mg/dL. A kidney biopsy confirmed moderate interstitial fibrosis and tubular atrophy with focal chronic inflammation and eosinophils suggestive of chronic interstitial nephritis. Both agents were held after third cycle secondary to AIN and prednisone 1mg/kg was initiated. SCR decreased to 1.38 mg/dL and AEC back down to 0 KU/L. Currently, the patient’s cancer is not progressing.

Discussion: Immune checkpoint inhibitors such as nivolumab and ipilimumab are known to cause AIN. Their combined use seems to confer an increased risk. Only one prior case exists of combined therapy leading to AIN in a native kidney. AIN appears to be related to an immune response to the kidney. It is essential for nephrologists and oncologists to understand this risk. Frequent monitoring of Scr during treatment and swift referral to nephrology for AKI can aid in early diagnosis of this newly recognized side effect and early initiation of treatment to prevent continued renal damage in these patients.

FR-PO009
Cytokine Storm and T-Cell Dysregulation Drives Acute Tubular Necrosis and Glomerular Disease in an SLE Patient with Hematopoagisch Lymphohistioctytosis (HLH)
Ashish Gummadi,1 Iris J. Lee, Swati Rao, Kamel Hatahet, Xu Zeng, Duncan B. Johnstone. Nephrology, Temple Univ Hospital, Philadelphia, PA.

Introduction: HLH is a rare condition of dysregulated activation of the innate immune system and abnormal T-cell function that can result in multi-organ failure and death. Renal involvement in HLH is not well characterized, but few cases report findings of acute tubular necrosis (ATN) and variable podocyte injury. Diffuse podocyte effacement and collapsing glomerulopathy have been described. We report a case of HLH in a woman with systemic lupus erythematosus (SLE) who presented with nephrotic range proteinuria and acute kidney injury (AKI).

Case Description: A 57 year old Caucasian female with history of hepatitis C cirrhosis was admitted to hospital for fever and placed on broad spectrum antibiotics. An extensive work up for infection was negative. The patient had a non-blanching erythematous macular rash, pancytopenia, splenomegaly, mental status changes and continued fevers.Peripheral smear and bone marrow biopsy were non-diagnostic. Ferritin levels >7500ng/ml, prompted consideration of HLH. Clinical findings and levels of soluble IL-2 Receptor (5295U/ml) later confirmed HLH. Treatment was started with steroids, IVIG and Etoposide. Inflammatory markers, CRP and Ferritin improved, but patient then developed AKI and nephrotic range proteinuria (5 grams) with microscopic hematuria. Serologies were positive for ANA (1:160), P-ANCA (1:80), and low complement. Renal biopsy confirmed a diagnosis of SLE, but only demonstrated class II lupus nephritis. A severe nephrotic ATN was seen on biopsy.

Discussion: We found both features of ATN and nephrotic range proteinuria in our patient with SLE and HLH. Our patient unexpectedly showed minimal glomerular damage related to SLE, as we only found class II lupus nephritis, which uncommonly presents with severe nephrotic range proteinuria. It has been proposed that in HLH, a soluble factor, and/or yet to be identified cytokine or lymphokine may contribute to podocyte damage and modifications resulting in nephrotic range proteinuria which was present in our patient.

FR-PO060
Severe Cisplatin Induced Renal Salt Wasting
Pavani Reddy,1 Ashvin Kamath,1 Golriz Jafari,1 Phuong-Thu T. Pham,2 Phuong-Chi T. Pham.1 OVMC; 2UCLA.

Introduction: Cisplatin is known to induce Fanconi syndrome and renal salt wasting (RSW). RSW typically only requires transient normal saline (NS) support. We report a severe RSW case that required >12L of 3% saline.

Case Description: A 57-year-old woman with limited stage small cell cancer was admitted for cisplatin (80 mg/m²) on day 1, and etoposide (100 mg/m²) daily, day 1, 2, 3, 4. On day 3, patient’s serum sodium (SNa) decreased from 133 to 125 within 24 hours. A diagnosis of syndrome of inappropriate antidiuretic hormone secretion was made. Urine studies revealed osmolality (Uosm) 693 mosm/kg, UNa 205 mEq/L, and potassium (UK) 40 mEq/L. While plan for strict free H₂O restriction was being placed, patient’s SNa fell to 209 mEq/L on day 5. Five hours in association with 4 hours of headache, nausea, and dizziness. The patient had severe RSW that resolved within 48 hours with 3% saline. The patient’s SNa improved to 139 mEq/L and serum creatinine (SCr) improved to 0.8 mg/dL post-operatively. LDH 3,116 U/L, myoglobin 207 ng/mL, CPK 960 U/L, reticulocytes 7.26%, unconjugated bili 2.1 mg/dL, lactate dehydrogenase < 4, normal G6PD, ADAMTS13, ANA, ANCA, C3, C4. He received RBC transfusions without improvement in his Hgb. MRI showed focal kinking of the ascending aortic graft with resultant turbulent jet (see Figure).

Proximal tubule injury. Left, LM: sloughing of necrotic proximal tubule epithelial cells into the lumen (L), absorption droplets (RD), degeneration of brush border (BB). PAS stain 20X. Right, EM: proximal tubule with only residual brush border microvilli (MV) and basolateral processes (BL), numerous cytoplasmic vacuoles (V). 2700X.

Discussion: The clinical picture, pathology and time course of ATN coincided with alirocumab as the cause, and renal function returned to baseline 1 month following cessation of this agent. A mechanism of alirocumab-induced ATN may be suppression of the PCSK9 overexpression in the kidney that occurs during inflammation, likely a cellular protective response to injury. CKD may be an additional risk factor. Of note, ATN was also documented as an effect of SPC3001, an antisense oligonucleotide which interferes with PCSK9 expression. Interstitial, cardiologists and nephrologists need to be aware of ATN as a potential side effect of alirocumab, and possibly other drugs that downregulate PCSK9 expression.

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

379A
FR-PO061
A Rare Case of Harvoni (Ledipasvir with Sofosbuvir) Induced Acute Interstitial Nephritis
Dilek Yarar1, Jean L. Franck2, John J. Doran3, Carla L. Ellis4
1Renal Pathology Dept, Emory University, Atlanta, GA; 2Nephrology Dept, Grady Memorial Hospital, Atlanta, GA; 3Dept of Medicine, Emory University, Atlanta, GA.

Introduction: Harvoni is a novel agent approved by the FDA for the treatment of hepatitis C infection. Scant data concerning Harvoni and its nephrotoxicity profile are available; we report a case of biopsy proven acute interstitial nephritis (AIN) associated with Harvoni.

Case Description: A 62-year-old female with hypertension, insulin dependent diabetes mellitus, chronic liver disease secondary to hepatitis C infection and chronic kidney disease stage 3 was admitted to Grady Memorial Hospital due to a recent rise in her serum creatinine level. Beside starting on Harvoni four weeks prior to presentation, the patient denied other changes in her medications which included insulin, amlodipine, hydralazine and losartan. She denied use of non-steroidal anti-inflammatory agents or herbal products. Her physical examination was only remarkable for a bilateral lower extremity pitting edema. Admission labs were notable for a creatinine level of 2.5 from a baseline of 1.7. Urine sediment analysis showed presence of white blood cells casts. Those findings prompted a renal biopsy which was performed. Histopathological findings showed mild to moderate acute interstitial nephritis with focally increased interstitial eosinophils and neutrophils and evidence of diabetic nephropathy. The decision to hold Harvoni was made, and on follow up the patient had near complete resolution of her acute kidney injury with her creatinine almost back to baseline.

Discussion: Harvoni is a novel medication for the treatment of chronic hepatitis C infection. To our knowledge this is the second case of biopsy-proven AIN induced by Harvoni. This report cases this need for nephrologists and hepatologists to be aware of this potential side effect of Harvoni.

FR-PO062
Bile Acid Nephropathy Successfully Treated with Plasmapheresis
Sam Kang1, 2, Orla M. Croiste1, 2, Syed Akbar Zulagha1, 2, Liam Plant3, 4
1Dept of Renal Medicine, Cork University Hospital, Cork, Ireland; 2Dept of Gastroenterology, Cork University Hospital, Cork, Ireland.

Introduction: Anabolic steroids are well documented to cause cholestatic jaundice. With the institution of supportive care, predominantly withdrawal of offending agent, recovery usually ensues. Concomitant acute kidney injury secondary to bile acid nephropathy, is increasingly being recognised in this cohort of patients.

Case Description: A 44 year old man presented with severe jaundice and pruritis. He had been consuming testosterone enanthate and oxymetholone for the past 12 weeks. Of note, his sister has a history of end stage liver disease, on the waiting list for a liver transplant, and 8 first degree relatives (including a 15 year old daughter) have a history of cholelithocholestastomy. On admission, bilirubin was 513 umol/L and creatinine 113 umol/L. Subsequent Magnetic Resonance Cholangiopancreatography did not reveal any evidence of pathology, along with normal viral, autoimmune and hereditary liver disease screens. Liver biopsy demonstrated severe cholestasis with neutrophilic infiltrate around bile ducts and central veins. Concomitantly, creatinine worsened and in the absence of clear etiology, a renal biopsy was performed, which demonstrated evidence of tubular injury with bile acid casts in the distal tubules. In light of progressive worsening of bilirubin, pruritis and renal function(creatinine peaking at 650 umol/L), plasmapheresis was initiated. He underwent 7 cycles, which led to a progressive improvement in the bilirubin and creatinine levels and offsetting the need for dialysis.

Discussion: Anecdotal evidence exists that plasmapheresis help reduce bile acid associated pruritis, and a recent case report, demonstrated success in a very similar setting of bile acid nephropathy. With respect to our patient, sustained improvement in overall clinical status was noted post plasmapheresis. A hypothesis for a genetic bile transporter defect, considering family history, is being entertained. This case highlights that plasmapheresis can be an effective treatment to arrest acute kidney injury secondary to bile acid nephropathy, which in turn emanates from cholestatic jaundice, especially in a population that consumes predisposing agents.

FR-PO063
Progressive AKI after Relief of Urinary Tract Obstruction
Volodymyr Chornyy1, Muna T. Canales2
1Nephrology, Hypertension and Renal Transplantation, Univ of Florida, Gainesville, FL.

Introduction: Urine output (UOP) is not a good indicator of urinary tract obstruction (UTO) as damage to the kidney may occur in the presence of only partial obstruction. Herein we present a case of partially relieved UTO with adequate UOP which progressed over time to complete renal failure.

Case Description: An 82 year old man with history of CKD stage 3 and chronic urinary retention due to enlarged prostate requiring clean intermittent self-catheterizations (CISC) presented with generalized weakness & 20 lbs unintentional weight loss over 6 months. He was noted to void naturally 3-4 x/day & while being busy on his farm, decreased the amount of CISC. He presented with elevated serum creatinine (SCr) of 4.8 mg/dL from baseline of 1.2 mg/dL 6 months prior. Ultrasound demonstrated severe bilateral (b/l) hydroureteronephrosis. Upon decompression with Foley catheter, 1500 cc of urine was evacuated. Given history of non-adherence with CISC, post-obstructive urethropy is diagnosed & recovery was anticipated. However, despite urinary output (UOP) of ~1500 cc/day, his renal function continued to deteriorate.
FR-PO065
Estimation of Renal Function in Patients with Acute Kidney Injury or Chronic Kidney Disease Who Are Receiving Dolutegravir
Hafiz Ali Sroya, Faisal Anwar, Christos Argyropoulos.
UNM School of Medicine.

Introduction: Dolutegravir (DTG) is integrase inhibitor used for the treatment of HIV infection. Data suggests that DTG increases serum creatinine by inhibiting organic cation transporter 2, which is responsible for tubular secretion of creatinine. It has been shown that DTG increases serum creatinine clearance (CrCl) by 14% in healthy individuals. However, in patients with impaired renal function (either AKI or CKD), the effect of DTG on CrCl is likely to be quantitatively more important, as tubular secretion contributes significantly in CrCl under these conditions. Measuring CrCl and using eGFR equations in this situation may significantly underestimate the GFR that can adversely affect the patient’s management. We present a case that illustrates these points.

Case Description: A 57 YO female with HIV/AIDS and CKD3bA3 was admitted with non-oliguric AKI on CKD. Her HIV/AIDS was controlled since diagnosis on a regimen of Trabact (cobasvacirilavdrag/entecitabine/tenofovir) with most recent CD4 count 393 and viral load <20. A native kidney biopsy was consistent with ATN and mild tubular atrophy. She was started on hemodialysis due to worsening metabolic acidosis, uremia and hyperkalemia. Stribild was discontinued and a regimen of Abacavir, Lamivudine & Dolutegravir was started. She remained dialysis dependent with no signs of renal recovery based on pre & post dialysis creatinine levels. Her eGFR calculated by MDRD equation was consistently <2ml/min and 24hr urine CrCl that was 1ml/min. We measured serum Cystatin C level (3.4 mg/l) and did eGFR calculations using CKD Epi, CKD Epi Cystatin C, CKD Epi Cys-C equations with eGFR 1, 1.4 and 10ml/min respectively. Finally, we did NM GFR measurement using Tc-99m DTPA that was 22 ml/min/1.73sq.m. We stopped dialysis and patient remained stable for 2 weeks but her recovery was complicated by another episode of AKI necessitating initiation of dialysis.

Discussion: Dolutegravir’s effect on CrCl is probably more pronounced in patient with low eGFR. GFR should be calculated using compounds that are freely filtered, not secreted or reabsorbed instead of eGFR or CrCl for correct estimation of renal function in patients with AKI or CKD receiving dolutegravir.

FR-PO066
Gemcitabine Associated Interstitial Nephritis
Maryam Gondal,1
Namrata Krishnan.2
1Nephrology, Yale New Haven Hospital, New Haven, CT; 2Nephrology, VA, West Haven, CT.

Introduction: Gemcitabine is widely used as a first line chemotherapeutic agent for various solid organ malignancies. Nephrotoxicity with this agent is rare and typically presents as hemolytic uremic syndrome (HUS). Acute interstitial nephritis (AIN) has not been previously reported with its use. We describe a case of gemcitabine induced AIN.

Case Description: A 69 year old male diagnosed with pleomorphic rhabdomyosarcoma of the neck and left supraclavicular fossa with osseous metastases was started on Adriamycin/ifosfamide and Mesna for treatment. He developed severe biopsy proven acute tubular injury(AKI) and acquired fanconi syndrome related to ifosfamide use within 3 months of starting treatment. Ifosfamide was stopped and patient was switched to gemcitabine for further therapy of his sarcoma. After receiving 3 cycles of gemcitabine, he was found to have evidence of further acute kidney injury (creatinine rose from 2.9mg/dl to 5.9mg/dl) associated with the development of a morbilliform, diffuse, skin rash. Urine sediment was noted to be bland. Renal US showed mild self-limited hydronephrosis secondary to mild benign prostatic hyperplasia. No evidence of HUS was found. Renal biopsy revealed areas of robust acute and chronic interstitial nephritis with a mixed infiltrate (neutrophils/lymphocytes/monocytes) along with persistent severe ATI from previous ifosfamide exposure. Patient was diagnosed with a gemcitabine induced AKI. He was pulsed with IV solumedrol and transitioned to a 3 month oral prednisone taper. His creatinine improved down to 2.9mg/dl-3.1 mg/dl after completion of therapy.

Discussion: Acute interstitial nephritis secondary to gemcitabine is rare. The present case emphasizes the need for renal replacement therapy in patients with acute kidney injury on Gemcitabine therapy. It also presents as hemolytic uremic syndrome (HUS). Acute interstitial nephritis (AIN) has not been previously reported with its use. Based on our experience, we conclude that gemcitabine is a nephrotoxic agent and should be used with caution in patients with renal dysfunction.

FR-PO067
Kidney Recovery after Three Years of Dialysis for Hepatorenal Syndrome
Type 1
Louise Suess, Sandeep Aggarwal, Gregory Malat, Ellie Kelepouris, Alden Michael Doyle.
Transplant Nephrology, Drexel Univ College of Medicine.

Introduction: Kidney recovery from Hepatorenal Syndrome (HRS) type 1 that requires dialysis is unusual but is sometimes possible with the combination of albumin, octreotide and midodrine; terlipreserin, or norepinephrine. HRS is generally felt to be irreversible after initiation of dialysis therapy is required but has occasionally been described after a few months of dialysis in the setting of successful liver transplantation. Here, we describe a case of kidney recovery after 3 years of dialysis without transplantation.

Case Description: A 51 y/o M with a history of alcoholic cirrhosis, hepatic encephalopathy, nephrological varices, portal hypertension, and ascites requiring paracentesis, who presented with decompensated liver failure. Patient had a MELD score of 42, worsening jaundice, ascites, thrombocytopenia, coagulopathy, hyponatremia and AKI. He was oligoanuric with a serum creatinine of 9 mg/dl, low urine sodium, bland UA and a normal kidney USG. Patient was diagnosed and treated for HRS type I with albumin, octreotide, and midodrine. Despite therapy, patient remained oliguric and required dialysis. Patient was listed for simultaneous liver and kidney transplant and was discharged to our outpatient dialysis unit where he remained stable but virtually anuric. Over the next 3 years, patient was abstinent from alcohol and had slow but steady improvement in liver function and decreased MELD score.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underlines represents presenting author.
FR-PO069

A Very Rare Case of HARVONI Causing Acute Tubular Necrosis

Introduction: With the approval of the newer agents, patient with Hepatitis C virus (HCV) are now having an effective cure. One of these agents is HARVONI, a combination pill containing Ledipasvir and Sofosbuvir, an effective and more importantly an interferon free regimen. It was approved in 2014 for the treatment of hepatitis C genotype 1 virus infection with sustained virological response of more than 95%. Although there were no cases of Acute Kidney Injury (AKI) seen in the trial phase, lately some case reports of HARVONI induced AKI have surfaced. Recently, one case of Acute Interstitial Nephritis was published but we are reporting another unique case of Acute Tubular Necrosis mediated by HARVONI.

Case Description: 58 year old female with history of HCV on HARVONI, Hypertension and DM, presented to the ER with 5 days of dysphagia and odynophagia. She was subsequently found to be in AKI with serum creatinine (SCr) of 11.06 and potassium of 7.2. She had no known history of kidney disease with baseline SCr 0.9mg/dl. She was eventually started on hemodialysis. Urinalysis showed 1+ protein but no blood which on quantification was 625mg in 24 hours and negative for monoclonal pattern on immunofluorescence. Serum HCV quantitative was less than 15, cryoglobulins were negative, and C3, C4 were normal respectively. ANA was elevated at 63.3 yet double stranded DNA antibodies were negative. Her renal ultrasound showed normal size kidneys with no evidence of hydronephrosis. She underwent percutaneous renal biopsy which revealed acute tubular injury associated with widespread oxalate deposits and very scant eosinophils. Eventually the patient was weaned off dialysis and discharged with Scr of 2.5mg/dl.

Discussion: Our patient had a normal creatinine just a few months ago and the only new drug introduced to her was HARVONI, thus it is most likely caused the ATN and responsible for the AKI. HARVONI is a very effective medication but as its growing use, more and more of these cases are being discovered. We are reporting, to our knowledge, the first ever case of ATN caused by this agent. The exact mechanism is unclear and more studies should be done in pursuit of clearly identifying the renal adverse effects of this highly marketable drug.

FR-PO070

Worcestershire Sauce Induced Nephropathy: Case Report
Juan Camilo Trimmel, Bernardo Moguel. 1 Internal Medicine, Hospital Español de Mexico, Mexico City, DF, Mexico; 2Nephrology Div, Hospital Español de Mexico, Mexico City, DF, Mexico.

Introduction: Histopathology damage by Worcestershire sauce was unknown; however, the excessive use causes oxalate deposition. Acute oxalate nephropathy (AON) due Worcestershire sauce is a rare cause of kidney failure. It’s secondary to calcium oxalate crystals deposits that induce chronic tubular damage, tubulointerstitial fibrosis and progressive kidney failure. A high load of oxalate, causes hyperoxaluria that increases the risk of nephro lithiasis and nephro calcinosis; also, triggers like dehydration and/or metabolic acidsis, could cause acute kidney injury.

Case Description: 51-year-old latin american male, without past medical history, presented to the emergency room with a 2 week history of diarrhea, approximately 10 stools per day, with abdominal cramping during defecation. Blood Chemistry: Creatinine: 23.06 mg/dL; BUN: 117.5 mg/dL; Na: 134.8 mmol/L; K: 4.22 mmol/L; Cl: 96.8 mmol/L; Albunin: 3.46 g/dl; Cr: 1.8 mg/dl; Hemoglobin: 9.8 g/dl; Platelet Count: 5.90. Chest X-Ray: Bilateral parenchymal 70%. 24-hour urine protein: 9820 mg. Urine protein/creatinine ratio: 12.27 g/g. Renal ultrasound: 3.47 g/dL, BUN/Cre: 5.09. Chest X-Ray: Bilateral pleural effusion of approximately 30%.

Discussion: Our patient had normal creatinine just a few months ago and the only new drug introduced to her was HARVONI, thus it is most likely caused the ATN and responsible for the AKI. HARVONI is a very effective medication but as its growing use, more and more of these cases are being discovered. We are reporting, to our knowledge, the first ever case of ATN caused by this agent. The exact mechanism is unclear and more studies should be done in pursuit of clearly identifying the renal adverse effects of this highly marketable drug.

FR-PO071

Acute Renal Failure, Aneurysm and Deep Vein Thrombosis
Camilo Naga, 1 Pavan Chugh, Rahul N. Pawar. 1 Internal Medicine, Loma Linda Medical Center; 2Loma Linda VAMC, Loma Linda, CA.

Introduction: Anuric Acute kidney injury (AKI) is uncommon but it can be seen with acute tubular necrosis, renal cortical necrosis and bladd er outlet obstruction. Here we report an unusual case of anuric AKI.

Case Description: A 62-year-old man with a solitary left kidney, presented to the ER, with complaint of low back pain and anuria for 4 days. His past medical history included, hypertension, HTN & CKD stage 3 with eGFR 53ml/min. On exam, BP was 165/110mmHg with swelling and pain of left hip and thigh. Lab values were: K 6.5 meq/l, BUN 119mg/dl, Cr 13.1mg/dl. A Foley catheter insertion did not yield urine. The Patient was given insulin- D50, kAYexalate & IV NaHCO3. Renal US showed left kidney length of 16 cm, with moderate hydronephrosis. US duplex of left thigh veins showed DVT extending from left common femoral vein to the trifurcate veins. Nephrology consult recommended a non-contrast CT scan of the abdomen and pelvis, repeat doses of kAYexalate, insulin-D50 & and NaHCO3, and pain of left hip and thigh. Lab values were: K 6.5 meq/l, BUN 119mg/dl, Cr 13.1mg/dl. A Foley catheter insertion did not yield urine. The Patient was given insulin- D50, kAYexalate & IV NaHCO3. Renal US showed left kidney length of 16 cm, with moderate hydronephrosis. US duplex of left thigh veins showed DVT extending from left common femoral vein to the trifurcate veins. Nephrology consult recommended a non-contrast CT scan of the abdomen and pelvis, repeat doses of kAYexalate, insulin-D50 & and NaHCO3, and pain of left hip and thigh. Lab values were: K 6.5 meq/l, BUN 119mg/dl, Cr 13.1mg/dl. A Foley catheter insertion did not yield urine. The Patient was given insulin- D50, kAYexalate & IV NaHCO3. Renal US showed left kidney length of 16 cm, with moderate hydronephrosis. US duplex of left thigh veins showed DVT extending from left common femoral vein to the trifurcate veins. Nephrology consult recommended a non-contrast CT scan of the abdomen and pelvis, repeat doses of kAYexalate, insulin-D50 & and NaHCO3, and pain of left hip and thigh. Lab values were: K 6.5 meq/l, BUN 119mg/dl, Cr 13.1mg/dl. A Foley catheter insertion did not yield urine. The Patient was given insulin- D50, kAYexalate & IV NaHCO3. Renal US showed left kidney length of 16 cm, with moderate hydronephrosis. US duplex of left thigh veins showed DVT extending from left common femoral vein to the trifurcate veins. Nephrology consult recommended a non-contrast CT scan of the abdomen and pelvis, repeat doses of kAYexalate, insulin-D50 & and NaHCO3.

Emergent laparotomy confirmed a massive left IAA and thrombosis of the thigh veins. The patient underwent open repair of AAA and the left IAA with a bifurcated prosthetic nitroin with placement of a ureteral stent. At 3-month follow-up, Cr was 50ml/min suggesting a favorable outcome.

Discussion: Obstructive anuria from IAA (in a solitary kidney) is rare, with only 4 cases reported in the literature. Our case illustrates IAA should be considered in the differential diagnosis of anuric AKI. This case emphasizes the utility of CT scan of abdomen and pelvis as a diagnostic tool in the evaluation of anuric AKI.

FR-PO072

A Rare Cause of AKI in a Renal Allograft: A Case Report

Introduction: AKI is common complication in renal transplant recipients. Differential diagnosis is broad and includes multiple infectious etiologies. However, it is rare for mycobacteria to infect the allograft and cause AKI. We present here the case of a renal transplant recipient who presented with an FUO and was diagnosed with disseminated MAC with renal allograft involvement.

Case Description: Soyo M ESRD 2/2 PCKD is s/p LURT (alemtuzumab induction,rapid steroid withdrawal,maintained on tacrolimus and mycophenolate). No history of acute rejection and his creatinine stabilized at 1.5. Twenty months post-transplant, he presented with 2wk of worsening fevers (99-103F in past 3 months) and dry cough. No weight loss, dyspnea, or GU symptoms. Routine blood work was notable for AKI (Cr 2.2). Chest CT with left paraaortic mass and an enlarged retroperitoneal lymph node. Lymph node biopsy was positive for acid fast bacilli, NAAT testing neg for TB). Blood and urine ex were negative, IGRA indeterminate and Fengtill positive. He was started on azithromycin, ethambutol and rifampin. His Cr rose to 3. Renal allograft biopsy showed severe interstitial inflammation,lymphohcytic tubulitis and rare acid fast bacilli identified on special stain. At this time MAC speculated from the lymph node biopsy. By hospital day 11, Cr decreased to 2.2. IVIg was given for treatment of possible concurrent allograft rejection. High grade fevers persisted throughout the 2wk admission. He was discharged on a 12mo course of Rifampin, Ethambutol, and Azithromycin. Cr was 1.8 upon discharge. Blood cultures sent on admission ultimately were positive for MAC. Three months after his initial presentation, he was clinically improved, with resolution of fevers. His Cr had decreased to 1.7.

Discussion: This case underlines the importance of recognizing the atypical and rare causes of AKI in a renal transplant recipient, especially in the setting of a known ongoing infection.
FR-PO073
Prolonged AKI Caused by Severe Rhabdomyolysis due to Genetic Disorder of Muscle ATP Metabolism
Kilian Steden, Sahana R. Kamalانbanahai, Joachim Hoyer. Internal Medicine and Nephrology, Univ Marburg, Marburg, Hessen, Germany.

Introduction: Caminute Palmitolytransferase (CPT) II deficiency is an autosomal recessive disorder characterized by a disruption of mitochondrial oxidation of long-chain fatty-acids, thus leading to an impaired ATP catabolism. First clinical symptoms of the myopathic form are observed in childhood and are characterized by weakness, exercise-induced muscular pain and myoglobinuria often triggered by fasting, lengthy muscular activity, viral infection or cold temperature.

Case Description: A 54 year old female physiotherapist returns from a skiing trip, complaining of pain in the proximal lower limbs as well as brown coloured urine. Laboratory reports showed a fulminant rhabdomyolysis (CK 235.000 U/l) accompanied by an acute kidney failure (serum creatinine 10.3 mg/dl). Treatment included alkalization of urine and volume management. As kidney function only slowly recovered, a more thorough evaluation of the underlying cause of rhabdomyolysis was performed. The patient did not report any trauma, chronic alcohol use, steroid medication or necrosis. Serological testing ruled out autoimmune disorders. MR imaging showed disseminated muscular edema and signs of myositis. The muscle biopsy showed single fibre necrosis and type-II fibre-hypotrophy with no signs indicating myositis or myocardial disease. We considered a genetic disorder. The patient reported of occasionally suffering from muscular pain since childhood. Testing for genetic myopathies revealed CPT II deficiency due to two heterozygous mutations in exon 1 and 3 of the CPT II gene. Over a prolonged time period of 5 weeks kidney function improved significantly with an almost normalized kidney function to this date (GFR 75 ml/min).

Discussion: Besides common causes for rhabdomyolysis such as trauma, arterial thrombosis, infections and autoimmune diseases, genetic disorders need to be considered in conclusive or complex cases. CPT II deficiency is a rare disorder (currently 300 reported cases), but should be considered as differential diagnosis. Therapy includes strict low-fat diet high on carbohydrates in addition to oral intake of L-carnitine to prevent rhabdomyolysis and muscle pain.

FR-PO074
Hand2 Inhibits Kidney Specification while Promoting Vein Formation within the Posterior Mesoderm
Elliot Perens. Div of Biological Sciences and Dept of Pediatrics, Univ of California, San Diego, La Jolla, CA.

Background: The kidneys and urinary tract are derived from the intermediate mesoderm (IM), yet the regulatory pathways that determine precise IM dimensions and that separate the IM from neighboring portions of the posterior mesoderm are poorly understood.

Methods: To study the genetics of early kidney development, we are using zebrafish. Like mammalian kidneys, zebrafish kidneys are derived from the IM, which expresses the same conserved transcription factors (such as lim1 and pax2) as the mammalian IM. Using a combination of loss-of-function and gain-of-function analysis, we have sought to determine the role of hand2 in IM development.

Results: We have found that the MHLH transcription factor Hand2 limits the size of the embryonic kidney by refining IM dimensions. In zebrafish hand2 mutants, the IM is expanded, and it is diminished when hand2 is overexpressed. hand2 is expressed within the posterior mesoderm, laterally adjacent to the IM. A set of venous precursors arise at the junction of these two territories, and hand2 promotes this transition by suppressing IM formation in this region. Furthermore, Hand2 and the similarly localized zinc-finger transcription factor Osr1 have functionally antagonistic actions on proepithelial formation.

Conclusions: Together, our data illuminate a previously unrecognized regulation of IM development and suggest a model in which hand2 functions in opposition to osr1 to balance the formation of IM and venous progenitors by regulating cell fate decisions in the posterior mesoderm. Our findings have implications for understanding the genetic basis of congenital anomalies of the kidney and urinary tract (CAKUT) and for developing new approaches in regenerative medicine.

Funding: Other U.S. Government Support, Private Foundation Support

FR-PO075
Heterozygosity for Six2 Increases Ureteric Branching and Final Nephron Number
Alexander N. Combes,1 2 Sean Wilson, Belinda Pipson,2 Brandon Binnie,1 Ali Ju,3 Cristina Cebrian Ligero, Sarah L. Walton,3 Karen M. Moritz,2 Alicia Oshlack, Melissa H. Little.1 2 3 Anatomy and Neuroscience, Univ of Melbourne, Melbourne, Vic, Australia; 3 Murdoch Childrens Research Inst, Melbourne, Vic, Australia; 1 Inst for Molecular Bioscience, Univ of Queensland, Brisbane, Qld, Australia; 2 Translational Research Inst, Univ of Queensland, Brisbane, Qld, Australia; 3 Dept of Internal Medicine, Univ of Michigan, Michigan, MI; 4 School of Biomedical Sciences, The Univ of Queensland, Brisbane, Qld, Australia; 5 Dept of Paediatrics, Univ of Melbourne, Melbourne, Vic, Australia.

Background: SIX2 is a transcription factor that regulates the maintenance of progenitor state within the cap mesenchyme (CM) during kidney development. Complete loss of Six2 in mouse results in premature differentiation of the CM and a failed kidney development. In this study, we examined kidney development in mice heterozygous for Six2 (Six2+/−) using quantitative multiscale imaging and transcriptional profiling.

Results: Six2 mRNA and SIX2 protein levels were reduced by 50% in the Six2+/- mice. Surprisingly, these mice had an average of 18% more niches than wild-type mice from 15.5 dpc to postnatal day (P)2. Total glomerular number was also 18% higher. RNA-Seq of Six2+/-Het kidneys revealed a decrease in genes associated with the uninduced CM state, including Citedl, Crem, and Mecsl. Several renal vesicle-enriched genes, such as Tcf23 and MyoD, were unregulated, whereas there was evidence for upregulation of mesenchyme progenitors. Six2+/-Het mice had increased CM and ureteric tip proliferation and upregulation of CM-expressed genes associated with proliferation and metabolism. Direct and dose-sensitive SIX2 targets were identified by further analysing transcriptional changes in CM from 11.3 dpc. Six2 KO and heterozygous mice, with these genes, showed a high overlap with published SIX2 ChIP data.

Conclusions: In summary, this represents a rare example of a genetic change resulting in increased nephron number by subtly shifting the molecular regulation of proliferation and differentiation in the CM. It also suggests a dose-sensitive separation between the role of SIX2 in regulating CM proliferation and the maintenance of CM identity.

Funding: Government Support - Non-U.S.

FR-PO076
Increased Hedgehog Signaling in Renal Progenitors Disrupts Stomatal Development and Nephrogenesis

Background: Foxd1+ stromal cells are essential for renal development. Abnormal stroma is a signature feature of CAKUT. While Foxd1+ stromal as well as SIX2+ nephrogenic cells both arise from Osr1+ and their daughter Sat1+ progenitor cells, the molecular mechanisms that control the specification and the relative proportion of Foxd1+ stromal cells are undefined. Since a renal injury causes Hedgehog (HH)-dependent proliferation of stroma-derived cells, we hypothesize that HH signaling controls specification of Foxd1+ cells during embryogenesis.

Methods: HH signaling was activated in a temporal manner in vivo with Tamoxifen (TM) in mice expressing Ptc1loxP and Sat1-CreERT2 or Osr1-GFP-CreERT2 alleles. Lineage tracing was performed using a ROSA tdTomato allele. Cell proliferation was analyzed using Ki-67 and phospho-histone H3. Osr1+GFP+ cells were purified from metameric mesenchyme by FACS.

Results: TM injection at E9.5 in Sat1-CreERT2;ROSAtdTomato mice induced TOMATO expression in both SIX2+ nephrogenic and PBX1+ stromal cells. TM injection at E9.5 in Sat1-CreERT2;PtdTomato mice decreased Ptc1 mRNA by 50% and increased expression of the HH signaling reporter, Ptc1-lacZ, in situ. E14.5 mutant kidneys demonstrated a 78% increase in PBX1+ cells and ectopic expression of Raldh2 in the medulla and presumptive ureteropelvic region. Also at E14.5, PBX1+ cells associated with ureteric bud tips were mis-patterned and were increased in number by 20% (n=4, p<0.05). Proliferation of PBX1+ cells was not significantly changed. The number of Ncam4+ nephron progenitor structures and WT1+ glomeruli was decreased by 28% and 20%, respectively (n=4, p<0.01). Yet, the number of SIX2+ cells was not significantly different than controls. In Osr1+ cells isolated from metameric mesenchyme of E11.5 Osr1-CreERT2;PtdTomato mice injected with TM at E9.5, Foxd1 mRNA was increased by 60% but SIX2 mRNA was unchanged compared to in control Osr1+ cells (n=5, p<0.05).

Conclusions: Increased HH signaling in renal progenitor cells increases generation of stromal cells, disrupts stromal patterning, and decreases nephron formation.

Funding: Government Support - Non-U.S.

FR-PO077
Bim Gene Dosage Is Critical in Modulating Nephron Progenitor Survival in the Absence of Dicer Activity
Debora Malta C.S. Santos, Andrew J. Bodnar, Yu Leng Phua, Neil A. Hukriede, Jacqueline Ho. Dept of Pediatrics, Children's Hospital of UPMC, Pittsburgh, PA.

Background: Low nephron endowment has been implicated in an increased risk of hypertension and chronic kidney disease. We have previously reported that in Six2-GC10−/−;Dicer−/− mutant kidneys, nephron progenitors lacking mature miRNAs undergo increased apoptosis and express increased levels of the pro-apoptotic protein, Bim.

Methods: In this study, we investigated the functional significance of increased Bim expression in Six2-GC10−/−;Dicer−/− mutant kidneys. To address this question, we generated a mouse model with conditional deletion of both Dicer and Bim from nephron progenitors in the developing kidney.

Results: While mutant kidneys exhibited a reduced number of nephron progenitors and developing nephron structures, the deletion of a single allele of Bim was sufficient to reduce the apoptotic rate of nephron progenitors and improve nephron formation. Next we used the same methods to identify potential binding sites for the nephron progenitor-enriched miRNAs, miR-10a, miR-17, miR-24-1 and miR-106b, in the 3'-untranslated region (3′-UTR) of Bim. All four miRNAs negatively modulated the endogenous expression of Bim and the activity of a luciferase reporter containing the intact Bim 3′-UTR in vitro. Furthermore, pri-miR-miR-10a, pri-miR-miR-17, pri-miR-miR-24-1 and pri-miR-miR-106b could downregulate the expression of EGFP expression in Xenopus laevis embryos injected with a synthetic miRNA containing the EGFP sequence fused to mouse Bim 3′-UTR.

Conclusions: Together these data suggest that the coordinated action of miR-10a, miR-17, miR-24-1 and miR-106b sets a threshold of Bim expression, regulating the balance between apoptosis and survival in nephron progenitors.

Funding: NIDDK Support
Temporal Down-Regulation of Spontaneous Calcium Activity in Metanephric Mesenchymal Cells Inhibits Branching Morphogenesis

The Cardiovascular Inst, Perelman School of Medicine, Univ of Pennsylvania, FR-PO087

Background: Calcium signaling is of fundamental importance for the development of early vertebrates, but little is known about the role of calcium in mammalian embryogenesis. In this study, we have used explanted kidneys from 14-day-old rat embryos cultured for 1 or 2 days to study calcium activity in metanephric mesenchymal (MM) cells, branching morphogenesis and synaptotagmin expression.

Results: We have recorded spontaneous calcium activity, characterized by stochastic calcium spikes of different amplitude and shape, in MM cells. This pattern of irregular calcium spikes is compatible with the calcium activity observed in cultured mesenchymal cells exposed to mechanical forces. Spontaneous activity was abolished following inhibition of the SERCA pump in the endoplasmic reticulum (ER) membrane, but remained intact during exposure to caffeine, suggesting a contribution to calcium stores. Depletion of ER calcium stores for 24 hours caused a temporal down-regulation of the spontaneous calcium activity. This result demonstrated a significant reduction of ureter branching points and order and fewer newly formed renal vesicles. Proliferation of MM cells remained intact. We have hypothesized that metanephric spontaneous calcium activity is required for secretion of the morphogenic factors that mediate the reciprocal interaction between the MM cells and the ureter bud, a prerequisite for ureter branching morphogenesis and nephron formation. In support of this hypothesis we demonstrate expression of the calcium dependent exocytory protein synaptotagmin 1 in MM cells.

Conclusions: This study has identified calcium as a novel indispensable link in the events involved in development of the mammalian kidney.

Funding: Government Support - Non-U.S.

The Transcription Factor tfap2a Directs Progenitor Fate Decisions during Nephron Development

Development Bio, University of Pennsylvania, FR-PO079

Background: Vertebrate kidney development consists of the differentiation and intratric patterning of specialized epithelial cells into discrete segments that form the nephron. However, the molecular and genetic pathways involved in cell fate decisions during nephrogenesis remain poorly understood.

Methods: By performing a forward genetic screen and utilizing whole mount in situ hybridization to assess nephron segmentation, we identified a mutant line with abducted distal segment development. Whole genome sequencing revealed that the genetic lesion disrupted splicing of transcription factor AP-2 alpha (tfap2a), which has been described as essential for neural crest and epidermis differentiation, but was not known to be active during renal ontogeny.

Results: We found that tfap2a exhibits a dynamic expression pattern in renal progenitors, eventually restricting to the distal segments of developing nephrons. Deficiency of tfap2a recapitulated the mutant phenotype, and tfap2a mutants also failed to complement a previously characterized tfap2ava105 strain, which encodes a missense mutation that also disrupts transcriptional splicing. In addition to distal tubule defects, tfap2a abrogation was associated with a significant increase in multiciliated cells, which supports the hypothesis that tfap2a may mediate cell fate choice within the nephron. Taken together, these studies support a novel role for tfap2a in epithelial cell fate decisions during nephrogenesis. Interestingly, during mouse embryogenesis, tfap2a expression is abundant within the developing urogenital tract encompassing structures such as the ureteric tip, early tubules, and late tubule.

Conclusions: Thus, our continuing efforts to characterize the molecular activities of tfap2a in renal progenitors may uncover aspects of nephron formation that are relevant to human kidney disease and disease states.

Funding: NIDDK Support

Hoxp-Expression Marks a Multipotent Progenitor Cell Pool during Kidney Development in Mice

Nikhil Singh, Rajan Jain, Li L, Lloyd G. Cantley, Jonathan Epstein, 1 Section of Nephrology, Yale Univ, New Haven, CT; 2 Dept of Cell and Developmental Biology, Univ of Pennsylvania, Philadelphia, PA; 3 The Cardiovascular Inst, Perelman School of Medicine, Univ of Pennsylvania, Philadelphia, PA.

Background: The homeodomain-containing transcription factor Hoxp has been recently identified as a marker of progenitor cells in a variety of embryonic and adult tissues, including kidney, lung, skin, heart, brain, taste bud and gut. We sought to determine whether Hoxp-expression marks a progenitor cell population during kidney development.

Methods: We used quantitative PCR and a Hoxp3xF-FGP reporter mouse to analyze the expression of Hoxp during murine nephrogenesis. We used a Hoxp-Cre and a tamoxifen-inducible Hoxp-Cre-ER line to fate map Hoxp-expressing derivatives during embryonic development.

Results: We found that Hoxp is expressed in the metanephros as early as E13.5 with expression increasing through gestation and peaking postnataally at P7. At E13.5, Hoxp-positive cells localize to the condensing metanephric mesenchyme and by E14.5, they have proliferated in number and are surrounded by precursor and mesenchymal cells. Hoxp-positive cells at E13.5 stain for mesenchymal markers, and these cells fate map to mesangial cells and the Renin-expressing cells of the juxtaglomerular apparatus - suggesting a common progenitor population for both populations of the nephron. Hoxp-expression is maintained in mesangial and Renin-positive cells, as well as in scattered proximal tubular cells and cells in the renal papilla; the latter two areas having previously been cited as potential stem cell niches in the adult.

Conclusions: Hoxp-expression marks a progenitor cell pool during embryogenesis that gives rise to Renin-expressing cells in the JGA as well as intraglomerular mesangial cells. Hoxp is also expressed in several putative stem cell niches in the postnatal murine kidney, an area which requires further investigation.

Funding: Other NIH Support - Analysis of a Novel Homeobox Gene in Cy Development

mTORCI Activity in Renal Progenitor Cells Is Correlated with Nephrogenesis and Kidney Size

Joseph M. Chambers, Shahram Jevin Poureetezadi, Rebecca A. Wingert, Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: Low nephron number is correlated with adverse health outcomes, including hypertension and chronic kidney disease in adulthood. mTORC1 complex is a member of the serine/threonine kinase family and is a central regulator of cell metabolism, growth, proliferation and survival. TSC1 is an inhibitor of the mTORC1 complex together with TSC2. Although mTORC1 has been shown to regulate stem cells of the hematopoietic system, its role in regulating stem cells in the kidney and nephrogenesis has not been defined.

Methods: Knockout of mTORC1 or TSC1 in progenitor cells in embryonic mice was achieved using Cre-LoxP Technology. Six2-CRE/FP:mTORC1-1 or Six2-CRE/FP:TSC1-1 heterozygous females were mated with mT/mG line, or TSC2+/- females to generate embryos carrying a homozygous deletion or CD1 females to generate heterozygous deletion. Kidney weight was measured relative to the body mass. Kidney morphology was evaluated and nephron counts were determined using acid digestion. In addition, kidney function was measured using serum urea at 5 to 6 months.

Conclusions: Tissue-specific deletion of mTSC1 in renal cell progenitors led to renal agenesis and severe dysplasia of the kidney, resulting in death a few days after birth. Analysis of mTORC1+/f animals reduction in nephron endowment compared to control mice. Furthermore, kidney function in mTORC1-/- animals was reduced as well. On the other hand, complete deletion of TSC1 led to significant increase in kidney size and their death few days of birth but apparently secondary to tubular injury. Heterozygous deletion of TSC1 led to significant nephromegaly compared to control in addition to 50% increase in nephron numbers compared to controls. Kidney function in adult mice with heterozygous deletion of mTORC1 or TSC1 has decreased kidney function as measured by urea level.

Funding: NIDDK Support

PPAR Signaling Regulates Nephron Development

Joseph M. Chambers, Shahram Jevin Poureetezadi, Eric Donahue, Rebecca A. Wingert, Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: At present, the genetic and molecular mechanisms directing nephron segmentation during kidney development are not well understood. Embryonic zebrafish have been identified as a suitable model system. Zebrafish provide a powerful, conserved system to discover developmental mechanisms driving nephron formation.

Methods: Through a novel chemical genetic screen, we discovered that peroxisome proliferator-activated receptor (PPAR) signaling is essential for normal nephron segment development. PPARs are a group of nuclear receptor proteins that are activated by agonists such as fatty acids and act as transcription factors by heterodimerization with retinoid X receptor (RXR) to regulate cell differentiation and, in addition, have diverse roles in metabolism.

Results: We found that treatment with the PPAR agonist bezafibrate during nephrogenesis resulted in a decreased length of the distal tubule while increasing the proximal straight tubule domain. Interestingly, the co-activator, pparγ1a, which binds to activated PPARs to regulate transcription of target genes, is expressed specifically in renal progenitors. To test the functional role of this co-activator during nephrogenesis, we used mice deficient in pparγ1a and found deficiency reduced distal tubule formation. Next, we examined nephron development in pparγ1a+/1 mutant zebrafish and found that the distal tubule was likewise abrogated.

Conclusions: Taken together, our studies reveal for the first time that PPAR activity is required for nephrogenesis. These findings may lead to a better understanding of the therapeutic value of PPARs in relation to the human kidney, as they have been shown to have renoprotective properties.

Funding: NIDDK Support

Genetic Mechanisms of Multiciliated Cell Genesis during Renal Ontogeny

Amanda N. Marra, Shahram Jevin Poureetezadi, Rebecca A. Wingert, Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: The differentiation of multiciliated cells (MCCs) has become an increasingly attractive area of research because of their association with fluid flow and disease across tissues, including the kidney. There is evidence for a core, conserved pathway of MCC development that includes the Notch signaling pathway as an important MEC factor.
FR-PO084 Multiciliated and Transporter Cell Fate Decisions Are Regulated by the Iroquois Transcription Factors irx2a/3b during Nephrogenesis Christina N. Cheng, Rebecca A. Wingert. Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: The genetic mechanisms that control cell fate decisions during kidney development remain poorly understood. The zebrafish pronephros provides a simplified tool to study multiciliated cell genesis, where the transcription factor irx2/3b has conserved roles in proximodistal segmentation. Here, we have used a combination of expression and functional studies to study the roles of irx genes during nephrogenesis.

Results: We found that irx2a and irx3b influence MCC fate as the loss of irx2a or irx3b resulted in decreased MCC density. Interestingly, the proximal straight tubule became expanded in irx2a or irx3b deficient embryos suggesting that these genes may help modulate the balance between MCC versus transporter cell lineages during nephrogenesis. Furthermore, irx2b, the zebrafish paralog of irx3b, was found to have conserved roles in proximodistal segmentation.

Methods: Here, we have used a combination of expression and functional studies to study the roles of irx genes during nephrogenesis.

Results: We found that irx2a and irx3b influence MCC fate as the loss of irx2a or irx3b resulted in decreased MCC density. Interestingly, the proximal straight tubule became expanded in irx2a or irx3b deficient embryos suggesting that these genes may help modulate the balance between MCC versus transporter cell lineages during nephrogenesis. Furthermore, irx2b, the zebrafish paralog of irx3b, was found to have conserved roles in proximodistal segmentation.

Conclusions: This study reveals exciting novel roles for irx2a/3b during renal epithelial cell specification. Further investigation of the genetic regulators involved in these events will generate a better understanding of the developmental pathways that govern kidney development, and may have significant implications for CAKUT therapies and renal regeneration in the near future.

Funding: NIDDK Support

FR-PO085 New Strategy for Kidney Regeneration Using DISCAS: The Drug-Induced Specificity Cell Ablation System Shuchiro Yamana, Tomohiro Fujiyama, Takashi Oginata, Hiromi Uchida, Madoka Shiraishi, Y mans Takaoka, Satoru Kato. Internal Medicine (Nephrology and Hypertension), Jikei Univ School of Medicine, Japan.

Background: The kidneys develop through reciprocal and sequential interactions between the ureteric bud (UB) and surrounding cap mesenchyme (CM). To date, the cell type specification and niche has achieved multi-faceted genetic dissection. Whereas transplantation studies reveal that the competition with the existing native host cell occupying a niche is considered to be its underlying cause. We demonstrated the development of living scaffold for kidney regeneration using the drug-induced specificity cell ablation system (DISCAS). We found that DsRed is an efficient kidney regeneration method to eliminate the existing native newborn progenitor cells (NPCs) that behave competitively in the nephrogenic niche.

Methods: We generated a mouse model with ablation only NPCs using an induction drug. Subsequently, metastases (MN) was isolated from the embryos and an induction drug was added to the organ culture dish for the elimination of native NPCs only. MN through DISCAS provided a scaffold mainly comprising living UBs. Donor mouse NPCs that were not affected by the drug were then transplanted into MN through DISCAS. We examined donor NPC engraftment to CM and their differentiation to a neo nephron. We analyzed the organ culture of MN using immunostaining.

Results: Donor NPCs were noted in the broad engraftment in CM, which ablated native NPCs using the drug. In addition, regenerative nephrons comprising only transplant cells were provided. The neo nephron expressed glomerular and tubular markers. We observed the engrafted with host collecting ducts and neo nephrons. The engraftment range of the transplant cells accounted for 48.7% of MN with DISCAS and obtained a wide range of neo nephrons.

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

Underline represents presenting author.
Results: Using whole mount in situ hybridization, we found that emx1 is dynamically expressed during kidney development. Expression of emx1 in the distal segments decreased in emx1 deficient embryos, which had a normal distal nephron territory, but had alterations of the individual segments within it, with an expanded distal early (DE) segment and a reduced distal late (DL) segment. These data suggest that emx1 is essential to promote the DL, and that it may restrict the DE and/or regulate the site of the DE-DL boundary. emx1 deficient embryos had reduced expression domains of several components that direct distal nephron segmentation, such as irx3 and simla, suggesting emx1 acts upstream of these factors. However, expression of mecoc was unchanged in emx1 deficient embryos, suggesting mecoc acts upstream or independently. Furthermore, emx1 expression in mesenchymal progenitors was found to change to changes in retinoic acid (RA), a morphogen which is essential to induce proximal segments and repress distal segments during nephrogenesis. RA treated embryos had a restricted emx1 domain, while exposure to the RA biosynthesis inhibitor DEAB conversely expanded emx1 expression, indicating that RA signaling acts to negatively regulate emx1 expression within renal progenitors.

Conclusions: Taken together, this work reveals for the first time that emx1 has essential roles in distal nephron patterning. As expression of Emx1 has also been annotated in the mouse mesenchyme, and because of the similarity between the zebrafish and mammalian genomes, this research can provide insights into regulatory networks that direct renal progenitor patterning during nephrogenesis.

Funding: NIDDK Support, Private Foundation Support

FR-PO089

Differential Usage of Enhancers for Bmp7 in Different Lineages of Kidney Development In Vitro Koutaro Ide, 1 Yoshihiro Rizaldy, 1 Keiichi Tsujimura, 2 Yoshihiko Mita, 2 Kana Ide, 2 Tatsuya Takase, 1 Gaku Sato, 1 and Taro Tsujimura 1,2

Methods: We first investigated the publicly available ChIP-seq data from ENCODE of H3K27ac marks around the locus in the kidney at different stages. We next generated deletion lines of mouse Emx1, each for the ureteric bud (UB), and downstream region of the Bmp7 locus, as previously described. We used these deletion lines to test the functionality of the deleted regions.

Results: We found that the pattern of H3K27ac was conserved in different cell types at different times and spaces. Upon differentiation towards intermediate mesoderm via activation of Otx1 (Mae et al. 2013), the deletion of the intraembryonic enhancer showed significant reductions in the Bmp7 expression, while those of the others did not. Interestingly, however, none of the deletions changed the expression level of Bmp7 upon differentiation specifically towards UB lineage (Takasato et al. 2015).

Conclusions: Taken together, these results show that different enhancers, particularly within the introns that were not tested yet, appear to regulate the expression of Bmp7 in different cell types of the kidney. Deletion of these elements individually in vivo should further clarify their roles in regulation as well as the precise functions of Bmp7 secreted from different domains of the kidney.

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

FR-PO090

The Basic Helix-Loop-Helix Transcription Factor, Tcf21/ Podl in Renal Strroma Is Essential for Crossstalk between Neprons and Interstitia Shintaro Ide, 1 Yoshio Maezawa, 1 Rizaldy P. Scott, 1 Tuncer Onay, 1 Yoshhiro Akimoto, 1 Kana Ide, 1 Minoru Takemoto, 1 Susan E. Quaggini, 1 Koutaro Yokote, 1,3 Clinical Cell Biology and Medicine, Chiba Univ Graduate School of Medicine, Chiba, Chiba-ken, Japan; 1Dept of Anatomy, Kyorin Univ School of Medicine, Mitaka, Tokyo-to, Japan; 1Feinberg Cardiovascular Research Inst and Div of Nephrology and Hypertension, Northwestern Univ, Chicago, IL.

Background: Renal stroma cells provide a supportive scaffold for nephrons and the collecting duct system, produce erythropoietin, undergo myofibroblast-like transformation to induce renal fibrosis Tcf21/Podl is an bHLH transcription factor highly expressed in both renal stromal and nephron progenitor population. A standard Tcf21 KO mouse died in the perinatal period with disrupted nephron development and disorganized interstitial patterning. However, given the complexity of the Tcf21 KO phenotype and early lethality, the precise role of Tcf21 in stromal cells remains unclear.

Methods: In order to elucidate the role of Tcf21 in renal stromal development and function, Tcf21 flox mice were bred with FoxD1Cre mice that provide specific gene deletion in renal stromal cells and its derivatives.

Results: Mice that lack Tcf21 in renal stroma (Tcf21crecre) develop massive polyuria with significantly reduced urinary creatinine and osmolality, increase of urinary sodium and chlorine excretion. Mutant kidneys are significantly smaller, show disorganized stromal structure, and prominent decrease in collecting ducts and loops of Henle. Ultrastructural analysis show thinning of endothelial cells, morphological changes of interstitial fibroblasts, and disorganized localization of glomerular capillary loops. Genomic expression profiling using RNA-seq reveals possible downstream targets of this transcription factor including type 6 and type 7 collagens.

Conclusions: Together, these data demonstrate a crucial role of stromal Tcf21 in the development of tubular/collecting duct system. Identification of direct targets of this transcription factor could provide a novel insight into the interaction between stromal compartment and nephrons.

Funding: NIDDK Support, Private Foundation Support

FR-PO091

Stromal-Expressed B-Catenin Controls Proper Differentiation of the Medullary Struma Felix Julien Boisvin, Darren Bridgewater. Pathology and Molecular Medicine, McMaster Univ, Hamilton, ON, Canada

Background: The renal stroma is a population of fibroblast cells essential for proper kidney development. Yet, stromal lineage formation, maintenance, and differentiation are poorly understood. In stromal progenitors, β-catenin is essential for establishing cortico-medullary patterning and formation of the medulla. While deletion of β-catenin specifically in stromal progenitors results in the absence of medulla, its underlying mechanism is not clear. We hypothesize stromal β-catenin is essential to regulate differentiation of the medullary stroma.

Methods: We generated mice with a β-catenin deficiency in stromal progenitors (B-cat−/−). Results: The overall stromal population in β-cat−/− kidneys revealed a 16.67% reduction using the stromal nuclear marker Pbx1 at E15.5. Analysis of the cortical stroma using FoxD1 and Tenascin-C did not reveal significant changes in their expression in β-cat−/− by IF and qPCR, suggesting β-catenin is not essential for cortical stroma progenitor formation. In contrast, the analysis of medullary stroma markers Pod1, Wnt4, Bmp4, and p53Kip2 revealed marked reductions of medullary stroma in β-cat−/−. To further investigate the contribution of β-catenin to the regulation of genes essential for medullary stroma formation, we developed a mouse model where β-catenin is overexpressed in stromal cells (β-cat+lox+loxS880). The levels of Bmp4, Bmp6, genes necessary for medullary stroma formation, were significantly increased in β-cat+loxS880 in an expanded cell population overexpressing β-catenin. This demonstrates β-catenin regulates the expression of genes essential for medullary stroma differentiation and medulla formation. Considering the reduced medullary stroma in β-cat−/−, we suspected stromal cells that did not differentiate properly to form the medullary stroma were eliminated by apoptosis. Analysis of apoptosis revealed a significant increase in TUNEL and Casp3+ stromal cells. These apoptotic cells were found in clusters below the nephrogenic zone just prior to medullary stromal formation.

Conclusions: Taken together, our results suggest β-catenin specifically regulates medullary stroma differentiation and survival by regulating Bmp4 and Wnt4 for proper medulla formation.

Funding: Government Support - Non-U.S.

FR-PO092

Loss of Zeb2 in Stromal Progenitors in Developing Mouse Kidney Leads to Renal Fibrosis Sudhir Kumar, Hila Milo Rosauly, Richa Sharma, Xueping Fan, Weining Lu. Renal Section, Boston Univ Medical Center, Boston, MA.

Background: Renal fibrosis is a leading cause of chronic kidney disease and renal failure worldwide and is characterized by fibroblasts to myofibroblast transition and deposition of fibrous matrix such as collagen. Zeb2 is a SMAD-interacting transcription factor expressing in stromal cells and fibroblasts in developing kidney. However, the link between ZEB2 and renal fibrosis is not known.

Methods: We generated Zeb2 stroma-specific conditional knockout mice (cKO) by crossing Zeb2 flox mice with FoxD1Cre mice and analyzed the phenotype of homozygous Zeb2flox/flox;FoxD1Cre mice (Zeb2 cKO) and their wild-type littermate controls. Kidney histology, renal function, and lifespan were studied in Zeb2 cKO. Protein expression analyses were performed by immunostaining of ZEB2, Phospho-SMAD3 and several markers for stromal progenitors, fibroblasts, and myofibroblasts in Zeb2 cKO and wild-type controls.

Results: We found that ZEB2 is highly expressed in FOXD1+ renal stromal progenitors and PDGFR-β+ fibroblasts during mouse kidney development. Deletion of Zeb2+ allele using FoxD1Cre mice leads to growth retardation, renal failure, and early mortality in homozygous cKO. Immunohistochemical analysis showed that newborn Zeb2 homozygous cKO kidneys have reduced expression of PDGFR-β and Tenascin-C, two stromal cell and fibroblast markers. At 3 weeks of age, interstitial fibroblasts showed markedly increased expression of α-smooth muscle actin indicating fibroblast to myofibroblast transition. Increased myofibroblasts lead to renal fibrosis with expanded collagen deposition as measured by Masson trichrome, picrosirius red and collagen-I staining. Further analysis showed that Zeb2 homozygous cKO mice have increased number of p-SMAD3+ interstitial cells suggesting enhanced TGF-β/SMAD3 signaling activation.

Conclusions: ZEB2 is important for renal interstitial fibroblast development and loss of Zeb2 in stromal progenitor cells during mouse kidney development leads to fibroblast to myofibroblast transition and renal fibrosis via enhanced TGF-β/SMAD3 signaling.
FR-PO093
Prorenin Receptor Controls Renal Branching Morphogenesis via Wnt/β-Catenin Signaling Renfang Song, Adam T. Janssen, Yuwen Li, Samir S. El-Dahr, Ibor V. Yosypov. Pediatrics, Tulane Univ, New Orleans, LA.

Background: The prorenin receptor (PRR) is a receptor for renin and prorenin, and an accessory subunit of the vascular proton pump H+-ATPase. Renal branching morphogenesis, defined as growth and branching of the ureteric bud (UB), is essential for mammalian kidney formation. Here, we demonstrated that conditional ablation of the PRR in the UB in PRR−/− mice causes severe defects in UB branching, resulting in marked kidney hypoplasia at birth (PLOS ONE, 2013).

Methods: Here, we investigated UB transcriptome using whole-genome-based analysis of gene expression in UB cells FACs-isolated from PRR−/− and control kidneys at birth (P0) to determine the primary role of the PRR in terminal differentiation and growth of UB-derived collecting ducts.

Results: Three genes with expression in UB cells previously shown to regulate UB branching morphogenesis, including Wnt9b, β-catenin and Fgf2, were upregulated whereas the expression of Wnt11, Bmp7, Etv4 and Gfra1 was downregulated. We next demonstrated that infection of immortalized UB cells with shPPR in vitro or deletion of the UB PRR in double-transgenic PRR−/−/BarGal mice, a reporter strain for β-catenin transcriptional activity, in vivo increases β-catenin activity in the UB epithelia. In addition to UB morphogenetic genes, the functional groups of differentially expressed genes within the downregulated gene set in UB cells FACs-isolated from PRR−/− mice included genes involved in molecular transport, metabolic disease, aminoacid metabolism and energy production.

Conclusions: Together, these data demonstrate that UB PRR performs essential functions during UB branching and collecting duct morphogenesis via inhibition of β-catenin signaling and control of hierarchy of genes that control UB branching and terminal differentiation of UB-derived collecting ducts.

FR-PO094
Grainyhead-Like 2 Regulates Urinary Concentrating Ability by Facilitating Collecting Duct Barrier Function Christine Jin,¹,² Janett Ruffert,²,³ Katharina Walentin,¹ Jonathan M. Barasch,¹ Keram Mutig,¹ Sebastian Bachmann,² Nina Himmerkus,² Markus Bleich,¹ Kai M. Schmidt-Ort,² Charlotte, Berlin, Germany; ¹Max Delbrueck Center for Molecular Medicine, Berlin, Germany; ²Urological Research Laboratory, Berlin, Germany; ³Columbia Univ, New York; ¹Univ of Kiel, Kiel, Germany.

Background: The transcription factor grainyhead-like 2 (Grhl2) is highly expressed in the collecting duct, Grhl2−/− mice, which lack functional proximal and distal segments, comparable to mammals. The zebrafish pronephros, has become a progressively prevalent model to analyze renal development and disease. The zebrafish pronephros is composed of two nephrons that contain a series of functional proximal and distal segments, comparable to mammals.

Aim: To discover the repertoire of genes that define nephron segmentation, a novel haploid forward genetic screen was conducted after random mutagenesis with ethynitrosourea.

Results: The screen was performed on approximately 700 genomes and resulted in the collection of 15 mutant lines to date. Ongoing complementation studies have suggested that these mutations represent at least 12 different nephrogenesis genes. The kidney phenotypic classes include models of podocyte deficiency, as well as expansions or reductions in the domains of individual proximal and distal tubule segments. Here, we report the characterization of several recessive, embryonic lethal mutations affecting kidney development. For example, line 363 lacks the proximal straight tubule, such that the proximal convoluted tubule and distal tubule form adjacent to one another. Current efforts are directed at identifying the genetic lesion underlying mutation 363. In comparison, line 154 had reduced proximal and expanded distal segments, hallmark of a defect in retinoic acid (RA) biosynthesis. To test this, we performed complementation analysis with aldehyde dehydrogenase la2−/− (aldh1a2), as well as rescue studies, which revealed that 154 is a novel allele of aldhl2a.

Conclusions: This collection of kidney mutations will provide a useful resource to uncover the genes that direct nephrogenesis pathways and may provide new models to study human congenital kidney defects.

Funding: NIDDK Support

FR-PO095
The Role of Planar Cell Polarity Signaling in Nephrin Cilogenesis and Tubulogenesis Rachel Katherine Miller,¹ Bridget D. Delay,¹ Vanja Stankic,¹ Mark E. Corkins,¹ Tonya A. Balis,¹ Malgorzata Dzau,¹ Pierre D. Mccrea,¹ Andrew B. Gladden,²,³ ¹Pediatrics-Research Center, Univ of Texas McGovern Medical School, Houston, TX; ²Univ of Texas Graduate School of Biomedical Sciences, Houston, TX; ³Genetics, Univ of Texas MD Anderson Cancer Center, Houston, TX; ⁴Immu-Biology Laboratory, Houston Methodist Research Inst, Houston, TX.

Background: Kidney tubules consist of a ciliated epithelium, and disruption of cilia polarity leads to aberrant nephrogenesis and cyst development. Recent work suggests that planar cell polarity (PCP) genes influence the development of cilia, but the mechanism behind this involvement is unknown. Daam1, a gene involved in PCP signaling and ciliogenesis, is expressed during nephrogenesis, and knockdown of Daam1 leads to decreased kidney tubulogenesis in Xenopus laevis (frog) embryos. Dishevelled, a component upstream of Daam1 in the PCP pathway, is known to interact with Daam1. We hypothesize that Daam1 modulates kidney tubule formation through formation of cilia.

Methods: Using Xenopus laevis (frog) embryos, supplemented polarized mammalian kidney cell (MDCK), we assess the roles of PCP components in kidney tubule ciliogenesis and morphogenesis utilizing knockdown, CRISPR/Cas9-mediated knockout, overexpression, immunostaining, yeast-2-hybrid and biochemical techniques.

Results: Our preliminary data suggest that knockdown of Daam1 leads to reduction of cilia in X. laevis kidneys and MDCK cells, supporting a working hypothesis that a reduction in kidney tubule ciliogenesis may contribute to nephrogenesis defects. Our initial assessments using CRISPR/Cas9-mediated knockout of Daam1 support its role in ciliogenesis and nephric morphogenesis. Yeast-2 hybrid screening and co-immunoprecipitation assays indicate that Daam1 interacts with Tuba, a component of the exoyct complex that is required for ciliogenesis and cilia remodeling. We observe a reduction in functional proximal tubule and that CRISPR-Cas9-mediated Tuba knockouts also have defects in nephrogenesis.

Conclusions: Together, these results indicate that PCP signaling is necessary for tubulogenesis within the developing kidney, in part due to effects upon ciliogenesis.

Funding: NIDDK Support

FR-PO096
Genetic Analysis of Mutations Affecting Kidney Development Audrey White, Gary Gerlach, Rebecca A. Wingert. Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: How the segment cell types of the nephron arise remains a major unsolved question in the field of nephrology. The zebrafish embryonic kidney, or pronephros, has become a progressively prevalent model to analyze renal development and disease. The zebrafish pronephros is composed of two nephrons that contain a series of functional proximal and distal segments, comparable to mammals.

Aim: To discover the repertoire of genes that define nephron segmentation, a novel haploid forward genetic screen was conducted after random mutagenesis with ethynitrosourea.

Results: The screen was performed on approximately 700 genomes and resulted in the collection of 15 mutant lines to date. Ongoing complementation studies have suggested that these mutations represent at least 12 different nephrogenesis genes. The kidney phenotypic classes include models of podocyte deficiency, as well as expansions or reductions in the domains of individual proximal and distal tubule segments. Here, we report the characterization of several recessive, embryonic lethal mutations affecting kidney development. For example, line 363 lacks the proximal straight tubule, such that the proximal convoluted tubule and distal tubule form adjacent to one another. Current efforts are directed at identifying the genetic lesion underlying mutation 363. In comparison, line 154 had reduced proximal and expanded distal segments, hallmark of a defect in retinoic acid (RA) biosynthesis. To test this, we performed complementation analysis with aldehyde dehydrogenase la2−/− (aldh1a2), as well as rescue studies, which revealed that 154 is a novel allele of aldhl2a.

Conclusions: This collection of kidney mutations will provide a useful resource to uncover the genes that direct nephrogenesis pathways and may provide new models to study human congenital kidney defects.

Funding: NIDDK Support

FR-PO097
Genetic Networks of Distal Tubule Patterning during Nephrogenesis Bridgette Drummond, Yue Li, Nicole Handa, Amanda N. Marra, Christina N. Cheng, Rebecca A. Wingert. Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: The nephron is composed of a variety of cell types that are arranged into distinguishable proximal and distal segments. Previous studies have utilized the simplified nephron system of the zebrafish embryo to identify novel components of nephrogenesis, such as the key roles for retinoic acid (RA) signaling in inducing proximal nephron fates, and the transcription factor encoded by mecom, which is required for distal segment formation. Methods: In this study, the T-box transcription factors tbx2a and tbx2b were found to be expressed by renal progenitors that give rise to the distal tubule. Loss of function studies revealed that deficiency of tbx2a, tbx2b or both tbx2a/b led to similar reductions in distal tubule formation.

Results: Interestingly, knockdown of tbx2a reduced the domain of tbx2b expression in renal progenitors, and distal tubule development in tbx2a−/− deficient embryos was partially rescued by tbx2b overexpression, indicating that tbx2a acts upstream to induce or maintain tbx2b during distal tubule development. To test the relationship of tbx2a/b with the RA pathway, wild-type embryos were treated with exogenous RA or a RA biosynthesis inhibitor, revealing that tbx2a/b are negatively regulated by RA signaling. Next, using in situ hybridization, we found that mecom transcripts maintained a consistent expression domain in the distal segments of tbx2a, tbx2b, and tbx2a/b deficient embryos. In contrast, mecom deficient embryos had significantly decreased tbx2a and tbx2b domains. Further, the diminished distal tubule typically seen with loss of mecom was partially rescued by co-expression of tbx2a/b, capping RNA. This indicates that mecom acts to promote tbx2a/b expression, which in turn promotes the formation of the distal tubule.

Conclusions: Taken together, these findings demonstrate that mecom, tbx2a, and tbx2b are necessary and sufficient factors for distal tubule development, which is pertinent for other developmental and regenerative medicine studies.

Funding: NIDDK Support, Other U.S. Government Support
ELF5 is a Principal Cell Lineage Specific Transcription Factor That Contributes to Normal Expression of Aqp2 and Avpr2

**Background:** The collecting ducts of mammalian kidneys are populated by intermingled intercalated and principal cells that are critical for water, electrolyte and acid-base homeostasis. Comparison of the gene expression profiles of normal developing mouse kidneys versus kidneys with Notoch-signaling-deficient collecting ducts, in which most duct cells are aberrantly fated to become intercalated instead of principal cells, led us to identify ELF5 as a potential principal cell specific transcription factor. We have determined whether ELF5 is an early principal cell lineage specific factor and whether it is required for principal cell differentiation.

**Methods:** We determined the renal ELF5 expression pattern using transgenic mice in which GFP or reverse tetracycline transactivator (rtTA) are expressed under the control of the ELF5 regulatory region and mice in which LacZ is knocked into the ELF5 locus. Lineage tracing kidney embryos were performed to determine the fate of ELF5 expressing cells using ELF5–rtTA,Tet-o-cre; Rosa26mfox mice. We performed dual luciferase assays to test the ability of ELF5 to induce the transcriptional activity of proximal promoters of principal cell specific genes. We also analyzed mice with conditional inactivation of ELF5 in the collecting ducts.

**Results:** ELF5 is expressed prior to Aquaporin-2 within the developing collecting ducts as early as E14.5. Lineage tracing of ELF5–expressing cells between E16.5 and E17.5 revealed that ELF5–expressing cells develop into mature principal cells expressing Aquaporin-4, and that E17.5 ELF5–null mice had normal proportions of the principal and intercalated cells, consistent with a 20% reduction in Aqp2 and Avpr2 gene expression levels in the kidneys with ELF5–deficient collecting ducts.

**Conclusions:** Although ELF5 is expressed early in the developing collecting ducts and becomes restricted to the principal cell lineage by E16.5, the contribution of ELF5 to the principal cell specific gene is minimal. The ELF5–rtTA mice will be useful for genetically labeling principal cells and inactivating genes specifically in the principal cell lineage.

**Funding:** Other NIH Support - P20GM10335 and P20GM103620

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Prenatal Renal Tract Abnormalities in Murine Models of Spina Bifida Overexpressing Grainyhead-Like 2 and Grainyhead-Like 3

**Background:** Given the prenatal manifestation of spina bifida, associated renal tract abnormalities may originate prenatally. Mouse fetuses with spina bifida overexpressing the grainyhead-like genes, grainyhead-like 2 (Grhl2) and grainyhead-like 3 (Grhl3), could serve as a model of the human condition. The present study aimed to use this murine model to assess the potential for prenatal renal tract abnormalities in spina bifida.

**Methods:** Matings were performed of heterozygous Axsl mice, which overexpress Grhl2 (Grhl2tg21) and transgenic early tail mice, which overexpress Grhl3 (Grhl3tg). Renal tracts were dissected from fetuses at embryonic day (E)18.5, embedded, sectioned at 3 μm, and hybridized with histology and immunohistochemistry.

**Results:** Of Grhl2tg21 fetuses with spina bifida at E18.5, 2/4 (50%) had abnormal kidney morphology, with no histological abnormalities. 7/9 (77.8%) Grhl3tg fetuses with spina bifida exhibited ureteral tortuosity (n = 4, 44.4%) or dilation (n = 3, 33.3%) at E18.5. Ureteral dilation was also observed in Grhl2tg21 fetuses with spina bifida. Immunohistochemistry suggested indistinguishable smooth muscle differentiation in bladders and ureters of Grhl3tg fetuses with spina bifida (n = 2) compared to controls (n = 2). No renal tract abnormalities were observed in heterozygotes at E18.5, but 2/4 (50%) fetuses carrying both the Axsl allele and the Grhl3 transgene had spina bifida and renal pelvic dilation.

**Conclusions:** In conclusion, spina bifida is a feature of mouse fetuses overexpressing either Grhl2 or Grhl3 at E18.5, but associated renal tract abnormalities result from Grhl2 and Grhl3 overexpression, not from Grhl3 itself. This is suggested by the observation of renal tract abnormalities in fetuses without spina bifida, the variation in defects between strains and evidence of inervation in renal tracts of fetuses with ureteral abnormalities. This study provides insight into the importance and interaction of Grhl2 and Grhl3 during renal tract development.

**Funding:** Private Foundation Support

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Cubulin/AMN-Mediated Protein Reabsorption in Nephrocytes Affects Drosophila Lifespan through Regulating the Senescence of Brain and Muscle Tissues

**Background:** Cubulin/AMN are major causes of chronic kidney disease in children. They are phenotypically and genetically heterogeneous diseases, with more than 50 genes reported as mutated in patients, mostly in syndromic forms. Many of the mutations are heterozygous, with autosomal dominant inheritance and variable expressivity. The most frequently mutated genes are HNF1B, MX2, EYA1 and SIX1, all encoding transcription factors. Many of the other genes are mutated in only few patients and their implication is sometimes elusive.

**Methods:** To improve molecular diagnosis and identify new causative genes, we developed a targeted exome sequencing strategy ("cubakome") focusing on 388 genes including known causative or likely causative genes, genes whose knockout in mouse lead to CUBK, genes involved in cellular processes/signaling pathways relevant for aging and senescence, as well as candidate that we had previously identified by whole exome sequencing of CUBK familial cases. 214 unrelated patients were analysed, 63 previously tested for HNF1B, MX2, EYA1 and/or SIX1 mutations by Sanger sequencing, and 151 new cases.

**Results:** We found that defect in nephrocyte protein reabsorption leads to shortened lifespan, whereas, enhanced protein reabsorption in nephrocytes extends Drosophila lifespan. We also found that nephrocyte protein reabsorption affects the proteostasis in hemolymph using proteomic approach. Furthermore, we also observed declined neuronal and muscular activities in flies with protein reabsorption defect. Finally, we found that protein reabsorption defect in nephrocytes impairs proteostasis and organ ageing in muscle and brain tissues, suggesting that Cubulin/AMN-mediated protein reabsorption in nephrocytes may affect the senescence of other organs via the tele-protectostasis mechanism.

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FR-PO103
Low Nephron Number in Japanese Subjects without Overt Renal Disease: The Effect of Race and Hypertension
Go Kanzaki,1,2 Victor G. Puellcs,1,3 Luise A. Cullen-Mcewen,1 Wendy E. Hoy,1 Yusuke Okabayashi,4 Nobuo Tsboi4, Akira Shirimu,2 Takashi Yokoo,1 John F. Bertram,1 1Dept of Anatomy and Developmental Biology, Monash Univ, Australia; 2Dept of Internal Medicine, The Jikei Univ School of Medicine, Japan; 3Centre for Chronic Disease, The Univ of Queensland, Australia; 4Dept of Analytic Human Pathology, Nippon Medical School, Japan.

Background: Nephron number in normal human kidneys varies widely and some racial groups with low nephron number have a higher incidence of hypertension and chronic kidney disease (CKD). In Japan, CKD has reached epidemic proportions, but the reasons for this remain unclear.

Methods: Autopsy kidneys from 18 male Japanese subjects without overt kidney disease were collected at Nippon Medical School, Tokyo, Japan and were carefully age-matched to archival data from 18 Caucasian Americans from Mississippi, USA. Demographic data were obtained from autopsy reports and medical records. Total nephron number and mean glomerular volume were estimated by design-based stereology. Glomerulosclerosis was determined using a standardized glomerulosclerotic index.

Results: Significant differences were found between Japanese and Caucasian Americans for height, weight, and thereby BSA (P<0.001 for all). Japanese kidneys weighed 21.8% less than those from Caucasian Americans (P<0.01). Caucasian American kidneys (955,843±52,781) contained 42.4% more nephrons than Japanese kidneys (P<0.01, 550,392±41,787). This difference was still present after adjustment for BSA.

Conclusions: Vit D treatment reduced the BP and the renal disturbances provoked by losartan treatment during lactation. These effects were associated with renal cellular deterioration and decrease of inflammation in the rats treated with Vit D.

FR-PO104
Loss of the Planar Cell Polarity Gene Fuzzy Causes Severe Renal Hypoplasia
Elena Torbaia, Yanran Wang, Medicine, Div of Experimental Medicine, McGill Univ and McGill Univ Health Center Research Inst, Montreal, QC, Canada.

Background: Fuzzy is a PCC effector gene, originally identified in Drosophila, where it regulates actin organization in wing cells. Disruption of Fuzzy in mice causes severe malformations including neural tube defects, polydactyly and facial defects among others. In vertebrates, Fuzzy also affects ciliogenesis by interacting with other PCC effectors to regulate recruitment of some intracellular organelles such as transport vesicles. Thus, Fuzzy may affect organogenesis by acting on both planar cell polarity signaling and on ciliogenesis, two processes important for kidney development.

Methods: Fuzzy gene-trap embryos were harvested at E14.5 and genotyped. Fuzzy homozygous mutants and matching controls were paraffin-embedded, sectioned and processed for immunofluorescent microscopy with various markers: calbindin (ureteric bud), Sox2 (nephron progenitors), N-CAM (early mesenchyme-derived nephron structures), WT1 (glomerular podocytes). Hematoxilin and eosin were used to conduct morphometric studies. PNCA and Tunnel assay were used to visualize proliferating and apoptotic cells. To determine renal function in Fuzzy−/− mice, we performed a tyramide signal amplification assay using a D-amino acid substrate to detect cleaved caspase-3, a marker of apoptosis.

Results: We found that 5 Fuzzy−/− mutants display severe kidney hypoplasia (~ 50% of the size of control animals) accompanied by ~ 50% reduction in the ureteric bud structures and corresponding 50% reduction of early glomeruli. However, the size of the Six2-positive progenitor pool, the proportion of early nephron structures and the number of podocytes per glomeruli were unaffected. Proliferation and apoptosis within the mesenchyme-derived structures were similar to control, yet proliferation and apoptosis within the ureteric bud structures were affected. ISH study revealed that Fuzzy is highly expressed in the collecting duct and at a lower level in other structures.

Conclusions: These studies indicate that decorative UB branching is the major cause of renal hypoplasia in Fuzzy−/− mutants. We will investigate whether loss of Fuzzy affects c-REI/GDNF, Wnt and/or Shh signaling. Hippo kinase pathway and causes aberrant tubular elongation in the collecting duct lineage.

FR-PO105
Vitamin D Effect on the Disturbances of Renal Function and Structure Induced by Losartan Exposure during Lactation in Rats
Lucas Ferreira Almeida, Heloisa Francescato, Cleonice Silva, Terezila Machado Coimbra, Physiology, Univ of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil.

Background: Renal development in rats is completed between 10 and 15 days after birth. Exposure to angiotensin II antagonists during lactation prevents disturbances in renal development. Vitamin D (Vit D) has been involved in cellular differentiation and proliferation and in the regulation of renin gene. Besides the lack of tubulin differentiation in losartan treated rats can affect the Vit D activation. This study evaluates the effect of Vit D in the renal changes provoked by losartan exposure during lactation.

Methods: Male Wistar rats were divided in 4 groups: 1-Control and 2-Control+Vit D, pups treated or not Vit D; 3-Losartan and 4-Losartan+Vit D, pups treated or not Vit D from dams that received losartan. Treatment with losartan (100 mg/kg/day) was conducted during lactation. Vit D (6 mg/kg/calcitriol-Abbot), administered by a mini-osmotic pump (Alzet), was introduced on day 30 after birth and continued until day 60. Blood pressure (BP) was determined 30 days after birth, and after sacrifice, renal samples collected to measure creatinine levels. The kidneys were removed for morphometric and immunohistochemical studies.

Results: The animals exposed to losartan presented higher blood pressure (140.0±7.7 mmHg), decreased glomerular filtration rate (0.56±0.62 ml/min/100g) and albuminuria (50.78±13.80 mg/24h), compared to control. These alterations were attenuated by Vit D treatment (129.5±7.4 mmHg, 0.77±0.16, 49.93±3.00, respectively, p<0.05%). Rats treated with losartan also showed decreased glomerular area media (5,800 µm²), higher interstitial area (21.1±1.66%), macrophage number (13.5±4.70/0.100 mm²), and increased score for fibronectin and alfa-SMA expression in renal cortex (1.4±0.08, 19.0±18 respectively). These alterations less intense in Losartan/Vit D group (6,300 µm²), 15.8±1.75%, 8.9±0.49, 1.0±0.08, 1.3±0.10, respectively.

Conclusions: Vit D treatment reduced the BP and the renal disturbances provoked by losartan treatment during lactation. These effects were associated with renal cellular deterioration and decrease of inflammation in the rats treated with Vit D.

FR-PO107
Iron Deficiency Induces Cystic Chronic Kidney Disease
Rongjia Deng,1 Jacob Stauber,1 Christian Hinze,2 Christian Rosenberger,3 Andong Qiu,2 Jonathan M. Barash,1 1Medicine/Nephrology, Columbia Univ, New York, NY; 2Nephrology, Max Delbrueck Center for Molecular Medicine, Berlin, Germany.

Background: Iron deficiency is a threat to embryonic and early postnatal development. Methods: We investigated dietary and transferrin iron deficiency during embryogenesis and in the immediate postnatal period.

Results: Iron malnutrition produced a severe phenotype with nearly complete loss of the proximal tubule (E15) while TRIR−/− produced only a mild glomerular and tubular insufficiency (E15). However, after both birth iron deficiency and TRIR−/− produced fulminant phenotypes reflected by severe disruption of the renal tubule and severe defects in TAL development. TRIR−/− (Six2Cre) demonstrated striking hypoplasia, tubular dilation, interstitial fibrosis and widespread cortical cystic transformation with Bardet-Biedel (BBS) or Nephronothesis (NPHP) defects. These defects were due to iron deficiency because introduction of NTRI (venofer) normalized the growth abnormalities. In summary, relocating the TRIR knockout to the TALH (KspCre), relocated cystogenesis to the cortical-medullary junction, confirming a direct effect of defective iron traffic in cystogenesis. RNAseq revealed that both dietary and genetic models induced the HIF-1 pathway. TRIR−/− resulted in a decrease in kidney Epo and the duodenal iron transporters Duhring and transferrin receptor 1 increased and increased in Liver Hamp1. In contrast, after small molecule activation of HIF (FG-4592) the hypoplastic cystic phenotype was dramatically rescued, EPO increased in the kidney, HAMP expression decreased in liver, and iron transporters were normalized in the duodenum. Indeed, HIF activation rescued body weight, kidney weight, and serum creatinine.

Conclusions: In sum, while TRIR−/− was not absolutely essential for embryonic development, kidney TRIR−/− was critical after birth; TRIR−/− produced disrupted systemic iron balance and induced kidney cystic hypoplasia. These changes resulted from disregulation of HIF and altered iron-dependent gene expression. The phenotype was rescued with iron and HIF modulators which increased systemic iron. These results demonstrate an unexpected connection between iron deficiency and cystic kidney disease and CKD and to two parallel therapeutic interventions for the treatment of cystic CKD.

FR-PO108
A Clinical Perspective of Glomerular Hyperfiltration in Health and Disease
Jo Kanzaki,1,2 Victor G. Puellcs,1 Luise A. Cullen-Mcewen,1 Yusuke Okabayashi,4 Nobuo Tsboi4, Akira Shirimu,2 Takashi Yokoo,1 John F. Bertram,1 1Dept of Anatomy and Developmental Biology, Monash Univ, Australia; 2Dept of Internal Medicine, The Jikei Univ School of Medicine, Japan; 3Dept of Analytic Human Pathology, Nippon Medical School, Japan.

Background: It has been proposed that a nephron deficit marks the risk for renal disease. This hypothesis is supported by the development of glomerular hyperfiltration in settings of nephron deficiency. However, the clinical study of human glomerular hyperfiltration is problematic, mostly due to limited access to adequate tissue samples and functional data. This study combines for the first time clinical and morphological data for a comprehensive analysis of glomerular hyperfiltration in human health and disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 389A
Methods: Autopsy kidneys from 25 Japanese patients were collected and were divided into three age-matched groups: normotensive (n=12; age=70), hypertensives (n=9; GFR=60), and CKD (n=2; eGFR=52). Total nephron number (Ng) and mean glomerular volume (Vg) were estimated using light microscopy. Glomerular hypertrophy, assessed by glomerular hypertrophy, single nephron GFR (snGFR and eGFR), and mean glomerular volume were evaluated.

Results: Ng was slightly lower in hypertensives (423,106±98,137) than in normotensives (464,545±108,157), but was similar to normotensives and CKD. snGFR and eGFR were elevated in hypertensives (P<0.05 vs normotensives), but was similar in normotensives and CKDs. eGFR/Vg was reduced in hypertensives (P<0.05 vs normotensives) and in the CKDs (P<0.001 vs hypertensives).

Conclusions: This study shows the importance of hypertrophic glomerulopathy in hypertensives. While CKD patients showed glomerular hypertrophy and reduced eGFR/Vg, snGFR was unaltered. This suggests these glomeruli have already exhausted their physiological capacity to compensate for glomerular loss.

Funding: Government Support - Non-U.S.

FR-PO108
Impact of Enzyme Replacement Therapy on Cardiac and Renal Tissues: A Post-Mortem Case Series

Methods: Post-mortem cardiac and renal samples were compared with tissue collected prior to initiation of ERT. Renal function was determined by annual 51Cr-EDTA clearance after ≥ 12 yrs ERT.

Results: There was a clear correlation between the majority of the selected biomarker levels and the underlying primary renal disease. With regard to B-cell activation, patients with IgAN showed higher levels of serum biomarkers, with particular focus on factors known to be important in B-cell activation, are associated with mesangial deposition of IgA1-containing immune complexes. Two of the key events in the pathogenesis of IgAN are the appearance in the serum of polymeric IgA1 molecules and IgA and IgG anti-IgA1 autoantibodies directed against the aberrant O-galactosylation.

Conclusions: Our results suggested urinary IgA–IgG and J-IgA–IgG complexes were higher and negatively associated with renal function in patients with ERT. However, further research with larger sample sizes is needed to identify the role of urinary IgA–IgG and J-IgA–JgG complexes in IgAN.

Funding: Government Support - Non-U.S.

FR-PO110
The Levels of Urinary J Chain-Containing IgA-IgG Complexes Are Elevated in Patients with IgA Nephropathy

Methods: Spot morning urine samples were collected from 10 patients with biopsy-proven IgAN (IgAN group), 11 patients with non-IgA nephropathies (diseases control group) and 23 healthy volunteers (control group). The levels of urinary IgA-IgG and Jg-IgA-jg complexes were measured by sandwich enzyme-linked immunosorbent assay (ELISA), and the latter was measured with J chain specific monoclonal antibody generated by our laboratory.

Results: The levels of urinary IgA-IgG and Jg-IgA-jg complexes were significantly higher in IgAN group than in diseases control group (1.55±0.38 vs. 0.76±0.12; P=0.0377, respectively) and healthy control group (1.55±0.38 vs.0.13±0.03; P=0.0011, 2.54±0.29 vs. 0.90±0.07; P=0.0001, respectively). We observed that higher levels of urinary IgA-IgG complexes were significantly associated with higher levels of Jg-IgA-jg complexes (r=0.92, P=0.0001) in patients with IgAN. The levels of urinary IgA-IgG and Jg-IgA-jg complexes in patients with IgAN were associated positively with serum creatinine (r=0.92, P=0.0002; r=0.84, P=0.0025, respectively) and negatively with eGFR (r=−0.70, P=0.0251; r=−0.65, P=0.0438, respectively). The latter was not significantly associated with 24-hour urine protein (r = 0.62, P=0.0558; r=0.50, P=0.1462, respectively).

Conclusions: Our results suggested urinary IgA-IgG and Jg-IgA-jg complexes were higher and negatively associated with renal function in patients with ERT. However, further research with larger sample sizes is needed to identify the role of urinary IgA-IgG and Jg-IgA-jg complexes in IgAN.

Funding: Government Support - Non-U.S.

FR-PO111
Serum BCMA Levels Are Elevated in IgA Nephropathy

Methods: Serum samples were collected from 49 candidate biomarkers were measured using a bead-based multiplexing immunoassay (Luminex). We analysed the relationship of biomarker concentration with renal function (eGFR), a diagnosis of IgAN, risk of progression in IgAN, specificity of biomarker changes in IgAN by comparison with matched MN.

Results: There was a clear correlation between the majority of the selected biomarker serum concentrations and eGFR, suggesting that as renal function falls the levels of these biomarkers rise independent of the underlying primary renal disease. With regard to B-cell specific factors, levels of soluble BCMA (sBCMA, TNFRSF17, a receptor for B-cell survival factors BAFF & APRIL) were significantly higher in IgAN and MN compared to healthy subjects, independent of eGFR.

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

390A
Conclusions: Our results suggest levels of sBCMA are significantly elevated in patients early in the natural history of IgAN (patients with normal renal function) and elevated levels mark out a group of patients at high risk of developing progressive renal disease. Our results highlight the importance of B-cell activation in IgAN and suggest shedding of BCMA by plasma cells may provide a valuable biomarker for B-cell involvement in IgAN.

FR-PO112

VIS649-A Highly Potent Anti-APRIL Antibody for the Treatment of IgA Nephropathy

Background: IgA Nephropathy (IgAN) is the most prevalent cause of primary glomerular disease worldwide. There are currently no effective, disease specific therapies for treatment. The cytokine APRIL (A Proliferation Inducing Ligand, TNFSF13) is emerging as a potentially key player in IgAN pathogenesis and disease progression based on a compilation of genetic, biochemical, and clinically relevant data. We report here the discovery and optimization of VIS649, a highly potent, fully humanized anti-APRIL antibody for therapeutic consideration.

Methods: The VIS649 antibody scaffold was identified through epitope-targeted screening of a mouse hybridoma library designed for achieving maximal antagonism of APRIL-receptor interactions. Full humanization of antibody variable regions was successfully achieved using both standard and proprietary computational methods. Results: The attributes of VIS649 include pimoclar APRIL binding affinity and subnanomolar receptor blocking activity to both TACI and BCMA in vitro. VIS649 likewise demonstrates functional interference of APRIL mediated downstream cellular signaling through the canonical NFκB activation pathway. Further biological characterization of VIS649 in vitro demonstrates effective reduction of B-cell proliferation and directly relevant inhibition of APRIL-mediated IgA production. Early in vitro data indicate effective neutralization of biological activity based on targeted reduction in serum IgA levels with minimal perturbation of overall B and T cell homeostasis indicating a selective immunomodulatory mechanism of action. VIS649 has been successfully engineered as an IgG2 subtype for purposes of clinically mitigating against antibody-dependent exacerbation of complement recruitment in the kidneys of IgAN patients.

Conclusions: APRIL (TNFSF13) represents a logical biological target for the treatment of IgAN nephropathy. Toward this end, VIS649, a fully humanized IgG2 based anti-APRIL antibody with high biological potency and low complement activation is currently under pre-clinical development.

Funding: Pharmaceutical Company Support - Visterra, Inc.

FR-PO113

MicroRNA-155 Induced T Lymphocyte Subgroup Drifting in IgA Nephropathy

Background: This study was performed to explore the relationship between miR-155 in peripheral blood mononuclear cells (PBMCs), T lymphocyte subgroups, T lymphocyte regulators and clinical manifestations of IgAN patients.

Methods: Sixty IgAN patients and 25 healthy controls were included. Expression of miRNAs in PBMCs was determined using microRNA microarray and real-time RT-PCR. T lymphocyte subgroups (Th1, Th2, Treg and Th17), differentiation regulators (c-Maf, STATA-6, GATA-3, SOCS1 and Foxp3) cytokines (INF-γ, IL-5, IL-10 and IL-17), serum IgA1 glycosylation level and Cosmc expression were assessed.

Results: Microarray analysis and qPCR suggested that miR-155 level of PBMCs in IgAN patients was significantly higher (p=0.01). Expression level of Gata3, SATA-6 and SOCS-1 in IgAN patients were significantly higher, while Foxp3 and Cosmc expression were remarkably lower. Flow cytometry found that peripheral blood Th1 and Treg cells percentages were remarkably higher. However, Th2 and Th17 cells percentages were remarkably lower. ELISA results indicated that serum Th1 cytokine INF-γ and Treg cytokine IL-10 levels were apparently lower, while Th2 cytokines IL-5 and Th17 cytokine IL-17 were significantly higher in IgAN patients than normal controls. Significant correlations were found between miR-155 levels and Foxp3, Cosmc level, 24h urine protein amount, urine RBC count, serum IgA concentration and IgA1 ds-glycosylation level. In vitro study, we also found that miR-155 mimic treatment will reverse T lymphocyte drifting and decrease the IgA dys-glycosylation level; While miR-155 inhibitor treatment will aggravate the T lymphocyte drifting and increase the IgA dys-glycosylation level.

Conclusions: Remarkable lower expression of peripheral lymphocytes miR-155 was observed in IgAN patients, which leads to T lymphocyte subgroup drifting (increase of Th2 and Th17 along with decrease of Th1 and Treg), which inhibits Cosmc gene expression and worsen the aberrant glycosylation of IgA1 molecule in IgAN patients.

Funding: Government Support - Non-U.S.

FR-PO114

T-folicular Like Helper Cells Drive the Proliferation and Expansion of IgA Antibody Secreting Cells in IgA Nephropathy

Background: Dysregulated IgA1 response is a central defect in the development of IgAnephropathy (IgAN), but it is not clear if the altered IgA1 response is solely attributable to dysregulation of IgA-antibody secreting B-cells (ABS) or whether additional immune cells contribute.

Methods: We studied peripheral B-cells in 8 IgAN patients, 8 healthy controls (HC), 5 lupus nephritis (LN), and 5 CKD controls.

Results: In the steady state, IgAN individuals had an increased number of IgA-B (88 per 1000 activated B-cells) in the peripheral blood compared to the HC, LN and CKD controls (20, 58 and 27, per 1000 activated B-cells, respectively), correlating with increased levels of IgA and IgA1 detected in the serum. In vitro stimulation with IL-4, IL-6, IL-21 and CD40L demonstrated increased IgA-B cell proliferation of IgAN patients was heavily influenced by the expression of IL-21, followed by increased surface expression of IL-7 on non-class switched B-cells compared to the controls. We next asked the question whether this enhanced proliferative capacity was attributable to T-folicular (Tf) like helper cells, a subset of T-cells that secrete IL-21 upon contact with naive B-cells, and have been shown to drive naive cells into immunoglobulin secreting cells in vitro. Co-culturing Tf-like cells and naive B-cells, an enhanced capacity to drive the naive B-cells to activated B-cells in vitro was observed using cells isolated from IgAN patients, resulting in 13.5% of the B-cell population having an activated B-cell phenotype (vs 6.9% of the B-cell population in HC). IgA was detected in the supernatants of the co-cultures of IgAN patients (658ng/ml vs 518ng/ml of HC cell co-cultures (p < 0.05).

Conclusions: Collectively our data suggest that an altered balance of Th1, T follicular and B-cell interactions may contribute to increased expansion and proliferation of IgA-B cells in IgAN, leading to greater numbers of IgA-B cells in the peripheral blood in the steady state.

Funding: NIDDK Support

FR-PO115

Cationic Lipids Enhance Autoantigen Production in IgA1-Producing Cells from IgA Nephropathy Patients and Healthy Controls

Background: IgA nephropathy (IgAN) is an autoimmune disease characterized by elevated production of autoantigen, IgA1 with some O-glycans deficient in galactose (Gd-IgA1). Increased pro-inflammatory cytokines, such as IL-6, have been shown to increase synthesis of Gd-IgA1, but only in cells from patients with IgAN. Here we show, for the first time, that a cationic lipid can enhance Gd-IgA1 production in IgA1-producing cells of patients with IgAN as well as healthy controls.

Methods: Peripheral blood mononuclear cells were isolated from IgAN patients and healthy controls, EBV immortalized, and IgA1 producing cells were subcloned using limiting dilution. IgA1-secreting cells from IgAN patients and healthy controls were stimulated with cationic lipids, and IgA1 production and O-glycosylation were assessed.

Results: Cationic lipids were supplemented to the cell culture medium of a panel of IgA1-producing cells from IgAN patients and healthy controls. This supplementation dramatically increased Gd-IgA1 production of IgAN (HC 3.81 ± 1.73, IgAN 5.18 ± 2.17 U Gd-IgA1) and IgAN+Lipid 6.48 U Gd-IgA1) without affecting total IgA1 production. Together, these data for the first time identified a general mechanism controlling galactosylation of IgA1 O-glycans.

Conclusions: This is the first study that revealed an effect of cationic lipids on glycosylation. Specifically, these lipids reduced galactosylation of IgA1 O-glycans without affecting total IgA1 production. Ongoing experiments will identify mechanisms involved. Understanding of the pathways controlling glycosylation in IgA1-producing cells may identify targets for manipulation of IgA1 O-glycosylation in patients with IgAN.

Funding: NIDDK Support, Private Foundation Support

FR-PO116

Circulating CD89-IgA Complex Levels Can Predict the Renal Outcome in Patients with IgAN

Background: CD89-IgA levels can predict the renal outcome in patients with IgAN.

Methods: Sixty IgAN patients and 25 healthy controls were recruited from the Glomerulonephritis Registry of Yonsei University Health System.

Results: Higher levels of IgA and IgA1 detected in the serum. Associated with disease progression. Thus, this study aimed to delineate whether circulating levels of CD89-IgA complex is associated with disease progression.

Conclusion: CD89-IgA levels at the time of biopsy and did not differ among chronic kidney disease stages. During follow-up study outcome was a 30% decrease of eGFR during the follow-up.

Circulating CD89-IgA complex levels were determined by sandwich ELISA method. The study outcome was a 30% decrease of eGFR during the follow-up.

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

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391A
Deficiency of C3a/C5a Receptors Reduce Renal Injury in IgA Nephropathy
In Vivo and C3a/C5a Receptors Antagonism Inhibit Mesangial Cells Proliferation In Vitro
Guolan Xing, Ying Zhang. Dept of Nephrology, First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China.

Background: Complement activation has a deep pathogenic influence in IgA nephropathy (IgAN). C3a and C5a, as key pro-inflammatory effectors of complement system, contribute to the development of IgAN. Therefore, C3a, C5a and their receptors are potential therapeutic targets for the disease. This study aimed to investigate whether deficiency of C3a/C5a receptors could attenuate renal injury in IgAN mice model, and define the effect of C3a/C5a receptors inhibition on cultured human mesangial cells (HMCs).

Methods: An IgAN mice model induced by Sendai virus (SV) infection was employed on wild-type and severe Combined Immunodeficiency (SCID) mice. The injured mice were divided into 5 groups: 1) SV infection (SV); 2) Inactivated SV at gradually increasing dose intranasally for 14 weeks, combined with SCID (SV/SCID); 3) SCID only (SCID); 4) Inactivated SV at gradually increasing dose intranasally for 14 weeks, combined with SCID and C3aR deficient (SV/SCID-C3aR-knockout); 5) Inactivated SV at gradually increasing dose intranasally for 14 weeks, combined with SCID and C5aR deficient (SV/SCID-C5aR-knockout). C3a/C5aR knockout mice were generated by the CRISPR-Cas9 technique. HMCs were isolated from 8-week-old healthy male Balb/c mice. In vitro C3a/C5aR antagonist was synthesized. Production of cytokines and chemokines in response to C3a/C5aR antagonist were detected by ELISA and RT-qPCR. Cultured HMCs were pretreated with 100ng/L IgA. Cell proliferation was measured by MTT assay. Production of cytokines and chemokines in response to C3a/C5aR antagonist were analyzed by Western blot and RT-qPCR.

Results: In the SV-infected IgAN model, C3aR/C5aR deficient mice had significantly reduced proteinuria than WT mice, but not lower than BUN and Scr. C3aR/C5aR deficient mice also showed remarkably lower renal IgA and C3 deposition, less histologic damage and reduced mesangial proliferation compared to the WT mice. Furthermore, both C3aR and C5aR deficiency significantly inhibited the gene expression and protein synthesis of TNF-α, TGF-β, IL-1β, IL-6, and MCP-1, especially C3aR deficiency. In vitro C3aR/C5aR antagonist inhibition prevented IgA-induced HMCs proliferation and TNF-α, TGF-β, IL-1β, IL-6, MCP-1 production.

Conclusions: These results demonstrate that deficiency of C3a/C5a receptors reduce renal injury in IgAN mice model, and verify the inhibition of HMCs proliferation by C3a/C5a receptors antagonist in vitro. Our findings suggest that pharmacological targeting of C3aR/C5aR may have potential in the treatment of IgAN.

Funding: Government Support - Non-U.S.

Anti-Symmetric Dimethylarginine Autoantibodies (anti-sDMA) in Systemic Lupus Erythematosus
Andrew Z. Wei, Pan Liu, Cybele Ghossein, Jing Jin. Nephrology/Hypertension, Northwestern Univ Feinberg School of Medicine, Chicago, IL.

Background: Systemic lupus erythematosus (SLE) is a complex multi-system autoimmune disease characterized by the loss of tolerance to self-antigens and subsequent production of self-reactive antibodies. The most well-known and clinically-tested class of antibodies are the anti-nuclear antibodies (ANA), which include antibodies against ribonucleoproteins (anti-RNP)s such as the smiths proteins (anti-Sm). Glycine-arginine (GR) dipeptide repeats of the Sm protein contain symmetrical dimethylarginines (sDMA), a post-translational modification, which form an antigenic epitope for autoantibodies. The presence of anti-Sm has been associated with an increased risk of kidney involvement due to production of immune complex deposits. The purpose of this ongoing study is to elucidate the potential involvement of arginine methylase of GR repeats in neoantigenic responses of lupus.

Methods: Serum from 31 SLE patients with renal involvement and 6 healthy controls was collected (28 females and 3 males, age = 23-66yrs, median= 42yrs). The through the use of peptide-array technology, we generated an array containing 270 distinct antigen peptides (all 15 amino acids in length) derived from 76 human proteins, and screened SLE patient sera for antibody reactivity towards sDMA and non-modified epitopes. Serum from healthy subjects, antigen standard such as Y12 and SYM10 were used as negative controls.

Results: 17/31 SLE patients demonstrated strong selectivity of sDMA-containing vs. non-methylated epitopes. Anti-sDMA positive serum reacted to a wide range of proteins with low sequence specificity. Selectivity for sDMA epitopes were not seen in heterogeneous healthy controls.

Conclusions: Anti-sDMA that preferentially target sDMA epitopes are seen in a large sub-set of SLE patients with SLE. These antibodies bind to a wide variety of sDMA-containing epitopes found in human cells and may contribute to the pathogenesis of SLE and development of immune complexes in lupus nephritis. The EBNA-1 protein of the Epstein Barr virus contains a region rich in GR and provides an interesting hypothesis through the generation of anti-sDMA through molecular mimicry.

Annexin II-Binding Immunoglobulin Level Correlates with Renal Histological Features in Lupus Nephritis
Kwok Fan Cheung, Susan Yang, Mel Chau, Desmond Y.H. Yap, Daniel Tak Mao Chan. Dept of Medicine, The Univ of Hong Kong, Hong Kong.

Background: Annexin II on the surface of mesangial cells mediates anti-dsDNA antibody binding and downstream inflammatory and fibrotic processes in lupus nephritis. We investigated the relationship between annexin II-binding immunoglobulins and renal histology in lupus nephritis.

Methods: Archived serial samples from 28 patients with Class III/IV lupus nephritis were retrieved, and annexin II-binding immunoglobulin level was measured with an in-house ELISA. Glomeruli were isolated from NZBWFI mice, and annexin II gene and protein expression was investigated by real-time PCR and cytochemical staining respectively. Ultrastructural localization of annexin II was determined by immunogold staining and electron microscopy.

Results: Associations between serum annexin II-biding IgG level, anti-dsDNA level, and disease activity were observed in 42% of lupus nephritis patients. Annexin II-binding IgG level correlated with activity index (r=0.44, p<0.04), leukocyte infiltration score (r=0.52, p<0.01), and karyorrhexis/libidin necrosis score (r=0.60, p=0.002) as stated in the patients' renal biopsy reports, and also the semi-quantitative mesangial electron-dense deposits score (r=0.63, p<0.009). Glomerular annexin II expression increased with active nephritis and decreased with glomerulosclerosis in NZBWF1 mice. Annexin II expression co-localized with electron-dense deposits in the mesangium, along the glomerular basement membrane and around podocytes.

Conclusions: The association between annexin II-binding IgG level and histological features of severe nephritis and the co-localization of annexin II with electron-dense deposits both implicate annexin II in the pathogenesis of lupus nephritis.

Funding: Government Support - Non-U.S.

Interferon Regulatory Factor 5 Signaling in Myeloid Cells Is Not Required For the Development of Lupus and Lupus Nephritis
Abraham Cohen-Bucay, Kei Yasuda, Barry K. Horne, Prachi Shukla, Ian R. Rifkin, Ramon G. Bonegio. Renal Section, Boston Univ Medical Center, Boston, MA.

Background: Recent genetic studies have associated systemic lupus erythematosus (SLE) and gain-of-function polymorphisms in the interferon regulatory factor 5 (IRF5) gene with lupus-prone mouse strains. IRF5 knockout mice develop less active lupus and less severe lupus nephritis (LN). A growing body of literature indicates a critical role for myeloid cells including macrophages, monocytes, and neutrophils in the pathophysiology of autoimmunity. This led us to hypothesize that IRF5 signaling in myeloid cells may play a critical role in the development of autoimmunity and end-organ damage in SLE.

Methods: We generated an IRF5 conditional knockout (cKO) targeting myeloid cells using the Cre-loxP system in lupus-prone FcRIV/-/- knockout (R2) mice. Littermate R2 (R2/-/-) and R2.IRF5cKO (R2/-/-IRF5fl/fl.LysMCr+/-) mice were evaluated for evidence of SLE by measuring splenomegaly, lymphadenopathy, and analysis of albuminuria, renal histopathology and analysis of immune cell infiltrate of the kidney by flow cytometry. We used comparison the severity of lupus nephritis.

Conclusions: IRF5 signaling in neutrophils, monocytes and macrophages is not required for the development of SLE or damage to end organs like the kidneys in lupus-prone R2 mice.

Funding: NIDDK Support

Growth Factor Midkine Excacerbates Lupus Nephritis by NFAT-Regulated Activation of T Cells
Tomohiro Kosugi, Keiko Watanabe, Tomoki Yoshioka, Hiroshi Kojima, Yuka Sato, Tomoki Kosugi, Yukio Yuzawa, Shoichi Maruyama. 1Nephrology, Nagoju Univ, Nagoja, Aichi, Japan. 2Nephrology, Fujita Health Univ School of Medicine, Toyoake, Aichi, Japan.

Background: Midkine (MK), a heparin-binding growth factor, regulates cell growth, cell survival and migration in nephrogenesis and development. Its pathophysiological roles are diverse, ranging from the occurrence of acute kidney injury to progression of chronic kidney disease, often accompanied by hypertension and diabetes. In autoimmune diseases, however, molecular mechanism involving MK is unknown. In current study, we elucidated the role of MK in the activation and differentiation of T cellsubset in lupus nephritis (LN).

Methods: In vivo study, LN was induced in MK-deficient (MK−/−) or wild-type mice (MK+/+) with an intraperitoneal injection of pristane. Mice were sacrificed at 6 months later. Serum, urine, kidney and spleen were analyzed. In vitro study, we examined the activation of CD4− splenocytes and differentiation of T cell subset.

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RESULTS: In vivo study: Glomerular injuries in Mdk+/+ mice were severer than those of Mdk−/− mice. CD45+CD11b+Ly6G−/−Mφs and CD45−CD11b+Ly6G+Mφs were prominent in Mdk−/− mice, consistent with the profiles of albuminuria and renal function. In proportion to LN disease activity, the frequency of splenic CD69+ T cells and T helper (Th)1 cells, but not regulatory T cell (Treg), was increased in Mdk−/− mice with skewed cytokine profile. Mφs were also enhanced in activated CD4+ T cells. In vivo study: MK induction in splenocytes was found during the activation of T cells, and supplemental administration of MK protein to Mdk−/− activated T cells induced the activation of the nuclear factor of activated T cells (NFAT) signaling and CD69 expression with a profile similar to that in Mdk−/− activated T cells. In addition, MK selectively regulates population and differentiation into Th1 cells, which is independent of Treg population.

Conclusions: MK serves an indispensable role in the NFAT-regulated activation of CD4+ T cells and Th1 cell differentiation, eventually leading to the exacerbation of LN.

FR-PO122
Gene-Environment Interactions Promote Nephritis-Associated Autoimmunity
Amy G. Clark,1,2 Emma Zhao,1 Anastasiya Birukova,1 Elizabeth Sarah Buckley,1,2 Jeffrey Ord,1,2 Yohannes G. Asfaw,1 Robert Matthew Tighe,1,2 Mary H. Foster.2
1Medicine, Duke Univ Med Ctr; Durham, NC; 2Duke VAMC, Durham, NC.

Background: Occupational exposure to inhaled crystalline silica dust is clearly associated with autoimmune diseases such as lupus and ANCA-associated vasculitis with glomerulonephritis where autoantibody (autoAb) production is a prominent disease component. A key question is how lung exposure to silica breaks tolerance and unleashes autoreactive B cells and autoAb that destroy kidneys and other organs. We hypothesize that pathogenic B cell dysregulation occurs in ectopic/tertiary lymphoid structures (ELS) that develop in response to relevant environmental exposures in genetically susceptible individuals.

Methods: Wildtype (WT) and autoAb transgenic (Tg) mice of C57BL/6 (B6) and genetically distinct lupus-prone NZB, MRL, and BXSB backgrounds were exposed to inhaled silica or vehicle. After 1-3 months, lung pathology and lymphocyte infiltration were evaluated using H&E, PAS, and immunofluorescent stained sections. AutoAb levels in bronchoalveolar lavage fluid (BALF), supernatants from cultured lung and spleen cells, and serum were assayed by ELISA.

Results: All WT and autoAb Tg+ silica-exposed strains showed extensive lung pathology with B and T cell infiltrates and ELS compared to vehicle controls. The percentage lung area containing ELS following silica exposure was variably WT (B6XBXSB=MRL>B6>NZB, p=0.03). Significant increases in autoAb production (anti-DNA and anti-MPO) with silica exposure were seen using H&E, PAS, and immunofluorescent stained sections. AutoAb levels in bronchoalveolar lavage fluid (BALF), supernatants from cultured lung and spleen cells, and serum were assayed by ELISA.

Conclusions: In genetically susceptible subjects, pulmonary exposure to silica leads to B and T cell accumulation with ELS formation in lung, enhancing local as well as systemic autoAb production. This data suggests that a gene-environment interaction leading to autoAb production is a potential mechanism promoting nephritogenic autoimmunity.

Funding: NIDDK Support, Other NIH Support - NIEHS, VA Support

FR-PO123
Major Glomerular Infiltrating Alternatively Activated Macrophage in Lupus Nephritis and Emigration Dependence on CD11b
San-Sang J. Sung,1 Yan-Chao Dai,1 Hong-Yang Wang,1 Jing Yu,1 Rahul Sharma,1 Young Hahn,1 Thera L.1,2 Mark D.1,2 and Linele Bolton.1,2
1Medicin, CIB, U of Virginia, Charlottesville, VA; 2Cell Biology, U of Virginia; U of Virginia.

Background: Despite the general acceptance that glomerulus-infiltrating leukocytes play critical roles in glomerulonephritis (GN), studies on the dynamics of leukocyte emigration into the glomerulus during disease progression and functional attributes of the leukocyte populations are lacking.

Methods: The lupus-prone NZM2328 (NZM) mice developing spontaneous LN with chronic GN (cGN) or anti-GBM-induced LN with acute GN (aGN) were studied. Confocal microscopy were used to identify marker expression. Highly purified glomeruli obtained from magnetic bead trapping were used to prepare single cell suspensions for flow cytometry analysis.

Results: Both MHCII+ and F4/80+ macrophages expressing high levels of the M2 markers Mac2, PD-L1, MMR, and Mgl1/2, and other macrophage markers CD11b, CD14, and SLAMF9 constituted the largest population of infiltrating leukocytes in NZM mice with cGN, comprising 60% - 80% of total CD45+ cells and their numbers correlated and proteinuria severity. I-A CD11b+ DC-like cells constituted the next largest leukocyte population (10% - 20%). PMN and T cells were only about 2% of total leukocytes. Leukocytes in young NZM mice lacking GN have 10 - 30 times fewer infiltrating leukocytes and lower percentages of PMN. In anti-GBM-treated NZM mice, CD11b+ I-A+ macrophages remained the largest glomerular leukocyte population (50%) whereas PMN increased to 30% of CD45+ cells at the expense of reduced CD11b+ DC numbers (4%). Blocking of CD11b, the predominant marker on both macrophages and PMN with anti-CD11b or anti-ICAM-1 mAb reduced macrophage and PMN infiltration by 80% and 70% respectively, and reduced proteinuria by 95%.

Conclusions: The results showed that in cGN, M2 macrophages are the predominant glomerular infiltrating leukocytes whereas contribution of infiltrating PMN and reduced numbers of DC occur in aGN. Infiltration of both macrophages and PMN are heavily dependent on CD11b-ICAM-1 interaction. Controlling macrophage infiltration and function is potentially beneficial in GN treatment.

Funding: Clinical Revenue Support

FR-PO124
Macrophage Mediators of Tissue Fibrosis Are Found in Murine Kidneys after Experimental Glomerulonephritis
Gaia Mualem,1,2 1Renal, Hypertension, and Electrolyte Div, Univ of Pennsylvania, Philadelphia, PA; 2Dept of Pathobiology, Univ of Pennsylvania, Philadelphia, PA.

Background: Crescentic glomerulonephritis (GN) is an important cause of kidney injury, and immune-mediated damage is thought to be a significant contributor to chronic kidney fibrosis. A transition in macrophage phenotype from classical (M1) to alternative (M2) activation has been associated with tissue fibrosis in other organ systems, and limiting this transition has attenuated fibrotic lung and liver injury in preclinical studies. Understanding whether this pathway contributes to renal fibrosis in GN could have significant implications for monitoring and abrogating disease progression.

Methods: Wild type (WT) C57BL/6 mice were treated with sheep IgG on day 0. Nephrotoxic serum (NTS) or control IgG was then injected intravenously on day 3 to induce immune complex deposition at the glomerular basement membrane. Kidneys were harvested at day 9. Half of the kidney was fixed in formalin for histology and half was preserved in Trizol for qPCR. Paraffin-embedded slides were stained with fluorescent antibodies against the macrophage marker CD68 and the M2 macrophage marker Ym1. qPCR was performed to evaluate for macrophage markers and regulatory cytokines.

Results: Preliminary experiments confirm an influx of M2 macrophages in the glomeruli, as identified by the markers CD68 and Ym1 that occurs as early as 3 days after NTS injection. Furthermore, qPCR analysis of whole kidney tissue reveals an increase in transcripts of the cytokine IL-13, which is produced by M2 macrophages, and of Fizz1 and Ym1, two markers of alternative activation in macrophages.

Conclusions: This work identifies a clear population of M2 macrophages in inflamed kidneys during GN that can be identified by markers CD68 and Ym1 that occurs as early as 3 days after NTS injection. Furthermore, qPCR analysis of whole kidney tissue reveals an increase in transcripts of the cytokine IL-13, which is produced by M2 macrophages, and of Fizz1 and Ym1, two markers of alternative activation in macrophages.

Funding: This work was supported by National Institutes of Health Grant R01DK111058.

FR-PO125
Plasma from Patients with Anti-Glomerular Basement Membrane Disease Could Recognize Microbial Peptides
Jian-Nan Li,1 Xiao-Yu Jia, Zhao Cui, Ming-Hui Zhao. Renal Devisio, Dept of Medicine, Peking Univ First Hospital, Beijing, China.

Background: Infection has long been suspected as one etiology of anti-glomerular basement membrane (GBM) disease, however, the evidence is insufficient and the mechanism is unclear. Molecular mimicry to the T cell and B cell epitopes on α3(IV)NC1 domain of GBM as their targets is hypothesized in this study.

Methods: Microbe originated peptides were searched from UniProt database based on a previously defined critical amino acid motif within α3(IV)NC1, which is α3(IV)-like, with five critical amino acid residues, isoleucine137, tryptophan140, glycine142, phylalein143 and phenylalanine144. Seven human-infected microbial peptides were identified and were further synthesized. Circulating IgG and IgM antibodies against these peptides were detected using ELISA from plasma of 76 patients with anti-GBM disease.

Results: Four peptides were recognized by both IgG and IgM antibodies, and one peptide was recognized by IgG antibodies only. Peptides from Bacteroides, Saccharomyces cerevisiae, and Bifidobacterium thermophilum possessed the highest recognition frequency with the prevalence of 73.7%, 61.8% and 67.1% for IgG, and 56.6%, 44.7% and 67.1% for IgM, respectively.

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FR-PO126
Pathogenesis of Antimicrobial Peptides LL-37 and CpG-ODN in ANCA Associated Vasculitis Guangquan Xing, Nephrology Dept, Affiliated Hospital of Qingdao Univ, Qingdao, Shandong, China.
Background: We hypothesized that AAV patients have ANCA-producing B lymphocytes in the circulation, and that these cells can be triggered and prone to produce ANCA in response to LL-37 and (or) CpG-ODN of which related to infection.
Methods: 15 patients with AAV were enrolled. 16 patients with chronic bronchitis (CB) were selected as disease control groups. 15 cases of healthy people were as healthy control groups. PBMC collected from those groups were cultured and stimulated by LL-37 and (or) CpG-ODN for 7 days. The IFN-α and ANCA in vitro were measured by ELISA.
Results: The level of IFN-α in AAV group much higher than that in CB group, and that in healthy control group. The serum level of LL-37 in AAV group was much higher than that in CB group, and that in healthy control group. The level of ANCA in vitro was measured by ELISA. The serum level of IFN-α and LL-37 was measured also.
Results: The level of IFN-α in AAV group much higher than that in CB group, and that in healthy control group. The serum level of LL-37 in AAV group was much higher than that in CB group, and that in healthy control group. Also the level of ANCA in vitro was measured by ELISA. The serum level of IFN-α and LL-37 was measured also.
Conclusions: There was level of IFN-α in the peripheral blood of AAV patients. IFN-α could reach a higher level stimulated by LL-37 and CpG-ODN. ANCA production in vitro in AAV groups were statistically significantly higher than that in CB group and that in healthy control group.
Funding: Government Support - Non-U.S.

FR-PO127
Atypical Glycosylation of the Constant and Variable Domains of Immunoglobulin G from Patients with ANCA-Associated Systemic Vasculitides: Relation to Disease Activity Olivier Lardinois,1 Leesa Deterding,2 Caroline J. Poulton,1 Candace Henderson,1 Patrick H. Nachman,1 J. Charles Poulton,2 Ronald J. Falk,1 1UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC; 2Collaborative Mass Spectrometry Group, National Inst of Environmental Health Sciences, Research Triangle Park, NC.
Background: Anti-neutrophil cytoplasmic autoantibodies (ANCA) directed against myeloperoxidase (MPO) and proteinase 3 (PR3) are considered pathogenic in ANCA-associated vasculitides (AAV). The aim of the present study is to investigate the changes in Fe and Fab glycosylation with disease activity in detail, and examine the association of glycosylation aberrations with disease parameters in a cohort of AAV patients.

Methods: IgGs were isolated from serum samples from 30 patients with AAV and 23 control subjects. Isolated IgGs were digested with trypsin and the released peptides were analyzed for subclass-specific Fe glycosylation by LC-MS. Fab glycosylation was determined by fluorescence labeling and chromatography of glycans released by PNGase treatment. The hydrazide glycoprotein capture approach and MS were used to determine the exact localization of N-glycosylation on Fe and Fab fragments.

Results: IgG Fe glycosylation and sialylation of total IgG purified from plasma was significantly reduced in AAV patients compared to controls. The levels of galactosylated and sialylated glycans on Fe portion of total IgG from PR3-ANCA patient significantly increased during disease remission. In contrast, Fe N-glycans levels of total IgG from MPO-ANCA patient did not correlate with disease activity. Hydrazide capture and LC-MS/MS analysis identified six N-glycosylation sites on Fab fragments of anti-MPO specific IgGs.

Conclusions: Significant differences exist between MPO and PR3-ANCA diseases regarding the changes in amounts and types of glycans on Fe portion of total IgGs with disease activity. A major fraction of anti-MPO specific IgGs isolated from serum samples of MPO-ANCA patients harbor extensive glycosylation within the variable domain on the Fab portion. These differences may contribute to significant clinical differences in the disease course, severity, or relapse rate observed between the two diseases.
Funding: NIDDK Support

FR-PO128
Assessment of HLA-DPB1*04:01 and Time to Relapse in an Evenly Divided Cohort of PR3-ANCA and MPO-ANCA Vasculitis Patients Katherine G. Stember,1 Yichun Hu,2 Susan L. Hogan,2 Caroline J. Poulton,1 Candace Henderson,1 J. Charles Jennette,2,1 Ronald J. Falk,3 Meghan E. Free,3 Dominic J. Ciavatta,2,3 1Pathology and Laboratory Medicine, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; 2UNC Kidney Center, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; 3Genetics, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.
Background: GWAS identified HLA-DPB1 as a risk factor for ANCA-associated vasculitis (AAV), specifically for patients with PR3-ANCA. Whether specific HLA-DPB1 alleles predict patient outcome is unclear. One recent study (Arthritis & Rheum. 2016 DOI 10.1002/art.39620) found that carriers of HLA-DPB1*04:01 (DPB4) had a significantly increased risk of relapse compared to non-carriers, regardless of ANCA subtype.
Methods: We sequenced the HLA-DPB1 gene in 203 patients with AAV. Differences in DPB1 alleles (null, heterozygous, or homozygous) between ANCA subtype were analyzed by Fisher’s exact test. Kaplan-Meier estimates and log rank test were used to analyze the relapse probability of DPB4 genotypes in all AAV patients and ANCA subtypes alone.
Results: In our cohort the DPB4 allele frequency was 81% and 68% among patients with PR3-ANCA and MPO-ANCA, respectively, compared to 43% among US Caucasians (Allele Frequency Net Database). Patients with PR3-ANCA were more likely to be homozygous for DPB4 compared to patients with MPO-ANCA (p=0.0012). In our cohort of 96 PR3-ANCA and 107 MPO-ANCA patients, the risk of relapse was not different based on DPB4 genotype (p=0.5). When stratified by ANCA subtype, PR3-ANCA patients showed a trend toward increased risk of relapse in DPB4 heterozygotes and homozygotes compared to non-carriers (p=0.06). In contrast, MPO-ANCA showed no difference in risk of relapse, regardless of DPB4 genotype (p=0.6).
Conclusions: Contrary to previous work, in our cohort of AAV patients, DPB4 carriers did not have a significantly greater probability of relapse. The difference may be a consequence of 65% MPO-ANCA patients in our cohort compared to 25% in the previous cohort. We conclude that DPB4 carrier status may be informative for PR3-ANCA patients, but is not predictive of relapse in a combined or MPO-ANCA only cohort.
Funding: NIDDK Support

FR-PO119
Circulating Complement Activation Products in MPO and PR3 ANCA Vasculitis Eve Wu,1 Sonia Brigitte Boyer,1 Elizabeth Alderman McNimmis,1 Yichun Hu,2 Susan L. Hogan,2 Caroline J. Poulton,1 Peiqi Hu, Hong Xiao, Ronald J. Falk,3 J. Charles Jennette, Patrick H. Nachman,3 Donna O. Bunch,1 Unv of North Carolina.
Background: An anti-MPO murine model suggests complement activation is important in ANCA-associated vasculitis (AAV). Correlation between complement activation products and disease activity has also been shown in an MPO-AAV cohort. These observations have not been confirmed in others, and complement activation has not been studied in PR3-AAV.
Methods: Subjects included 31 active AAV (BV=3), 14 MPO, 17 PR3, 36 remission AAV (BV=0, 15 MPO, 21 PR3), and 23 age- and gender-matched healthy controls (HC). Plasma samples were obtained on ice in EDTA tubes including no or 100mcg/mL of futhan. Propensity score (PS) and 1:Bc, 1:C5a, 1:C5b-9 were measured by ELISA. No futhan samples were used for analyses except Bb and C5b-9, where futhan significantly affected values. Group comparisons were made using Wilcoxon two-sample test. After Bonferroni correction, p<0.0083 was considered statistically significant.
Results: In BV=3, AAV, Bb, C3a, and C5b-9 were higher in active disease compared to HC (Table, median values). Bb and C3a were higher in remission compared to HC. C5a in remission was lower than in active disease, but Bb did not differ by disease state. C5a was not different. In MPO-AAV, C5a, C5a, and C5b-9 were higher in active disease compared to HC. Bb and C3a were higher in remission compared to HC, but did not differ from active disease. There was no difference in propensity among groups.

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to suppress anti-CD3-induced T-cell proliferation. In patients with inactive AAV, B-cells showed a diminished production of GrB upon IgG+IgM CD40L stimulation in presence of IL-21 (AAV vs. HC; IgG+IgM: 21.1±17.8% vs. 29.4±15.2%, p=0.0427; CD40L: 3.4±2.6% vs. 6.5±3.8%, p=0.0111).

**Conclusions:** Depending on the cytokine environment, a separate GrB producing B-cell population can be induced. GrB confers cytotoxic capacity to B-cells and allows suppression of T-cells. Thus, GrB**pos** B-cells can be regarded as an additional Breg subpopulation. This GrB**pos** B-cell population is diminished in patients with ANCA-vasculitis.

**Funding:** Private Foundation Support

**FR-PO132**

**Investigating the Role of MCT Pathway in ANCA Associated Vasculitis**

**Fernanda Florez-Barros,** 1 Graham Paul Belfield, 2 Alan D. Salama, 1 Centre for Nephrology, UCL Medical School, Royal Free Hospital, Univ College London, London, London, United Kingdom; 2 Respiratory, Inflammation, Autoimmunity, iMed, AstraZeneca, Sweden.

**Background:** Monocarboxylate transporters (MCT) are critical for exporting lactate from actively proliferating cells and if inhibited lead to an intracellular accumulation of lactate and cell death. MCT1 inhibitors are currently in clinical oncology trials, but there is only limited knowledge of their role in the context of kidney inflammation and autoimmune disease. The aim of this study was to investigate MCT1 inhibition in vasculitis and glomerulonephritis.

**Methods:** *in vivo* experiments with samples from acute and remission ANCA vasculitis patients and healthy controls. We studied MCT1&4 expression in B and T cells, and also the effect of MCT1 inhibition on cytokine production and changes in B and T subsets. *In vitro* experiments using the MCT1 inhibitor in the nephrotoxic nephritis model, evaluating the potential benefit on different parameters of renal function.

**Results:** a) There was a significantly lower expression of MCT1 in regulatory B cells compared with non-regulatory B cell subsets in patients with acute disease (p<0.05).

**Conclusions:**}

**FR-PO131**

**Annexin A1 Plays a Protective Role in Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibody Associated Glomerulonephritis**

**Takeshi Fujita,** 1 Poh-Yi Gan, 2 A. Richard Kitching, 3 Stephen R. Holdsworth, 5 *Nephrology, Hirosaki Univ, Hirosaki, Aomori, Japan; 2 Dept of Medicine, Monash Univ, Melbourne, Victoria, Australia; 3 Dept of Nephrology, Monash Univ, Melbourne, Victoria, Australia.

**Background:** Myeloperoxidase-ANCA associated glomerulonephritis (MPO-ANCA GN) results from autoimmunity to MPO. To date, corticosteroids are still first line therapy despite their adverse effects. Annexin A1 (AnxA1) is an endogenous anti-inflammatory protein ubiquitously expressed by glomerular cells and significantly overexpressed in inflammatory diseases. This study aimed to assess the role of AnxA1 and its importance in immunomodulating this disease model.

**Methods:** We compared the development of anti-MPO autoimmunity and the extent of induced GN in C57BL/6 (WT, n=8) and AnxA1**−/−** (n=7) mice developing experimental MPO-ANCA GN. MPO autoimmunity was induced by immunizing mice with MPO in Freund’s adjuvant and GN triggered using subnephritic dose of anti-glomerular basement membrane globulin.

**Conclusions:** Annexin A1 (AnxA1) is an endogenous anti-inflammatory protein ubiquitously expressed by glomerular cells and significantly overexpressed in inflammatory diseases. This study aimed to assess the role of AnxA1 and its importance in immunomodulating this disease model.
Results: ANxA1 deficiency significantly augments MPO-ANCA GN. ANxA1−/− mice developed more severe functional renal injury as measured by urinary albumin/creatinine ratio (2.0±0.5 vs 5.1±0.0, P<0.01) and structural glomerular damage (glomerular segmental necrosis; 21±2 vs 60.3%, P<0.0001), compared to WT mice. Additionally, ANxA1−/− mice had significantly increased infiltration of glomerular macrophages (0.2±0.05 vs 0.5±0.07 cells/glomerular cross section [c/gcs], P<0.05), CD4+ T cells (0.4±0.2 vs 0.8±0.2 c/gcs, P<0.05) compared to WT mice. To determine the role of ANxA1 in the development of systemic MPO-ANCA GN, spleens from WT and ANxA1−/− mice with induced MPO-ANCA GN were assessed. ANxA1−/− mice had increased numbers of activated splenic CD4+ T cells (CD4+CD44+; 26±2 vs 34±2%, P<0.05) and CD69+ T cells (CD8+CD44+; 20.0±5.5 vs 30.1±0.001 and CD8+CD69+; 13±2 vs 20.1±1, P<0.05) compared to WT mice.

Conclusions: This study highlights the importance of Annexin A1 in modulating the extent of MPO-ANCA GN and deficiency in Annexin A1 increases the severity of GN.

Funding: Government Support - Non-U.S.

FR-PO134

Deoxyribonuclease 1 Treatment Attenuates Neutrophil Extracellular Trap Formation, Leukocyte Infiltration and Inflammation in Experimental Anti-Myeloperoxidase Glomerulonephritis

Kim M. O’Sullivan,1 Poh-Yi Gan,1 A. Richard Kitching,2,3 Stephen R. Holdsworth,1,2,3 Centre for Inflammatory Diseases, Dept of Medicine, Monash Univ, Clayton, Australia; 2Dept of Nephrology, Monash Health, Clayton, Australia.

Background: Accumulating evidence suggests that a dysregulation of neutrophil extracellular trap (NETs) could be associated with the pathogenesis of anti-neutrophil cytoplasmatic antibody (ANCA) vasculitis. This study investigates the contribution of NETs in the development of experimental anti-myeloperoxidase ANCA associated glomerulonephritis (MPO-ANCA GN), and investigates the therapeutic possibility of deoxyribonuclease 1 (DNase1) to disrupt NET formation in vivo.

Methods: Experimental MPO-ANCA GN was induced using a standard protocol, by MRL-lpr/lpr mice intraperitoneally injected with NEP (0.02 mg/mouse) and MPO (1 mg/mouse) associated with glomerular basement membrane (GBM) proteins. DNase1 (1 mg/mouse) was administered intraperitoneally to mice at day 0, 7, and 14 after the induction of MPO-ANCA GN. The extent of NETs was determined by ELISA, cumulated neutrophil DNA, lactate dehydrogenase and MPO-specific recall responses (2.7±0.6 vs 7.5±0.8%). Leukocyte infiltration was evaluated by immunostaining and flow cytometry. Inflammation was assessed by Human Amniotic Epithelial Stem Cells (hAECs) co-culture with murine macrophages and neutrophils. Histological assessment of kidneys demonstrated prominent segmental necrosis in the saline treated group (38±5.6%) compared to DNase 1 treated group (16±2.4%, P<0.05).

Results: Delayed Type Hypersensitivity assessed by footpad swelling was significantly reduced in the DNase 1 treated group (0.4±0.06Δmm, p<0.05).

Conclusions: These findings indicate a specific function of the IL-17C/IL-17RE axis in regulating renal autoimmunity.

Funding: Government Support - Non-U.S.
**Methods:** Using quantitative mass spectrometry, we analyzed proteomes from mice control and treatment groups. Treatment groups included: 1) controls, 2) NTN, 3) NTN + PKC-α inhibitor Ro-32-0432 given i.p. after induction of nephritis on day 2, and 4) NTN + PKC-α inhibitor conjugated to the human mAb F1.1, directed against α3(IV) collagen. Mitochondrial function was investigated by measuring mitochondrial respiration (assessed as OCR), and glycolytic lactic acid production, as assessed by ICAR) in cultured kidney endothelial cells.

**Results:** Combined analysis of microdissected cortices identified total of 4187 proteins in all four samples. Functional protein groups most affected by NTN were mitochondrial proteins associated with respiratory processes, such as ATP synthase, Cytochrome b-c1 complex, and superoxide dismutase, which were down regulated. By contrast, expression of NTN mice (fold changes compared to the same protein levels found in healthy mice were 0.52±0.15), while their expression was restored with PKC-α inhibition (both systemic and glomerular specific, with fold changes 0.90±0.14, p<0.054E-14), suggesting a role for PKC-α in maintaining coupled oxidative phosphorylation. In cultured kidney endothelial cells, NTN reduced basal oxygen consumption rates (OCR) from 225 pmol/min to 185 pmol/min and increased ECAR from 42 to 62 mgH2O/min. The PKC-α inhibitor (at 10mM and 50mM) normalized NTN mediated changes in OCR and ECAR levels.

**Conclusions:** The results suggest that PKC-α is an important regulator of proteinuria development in mice, and zebrabfish. It exerts its function through modulation of its target nephronectin. miR-378a controlled nephronectin expression is a novel mechanism for proteinuria development in active glomerular diseases in patients.

**Funding:** Private Foundation Support

**FR-PO141**

**Podocyte Specific ZHX2 Overexpression Worsens Focal Segmental Glomerulosclerosis and Improves Minimal Change Disease**

**Maria Del Nodal Avila, Hector Donoro Blazquez, Camille E. Mace, Caroline B. Marshall, Lionel C. Clement, Sunant S. Chugh. Div of Nephrology, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL.**

**Background:** Zinc fingers and homeoboxes (ZIX) transcriptional factor family are major regulators of podocyte gene expression and are mostly expressed as heterodimers bound to transcriptional response elements of ZHX2 podocyte-specific transgenic rats. ZHX2-ZHX1 heterodimers are present mostly in the podocyte body and ZHX2-ZHX3 in the slit diaphragm. Loss of heterodimerization, is common in podocyte diseases and promotes nuclear entry of ZHX proteins.

**Methods:** To induce loss of heterodimerization of ZHX2 related complexes, podocyte-specific ZHX2 transgenic rats were generated. Following baseline characterization, we induced Adriamycin nephrosis, a model of FSGS, and puromycin aminonucleoside, a model of MCD.

**Results:** Three founder lines of ZHX2 podocyte-specific transgenic rats were characterized (TG 14, TG 142, TG 144). Glomerular RNA expression of ZHX2 in heterozygous rats showed a fold-increase of 1.13 ± 0.10 in TG 14, 1.50 ± 0.09 in TG 142 and 4.09 ± 0.69 in TG 144. Confocal characterization of heterogeneous TG 144 rats revealed increase expression of ZHX2 in podocyte cell membrane distribution. Expression of ZHX3 and ZHX1 was unchanged. None of the ZHX2 transgenic lines had proteinuria at baseline. When compared with Sprague Dawley rat, NPHS2-promoter/ZHX2 TG rats had more proteinuria and more severe glomerular disease than controls (TG 144 and TG 142 > WT; proteinuria/18h: 310.4 ± 41.5 mg, 208.4 ± 29.9 mg and 102.6 ± 20.3 mg, respectively) (p<0.01). Also, backcross of the ZHX2 transgene into the Buff/Mna background, a model of FSGS, for 8 generations was associated with more proteinuria (301.9 ± 27.4 mg in 18 h) than the Buff/Mna at age 8 month (193.8 ±23.7 mg in 18 h) (p<0.05). By contrast, proteinuria in PAN was less severe 10 days after treatment (TG 144 and TG 142 < WT; proteinuria/18h: 178.9 ± 13.4 mg, 169.1 ± 37.8 mg and 351.7 ± 33.9 mg, respectively)(p<0.05).

**Conclusions:** Loss of heterodimerization caused by overexpression of ZHX2 in podocytes had a protective effect in MCD but worsens the development of FSGS. These findings suggest a major role of ZHX2 in nephritic syndrome.

**Funding:** NIDDK Support, Private Foundation Support

**FR-PO140**

**Podocytes Regulate Expression of Glomerular Basement Membrane Protein Nephronectin via miR-378a in Glomerular Diseases**

**Jenny C. Nystrom,4 Jeremy H. Miner,3 Johan Lorenzen,3 Thomas Thum1 and Mario Schieffer.1 1Dept of Medicine/Nephrology, Hannover Medical School, Hannover, Germany; 2Dept of Physiology and Dept of Nephrology Sahlgrenska Academy, Washington Univ School of Medicine, Univ of Gothenburg, Gothenburg, Sweden; 3Div of Nephrology, Washington Univ School of Medicine, St. Louis.**

**Background:** MicroRNAs (miRs) play an important role in gene regulation and therefore seem to be promising candidates involved in glomerular diseases.

**Methods:** We used the zebrafish and mouse model to investigate the role of miR-378a in glomerular diseases.

**Results:** We identified miR-378a, as specifically increased in urine samples of patients with nephrotic primary membranous glomerulonephropathy, focal segmental glomerulosclerosis and minimal change disease. Nephronectin is a predicted target of miR-378a, which is differentially located in the glomerular basement membrane (GBM). In patients, glomerular miR-378a expression was increased and glomerular nephronectin levels were reduced in focal segmental glomerulosclerosis and membranous glomerulonephropathy. In our zebrafish model, nephronectin knockdown by morpholino or miR-378a overexpression caused edema, proteinuria and structural impairments of the glomerular filtration barrier with podocyte effacement and widening of the lamina rara interna of the GBM.

**Conclusions:** In mice pharmacological overexpression of miR-378a confirmed the phenotype with increased levels of albuminuria, podocyte effacement and altered expression of GBM proteins.

**Funding:** NIDDK Support

**FR-PO139**

**Loss of DNA Methylation Triggers Transcription of Silenced Laminin Genes in Aging Kidneys**

**Oleg N. Denisenko, Karol Bomszytk. Medicine, Univ of Washington, Seattle, WA.**

**Background:** Aging kidney is associated with aberrant gene expression of extracellular matrix components that leads to gradual structural changes and progressive decrease in glomerular filtration rates. We examined contribution of epigenetic changes to dysregulation of laminin genes in aging rat kidneys.

**Methods:** RT-qPCR was used to examine renal expression of all 11 laminin genes in kidneys from 4, 24 and 28 months old (mo) F344 rats, and from 4, and 30 mo FBN-F1 hybrid rats. Chromatin immuno-precipitation (ChIP) and DNA methylation (MeDIP) assays were used to assess renal histone and DNA modifications, respectively.

**Results:** While no changes were detected in the abundant laminin transcripts LAMA2, LAMB2, LAMC1, silenced genes LAMA3, LAMB3, and LAMC2 were transcriptionally upregulated in old animals (p<0.05). ChIP and MeDIP analyses revealed reduction in the density of silencing marks H3K27m3 and DNA methylation (5mC) at Lamc2 gene in old rats. Chromatin immuno-precipitation (ChIP) and DNA methylation (MeDIP) assays were used to assess renal histone and DNA modifications, respectively.

**Conclusions:** The results suggest that PKC-α is an important regulator of antibody mediated nephronectin inhibition that targets inhibition of this enzyme protects the kidneys from the damage associated with severe inflammation by restoring oxidative phosphorylation at the glomerular cell level. This has therapeutic implications for treatment of human disease.

**Funding:** NIDDK Support

**In vivo**
we developed 2PGM and coupled this with simplified nanoproteomics (SN), developed at the Pacific Northwest National Laboratory, to test the hypothesis that LR2 pigments may be quantified in glomerular filtrate.

Methods: Cortical glomeruli were accessed in anesthetized C57BL/6 mice with 2 photon guidance using the novel technique. Imaging excluded vascular injury. GF was aspirated, frozen, and underwent in-column trypsin digestion and inline LC/MS analysis with MS identification against the Uniprot mouse proteome. Urine from mice with mosaic PT deletion of LRP2 (LRP2 fl/fl;ApoE cre) was assessed by conventional proteomics to confirm the findings obtained with novel techniques.

Results: Cortical glomeruli (depth 63±7µm) were accessed with 100% survival. In GF, 18 proteins were identified (MW 57.5±12kD), albumin the most abundant, consistent with GF. Urine of LR2 fl/fl;ApoE cre mice was selectively enriched in 320 proteins relative to cre-control, including all known LR2 pigments. 38% of the GF identifications were among the 320 LR2 deletion-selective proteins.

Conclusions: We identified known and possible LR2 ligands in glomerular filtrate using novel methodology. 2PGM allows access to subsurface glomeruli, enhancing micropuncture. 2PGM coupled with SN may provide important data regarding glomerular protein filtration.

FR-PO143

Podocyte-to-Podocyte Propagation of Damage Takes Place in an Accelerated Manner in Males

Masahiro Okabe,1,2 Masaru Motojima,1 Yoichi Miyazaki,1 Takashi Yokoi,3 Taji Matsusaka,4 1Tokai Univ School of Medicine, Isehara, Japan; 2Jikei Univ School of Medicine, Tokyo, Japan.

Background: Our recent studies demonstrated that injury incurred in a fraction of podocyte population causes secondary damage in other initially intact podocytes. This podocyte-to-podocyte propagation of damage may drive the progressive nature of glomerulosclerosis. Since male patients commonly develop renal failure faster than females following various kidney diseases, we hypothesized that male podocytes are more susceptible to this secondary injury.

Methods: We established a new mosaic mouse model in which approximately 50% of podocytes express hCD25 and the other podocytes express EGFP. Injection with hCD25-targeted immunotoxin, LMB2, injured not only hCD25-positive but also negative podocytes, and the mice developed FSGS without increase in blood pressure. To study impact of sex on secondary podocyte injury, five male and five female mosaic mice (28 days) were injected with LMB2.

Results: FACS analysis in mosaic mice without LMB2 revealed that the proportion of hCD25-positive podocytes was not different between the male and female mice. Seven days after the induction of podocyte injury, urinary Alb/Creatinine ratios (ACR) were similarly increased in both groups (male 8.4±1.14 vs. female 8.5±1.12 mg/mg). Thereafter, the male mice continuously showed high ACR (89.2±50 at day 21) and two died at day 18 and 24. In contrast, ACR in the female mice decreased (19.2±16 at day 18, P<0.01 vs. male). Renal histological analysis at day 25 revealed that male glomeruli showed severer sclerosis, higher desmin expression, and fewer EGFP-positive cells than female glomeruli. Glomerular nephron was diminished globally in the male mice while only segmentally in the female mice. To verify that LMB2 causes similar primary podocyte injury in males vs. females, NEP25 mice (5 males and 5 females), in which all podocytes express hCD25, were injected with LMB2. No sex difference was observed in proteinuria, glomerulosclerosis, nephrin or desmin expressions.

Conclusions: Propagation of podocyte-to-podocyte injury takes place more aggressively in males, which may underlie more rapid progression of renal failure in male than female patients with kidney diseases.

Funding: Government Support - Non-U.S.

FR-PO144

The Effect of Maternal Low Protein Diet on Podocyte Endowment


Background: It is well established that an adverse feto-maternal environment such as a maternal low protein diet (LPD) can result in low nephron endowment – a permanent deficit in nephron number. Given that podocytes are post-mitotic cells with limited capacity for regeneration, we investigated whether a maternal LPD also resulted in reduced podocyte endowment.

Methods: Kidneys were collected at postnatal day 21 in rat offspring exposed to a maternal LPD (8%) or normal protein diet (NPD; 20%) starting at 3 weeks prior to pregnancy until weaning. Total nephron number was estimated by design-based stereology. Podocyte number was determined using a combination of immunofluorescence, confocal microscopy and optical clearing; and glomerular volume by model-based stereology. Podocyte density was also calculated. A total of 300 whole glomeruli were analysed. 10 glomeruli from the outer cortex and the inner cortex of LPD and NPD rats were sampled for each diet condition. Podocyte number was determined by 60% in LPD offspring (P<0.001; 66% for outer and 50% for inner). Inner glomeruli were larger and had lower podocyte densities than glomeruli from the outer cortex in both NPD and LPD rats (P<0.001 for all). While there was no zonal difference in podocyte number in NPD rats, there were 14% more podocytes in glomeruli from the inner cortex in LPD rats (P<0.001).

Conclusions: This is the first report that podocyte endowment is directly affected by an adverse feto-maternal environment. The observation that outer glomeruli in LPD rats had particularly low podocyte number suggests glomeruli formed in the latter stages of nephrogenesis were particularly affected. Studies focused on the adult consequences of low podocyte endowment are underway in our laboratory.

FR-PO145

Podocyte Number Increases after Birth in Mice and Humans

Víctor G. Puelles,1 James William Van der Wolde,1 Luisa A. Cullen-McEwen,2 Peter G. Kerr,3 David J. Nikolic-Paterson,3 John F. Bertram.1 1Dept of Anatomy and Developmental Biology, Monash Univ, Melbourne, Australia; 2Nephrology, Monash Medical Centre, Melbourne, Australia.

Background: Podocyte depletion is a direct cause of glomerulosclerosis and is observed in a wide range of glomerular diseases. However, the presence of postnatal podocyte gain remains a controversial topic.

Methods: Kidneys were collected from PodcreiDTR mice injected with 50ng/kg of diphtheria toxin (DT) and age-matched controls (6-14 weeks of age). Total podocyte number per glomerulus was obtained using a combination of immunofluorescence, optical clearing and confocal microscopy. A total of 740 whole glomeruli were analysed (20 per mouse). Podocyte number was also estimated in human nephrectomy (n=3 adults) and autopsy tissue (n=18 children) using model-based stereology in 10-20 glomeruli per subject for a total of 350 glomeruli.

Results: Podocyte number increased approx. 20% in control mice from 6 to 14 weeks of age (P<0.0001). Podocyte number increased by 13% (P<0.0001) 1 week after DT injection (7 weeks of age). However, by week 14 of age, podocyte number increased by 12% (P<0.0001) in DT-injected mice. While there was no statistical difference in podocyte number between 6-week control mice and 14-week DT-injected mice (P=0.59), the difference between DT-injected and age-matched control mice at 14 weeks remained at 15% (P<0.0001). Body weight increased in both control (37%; P<0.001) and DT-injected mice (47%; P<0.001). Glomeruli from children 3-36 months of age and adults contained approx. 30% more podocytes than children 0-2 months of age (P<0.0001). Podocyte number was similar in children 3-36 months of age and adults. Body surface area increased dramatically in children 3-36 months of age (50%; P<0.001), 12-36 months of age (154%; P<0.01), and adults (80%; P<0.001) compared to children 0-2 months of age.

Conclusions: These findings suggest that podocyte number increases by 20-30% after birth in both mice and humans. This increase in podocyte number may align with normal physiological growth in the early period of postnatal life. Future studies using cell fate tracking are urgently needed to confirm these findings.

FR-PO146

Podocyte Injury Is Involved in Albuminuria in the Rat Model of Hyperuricemia

Shin-Ichiro Asakawa, Shigeru Shibata, Daigo Toyokoy, Yosuke Kawamorita, Yoshifuru Tamura, Yoshihide Fujigaki, Shunya Uchida. Dept of Intern Med, Teikyo Univ School of Medicine, Tokyo, Japan.

Background: We have recently shown that high level of serum uric acid (UA) may deteriorate kidney function in CKD patients using propensity score analysis (Uchida S et al. PLoS One 2015). In the present study, we have evaluated the kidney injury and its mechanism in a rat model of hyperuricemia.

Methods: Male Sprague-Dawley rats received 2% oxonic acid (OA group) as a uricosuric inhibitor to increase serum UA level. Blood pressure and urinary albumin excretion were measured for 8 weeks during the experiment. Urine 8 weeks, kidney histology and urine albumin excretion were evaluated by immunostaining.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
**Results:** Rats received OA had significantly higher levels of uric acid than control group (1.3 ± 0.1 mg/dl vs. 0.7 ± 0.1 mg/dl, n=10; P < 0.002). OA group showed time-dependent increase in systolic blood pressure and thickening of accurate arteries andafferent arterioles as assessed by a smooth-muscle actin staining. Of note, OA caused significant increase in urinary albumin excretion, and the immunostaining of desmin, a podocyte injury marker, showing that OA induced podocyte injury in this OA model was further confirmed by electron microscopy. To address the mechanism of UA-induced kidney injury, we analyzed the levels of ROS formation, the oxidative stress marker, and cell injury shown by increased 8OHdG. Moreover, urinary 8OHdG was highly correlated with UAE (R² = 0.49, p<0.01), suggesting the importance of oxidative stress as a cause of podocyte injury. However, oral administration of tempol, a potent antioxidant, decreased blood pressure but not UAE, suggesting that the cause of UAE is distinct from that of blood pressure and is relevant to podocyte injury.

**Conclusions:** High levels of serum UA can cause arteriopathy/arteriolopathy and albuminuria, the latter of which is attributable to podocyte injury. Oxidative stress induced by higher serum UA may underlie the mechanism of the kidney injury.

**FR-PO147**

miR-21 Mediates Podocyte Injury and Mitochondrial Dysfunction via Targeting Mitochondrial Gene Dnm1l

Aihua Zhang, 1 Mi Bai, 1 Guixia Ding, 1 Yue Zhang, 1 Songming Huang, 1 Zhanjun Jia. 2 Depart of Nephrology, Nanjing Children’s Hospital affiliated to Nanjing Medical Univ, Nanjing, China; 1Nanjing Key Lab of Pediatrics, Nanjing, China.

**Background:** Emerging evidence indicated that the maintenance of mitochondrial structure and function is critical for preventing podocyte injury. Recently, some miRNAs have been proven to play roles in modulating mitochondrial function. Our preliminary data from a miRNA array analysis showed a remarkable elevation of renal miR-21 in a podocytopathy mouse model. By bioinformatics analysis, mitochondrial Dnm1l was predicted to be a direct target of miR-21. Thus we conducted experiments to determine the role of miR-21 in podocyte injury and mitochondrial dysfunction.

**Methods:** Purumycin aminonucleoside (PAO) or Adriamycin (ADR) was used to induce podocyte injury in cultured podocytes or animals. Genetic approaches were applied to define the roles of miR-21 in mediating podocyte injury and mitochondrial dysfunction in vitro and in vivo.

**Results:** Following PAN treatment in SD rats and podocytes, miR-21 was dramatically induced by 4.8-fold in kidney and 4.2-fold in cells, respectively. Strikingly, overexpression of miR-21 alone in podocytes induced mitochondrial dysfunction evidenced by the increase of ROS (2.1±0.6 folds) and decrease of mitochondrial membrane potential (MMP) (-27%) with mitochondrial DNA (mtDNA) copy number (-24%), and cell injury shown by increased apoptosis (+81%) and decreased nephrin (-70%) and podocin (-45%) expression. By luciferase reporter assay and miR-21 overexpression, we identified that Dnm1l is a direct target of miR-21. And overexpression of Dnm1l could largely abolish miR-21 effects on inducing mitochondrial dysfunction and podocyte injury. Moreover, the miR-21 inhibitor attenuated PAN/ADR-induced podocyte injury in both in vitro cells and in vivo animals shown by 70% blockade of albuminuria and remarkable amelioration of podocyte injury markers in line with markedly attenuated mitochondrial dysfunction.

**Conclusions:** miR-21 mediated podocyte injury and mitochondrial dysfunction via targeting mitochondrial gene Dnm1l.

**FR-PO148**

Succinate Receptor GPR91 Regulates Mitochondrial Metabolism and Contributes to Diabetic Nephropathy Progression

Ju Young Moon, 1,2 Dorinne Desposito, 1 Anne Riquer-Brison, 1 Bahram Nadim, 1 Janes Petri-Pedrì. 1 Dept of Physiology and Biophysics, Univ of Southern California, Los Angeles, CA; 2 Dept of Internal Medicine, College of Medicine, Kyung Hee Univ, Seoul, Korea.

**Background:** Succinate is traditionally known as an intermediate of the mitochondrial citric acid (TCA) cycle, but its novel signaling role as a ligand of the cell membrane GPCR GPR91 receptor (also called SUCNR1) is emerging. Succinate and GPR91 have been implicated in metabolic diseases including hyperoxia (sclerosis), lipolysis (obesity), and diabetic nephropathy (DN), however the pathophysiological role of GPR91 signaling in DN has been elusive. The purpose of the studies was to validate the importance of GPR91 in DN, and to investigate the pathomechanisms of succinate/GPR91 signaling. We hypothesized the genetic GPR91 inhibition attenuates the progression of DN by regulating mitochondrial metabolism and hypoxia response in the kidney.

**Methods:** Our study included four mouse groups: 1) C57BL6 (Wild type, WT CON); 2) C57BL6/Stz-LNAME (KO CON); 3) C57BL6/Stz-LNAME (KO STZ CON); and 4) C57BL6/Stz-LNAME (KO STZ CON). Intravitreal photomicroscopy was used to measure mitochondrial metabolism in the intact kidney in vivo, by quantitatively visualizing mitochondrial ROS generation (using Mitoxon) and depolarization of the mitochondrial membrane potential (using MitoTracker-Red).

**Results:** We found significant reductions in hyperglycaemia-induced mitochondrial ROS generation and depolarization of the mitochondrial membrane potential in distal tubular epithelial cells and is nontenous and is resistant to GPR91 KO. GPR91 KO mice showed significantly decreased intertubular cast formation and glomerular sclerosis index. GPR91 mice, however, had significantly higher levels of nephrin mRNA and protein in the kidney in response to CKD.

**Conclusions:** GPR91 deficiency resulted in a decrease in proteinuria and improved glomerular structure as well as increased nephrin expression. These findings indicate GPR91 inhibition as a mechanism to maintain glomerular integrity. Funding: Government Support-MOP-133484.

**FR-PO150**

CHOP Deficiency Inhibits Proteinuria by Promoting Nephrin Expression in a Mouse Model of Chronic Kidney Disease

Zahraa Mohamed-Ali, 1 Mandeeep K. Marwah, 1 Chao Lu, 1 Kjetil Ask, 1,2 Jeffrey G. Dickhaut. 1,2 Health Sciences, McMaster Univ, Hamilton, ON, Canada; 1Nephrology, St. Joseph’s Healthcare Hamilton, Hamilton, ON, Canada; 1Firestone Inst for Respiratory Health, St. Joseph’s Healthcare Hamilton, Hamilton, ON, Canada.

**Background:** CHOP (GADD153/DDIT3) is a transcription factor that is upregulated during endoplasmic reticulum (ER) stress in chronic kidney disease (CKD). CHOP impacts areas of chronic kidney disease such as inflammation, apoptosis, and fibrosis. CHOP is shown to be preferentially translated. Therefore, we hypothesized that CHOP deficiency would result in higher nephrin expression, a more intact glomerular structure, and lower proteinuria in response to CKD.

**Methods:** Our model of CKD was based on reduced renal mass and Angiotensin II/DOCA infusion in C57BL/6 male mice. CHOP deficient mice on the C57BL/6 genetic background were used to test the effect of CHOP knockout in the CKD model. CKD was assessed using blood pressure and 24h total urinary protein and albumin excretion. On day 21 of the model, mice were sacrificed. PAS staining was used to evaluate renal pathology and damage. Nephrin mRNA levels were measured using Nanostring analysis and nephrin protein levels from renal tissue lysates.

**Results:** In response to the CKD model, both CHOP+ and wild type (WT) mice showed similar significant increases in systolic and diastolic blood pressure. However, CHOP+ mice showed significantly lower proteinuria and albuminuria. In addition, CHOP deficiency significantly decreased intertubular cast formation and glomerular sclerosis index. CHOP+ mice, however, had significantly higher levels of nephrin mRNA and protein in the kidney in response to CKD.

**Conclusions:** CHOP deficiency resulted in a decrease in proteinuria and improved glomerular structure as well as increased nephrin expression. These findings indicate CHOP inhibition as a mechanism to maintain glomerular integrity. Funding: Government Support-MOP-133484.

**Funding:** Government Support - Non-U.S.
FR-PO151

Caspase-1 Activation Contributes to Hypertension-Induced Glomerular Injury and Focal Segmental Glomerulosclerosis 
Jinghui Luo,1 Yingbao Yang,1 Stephanie Wylie,1 Tamra J. Reed,2, J. Michelle Kahnleberg,2 Jeffrey B. Hodglin.2 1Pathology, Univ of Michigan; 2Rheumatology, Univ of Michigan, Ann Arbor, MI.

Background: Hypertension is a leading cause of end-stage kidney disease and a significant determinant of focal segmental glomerulosclerosis (FSGS). However, the cellular and molecular responses to glomerular hypertrophy are not well understood. Recent studies highlight the inflammation in the pathogenesis of diabetic nephropathy and related podocyte injury. We find a robust upregulation (priming) of inflammasome-related gene expression in glomeruli of diabetic and non-diabetic patients with FSGS and/or hypertension. We hypothesize that caspase-1 activation contributes to hypertension-mediated albuminuria and FSGS.

Methods: Caspase-1 knockout (KO) and wildtype (WT) BALB/c mice (n=8-10 per group) were uninephrectomized, implanted with osmotic minipumps releasing Ang2 (1.2 ug/kg/min), and given 1% salt water for 4 weeks (wks). Control groups received sham, saline infusion, and normal water. Blood pressure (BP) and albumin/creatinine ratio (ACR) were measured at 2-wk intervals and kidneys harvested for histology. Immortalized human podocytes were treated with Ang2, LPS, +ATP to investigate caspase-1 activation.

Results: Ang2 similarly elevated BP in both WT and KO mice at 2 and 4 wks versus control. At 2 weeks, ACR was increased in both groups (10mg/kg), however ACR in WT >doubled by 4 wks, whereas KO mice remained stable (p<0.01). Histologic analysis revealed 3-fold more FSGS in Ang2 treated WT vs KO mice (p=0.05). In cultured podocytes, Ang2 alone (500nM & 1mM) activated caspase-1 6-8-fold vs controls, and 8-10-fold combined >doubled by 4 wks, whereas KO mice remained stable (p<0.01). Histologic analysis revealed 3-fold more FSGS in Ang2 treated WT vs KO mice (p=0.05). In cultured podocytes, Ang2 alone (500nM & 1mM) activated caspase-1 6-8-fold vs controls, and 8-10-fold combined >doubled by 4 wks, whereas KO mice remained stable (p<0.01).

Conclusions: Caspase-1 loss significantly abrogates albuminuria and FSGS in models of hypertension, and Ang2 primes and activates the inflammasome in podocytes. This may provide therapeutically targetable.

Funding: NIDDK Support

FR-PO152

RNA-seq Based Differential Expression Analysis in Rats with Slit Diaphragm Specific Dysfunction: The Glomerular Gene Expression Profiles of Nephropathy Induced by Anti-Nephrin Antibody 
Ying Zhang, Yoshiyusu Fukusumi, Hiroshi Kawachi. Dept of Cell Biology, Kidney Research Center, Niigata Univ, Niigata, Japan.

Background: Slit diaphragm (SD) dysfunction is understood to be involved in the development of proteinuria in several types of glomerular diseases. However, the pathogenic mechanism of the SD dysfunction is not well elucidated. The aim of this study is to identify novel molecules involved in the SD dysfunction.

Methods: The glomerular gene expression profiles of rat nephropathy induced by the injection of anti-nephrin antibody were examined by RNA sequencing (RNA-seq) with the Next-Generation Sequencer. Differentially expressed molecules were further analyzed by Gene Ontology (GO) and KEGG pathway analysis using DAVID.

Results: mRNA expressions of 870 genes were reduced to less than 50% at 1h when abnormal proteinuria was not detected yet, and those of 601 genes were reduced on day 5 when proteinuria peaked. mRNA expressions of 880 and 794 genes were increased to more than 2 folds at 1h and on day 5, respectively. We focused on 870 molecules which are down-regulated at 1h, since they are supposed to be potential molecules involved in the onset of proteinuria. GO analysis indicated 163 of the 870 genes were clustered in plasma membrane, and enrichment analysis revealed transmembrane receptor tyrosine kinase activity was the most significant over-represented molecular function for these 163 plasma membrane molecules. KEGG pathway analysis showed RAP1 signaling pathway is most significantly enriched. In the 870 molecules the most evidently down-regulated molecule is Hmgs2 (3.8% to normal) and the second is Slc5a8 (4.3%). The reduction in gene expression levels of these two molecules were validated by real-time PCR. Glomerular expressions of these molecules were detected by Western blot analysis and the distribution of Slc5a8 in podocyte was observed by immunohistochmical analysis.

Conclusions: RNA-seq analysis with nphoretic glomeruli showed Hmgs2 and Slc5a8 are involved in the early event of the SD dysfunction. GO and KEGG analyses showed the altered RAP1 pathway modulated by receptor tyrosine kinases participates in the development of proteinuria in the SD dysfunction.

Funding: Government Support - Non-U.S.

FR-PO153

Preservation of Glomerular Architecture in Aged Mice via Systemic Late-Age Intervention with SS-31 
Mariva T. Sweetwanye,1 Jeffrey W. Pippin,1 Diana G. Eng,1 Kelly L. Hudkins,2 Charles E. Alpers,2 Ying Ann Chiao,2 Hazel H. Szkto,2 Peter S. Robinowitch,2 Stuart J. Shankland.1 1Nephrology, Univ of Washington, Seattle, WA; 2Pathology, Univ of Washington, Seattle, WA; 3Pharmacology, Weill Cornell Medical College, New York, NY.

Background: The mitochondrial targeted peptide, SS-31, prevents mitochondrial damage and reduces cellular injury. Mitochondrial damage and oxidative stress accumulate with age. Thus, we hypothesized that SS-31 peptide would prevent/limit the progression of glomerular disease with aging.

Methods: 24-month old mice (~70-yr-old human) received either 8w of SS-31, or saline, by osmotic pump. Animals were sacrificed at 26m (~79-yr-old human) and tissues analyzed by quantitative histology. Untreated 24m-old animals were used to perform baseline measurements.

Results: SS-31 partially but significantly, inhibited the development of glomerulosclerosis (PAS). The age-associated decrease in podocyte density was not altered, but SS-31 treatment limited podocyte injury (desmin), and improved podocyte integrity (synaptopodin). 26m-old 8w SS-31 treated mice also had higher glomerular endohelial cell density (CD31). Parietal epithelial cells (PEC) were the most protected glomerular cell as SS-31 treatment significantly increased PEC density above baseline and yet decreased PEC activation markers (staining for active phospho-ERK1/2, α-smooth muscle actin, COLIV). Thus suggesting that PEC responses are still malleable at late age. Glomerular mitochondrial damage was evident in 26m-old saline treated mice by electron microscopy but was attenuated in PECs and podocytes in SS-31 treated aged mice. Consistent with decreased oxidative activity, SS-31 reduced NOx staining in podocytes, mesangium and PECs. Cellular senescence (p16) was also reduced in tuft cells and PECs of aged SS-31 treated mice as compared to saline controls.

Conclusions: In mice of advanced age, mitochondrial protection via SS-31 intervention lowers glomerulosclerosis, increases PEC density but lowers their activation, improves podocyte and endothelial cell integrity, and reduces senescence. This demonstrates that age-induced renal injury can be attenuated even in individuals of advanced age.

Funding: NIDDK Support, Other NIH Support - NIA

FR-PO154

Morphologic Changes in Human Parietal Epithelial Cells Using 3D Capsular Reconstructions 
Parker C. Wilson,1 Gilbert W. Moeckel,2 Robert L. Safirstein,2 Richard Torres.1 1Pathology and Laboratory Medicine, Yale Univ School of Medicine; 2Nephrology, Yale Univ School of Medicine.

Background: There has been recent interest in the role of parietal epithelial cells (PEC) in the evolution of kidney disease. However, PEC morphology cannot be adequately visualized using traditional microscopy due to the limitations of 2D histologic sections. We employed a new imaging method based on multiphoton microscopy and chemical clearing to improve glomerular capsule visualization.

Methods: High-resolution 3D microscopic images of entire glomeruli were obtained from autopsies with well-preserved kidneys and varying degrees of chronic kidney disease (CKD). Tissue clearing was performed to enable high resolution deep tissue imaging on a home-built multiphoton microscope. Glomeruli were digitally removed to reveal capsular surface morphology on 3D reconstruction.

Results: Individual kidneys showed a range of capsular morphologies. In the absence of CKD, parietal epithelial cells (PEC) had rounded nuclei and were evenly-spaced in a single layer covering the capsule (1A,1B). In patients with CKD, disorganized architecture and severe obliteration of the capsular space was seen (2A,2B). Severely affected capsules from patients with CKD showed marked reduction in epithelial cell number and was associated with capsular thickening, fibrotic capsules with coarse contours, and damaged proximal tubules (3A,3B).

Conclusions: Multiphoton microscopy with optical clearing is a powerful tool for visualization of glomerular capsules, atubular glomeruli, and associated proximal tubule changes in human specimens. Glomerular capsule changes may be linked to proximal tubule damage in chronic kidney disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 400A
Progressive Pathological Profile of the Passive Nephrotic Nephritis Model in CD1 and C57BL/6 Mice
Maria Katarina Ougura,1,2 Peter Hedling Kivist,1 Henrik Elvang Jensen,3 Constanze Hess,2 Claus Haase,2 Henrik Søndergaard,2
1Diabetes Complications Pharmacology, Novo Nordisk A/S, Denmark; 2Dept of Veterinary Disease Biology, Univ. of CPH, Denmark.

Background: When modelling human diseases in mice, different susceptibility to specific diseases needs to be considered. CD1 mice are commonly used outbred stock of mice for studies of chronic kidney disease, such as the lupus-like syndromes to develop kidney fibrosis. In this study C57BL/6 (B6) and CD1 mice were compared for their susceptibility to develop nephropathy in the passive nephrotic nephritis (NTN) model.

Methods: Initially, 100 and 250 μl of sheep anti-rat GBM antibody containing nephrotic serum (NRS) was injected i.p. in CD1 and B6 mice. NRS was identified as the preferred doses to induce NTN in CD1 and B6 mice, respectively. In a longitudinal study, the urinary albumin excretion rate (UAER) was measured on day 2-3, 6-7, 16-17, and 36-37 post NTN injections. On day 7, 21, and 42 post NTN injections, kidneys were harvested and stained with Perl, PAS, and collagen to study immunohistochemistry. Mesangial expansion (ME) was graded from 0 to 3, in a blinded fashion.

Results: NTN induction resulted in significantly increased UAER already on day 2-3 in CD1 and B6 mice (mean±SD 233.7±24/134.4; 68.2±24/75.5) compared to their healthy controls (mean±SD 97.1±24/31.2; 40.1±17.7), and this continued until day 36-37. On day 2-3, 6-7, and 16-17 UAER was significantly increased in CD1 NTN mice compared to the B6 NTN mice. Both CD1 and B6 NTN mice revealed significant, but similar progressive ME on day 7, 21, and 42, suggesting that disease might exacerbate beyond day 42. Perl staining showed increased renal iron accumulation on day 21 and 42 in both CD1 and B6 NTN mice, suggesting that iron accumulation is a pathological feature in this model. An increased deposition of collagen III was observed in the renal cortex in CD1 and B6 NTN mice on day 21 and 42, suggesting a similar renal fibrosis development in CD1 and B6 mice.

Conclusions: Taken together, CD1 and B6 mice show significant, progressive, but similar renal pathology up to day 42 when subjected to NTN. Moreover, both murine strains are useful for studies related to UAER, ME progression, and renal fibrosis, when subjected to NTN.

Gene Expression Profiling of Proximal Tubular Cells - A Novel Experimental Technique
James Alexander Tomlinson,1,2 Claude Bruce-Cobbold,1 James M. Leiper,1 MRC CSc, Imperial College, London, United Kingdom; 2Renal Section, Dept of Medicine, Imperial College, London, United Kingdom.

Background: Gene association and experimental studies implicate the proximal tubule (PT) as a major effector cell in progressive renal fibrosis but PT-specific maladaptive responses to injury in vivo are not well defined. Previous techniques to isolate tubular cell gene material remain limited by residual contamination from other kidney cell-types and gene expression changes elicited by the isolation technique itself. We have developed a novel ribosomal protein tag-and-capture technique to isolate proximal tubular cell messenger RNA (mRNA) transcripts from whole kidneys.

Methods: The RiboTag mouse strain has a mutated ribosomal protein L22 (Rpl22) locus with three copies of the haemagglutinin (HA) epitope after a STOP codon. We have developed and validated a proximal tubule-specific kidney androgen-sensitive protein Cre recombinase (KAPiCre) strain, female mice expressed HA-tagged Rpl22 protein to confine to kidney proximal tubular cells induced by testosterone treatment.

Results: Western blot analysis of whole kidney tissue showed strong HA protein expression in Ribotag homozygous mice, ~50% less in heterozygous mice and not in the absence of KAPiCre or RiboTag genes. Immunohistochemical staining revealed strong HA protein expression within proximal tubules and not in other kidney structures. Ribosomal immununoprecipitation yielded 100-300ng/μL of RNA from a single kidney, with negligible yield from control KAPiCre negative animals (~5ng/μL). Proximal tubular-specific gene markers including megalin, NHE3 and AQP1 were enriched (2 – 3-fold), whilst gene markers associated with other cell types, aSMA (mesenchymal cells/foamblasts) and UMOD (thick-ascending limb cells) were reduced (up to 10-fold) compared to whole kidney extract.

Conclusions: This novel technique permits proximal tubular gene expression analysis at any given time-point during the evolution of renal fibrosis using targeted RT-qPCR or non-biased RNA sequencing. Future studies using this experimental tool will provide new insights into how the proximal tubule responds to renal injury and repair, thus making a valuable contribution to our understanding of CKD pathogenesis.

Proximal Tubule-Specific Intracellular-Type Nampt Conditional Knockout Mice Exhibited Renal Fibrosis and Basement Membrane Thickening via Suppression of Sirt1 and/or 6
Hirokazu Muroaka, Kazuhito Hasegawa, Sho Uno, Hiroshi Itoh, Dept of Endocrinology, Metabolism and Nephrology, Keio Univ, Shinanomachi, Tokyo, Japan.

Background: Intracellular-type Nicotinamide phosphoribosyltransferase (iNampt) cooperates with NAD-dependent deacetylase Sirtuins, to exert the potential of stress resistance and longevity. We previously reported that proximal tubule (PT)-specific Sirt1 transgenic mice are protected against diabetic nephropathy (DN), and that PT conditional knockout (CKO) mice exhibited aggravation of DN (Nature Medicine,2013). We also showed that the high expression level of Nampt in PTs contributes to the sufficient supply of nicotinamide mononucleotide (NMN), a precursor of NAD, to glomeruli. In this study, we established PT-specific conditional Nampt-deficient mice to investigate the role of iNampt in DN.

Methods: We generated PT-specific, iNampt-deficient mice by crossing Namptfl/fl mice with γ-GT-Cre mice. Wild-type (WT) and CKO mice were injected with saline (SA), control or peritubular (STZ) to induce DN. The phenotypes of mice, WT+Sal, CKO+Sal, WT+STZ, and CKO+STZ, were analyzed at 8 and 24 weeks after treatment.

Results: Periodic acid methenamine silver, Masson-trichrome, and Elastica von Gieson staining revealed notable thickening of the tubular basement membrane and basement membrane thickening accompanied with peritubular and perivascular fibrosis surrounding interlobular arteries and veins in the medulla were clearly detected in CKO mice. DNA microarray showed that expression of tubular tissue inhibitor of metalloproteinase 1 (TIMP-1) and latent transforming growth factor beta binding protein 2 (LTBP-2) was elevated in CKO mice, which might cause the histological changes. Among all isoforms of sirtuin proteins, the activity of SIRT1 and SIRT6 were significantly decreased in the CKO mice.

Conclusions: We revealed that iNampt deficiency in PTs has unfavorable effects on the phenotype of broad bridging fibrosis through the overproduction of TIMP-1 and LTBP-2. These results would be responsible for this change. Nampt in PTs is a safeguard against the initiation and progression of DN-induced fibrogenic progression.

Modulation of Proximal Tubule Endocytic Capacity by Shear-Stress Stimulated Cell Differentiation
Kimberly R. Long,1 Katherine Shipman,1 Youssef Raibii,1 Megan Eshbach,1 Ora A. Weiss,1,2 Medicine - Renal Electrolyte, Univ of Pittsburgh School of Medicine, Pittsburgh, PA; 2Cell Biology, Univ of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: Epithelial cells that line the proximal tubule (PT) of the kidney are responsible for the reabsorption of low molecular weight proteins and other small molecules from the glomerular ultrafiltrate. Efficient uptake of these filtered proteins is essential to prevent tubular proteinuria.

Methods: Because cells in the kidney are continuously exposed to flow and the accompanying fluid shear stress (FSS), we asked whether continuous growth under FSS affects cell morphology and constitutive endocytic capacity. To this end, opossum kidney cells were plated on permeable filter supports, and the following day were exposed to orbital FSS or maintained under static conditions for an additional four days.

Results: Filters exposed to FSS had roughly 25% more cells than those maintained under static conditions as quantified using DAPI staining. Additionally, cells exposed to FSS were taller, had a more extensive brush border, and contained more apical endocytic compartments than cells grown under static conditions. Endocytic capacity per cell, quantified based on uptake of fluorescently-labeled albumin, was also dramatically increased (~2-fold) in cells cultured under FSS. This effect could be furthered by overnight incubation under static conditions prior to albumin uptake. Interestingly, cells exposed to twice our normal orbital speed had a 5-fold increase in endocytic capacity per cell, and albumin uptake could be rapidly modulated by changes in FSS in these cells. Ultrastructural analysis revealed striking differentiation of the apical brush border and endocytic pathway in these cells, similar to that observed in PT cells in vivo.

Conclusions: Growing cells under continuous FSS better replicates the characteristics of PT cells in vivo and may represent a more physiologic in vitro model system in which to study protein uptake and the endocytic pathway in PT cells.

Deletions of the TGF-β Receptor in the Proximal Tubule Worsens the Response to Chronic Injury due to Altered β-Catenin Activation
Stellar Nlndhi Khod,1 Sirkhala Neelsetty,1 Melanie Phillips,1 Raymond C. Harris,1 Leslie S. Gewin,2 Medicine, Vanderbilt Medical Center, Nashville, TN; 2Medicine, Veterans Affairs Hospital, Nashville, TN.

Background: TGF-β is arguably the strongest profibrotic factor in chronic kidney disease (CKD), but its effects vary depending upon the target cell type. We previously demonstrated that blocking TGF-β signaling in the proximal tubule (PT), the main target of renal injury, protected renal function after acute kidney injury (AKI) in mice; how TGF-β signaling in the PT affects CKD progression is still uncertain. Method: To address this, we selectively deleted the TGF-β type II receptor (TIRII) in the PT using the γGT-Cre. These conditional knockout (KO) mice and littermate controls were injected by either aristolochic acid (AA) or uninephrectomy/angiotensin II. To define the mechanism underlying the observed response, we used PT cells with and without TIRII as well as mice with conditional stabilization of β-catenin in the PT.

Results: Surprisingly, conditional KO mice had a worse response to chronic injury as assessed by increased tubular injury (histology, KIM-1 levels), fibrosis (collagen I expression), and renal function. In addition, deleting the TIRII increased epithelial apoptosis both in vitro and in PT cells. AκA/κA mice with TIRII signaling interacts with the β-catenin pathway, and β-catenin activation has been shown to reduce apoptosis in murine AKI, we investigated how abrogating TGF-β signaling alters β-catenin activity. Both renal cortices from injured conditional KO mice and TIRII-/- PT cells had reduced nuclear β-catenin and axin2 mRNA compared to tissue and cells with the receptor intact. The increased apoptosis in AA-treated TIRII-/- PT cells was reduced by pharmacologically augmenting β-catenin activity. We crossed our conditional KO mice with those containing conditional activation of β-catenin and injured them using AA. The activating β-catenin construct would decrease the renal injury and fail blocking TIRII in the PT.
Conclusions: In conclusion, genetically inhibiting TGβ-β signaling in the PT worsened the response to chronic injury by increasing epithelial apoptosis, in part, due to compromised β-cat signaling.

Funding: VA Support

FR-PO160
Thioredoxin Interacting Protein: A Novel Regulator of Tubular Autophagy and Mitophagy in Diabetic Nephropathy
Chunling Huang, Xinning Chen, Carol A. Pollock. Renal Lab, Kolling Inst, Univ of Sydney, Sydney, NSW, Australia

Background: Dysregulation of autophagy contributes to the development of diabetic nephropathy. Hyperglycemia upregulates TXNIP expression, which in turn induces the generation of reactive oxygen species (ROS), inflammatory and fibrotic responses in diabetic nephropathy. The aim of this study is to define the role of thioredoxin interacting protein (TXNIP) with autophagy/mitophagy in diabetic nephropathy.

Methods: Transgenic (mRen-2) rats with streptozotocin-induced diabetes were given TXNIP DNAzyme or scrambled DNAzyme for 12 weeks respectively. Total collagen deposition, type I collagen expression, mitochondrial function and mitochondrial ROS (mROS) production were assessed. The formation of autophagosomes and autolysosomal clearances were determined in kidneys from both human and rats with diabetes. The colocalization of LC3 and P62 within mitochondria was used to monitor mitophagy. Autophagic signaling molecules including mTOR, p70s6, and p62 were examined.

Results: TXNIP DNAzyme dramatically attenuated total collagen deposition and type I collagen expression in the kidneys of diabetic rats compared to the control DNAzyme. LC3 and P62 expression were increased in the renal tubular cells of human diabetic kidneys compared to non-diabetic controls, which indicates accumulated autophagosomes and reduced autophagic clearance. The increased LC3 and P62 in the renal tubular cells of diabetic rats were reversed by TXNIP DNAzyme. High glucose induced mitochondrial dysfunction, mROS production, and inhibited mitophagy in the renal tubular cells, which were reversed by TXNIP siRNA. Inhibition of TXNIP suppressed diabetes-induced BNIP3 expression and activation of the mTOR signaling pathway.

Conclusions: Hyperglycemia-induced TXNIP contributes to the dysregulation of tubular autophagy and mitophagy in diabetic nephropathy through activating mTOR signaling pathway.

FR-PO161
Hypoxia-Inducible Factor Agonist Ameliorates Impact of Tubulointerstitial Injury on Subsequent Glomerular Injury
Jun Zou, Jianyong Zhong.1 Taiji Matsuoka,2 Volker H. Haase,3 Haichun Yang,2 Agnes B. Fogo.2 Pathology, Kolling Inst, Univ of Sydney, Sydney, NSW, Australia

Background: We previously found that tubulointerstitial injury sensitizes to subsequent glomerular injury, with increased peritubular capillary permeability and tissue hypoxia in follic acid-induced tubulointerstitial injury. Hypoxia-inducible factors (HIFs) regulate hypoxia and angiogenesis. In this study, we evaluated whether dimethylxalolglycine (DMOG), an inhibitor of HIF-a degradation, can ameliorate tubulointerstitial injury and its impact on subsequent glomerular injury.

Methods: Cel I-lucerase mice, with lucerase in the collagen I promoter, were mated with Npg25 mice, which express human CD25 receptor on podocytes, and develop glomerulonephrosis when LMB2 toxin is administered. Mice, 12 wk old males, received follic acid (FA, 240mg/kg BW, i.p.) or vehicle (VE), and subgroups were treated with DMOG (8 mg qd, p.o.) from wk 3 till 6. Uninephrectomy was performed at wk 7. Ten days later, mice were sacrificed.

Results: Kidneys from UnNx, before added glomerular injury, showed that DMOG elevated HIF-1a and HIF-2a mRNA in FA+DMOG vs FA. Pimonidazole, a tissue marker of hypoxia, was attenuated in FA+DMOG vs FA. VEGFA mRNA was significantly increased and collagen I reduced in FA+DMOG vs FA. CD31 staining, a marker of peritubular capillaries, was not different among groups. At sacrifice, body weight increase increased and collagen I reduced in FA+DMOG vs FA. At sacrifice, body weight increase increased and collagen I reduced in FA+DMOG vs FA.

Conclusions: Our findings indicate that hypoxia contributes to tubular injury sensitizing to subsequent glomerular injury, and restoring HIFs may blunt this adverse crosstalk of tubules to glomeruli.

Funding: NIDDK Support

FR-PO162
Darunavir Protects Renal Tubular Epithelial Cells against HIV-Induced Injury via Mechanisms Independent of HIV Replication
Xiaobo Gao, Alan Rosales, Heidi Karttunen, Michael J. Ross. Medicine, Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: HIV-associated nephropathy (HIVAN) is an important cause of end-stage renal disease (ESRD) in HIV-positive patients. HIVAN is caused by infection of renal epithelial cells, but viral replication in these cells is not necessary to induce disease. Expression of HIV Vpr and Nef proteins causes dysregulation of cellular signaling pathways, including disruption of Akt and ERK, and they were implicated in the induction of inflammation in HIVAN. Antiretroviral therapy (ART) markedly reduces the risk of progression to ESRD without eradicating HIV in the kidney and the mechanism(s) by which ART protects kidneys from HIVAN is poorly understood.

Results: Described in results section.

Conclusions: Since previous suggest that HIV protease inhibitors have pleiotropic effects on cell signaling, we tested our hypothesis that HIV protease inhibitors protect the kidneys from HIVAN via HIV-independent mechanisms. Conditionally immortalized human tubular epithelial cells (RTEC) were infected with gag/pol-deleted HIV (does not express HIV protease and cannot replicate), Vpr lentivirus, or control lentivirus and subsequently treated with the HIV protease inhibitor darunavir (DRV) or vehicle control. Western blotting studies demonstrated that DRV significantly attenuated HIV and Vpr-induced activation of STAT, ERK, and Src. DRV also decreased HIV and Vpr-induced expression of IL-6 and IL-8, which we had previously demonstrated to be important mediators of inflammation in HIVAN. Moreover, DRV also decreased cleavage of PARP1 in HIV and Vpr-transduced RTEC, suggesting that DRV prevented caspase-induced apoptosis.

Funding: NIDDK Support

FR-PO163
Renin Accelerates Progression of HIV via Enhanced HIV Gene Expression
Zhen Zhou, B. B. Ke;1,2,3,4 Volart B. Rai;1,2,3,4 Jiano K. Tembire;1,2,3,4 Vinita Vihnoi;1,2,3,4 Nairuti H. Shah;1,2,3,4 Judith Eng;1,2,3,4 Ashwani Malhotra;1,2,3,4 Pravin C. Singhal. Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.

Background: The activation of renin angiotensin system (RAS) has been demonstrated to play an important role for the progression of HIVAN. Recently, cells of renal lineage have been shown to convert into podocytes in deactivated RAS. We have previously demonstrated that HIV enhances kidney cell renin expression. Now we hypothesize that HIV-induced renin production might be causing kidney cell injury through enhancement of HIV gene expression.

Methods: Human podocytes (HPs) were transduced with either vector (V/HP) or HIV (NL-A, HIV/HP). To increase endogenous renin production, V/HPs and HIV/HPs were transduced with siRNA vitamin D receptor (siRNA-VDR/HIV/HP) or scrambled (Scr-siRNA/HIV/HP). siRNA; protein blots were probed for renin and actin. To evaluate the effect of renin in vivo, mRNA expressions of HIV genes from renal tissues of HIVAN (Tg26) mice with high endogenous renin (Tg26 mice either with 2, 3 and 4 copies of antigeneinogen (Ag) or lacking VDR) were quantified by qPCR. To down regulate renal tissue renin expression, Tg26 mice were treated with either vehicle or a VDR agonist (VDA) for 2 weeks and then renal tissues were evaluated for HIV gene expression in addition, gene expression and progression of renal lesions were compared in Tg26 mice and Tg26 mice lacking renin.

Results: HIV enhanced renin expression in HPs. Silencing of VDR in HIV/HPs further enhanced expression of Nef, Tat, and Vif. However, VDA down regulated HIV gene expression in HIV/HPs. Renal tissues of Tg26-Agt-4 displayed 2.4 fold increase in mRNA expression of gp120, Vpr, Tat, Nef and Pvu vs Tg26-Agt-2. Similarly, Tg26 mice lacking VDR displayed greater HIV gene expression when compared with Tg26 mice with intact VDR. VDA treatment of Tg26 mice not only down regulated renal tissue expressions of renin but also attenuated expression of HIV genes. Tg26 mice lacking renin, displayed augmented renal tissue HIV gene expression and slowed progression of renal lesions.

Conclusions: Renin enhances renal tissue and podocyte HIV gene expression and induces accelerated progression of renal lesions.

Funding: NIDDK Support

FR-PO164
Reciprocal Interaction between (Pro)renin Receptor and Wnt/β-Catenin Drive Kidney Injury and Fibrosis
Zhen Li,1 Lili Zhou,1 Xue Hong,1 Jinhua Miao,1 Youhua Liu.1,2 Div of Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China; 2Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA.

Background: The (pro)renin receptor (RP) is a newly discovered, multi-functional protein that plays a critical role in the activation of the renin-angiotensin system (RAS). However, its regulation and potential role in the pathogenesis of chronic kidney disease (CKD) are poorly understood. In this study, we show that RP not only is a downstream target but also an upstream regulator of Wnt/β-catenin signaling.

Methods: The expression of RP in three models of kidney disease induced by ischemia/reperfusion injury (IRI), adriamycin or chronic angiotensin II infusion was assessed by Western blot and immunostaining. Human kidney tubular cells (HKC-8) were transfected with Wnt1 and/or PRR expression vectors. In vivo expression of Wnt1 and/or PRR was also carried out in mouse model of IRI (Tg26) mice with high endogenous renin (Tg26 mice either with 2, 3 and 4 copies of antigeneinogen [Ag] or lacking VDR) were quantified by qPCR. To down regulate renal tissue renin expression, Tg26 mice were treated with either vehicle or a VDR agonist (VDA) for 2 weeks and then renal tissues were evaluated for HIV gene expression in addition, gene expression and progression of renal lesions were compared in Tg26 mice and Tg26 mice lacking renin.

Results: HIV enhanced renin expression in HPs. Silencing of VDR in HIV/HPs further enhanced expression of Nef, Tat, and Vif. However, VDA down regulated HIV gene expression in HIV/HPs. Renal tissues of Tg26-Agt-4 displayed 2.4 fold increase in mRNA expression of gp120, Vpr, Tat, Nef and Pvu vs Tg26-Agt-2. Similarly, Tg26 mice lacking VDR displayed greater HIV gene expression when compared with Tg26 mice with intact VDR. VDA treatment of Tg26 mice not only down regulated renal tissue expressions of renin but also attenuated expression of HIV genes. Tg26 mice lacking renin, displayed augmented renal tissue HIV gene expression and slowed progression of renal lesions.

Conclusions: Renin enhances renal tissue and podocyte HIV gene expression and induces accelerated progression of renal lesions.

Funding: NIDDK Support
genetic expression induced by Wnt1, suggesting that PRR is an obligatory component of the Wnt1 pathway. Our results also show that the PRR expression was independent of renin. In mouse model of IRI, expression of either exogenous PRR or Wnt1 promoted β-catenin activation and aggravated kidney dysfunction and fibrotic lesions. Furthermore, in vivo expression of both PRR and Wnt1 accelerated kidney function decline, and deteriorated interstitial fibrosis and inflammation after ischemic injury.

Conclusions: These results establish that PRR is both a target and an essential component of Wnt/β-catenin signaling. Our studies suggest that PRR induction and Wnt/β-catenin activation constitute a vicious cycle, which drives kidney dysfunction and fibrosis after injury. Funding: NIDDK Support, Government Support - Non-U.S. FR-PO165

Renal Tissue of HIV Transgenic Mice (Tg26 and Vpr) and Parietal Epithelial Cells Display Altered miR-193A Expression

Warshafsky, Nirupama Chandel, 1 Vinod Sharma, 1 Manoj K. Tenhbre, 1 Ashwani Malhotra, 1 Catherine Meyer-Schwesinger, 2 Pravin C. Singhal. 1 Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; 2 Medicine, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Background: MicroRNAs (miR) regulate genes transcription both in physiological and pathological conditions. Both parietal epithelial cells (PECs) and podocytes (PDs) are derived from mesenchymal lineage during embryogenesis. miR-193A is highly expressed in matured PECs but least expressed in immature PECs. Human, immortalized PECs and PDs were transduced with either HIV (NL-4.3) or vector. A microarray-based approach in combination with real-time PCR to profile the miR expression patterns in HIV-1 transgenic mice. Both renal tissues and transduced cells were evaluated for expression of miR193A using the miRscan kits from Qiagen. Renal cortical sections of control and HIV were also evaluated for kidney cell expression of miR-193A utilizing in situ hybridization technique.

Results: 13 miRNAs, which belong to 11 miR families, were down regulated in HIV when compared with control mice. Expression of miR-193A was down regulated by 5 and 10 fold in renal tissues of Tg26 and Vpr transgenic mice, respectively. In situ hybridization studies revealed down regulation of miR193A in PECs in HIV transgenic mice. In vitro studies, HIV-transduced PDs as well as PECs displayed attenuated expression of miR193A when compared to respective vector-transduced cells.

Conclusions: HIV down regulates miR193 both in podocytes and PECs in vitro as well as in vivo.

FR-PO166

PGC-1α Protects against Notch1-Induced Kidney Injury

Ja Min Park, 1 Boyoung Nam, 1 Meiyin Wu, 1 Jung Tak Park, 1, 2, 3 Hyun Yoo, 1, 2 Shin-Wook Kang, 1, 2 Seung Hyek Han, 2 Katalin Susztak, 1 Dept. of Internal Medicine, Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ, Seoul, Korea; 2 Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; 3 Renal Electrolyte and Hypertension Div, Perelman School of Medicine, Univ of Pennsylvania, Philadelphia, PA.

Background: PGC1α is known as a key regulator of energy metabolism and mitochondrial biogenesis. However, there is lack of evidence on whether PGC1α provides a protective effect against kidney damage. This study evaluated the effect of PGC1α on kidney fibrosis using mice with tubule-specific double overexpression of Notch1 and PGC1α.

Methods: For animal study, we crossed mice expressing Pax8-rtTA/tetO-Pparg-1a (Pparg1a) and Pax8-rtTA/tetO-Cdx2 (Cdx2) to create Pax8-rtTA/tetO-ICN1/rtO-Pparg-1a (NP) mice. Using kidney tissues from these mice, we examined fibrotic changes, fatty acid oxidation pathway, and cell death. To delineate relationship between Notch1 and PGC1α, chromatin immunoprecipitation (ChIP) assay and lucerase assay were performed using primary cultured tubular epithelial cells.

Results: Compared to control mice, normal renal architecture was lost and severe tubular dilatation and fibrosis developed in NP mice. In contrast, these findings were almost null in NP mice. Fatty acid oxidation was impaired in NP mice and this alteration was significantly restored by PGC1α overexpression. In addition, PGC1α overexpression attenuated the increased apoptosis rate in NP mice. These results validated that the transcriptional repressor Hes1, a downstream target of Notch1 signaling, directly regulated PGC1α in kidney tubular epithelial cells. Furthermore, Hes1 overexpression significantly inhibited Pparg1a promoter-driven lucerase reporter activity.

Conclusions: Tubule-specific Notch1 overexpression decreased PGC1α expression and impaired fatty acid oxidation, resulting in severe kidney fibrosis. Notch1-induced kidney injury was almost nullified by PGC1α. In addition, PGC1α was directly regulated by Notch signaling. Our findings suggest that restoring PGC1α activity can be a promising therapeutic strategy in the management of chronic kidney disease.

FR-PO167

Early Intervention through Induced Genetic Deletion of Cell Division Autoantigen 1 Attenuates Diabetes-Associated Renal Fibrosis

Pak, Ying Ying, 1 Yung Tai Shin, 1 Ting Chee Dai, 2 Tzeqiao Wu, 3 Mark E. Cooper, 2 Zhonglin Chai, 1, 2 Diabetic Complications, Baker IDI Heart and Diabetes Inst, Melbourne, Victoria, Australia; 3 Dept of Immunology, Monash Univ, Melbourne, Victoria, Australia.

Background: CDA1 plays a key role in the development of diabetic nephropathy, where it enhances the profibrotic actions of the TGF-β-signalling pathway. This was demonstrated in vivo where global CDA1 knockout mice exhibited an attenuation in renal fibrosis in a model of diabetic nephropathy. Whether inhibiting CDA1 activity after the development of disease can attenuate renal fibrosis has yet to be experimentally investigated. This study focuses on the effect of an early intervention by induced genetic deletion of CDA1 on the progression of renal fibrosis in a streptozotocin (STZ)-induced mouse model of diabetic nephropathy.

Methods: Male CDA1flox/ERCre mice were rendered diabetic and killed 10 weeks later for analysis of various metabolic and renal parameters. After 5 weeks of diabetes, these mice were administered either tamoxifen to delete the CDA1 gene or vehicle to leave CDA1 intact.

Results: Analysis showed that diabetic mice exhibited expected changes in metabolic parameters such as hyperglycemia, polyaemia and renal hypertrophy. Tamoxifen administration, while having no effect on any metabolic parameters in both non-diabetic and diabetic CDA1flox/ERCre mice, led to a reduction of renal CDA1 mRNA expression of ~70-80% (p<0.001). Expression levels of profibrotic genes, such as fibronectin, collagen I and MMP2, were elevated by ~2.6-3.5 fold (p<0.01) in vehicle-treated/CDA1 “wildtype” diabetic mice. However, this increase was attenuated by ~40-70% (p<0.05) in CDA1 deficient diabetic mice. Additionally, renal extracellular matrix deposition as measured by Masson's Trichrome staining was increased ~40% in diabetic mice (p=0.062), and this increase was attenuated in CDA1 deficient mice.

Conclusions: In conclusion, reduction in CDA1 expression at an early stage of diabetic nephropathy is able to attenuate diabetes-associated renal fibrosis, emphasising the potent antifibrotic potential of utilizing this approach in diabetic nephropathy.

FR-PO168

Metformin-Induced Inhibition of Mammalian Target of Rapamycin (mTOR) Pathway Slows Down the Progression of HIV-1 Infection

Sekhar, Ashwini, 1 Vinita Vishnoi, 1 Nairutir H. Shah, 1 Kanak K. Tawadrous, 2 Anil K. Mongia, 1 Seyyedeh Shafadarin Marashi Shohstari, 1 Judith Eng, 1 Ashwani Malhotra, 1 Pravin C. Singhal. 1 Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; 2 Pediatrics, Down State Medical Center, Brooklyn, NY.

Background: Since patients with HIV infection are now living almost a normal life-style including the development of metabolic syndrome, we hypothesized that use of metformin in this population would not only control insulin resistance but would also slow down the progression of kidney lesions in HIV-associated nephropathy. To test our hypothesis, we studied the effect of metformin on the progression of renal lesions in a mouse model of HIV (doxycycline-inducible Vpr [podocyte specific] transgenic mice). Human, immunized PECs and PDs were transduced with either HIV (NL-4.3) or vector. A microarray-based approach in combination with real-time PCR to profile the miR expression patterns in HIV-1 transgenic mice. Both renal tissues and transduced cells were evaluated for expression of miR193A using the miRscan kits from Qiagen. Renal cortical sections of control and HIV were also evaluated for kidney cell expression of miR-193A utilizing in situ hybridization technique.

Methods: Vpr mice in groups of eight were fed either doxycycline or with or without metformin for six weeks followed by evaluation for renal biomarkers (Blood urea nitrogen, urine protein:creatinine ratio, grading of severity of renal lesions and immunoblotting for phospho-mTOR and down stream molecular markers). In vitro studies, mouse proximal tubular epithelial cells (mPTECs) were transduced with either empty vector (EV) or NL4-3 without gag and pol (HIV). EV/mPTECs or HIV/mPTECs were incubated in media containing either buffer or metformin (0.5μM) for 48h. Protein blots of EV/mPTECs and HIV/mPTECs were probed for phospho-mTOR, phospho-p70S6 kinase, phospho-eEF2, p-eIF4B, and p-4EBP-1. The same blots were stripped and reprobed for actin.

Results: Vpr mice displayed sclerotic glomerular lesions, microcyst formation, proteinuria and activation of mTOR pathway; metformin not only attenuated proteinuria but also decreased severity of metabolic syndrome. Moreover, metformin downregulated activation of the mTOR pathway. In vitro studies, protein blots of HIV/mPTEC displayed 2-fold increase in phospho-mTOR, 2.5-fold increase in phospho-p70S6K, and 2-fold increase both in p-eIF4B and p-4EBP-1 when compared to EV/mPTECs. On the other hand, metformin inhibited HIV-induced mTOR phosphorylation and associated down stream signaling.

Conclusions: Metformin slows down the progression of HIV by down regulation of mTOR pathway. Funding: NIDDK Support FR-PO169

The Effects of Aminophylline and Adenosine on the Tubular Damage Induced by Methotrexate in the Rats

Harun Akar, 1 Emin Taskiran, 1 Dilek Taskiran, 2 Oytun Erbas. 1 Internal Medicine, Tepecik Education and Research Hospital, Izmir, Turkey; 2 Physiology, Ege Univ, Izmir, Turkey; 1Physiology, Bilim Univ, Istanbul, Turkey.

Background: Methotrexate (MTX) causes kidney damage in high doses. Adenosine is recently suggested in the prevention of tubular damage associated with diabetic nephropathy. Adenosine receptor antagonism is a potentiates the MTX-induced urinary fibrosis in adenosine receptor antagonism. We aimed to investigate the potential of adenosine and aminophylline for preventing MTX-induced renal tubular damage.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 403A
Methods: Twenty-eight Sprague-Dawley adult male rats were included in the study. No drug was administered to 7 rats (n=7), which served as controls. Twenty one rats were administered a single dose of 20mg/kg intraperitoneal injection of MTX to induce MTX toxicity. 21 rats with MTX toxicity were divided into 3 groups; one group was treated with 1 mL/kg saline/day (MTX + saline) intramuscularly for 5 days, second group was treated with 4 mg/kg/day adenosine (MTX + adenosine) intramuscularly for 5 days, third group was treated with 80mg/kg/day aminophylline (MTX + aminophylline) intramuscularly for 5 days. At the end of the fifth day, all animals were euthanized and blood and urine samples were collected. BUN and creatinine were measured in plasma samples. Kidneys were harvested for histopathological tubular damage scoring, determination of renal malondialdehyde (MDA) , and glutathione (GSH). Urine was examined by dipstick for proteinuria.

Results: In saline group. In MTX + aminophylline group, proteinuria, plasma BUN, creatinine levels and proximal tubular damage score were found significantly increased when compared to the other groups (p<0.05). In MTX + adenosine group, plasma creatinine and proximal tubular damage score were found significantly increased compared to MTX + saline group. In MTX + aminophylline group, plasma BUN, creatinine levels and proximal tubular damage score were found significantly decreased compared to MTX + saline and MTX + adenosine groups (p<0.05).

Conclusions: Aminophylline reduced proximal tubular damage score induced by MTX and aminophylline may be an useful therapeutic agent for preventing MTX toxicity.

FR-PO170
Sirt1 Prevents Age-Associated Kidney and Cardiac Dysfunction
Ashley R. Bellin,1,2 Yanling Zhang,1 Kim Connelly,1 Richard E. Gilbert,1,2 ‘Li Ka Shing Knowledge Inst, St. Michael’s Hospital, Toronto, ON, Canada; 2Univ of Toronto, Toronto, ON, Canada.

Background: Aging is a major contributing factor to both chronic kidney disease (CKD) and heart failure (HF). Sirtuin 1 (Sirt1), an NAD dependent, catalytically inactive Sirt1Y/Y mice (p<0.0001). Blood pressure, urinary albumin excretion, and heart weight were, however, similar in wild type and Sirt1Y/+ mice. Measures of cardiac function, including stroke volume (10.2±1.1 vs. 6.5±0.4µl, Sirt1+/+ vs. Sirt1−/−, p=0.01), ejection fraction (40.1±4.2 vs. 25.9±3.9%, p=0.03), and cardiac output (44.5±5 vs. 30.2±3/min, p=0.02), were lower in the 14 month Sirt1−/− mice.

Conclusions: These findings indicate that Sirt1 is both a determinant of glomerular endowment and age-associated cardiac aging. Strategies that increase the abundance of Sirt1 in old age may ameliorate age-related cardiac dysfunction.

FR-PO171
Functional Characterization of the Role of the Transcription Factor GRHL2 in Cystic and Neoplastic Kidney Disease
Zihua You,1,2 Xiuting Chen,1,2 Klaas Jung,1,2 Kai M. Schmidt-Ott,1 Max Delbrück Center for Molecular Medicine, Berlin, Germany; 3Dept of Nephrology, Charité Universitätsmedizin, Berlin, Germany; 4Dept of Urologic Research, Berlin, Germany; 5Inst of Pathology & Dept of Nephrology, Univ of Aachen, Aachen, Germany; 6Dept of Urology, Charité Universitätsmedizin, Berlin, Germany.

Background: Cystic and neoplastic kidney diseases are characterized by a dysregulation of epithelial morphogenesis and epithelial hyperproliferation. Grainyhead-like 2 (GRHL2) is a transcription factor specifically expressed in distal and collecting duct epithelia of the kidney. We have previously shown that GRHL2 regulates epithelial morphogenesis and formation and controls lumen expansion of kidney tubules. However, the functional role of GRHL2 in kidney disease remains unknown.

Methods: We conducted a comprehensive immunohistochemical analysis of GRHL2 expression in patient samples of age-associated cardio-renal disease and in parallel, studied GRHL2 functionality in genetic mouse models.

Results: GRHL2 expression was upregulated in chromophobe carcinomas and oncocytomas when compared with other renal carcinomas and its expression was partially lost in tumor areas of epithelia in ADPKD. To assess the role of GRHL2 in cystic and neoplastic kidney diseases in vivo, the proto-oncogene MYC was conditionally overexpressed in the collecting duct (HoxB7Cre;R26StopFLMYC). These mice developed cysts with epithelial hyperplasia which tended to transform to adenomas. Both cysts and adenomas displayed strong GRHL2 overexpression and the overexpressing ducts showed similar hyperplastic ducts as shown by their positivity for VATPaseB1/B2. Furthermore, conditional deletion of Grhl2 in the kidneys of these mice (HoxB7Cre;R26StopFLMYC; Grhl2 flox/flox) resulted in a marked aggravation of cyst development. While HoxB7Cre;R26StopFLMYC mice (DC101) worsened albuminuria and renal histological injury scores in db/db mice, an effect DC101 (anti-VEGFR2) prevented, while VEGFR1 blockade with MF1 also protected eNOS with Bevacizumab (Avastin). VEGFR1 blockade with MF1 also protected eNOS with Bevacizumab (Avastin). FR-PO172
Anti-Angiogenic Factors Regulate the Cytoprotective Thrombomodulin Pathway in the Kidney In Vitro and In Vivo
Janon Bos,1 Rosanne Jane Turner,1 Maria Elisabeth Penning,1 Pascal Bus,1 Aiko P.J. De Vries,1 Marion Schapfnercek,1 Lukas J. Hawinkels,1 Kitty Bloemkampen,1 Jan A. Brujin,1 Hans J. Baeudel,1 1Pathology, LUMC, Netherlands; 2Nephrology, LUMC, Netherlands; 3Gastroenterology- Hepatology, LUMC, Netherlands; 4Obstetrics, UMCU, Netherlands.

Background: An excess of angiogenic factors is associated with a variety of renal syndromes, e.g. preeclampsia and diabetic nephropathy. Levels of soluble thrombomodulin increase in these syndromes, but if endothelial thrombomodulin changes and if this affects anti-coagulative and cytoprotective signalling in the kidney is unknown. Hence, we investigated thrombomodulin signalling in patients and experimental models of preeclampsia and diabetic nephropathy.

Methods: HUVECs were treated with VEGF or soluble Flt-1. Kidneys from 12 mice treated with angioptin or VEGF receptor (VEGFR) and tissue factor was measured with FR-PO172. Thrombomodulin protein expression was investigated with immunohistochemistry.

Results: sFlt-1 decreased endothelial thrombomodulin in vitro. Glomerular thrombomodulin protein was increased in diabetic pigs and in mice treated with anti-angiogenic compounds. In diabetic pigs, thrombomodulin, EPCR, and VEGF mRNA increased (all P<0.05), which correlated inversely with tissue factor mRNA. In preeclampsia, thrombomodulin increased was correlated to pregnancy controls and correlated with podocyte nephrin expression (both P<0.01).

Conclusions: Angiogenic factors regulate renal thrombomodulin expression in vitro and in vivo. Increased thrombomodulin expression is accompanied by less tissue factor expression and increased podocyte nephrin expression, indicative of a protective effect on the glomerulus. These results indicate an effect of thrombomodulin endothelial cells to maintain anti-angiogenesis; interventions pathways through which thrombomodulin expression is increased in endothelial cells could reveal clues to restore or prevent endothelial kidney damage.

FR-PO173
VEGFR1 Neutralization Reverses Murine Diabetic Nephropathy
Zhonghua Qi,1 Dianna L. Jaqua,1 Yuan Su,2 Martin S. Cramer,1 Bhashkarjyoti Sarmah,1 Shannon Marie Harlan,1 Tamer Coskun,1 Kathleen Heinz-Taheny,1 JoseF.G. Heuer,1 Ying Tang,1 Matthew D. Breyer.2 Eti Lilly and Company, Indianapolis, IN.

Background: The role of VEGF in the pathogenesis of renal disease remains controversial. The proangiogenic effects of VEGF are primarily mediated by its receptor VEGFR2 where these effects are antagonized by ligand binding to its inhibitory receptor VEGFR1 (B1).

Methods: A specific VEGF monoclonal antibody (MF1) was studied in CKD mice. Results: The present study demonstrated that MF1 dramatically improved albuminuria and renal histology in three distinct mouse models of CKD including unipolycystic kidneys (DC101) and 5/6 nephrectomy (db/db mice, and 129Sm renal rat kidneys. MF1 treatment increased circulating VEGF levels consistent with ligand displacement from VEGFR1, and this was accompanied by increased renal VEGFR2 phosphorylation, suggesting VEGFR2 activation. Interestingly MF1 treatment was accompanied by a sustained decrease in blood pressure significantly and rapidly (approximately 10mmHg) in both MF1 and eNOS db/db mice (p<0.01). Of note the decreased blood pressure was not exclusively dependent on the downstream activation of eNOS by VEGFR2. In contrast to previous reports, we found blocking either VEGFR or VEGFR2 via administration of neutralizing antibodies to VEGF or VEGFR2 (DC101) worsened albuminuria and renal histological injury scores in db/db mice, an effect consistent with clinical observations of proteinuria and hypertension following treatment with Bevacizumab (Avastin). VEGFR1 blockade with MF1 also protected eNOS db/db mice from serum creatinine (Scr) increases and significantly reduced mortality in these
mic. The effects of MF1 were not dependent on the VEGFR1 tyrosine kinase (tk) domain since treatment of VEGFR1−/− remnant kidney mice with MF1 didn’t significantly impair its beneficial effects on albuminuria and renal histology.

**Conclusions:** These data demonstrate monoclonal antibody VEGFR1 blockade prevents renal failure progression by increasing VEGFA and VEGFR2 activity in diverse murine models of kidney disease. These findings are consistent with recent observations of reduced VEGFA levels in human DN and suggest they may contribute to the pathogenesis of DN.

**Funding:** Pharmaceutical Company Support - Eli Lilly and Company

**FR-PO174**

Bone Marrow Myeloid Progenitor Cells Are Contributing to a Wide Variety of suPAR Associated Kidney Diseases

Eunsih Hahn,1 David Changhi Wei,1 Jing Li,1 Nicholas J. Tardi,1 Shikha Wadhwani,1 Yanxia Cao,1 Vassil Peev,1 Christopher Lund O’Connor,2 Markus Bizzer,3 Vinee Gupta,3 Sanja Sever,3 Jochen Reiser,3 1 Rush Univ; 2 Univ of Michigan; 3 Massachusetts General Hospital.

**Background:** Systemic soluble urokinase plasminogen activator receptor (suPAR) is implicated in the onset and progression of chronic kidney disease (CKD). To investigate the potential relevance of suPAR in other renal diseases, we examined the levels of suPAR and Gr-1+ bone marrow (BM) myeloid cells in multiple animal models of proteinuria.

**Methods:** Bone marrow transplantation (BMT), adoptive transfer, ELISA, and flow cytometry analysis were performed. Results: BM chimera and adoptive transfer studies revealed that hematopoietic cells, specifically BM myeloid cells, are responsible for suPAR production and proteinuria development in lipopolysaccharide (LPS)-induced proteinuria mouse model. In this model, BM myeloid cells increased suPAR expression, and LPS stimulation led to a significant increase in the percentage of Gr-1+ cells in the BM. Next, we examined the levels of suPAR and Gr-1+ BM myeloid cells in 5 additional animal models of proteinuria. i) A genetic model of podocyte injury (Pod-Rac1), in which podocyte-specific Rac1 activation causes podocyte dysfunction, ii) Adriamycin (ADR)-induced nephropathy, iii) Albumin, TGF β1, transgenic (TGF β1, Tg) mice, iv) Neutrophilic serum (NNT) nephritis, and v) BTHR ob/ob diabetic mice with nephropathy. All tested animals exhibited proteinuria. Unlike LPS model, Pod-Rac1 and ADR models, in which podocytes are the direct target of injury, were not characterized by elevated suPAR levels. There was also no change in the BM Gr-1+ cell population. In contrast, TGF β1, Tg, NTS, and BTHR ob/ob mice, showed elevated suPAR levels, which was accompanied by an expansion in Gr-1+ BM myeloid cells. Transplantation of BM from healthy into NTS mice ameliorated the degree of kidney disease.

**Conclusions:** Expansion of Gr-1+ BM myeloid cells and their overproduction of suPAR may represent a common upstream event in immunologically associated kidney disease with high systemic suPAR. BM transplantation may be one new therapeutic strategy to combat a disturbed BM kidney disorder.

**Funding:** NIDDK Support

**FR-PO175**

Synergism of CD40 Autoantibodies and suPAR in FSGS Recurrence

Tara Sigdel,1 David Changhi Wei,2 Flavio Vincenti,1 Jochen Reiser,1 Minnie Sarwal.1 1 Surgery, UCSF; 2 Medicine, Rush Univ.

**Background:** FSGS is a histopathological lesion leading to end stage kidney disease recurrence and transplantation. Primary FSGS has however a 40-80% risk of recurrence of disease in the transplanted kidney, with resultant accelerated graft loss. The disease pathophysiology has been difficult to unravel despite a large body of evidence suggesting a role of circulating factors. Recent studies in recurrent FSGS (rFSGS) suggested a potential role suPAR and CD40 auto-antibody (autoAb) isolated from the sera of FSGS patients.

**Methods:** We evaluated affinity in between CD40 autoAb isolated from rFSGS patients with suPAR and synergistic role of suPAR and CD40 Ab from FSGS in rodent model in causing kidney damage in terms of proteinuria. Anti-CD40 autoAb isolated from rFSGS and non-recurrent FSGS (nrFSGS) were injected (i.v.) to C57BL/6 mice with predetermined amount of CD40 autoAb isolated from FSGS and nrFSGS. Injection of CD40 autoantibody was given 6 times, every other day. Six hours after the last dose of CD40 autoantibody, recombinant human suPAR protein was given i.v. at 5 µg/ml to all mice in order to analyze the additive effect of suPAR on proteinuria. Urine was collected before and every day after the first injection of CD40 autoantibody to analyze urinary albumin and creatinine. Surface plasmon resonance (SPR) was used to find affinity in between CD40 autoAb isolated from rFSGS and suPAR. The injection of suPAR along with CD40 autoAbs from rFSGS increased proteinuria significantly compared to CD40 autoAbs alone (p<0.004). CD40 autoAbs isolated from FSGS, nrFSGS patients directly demonstrated affinity towards integrin αvβ3 as a similar binding affinity (KD ~ 26 to 84 nM). Only human CD40 autoAbs from FSGS have specific interaction as the RUmax values of those from nrFSGS and no-FSGS patients are small. Only human CD40 autoAbs from FSGS patient, not from nrFSGS patients had specific affinity towards suPAR.

**Results:** There was an increase in proteinuria (p<0.04) with the injection of CD40 autoAb from rFSGS. The injection of suPAR along with CD40 autoAbs from rFSGS increased proteinuria significantly compared to CD40 autoAb alone (p<0.004). CD40 autoAbs isolated from FSGS, nrFSGS patients directly demonstrated affinity towards integrin αvβ3 as a similar binding affinity (KD ~ 26 to 84 nM). Only human CD40 autoAbs from FSGS have specific interaction as the RUmax values of those from nrFSGS and no-FSGS patients are small. Only human CD40 autoAbs from FSGS patient, not from nrFSGS patients had specific affinity towards suPAR.

**Conclusions:** Through this study we demonstrated that CD40 autoAbs and suPAR synergizes in vitro and in vivo.

**FR-PO176**

PAPRs and PAPARY Attenuate the Anti-Glomerular Basement Membrane Glomerulonephritis through the Actions on the Different Inflammatory Cells, T Cells and Macrophages

Yusuke Okabayashi,1 Go Kanzaki,1 Akira Shimizu,1 Takafumi Kanemitsu,1 Michiko Aoki,1 Yusuke Kajimoto,1 Dedong Kang,1 Kiyotaka Nagahama,2 Akira Shimizu.1 1 Dept of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan; 2 Massachusetts General Hospital.

**Background:** Peroxisome proliferator activated receptor-α (PAPARα) and -γ (PAPARY) agonists modulate inflammatory responses and attenuate the renal injury in glomerular diseases, but the mechanisms are not well understood. In this study, we examined the protective effects of PAPARα and PAPARY agonists, fenofibrate and pioglitazone, in anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) characterized by the invasion of inflammatory cells such as macrophages and CD8+ T cells.

**Methods:** Male Wister-Kyoto rats at 5 weeks of age were divided into 7 groups and received fenofibrate (30, 100, 300mg/kg/day), pioglitazone (12.5, 50, 100mg/kg/day) or vehicle (control) the day before induction of anti-GBM GN. At 7 days after the induction, 24-hr urine samples were collected and the kidneys were harvested. The expression of cytokines, chemokines and cell surface markers in isolated glomeruli were evaluated by real time PCR analysis.

**Results:** Both the treatments reduced the level of proteinuria, glomerular infiltration of CD8+ T cells and ED1+ macrophages and prevented the development of necroinflammatory and crescentic lesions dose dependently. Notably, pioglitazone showed greater reduction in infiltration of ED1+ macrophages with down-regulation of the M1 macrophage marker including TNF-α, IL-1β and iNOS, and increase in infiltration of ED2+ M2 macrophages with up-regulation of the M2 macrophage marker, TGF-β and mannose receptor. In contrast, fenofibrate showed greater reduction in infiltration of CD8+ T cells and up-regulation of Th2 cell-associated cytokines, IL-4 and IL-10.

**Conclusions:** PAPARα and PAPARY dose-dependently attenuated glomerular inflammation in anti-GBM GN through the regulation of the different inflammatory cells. Our results suggested that PAPARα suppresses CD8+ T cell infiltration with increase in the production of Th2 anti-inflammatory cytokines, and PAPARY suppresses macrophage infiltration with promotion of the anti-inflammatory macrophage infiltration.

**FR-PO177**

Whole Genome Transcriptome, Methylene, and Transcription Factor Binding in Nephroprotective Nephritis

Thomas Oates,1 Owen J.L. Rackham,2 Sarah R. Langley,1 Jacques Behmoaras,1 Enrico Petretto.1 1 UCL Centre for Nephrology, Univ College London, London, United Kingdom; 2 Duke-NUS Medical School, Singapore; Imperial College London, United Kingdom.

**Background:** Nephroprotective nephritis (NTN) is a macrophage dependent model of crescentic glomerulonephritis in which the Wistar-Kyoto (WKY) rat is susceptible to disease and the Lewis (Lew) rat is resistant. Previous work has suggested a role for the AP-1 transcription factor (TF), JunD, in the pathogenesis of NTN. TFs are fundamental regulators of gene expression but additional regulation may result from local methylation of DNA cytosine bases. Given the interaction between TF activity, DNA methylation and gene expression, we integrated distinct whole-genome datasets to try and identify novel determinants of NTN pathogenesis.

**Methods:** DNA methylation data were produced in WKY and Lew bone marrow-derived macrophages (BMDMs) by whole genome shotgun bisulphite sequencing and interrogated with previously generated RNA-seq and JunD ChIP-seq data.

**Results:** We identified 1,004 genomic regions that showed differential methylation between WKY and Lew BMDMs. 427 of these regions overlapped with known genes and integration with RNA-seq data elucidated three genes that showed differential expression and differential methylation within their promoter region. Using the ChIP-seq data, we also found that, interferon-induced transmembrane protein 3 (Ifitm3), had differential binding of JunD within its promoter.
Conclusions: Integration of distinct whole genome datasets in NTN allows consideration of multiple determinants of gene expression and has revealed a potential new candidate gene (Ittm3) for glomerulonephritis susceptibility.

Funding: Government Support - Non-U.S.

FR-PO178

The Association and Its Mechanism between Microbiota Alteration and Intestinal-Barrier Function in Mice with Chronic Renal Failure Seiji Isono, Minoru Satoh, Yuji Sogawa, Atsushi Uchida, Kengo Kidokoro, Hajime Nagasu, Tamaki Sasaki, Naoki Kashihara. Dept of Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.

Background: The intestinal microbial flora consists of diverse bacterial species. These bacteria are necessary for the ontogeny, regulation of the immune system, and for intestinal homeostasis. Alterations of the intestinal barrier and intestinal bacterial flora in chronic kidney disease have been reported to affect uremic toxin influx.

Methods: We used 13-week-old male ICR-derived glomerulonephritis (ICGN) mice as the renal-failure group and ICR mice as the control group. Gene expression patterns of the whole bacterial flora in the intestine were analyzed by means of terminal restriction fragment length polymorphism. Fecal and serum bacterial products (phenol, para-cresol, indole/indole sulfate, and skatole) were examined by quantitative chemical analysis.

Conclusions: The intestinal bacterial flora was altered and tight junctions were impaired in mice with chronic renal failure. Defensins beta-1 and beta-3 may contribute to these changes in bacterial flora.

FR-PO179

Acetate from Microbiota Contributes to Tubulo-Interstitial Inflammation and Fibrosis in Lupus Nephritis Daniel Tak Mao Chen, Qing Zhang, Mel Chau, Ping Lung Chan, Susan Yung. Dept of Medicine, The Univ of Hong Kong. Hong Kong.

Background: The gut microbiota is implicated in the pathogenesis of autoimmune diseases. Bacterial products can gain access into the bloodstream and exert effects on distant organs. Acetate is a short chain fatty acid (SCFA) produced by gut microbiota. We previously reported that lupus nephritis patients had higher serum acetate levels compared with healthy controls, and acetate level correlated with activity of nephritis. We further investigated the role of acetate and its receptors in inflammatory and fibrotic processes in murine lupus and cultured proximal renal tubular epithelial cells.

Methods: Renal expression of SCFA receptors GPR-41 and GPR-43 was examined in NZBWF1 mice with progressive lupus nephritis. HK-2 cells were incubated with acetate (1-50mM) or serum-free medium for 24h, and the secretion of IL-6, IL-8 and MCP-1, and laminin expression was also induced by acetate in a time- and dose-dependent manner.

Results: GPR-41 and GPR-43 expression was marked in NZBWF1 mice with active nephritis, and was predominantly localized in the tubulo-interstitium. Acetate induced ERK, p38 MAPK and JNK phosphorylation in HK-2 cells, accompanied by increasing proteasomal activity and reducing the accumulation of polyubiquitinated proteins. GPR-41 and GPR-43 upregulation was mediated in part through IL-6, IL-8 and MCP-1, which in turn increased fibronectin synthesis through activation of MAPK and PI3K signaling pathways.

Conclusions: The results show that acetate from microbiota may contribute to tubulo-interstitial inflammation and fibrosis in lupus nephritis.

Funding: Government Support - Non-U.S.

FR-PO180

Mechanisms and Pathophysiological Significance of Eryptosis in Chronic Kidney Disease and Anemia Grazia Maria Virzi, Alessandra Brocca, Anna Clementi, Massimo de Cal, Claudio Ronco. IRRI.

Background: Anemia is a common complication of CKD resulted from compromised erythropoiesis or decreased lifespan of erythrocytes(RBCs). Eryptosis, suicidal death of RBCs, is characterized by cell shrinkage and membrane scrambling with phosphatidylserine (PS)-exposure at the RBC surface. Exposed PS is recognized by macrophages that engulf and degrade the affected cells. Eryptosis is observed in CKD, which invariably leads to anemia. The purpose of this study was to assess and study eryptotic changes in RBC exposed in vitro to uremic toxins and CKD patients'plasma.

Results: Inducible overexpression of I93M UCH-L1 in cultured podocytes resulted in increased levels of monoubiquitin and polyubiquitin partly through increased transcription of ubiquitin precursor proteins. No changes in ubiquitin levels were observed in podocytes overexpressing wildtype UCH-L1. Specific analyses of proteins that were polyubiquitinated in I93M-overexpressing cultured podocytes demonstrated that I93M overexpression resulted in an enhanced K48-polysubiquitination and degradation of alpha-actinin-4. In mice, overexpression of wildtype enzymatic active UCH-L1 resulted in podocyte loss and the development of proteinuria with increased podosomal activity. Astonishingly, overexpression of enzymatic inactive I93M UCH-L1 on the other hand reduced podocyte-loss and proteinuria and decreased podosomal activity.

Conclusions: UCH-L1 influences podocyte integrity and function through its enzymatic activity.

Funding: Government Support - Non-U.S.

Methods: RBC from healthy subject were incubated at a hematocrit of 0.4% in RPMI solution with different concentrations of uremic toxins and with plasma from CKD patients for 24hours. CKD patients were divided in 2groups(eGFR<45/mi/1.73m2). RBC volume and morphology was estimated, PS exposure was estimated by flow cytometric. Each experiment was tested 3times.

Results: Increasing concentrations of uremic toxins significantly modify RBC's volume, dramatically derange their morphology and progressively enhance the percentage of PS in vitro. Moreover, the median values of eryptosis showed significant differences between the 2CKD groups. The RBCs exposed to CKD plasma from patients with eGFR<45/mi/1.73m2 show strong eryptotic changes and high eryptosis(p<0.003). Eryptosis increases with CKD progression.
FR-PO182

Long-Term Selective ETA Receptor Antagonism Prevents Renal Injury in Humanized Sickle Cell Mice Malgorzata Kasztan, Carmen De Miguel, Jennifer S. Pollock, David M. Pollock. Dept of Medicine, Div of Nephrology, Univ of Alabama at Birmingham, AL.

Background: Elevated plasma endothelin-1 (ET-1)-levels reported in sickle cell disease (SCD) patients correlate with microalbuminuria, suggesting a pathophysiologic link between ET-1 and sickle nephropathy (SN). The current study was designed to determine if early intervention with an endothelin antagonist would prevent renal injury in a mouse model of SCD.

Methods: Humanized sickle cell mice (HbSS) and genetic controls (HbAA) were treated with ambrisentan (ET, antagonist), A-182086 (ETm, antagonist) (10mg/kg/day) or vehicle for 10 weeks (beginning at the time of HbF to HbS switch into adulthood).

Results: Chronic administration of ambrisentan prevented histo-pathological lesions including hypertrophy, sclerosis, vascular congestion and tubulointerstitial fibrosis, as well as preserved glomerular permeability.

Conclusions: ETm contributes to SN via ETA receptor activation and long-term ETm receptor antagonism may provide a strategy for the prevention of renal complications of SCD.

Funding: Other NIH Support - NIH/NHLBI: U01 HL117684-01

FR-PO183

Topiroxostat, a Novel Xanthine Oxidase Inhibitor, Exerts Renoprotective Role via Antioxidant Effects in Puromycin Aminonucleoside Nephrotic Rats Yosuke Kawamoto, Yoshifuru Shibata, Shunya Shibata, Shunya Uchida. Teikyo Univ School of Medicine, Tokyo, Japan.

Background: Topiroxostat (Topi) is a newly developed drug for gout and hyperuricemia belonging to xanthine oxidase inhibitor (XOI) like allopurinol. It has been proposed that allopurinol not only reduces serum uric acid (UA) level but also urine protein excretion in puromycin-aminonucleoside (PAN) nephritic rats. Topi may decrease urine protein excretion (UPE) in addition to hypouricemic effects. In the present study we aimed to examine change in UPE in response to Topi and its molecular mechanism using PAN rats.

Methods: PAN nephrosis was induced by a single intraperitoneal injection of PAN (10 mg/100 g body weight). Rats were divided into four groups: Control rats (Cont); PAN rats (PAN); Control rats with Topi 0.5 mg/kg/day (PAN + Topi); PAN rats treated with Topi (PAN + Topi).

Results: Topi significantly decreased tissue UA in the kidney cortex and UPE by 30% at day 10 after PAN injection. To elucidate the protective effect of Topi we focused on the oxidative stress in the kidney. Firstly, PAN significantly decreased the number of WT-1-positive podocytes and reduced podocin immunoreactivity, both of which were partially improved by Topi. Next, nitrotyrosine and 8-OHdG in the kidney induced by PAN were significantly decreased by Topi treatment. Moreover, increased amounts of XO and NOX4 in the cortex induced by PAN were completely reverted in response to Topi. Of note was that serum UA did not vary significantly.

Funding: Government Support - Non-U.S.

FR-PO184

Pathological and Molecular Characteristics of Adenine-Induced Chronic Kidney Disease (CKD) Model in Rats Erika Abe, Li Xiao, Yuumi Iida, Naoko Oyama, Rika Fujino, Hirofumi Jono, Hideyuki Saito. 1Dept of Clinical Pharmaceutical Sciences, Kumamoto Univ School of Pharmacy, Kumamoto, Japan; 2Dept of Pharmacy, Kumamoto Univ Hospital, Kumamoto, Japan.

Background: The process leading to CKD from acute kidney injury (AKI) is known to be caused by strength and frequency of proximal tubule injury. Although attempts were made to develop experimental CKD model, a suitable animal model is not yet established. In this study, we generated the adenine-induced CKD model using rats, and characterized pathological and molecular aspects for investigating factors involved in the CKD progression.

Methods: Wistar rats (8-weeks-old) were fed diet powder without or with adenine (0.3, 0.5 and 0.75%, respectively) for 4 weeks, followed by control diet for 4 weeks. Rats were sacrificed after 8 weeks, and kidney tissues were collected. In adenine-induced CKD model rats, body weight, water intake, urine volume, kidney weight, index of renal function, renal tubular damage markers (Kim-1, Ngal), oxidative stress-related factors (Nrf2, 4-HNE), fibrosis marker (eNOS), uremic toxin indoxyl sulfate (IS), organic anion transporters OAT1 and OAT3 mediating basolateral uptake of serum IS, and autophagy-related factors LC3-2 were examined.

Results: Body weight was significantly decreased and urine volume/water intake were increased in adenine group. Adenine treatment caused the decreases in urine urea nitrogen, Cr and marked increases in BUN and Scr. The marked increases in renal Kim-1 and Ngal, and histochemical injury of renal tubules were evident in adenine group. In adenine rats, the elevated 4-HNE and Nrf2 levels in the kidney indicated induction of oxidative stress. Moreover, LC3-2, a maker of autophagy, which often increases with oxidative stress, was also induced. The expressions of OAT1&3 were downregulated in adenine rat kidney, resulting in serum accumulation of IS. The appearance of interstitial eNOS indicated fibrotic response in adenine rat kidney associated with Masson’s trichrome positive staining. Furthermore, we also induced oxidative stress by feeding adenine rat Pan-1&3, the expressions of OAT1&3 were downregulated in adenine rat kidney, resulting in serum accumulation of IS. The appearance of interstitial eNOS indicated fibrotic response in adenine rat kidney associated with Masson’s trichrome positive staining.

Conclusions: Adenine-induced CKD model rats exhibited a significant deterioration of renal function, severe tubule injury, elevation of oxidative stress, accumulation of serum IS and autophagic and fibrotic responses.

Funding: Government Support - Non-U.S.

FR-PO185

Omics Characterization of Ethanol and Lipopolysaccharide Impact on the Renal Cortex Christine E. Dolin, Lauren G. Poole, Daniel Wade Wilkey, Gavin E. Artest, Eric C. Rouachka, Michele T. Barati, Michael Merchant. 1Pharmacology & Toxicology, Univ of Louisville; 2Medicine, Univ of Louisville; 3Computer Engineering & Computer Science, Univ of Louisville.

Background: Chronic, heavy ethanol (EtOH) consumption impacts the kidney through the hepato-renal syndrome. The direct renal effects of moderate chronic EtOH consumption and sensitization to secondary hits are unclear. We hypothesized that moderate EtOH consumption can alter renal transcriptomic/proteomic responses to acute exposure to lipopolysaccharide (LPS).

Methods: Mice were pair fed EtOH-containing Lieber-DeCarli diet for 6 weeks and/or injected i.p. with LPS 4h prior to sacrifice. Kidney cortex sections were isolated and snap frozen. Comparative Omics studies used a two-dimensional liquid chromatography-mass spectrometric analysis with an Orbitrap Elite and TMT labeling reagents and (b) mirVana™ isolation of total RNA, library preparation using the TruSeq Stranded Total RNA LT Sample Prep Kit-Set A with Ribo-Zero Gold and data collected using Illumina NextSeq 500/550 with the RNASeq protocol. Proteomic and transcriptomic data were filtered by Benjamin-Hochberg (BH) corrected ANOVA p-value <0.05 and fold change (FC). Ingenuity Pathways Analysis (IPA) was used to identify pathways changed by EtOH, LPS, and/or the combination. Individual protein changes were validated with immunoblotting.

Results: 170 of 1863 proteins were significantly different abundance at FC ≥2 across 3 groups. 853 of 47,719 transcripts were significantly differentially abundant at FC ≥2 across 3 groups. The majority of these effects LPS derived. Expected increases in Fibrinogen A and C were observed. Increases in TNF-α and COX-2 were observed.

Conclusions: This study on the effects of EtOH and/or LPS on the renal transcriptome and proteome supported observed expectations and revealed new changes in proteins, transcripts and pathways. We hypothesize these changes will provide insight into mechanisms by which EtOH affects the kidney and alters response to a second pathologic stimulus.

Funding: NIDDK Support, Other NIH Support - NIGMS P20GM103436 (N.Cooper, PI); P20GM106396 (D. Miller, PI); NCI 5R25CA134283-03 (D.Hein, PI); NIAAA R101AA021978-01 (G.Artest, PI), Clinical Revenue Support
### FR-PO186

**In-Near-Autofluorescence Is Useful for Non-Invasive Imaging of Injured Kidneys in Mice**

Isao Matsui, Hiroshi Fushiki, Nobuhiro Hashimoto, Keiichi Kubota, Tatsufumi Oka, Daisuke Morii, Yusuke Sakaguchi, Takayuki Hamamoto, Yoshitsugu Takabatake, Yoshitaka Isaka.

**Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; Translational Science Research Laboratory, Dentsu Discovery, Astellas Pharm Inc., Tsukuba, Ibaragi, Japan; Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.

**Background:** Tubulointerstitial injury (TI) is a final common pathway leading to end-stage renal disease. One of the major problems in the field of TI is the lack of strategies that enable us to evaluate the progression of TI non-invasively.

**Methods:** Near-infrared autofluorescence (AF) of injured kidney was non-invasively evaluated using IVIS Imaging system. A combination of excitation filter 710-875 nm and emission filter 810-900 nm was employed. Two models, unilateral ureteral obstruction and folic acid induced nephropathy, in BALB/c mice were analyzed. The origin of the renal AF was also analyzed.

**Results:** The AF levels were positively correlated with the degree of TI in both animal models. Microscopic analysis of the kidney sections revealed that the AF was originated from the injured tubular cells. Because porphyrins are intrinsic fluorescent substrates that have near-infrared emission peak, we analyzed renal expression levels of enzymes that participate in the metabolism of porphyrin. Among 10 enzymes, only coproporphyrinogen oxidase (CPOX) was suppressed in the injured kidneys in both animal models, suggesting that coproporphyrinogen III and its spontaneously oxidized product, coproporphyrin III, were accumulated in the injured kidneys. Authentic sample of coproporphyrin III had identical chromatographic properties observed in the injured kidneys. Intraproperitoneal injection of Δ-aminolevulinic acid, a substrate of porphyrin synthesis, enhanced the AF of the injured kidneys. BALB/c-pcr/net mice, a mouse strain that contains only 15% of the wild type CPOX activity, showed the identical AF observed in the injured kidneys.

**Conclusions:** Near-infrared AF derived from coproporphyrin III is useful for non-invasive imaging of the TI.

*Funding: Pharmaceutical Company Support - Astellas*

### FR-PO187

**CTGF Is Critically Involved in Lymphangiogenesis of Obstructive Nephropathy**

Hiroshi Kimura, Luis Falke, Tri Nguyen, Yasuhiko Ito, Andrew Leck, Roel Goldschmeding.

**Pathology, Univ Medical Center Utrecht, Utrecht, Netherlands; Nephrology and Renal Replacement Therapy, Nagoya Univ Graduate School of Medicine, Nagoya, Japan; Schilich School of Medicine and Dentistry, Western Univer; London, ON, Canada.

**Background:** Lymphangiogenesis is correlated with the degree of renal interstitial fibrosis. TGF-β induces VEGF-C production, which is the main driver of lymphangiogenesis. CTGF (aka CCN2) is an important determinant of fibrotic tissue remodeling, but its possible role in renal lymphangiogenesis has not been explored.

**Methods:** Wild-type mice (WT, n=5) and CTGF knockout mice (CTGF-KO, n=9) underwent unilateral ureteral obstruction (UUO), and both the obstructed kidney (OKB) and contralateral kidney (CLK) were collected on day 14 after UUO. We analyzed the expression level of CTGF and VEGF-C in the obstructed and contralateral kidney, respectively.

**Results:** In vivo, CTGF knock-out inhibited lymphangiogenesis in OBK, as evidenced by reduction of the increase of LYVE-1-positive lymphatic vessels (p<0.05) and VEGF-C-positive area (p<0.001). LYVE-1 and VEGF-C mRNA was reduced in CTGF-KO OBK and contralateral kidney (CLK) of CTGF-KO mice as compared to WT OBK (p<0.05). In HK-2 cells, CTGF inhibited VEGF-C expression, while, CTGF siRNA suppressed TGF-β1-induced VEGF-C mRNA (p<0.05) and protein (p<0.01). Solid-phase binding assay revealed direct physical interaction between CTGF and VEGF-C. CTGF treatment of HK-2 cells enhanced VEGF-C stimulated growth and tube formation of human lymphatic endothelial cells (HMVEC).

**Conclusions:** CTGF is critically involved in renal lymphangiogenesis through interactions with VEGF-C.

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

### FR-PO188

**Swimming Exercise Training (EXE) Does Not Change Inflammatory Parameters but Increase Creatinine Clearance (CrCl) and Low Glomerulosclerosis and Mortality in Rats with 10 Weeks of Chronic Kidney Disease (CKD)**

Rafael DaSilva Luiz, Rodolfo Rossetto Rampaso, Kleiton Augusto Santos Silva, Luciana Jorge, Edson Andrade Pessoa, Maria A. Gloria, Mario Luis Ribeiro Cesaretti, Nestor Schor. Nephrol Div, Escola Paulista de Medicina/UNIFESP, Sao Paulo, SP, Brazil.

**Background:** We evaluated the EXE effects on serum inflammatory markers, renal function and glomerulosclerosis in rats with 5/6NX.

**Methods:** Adult Wistar rats were divided in groups (n=8): Control (C), Control-EXE (C-EXE), Sedentary-5/6NX(S) and 5/6NX-EXE (NE). The protocol was employed in 5/6NX rats after 7 days from the surgical procedures. EXE periods were 60min/day, 5 days a week/8 weeks. It was evaluated inflammatory parameters as IL-1 alpha and beta, IL-2, IL-6 and TNF-alpha (Lumines), mean arterial pressure (MAP), maximal exercise test (METs/s), CO2, KUN, proteinuria(μg/ml), glomerulosclerosis(%) as well mortality rate. **Results:** EXE did not modify the profile of inflammatory markers.

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

### FR-PO189

**SRGAPs Is Essential for Podocyte Cytoskeletons and Its Downregulation Facilitates Podocyte Injury and Diabetic Nephropathy**

Yu Pan, Song Jiang, Qing Hou, Dandan Qiu, Jingsong Shi, Zhao-Hong Chen, Ming-Chao Zhang, Zhihong Liu. National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.

**Background:** Podocyte injury is involved in the development of diabetic nephropathy (DN). Disruption of cytoskeletons in podocytes underlies podocyte foot process effacement and detachment from the glomerular basement membrane, leading to podocyte loss, proteinuria and glomerulosclerosis in DN. At present, the mechanism underlying podocyte cytoskeletal damage is incompletely understood.

**Methods:** We performed high-throughput microarray transcriptomics analyses of the micro-dissected glomeruli samples from the patients with early or late stage type 2 diabetic nephropathy. We performed bioinformatics analyses of the data to identify the gene that was associated with the progression of DN. We performed a variety of molecular and cell biology studies with cultured podocytes, db/db mice and zebrafish to investigate the role of the candidate gene in podocyte injury.

**Results:** Systems and network analyses of the microarray data identified that actin cytoskeleton is one of the top dysregulated pathways in the glomeruli of diabetic patients and that SRGAP2 downregulation is associated with the progression of DN. We further found that SRGAP2 is mainly expressed in podocytes in glomeruli and confirmed its downregulation in the podocytes of patients with DN at protein level. Consistently, SRGAP2 was also downregulated in the cultured podocytes treated with high glucose or TGF-β1. Furthermore, SRGAP2 knockdown was found to enhance podocyte mobility through altering RhoA/Cdc42 interaction, which was reversed by exogenous SRGAP2 overexpression. In vivo, SRGAP2 delivery ameliorated podocyte injury in db/db mice. A knockdown of SRGAP2 in zebrafish by morpholino oligonucleotide (MO) resulted in developmental defects of podocytes and proteinuria.

**Conclusions:** SRGAP2 is a critical regulator of RhoA/Cdc42 activity, through which it maintains cytoskeleton stability. In DN, its expression is downregulated in podocytes, leading cytoskeleton disruption and podocyte injury. It is a potential therapeutic target for the treatment of DN.

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

### FR-PO190

**Sphingomyelinase Induces Podocyte Ferroptosis in HIV In 米milieu**


**Background:** Loss of podocytes in HIV-associated nephropathy has been attributed to both apoptosis and pyroptosis; however, the role of ferroptosis in HIV-induced podocyte injury has not been investigated up to date. Ferroptosis is a programmed caspase independent cell death process driven by cellular non-chelated iron and altered lipid environment (reduced glutathione and lipid alterations) and condensed mitochondrial structures. We asked whether lipid alteration mediated ferroptosis contributes to the loss of podocytes in HIV-associated nephropathy (HIVAN). To elucidate this aspect, we examined the role of sphingomyelinase (SMase) in the induction of podocyte ferroptosis in HIV milieu, in vivo as well as in vitro.

**Methods:** Smase activities of renal tissues of control (FVB/N, n=5) and HIVAN (Tg26, n=6) mice and vector (VHP) - and HIV-transduced human podocytes (HIV/HPs) were determined. To evaluate the effect of sphingomyelinase inhibitor (GW4869), VHP's and HIV/HPs were incubated in media containing either buffer or GW48 for 48 hours. Subsequently,

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

*Underline represents presenting author.*

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**408A**
FR-PO191

APOL1 Risk Variants Down Regulate Podocytes Nephrin Protein Expression: Role of Endoplasmic Reticulum Stress. Xuan Lan, Seyedeh Shadafarin Marashi Shohistani, Judith Eng, Ashwani Malhotra, Pravin C. Singhal. Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.

Background: Two coding sequence variants (G1 and G2) in APOL1 gene have been implicated for higher rates of chronic kidney diseases in African Americans when compared to European Americans. Previous studies from our group as well as from other investigators have elucidated that the APOL1 G1 and G2 variant proteins are more toxic to kidney cells when compared with wild type APOL1 G0; nonetheless, the involved mechanisms are not clear. The ER is as is implicated in the alignment of the physiological and pathological conditions and the lack of this gene have been reported to develop massive hypercoplasia. We hypothesize that APOL1 risk variants down regulate translation of nephrin as a consequence of endoplasmic reticulum (ER) stress.

Methods: In these studies, we used human podocytes (HPs) stably expressing APOL1G0, G1 or G2 (Vec/HPs, G0/HPs, G1/HPs, and G2/HPs). After differentiation for 7 days, the cell lysates were collected, and were subjected to Western blot to examine the protein expression of nephrin. We also isolated RNA samples from these cells, and detected the nephrin mRNA expression levels using real time-PCR. To study the role of endoplasmic reticulum stress, we evaluated the effect of APOL1 variants on podocyte phosphorylation of eIF-2α. To establish a causal relationship, podocytes expressing APOL1G0/G1/G2 were incubated in media containing either buffer or ER stress inhibitors (either salubrinal or 4-PBA-1) during differentiation followed by immunoblot analysis for nephrin.

Results: Expression of nephrin protein in G1 and G2 podocytes was dramatically decreased when compared with that in G0. Since the nephrin mRNA levels didn’t change, it appears that APOL1 risk variants affect nephrin expression at translation step. APOL1G1 and G2 dramatically increased its phosphorylation of eIF-2α, indicating that they these cell undergoing the ER stress. ER stress inhibitors rescued nephrin expression in APOL1G1 and G2 podocytes.

Conclusions: APOL1 risk variants suppress nephrin translation through enhanced ER stress.

FR-PO192

Triptolide Attenuates Proteinuria and Podocytes Apoptosis in Zebrafish via GADD45 Ling Wang, Zhao-Hong Chen, Qing Hou, Xiao-Dong Zhu, Wei-Song Qin, Cai-Hong Zeng, Zhihong Liu. National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.

Background: Dysfunction or loss of podocytes causes proteinuria, which has been associated with both acute and chronic glomerular diseases. However, podocyte target treatments are still limited. Triptolide, a major active component of Tripterygium wilfordii Hook F, has dramatic antiproteinuric effect, but the mechanism is unclear. A transgenic zebrafish model of inducible podocyte injury has been established previously. In this transgenic zebrafish, the bacterial nitroreductase (NTR) is expressed specifically in podocytes under the control of zebrafish podocin promoter, the prodrug metronidazole (MTZ) can be converted into a cytotoxic only in podocytes, which leading to podocyte injury.

Methods: We examined the effect of triptolide on transgenic zebrafish model of inducible podocyte injury. We treated zebrafish embryos with triptolide, then observed edema, measured proteinuria level as well as analyzed changes of podocin expression and foot process by immunostaining and Transmission Electron Microscope respectively. Furthermore, we performed an activated caspase-3 staining and applied microarray in triptolide-treated human podocyte. Finally, we validated the result of microarray by qRT-PCR in vitro and in vivo.

Results: Triptolide effectively alleviated edema and proteinuria in zebrafish model. The antiproteinuric effect was associated with improvement of foot process effacement, restoration of podocin expression and distribution as well as inhibition of podocytes apoptosis. Compared with the mRNA profile by microarray analysis showed GADD45 family expression was downregulated in triptolide treated human podocytes in vitro. GADD45B has been implicated in podocytes apoptosis. Triptolide could suppress the expression of GADD45 in both MTZ-treated zebrafish glomeruli and PAN-treated human podocytes.

Conclusions: These results demonstrate that triptolide has direct effect on podocyte. Triptolide attenuates podocyte injury through reversing podocyte apoptosis and downregulation of gadd45 expression.

FR-PO193


Background: MicroRNA193a negative regulates Wilms tumor (WT1) gene and plays an important role in the development of focal segmental glomerulosclerosis (FSGS). PA induces FSGS through a loss of critical number of podocytes. PA has been shown to be an inducer of apoptosis in podocytes, both in vitro and in vivo studies. We asked whether pro-apoptotic effect of PA was mediated via miR193a-induced reactive oxygen species (ROS) production in podocytes.

Methods: Immortalized human podocytes (HPs) were incubated in media containing either buffer or PA (30 μg/ml) for 24 hour and 48 hours (n=3). To determine the dose response effect, HPs were treated with variable concentration of PA (0, 10, 20, 30 μg/ml) for 24 hours. Subsequently, RNAs were extracted and CDNA as were probe for miR193a. To establish a causal relationship, HPs were incubated in media containing either buffer, PA (30 μg/ml), miR193i inhibitor (mir, 50 nM), and PA + mir inhibitor for 24 hours followed by apoptosis assay. In parallel sets of experiments, effect of miR193a inhibitor on PA-induced podocyte FROS generation was measured after DCFDA loading of control and experimental cells followed by measurement of ROS by a fluorometer. In another set of experiment, mice (n=4) were administered either normal saline or PA. After 8 days, renal cortical sections were prepared for in situ hybridization for miR193a expression and immuno-histochemical analysis for glomerular cell WT1 expression.

Results: PA enhanced podocyte expression of miR193a in a dose dependent manner. PA promoted ROS generation and apoptosis in podocytes, however, these effects of PA were partially inhibited by an inhibitor of miR193. In situ hybridization studies displayed enhanced miR193a expression by scattered podocytes in PA mice. PA mice kidneys showed decreased number of glomerular cells (control, 27.2 ± 7.6 vs. PA, 13.2±3.7 rve cells/glomerulus, P = 0.05).

Conclusions: PA contributes to podocyte injury through enhancing podocyte miR193a expression.

Fund: NIDDK Support

FR-PO194

DNA Hypermethylation of sFRP5 Contributes to Indoxyl Sulphate-Induced Renal Fibrosis Yanlin Yu, Jinghong Zhao. Dept of Nephrology, Inst of Nephrology of Chongqing and Kidney Center of PLA, Xinqiao Hospital, Third Military Medical Univ, Chongqing, China.

Background: Renal fibrosis is the most common outcome of chronic kidney disease (CKD), whereas the molecular mechanisms underlying CKD-associated renal fibrosis are not fully understood.

Methods: In this study, we used high-performance liquid chromatography (HPLC), Masson’s trichrome staining, Immunohistochemistry, Methylation-specific PCR (MSP), bisulfite-sequencing PCR (BSP), Semi-Quantitative RT-PCR, Western blotting, Immunoprecipitation.

Results: In this study, we found that in CKD patients the progress of renal fibrosis was positively related to the increase in the serum indoxyl sulphate (IS), a typical protein-bound toxin, and there was a close correlation between serum IS level and β-catenin expression in the kidneys (r=0.908, p<0.001). It was then demonstrated that intraperitoneal injection with IS for 4 weeks was able to induce renal fibrosis, accompanied by significant activation of Wnt/β-catenin signaling in uninephrectomized mice. Further investigations revealed that in cultured human renal tubular HK-2 cells IS exhibited a strong ability to silence sFRP5, an extracellular Wnt antagonistic gene, by increasing DNA methylation level of the promoter CpG island. A significant increase in ROS production and ERK1/2 phosphorylation, accompanied by increased expression of DNA methyltransferases (DNMTs), were detected before sFRP5 decline in IS-treated HK-2 cells. Similar to the inhibition of ROS production and ERK1/2 activation, treatment with 5-aza-2'-deoxycytidine, the inhibitor of DNMTs, significantly constrained IS-induced sFRP5 down-regulation and Wnt/β-catenin activation. In vivo, intraperitoneal injection with recombinated sFRP5 protein or 5-aza-2'-deoxycytidine remarkably alleviated IS-induced Wnt/β-catenin activation and interstitial fibrosis in the kidney.

Conclusions: Our results demonstrate that DNA hypermethylation of sFRP5 is involved in IS-induced Wnt/β-catenin activation that contributes to the development of renal fibrosis, which provides new insights into the pathogenesis of CKD-associated renal fibrosis.

Fund: Government Support - Non-U.S.

FR-PO195

A Novel Mouse Model Demonstrates the Role of Bone Marrow-Derived Fibrocytes in Gadolinium-Associated Systemic Fibrosis Catherine Do,1,2 Chuyuan Tan,1 Viktor Drel,1 Brent Wagner,1,2 Medicine, South Texas Veterans Health Care System, San Antonio, TX, 1Medical, Univ of Texas Health Science Center at San Antonio, San Antonio, TX.

Background: Intravenous gadolinium (Gd)-based contrast is now associated with a number of conditions, including ‘nephrogenic’ systemic fibrosis/gadolinium-associated systemic fibrosis. The pathophysiology has been largely unexplored, particularly with mouse models.

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

Underline represents presenting author.
Methods: Mice with partial nephrectomies underwent lethal irradiation then salvaged with bone marrow from green fluorescent protein (GFP)-expressing donors. After an engraftment period, these recipients were randomized to control (n=5) or Gd-based contrast treatment (n=8, 2.5 mmol/kg, 20 doses intraperitoneally over 4 weeks). Gd was assessed with inductively-coupled plasma mass spectrometry. With Gd, the kidney, liver, and lung were removed, and the tissue was stained with hematoxylin and eosin (H&E). Kidney, liver, and lung were then processed for immunohistochemistry. The fluorescence of APE1/Ref-1, Smad2/3, and -7 as well as CCR2 ligand monocyte chemoattractant protein-1, are all increased in skin and kidney after TGF-β treatment.

Conclusions: Systemic fibrosis can be induced by Gd contrast in mice. That GFP levels and expression increase in an involved organ, the skin, in tandem with a fibrocyte marker—CD45RO—supports the blood-borne circulating fibrocyte hypothesis of the disease. Importantly, similar to what is observed in a rat model, our data strongly suggest that inflammatory chemokines play a critical role in the pathogenesis of Gd-induced systemic fibrosis. Our study demonstrates that mice are an appropriate model to investigate the deleterious effects of gadolinium and will allow proceeding with mechanistic studies using relevant genetically-modified mice.

Funding: NIDDK Support, VA Support

FR-PO199

The Novel sGC Stimulator IW-1973 Inhibits Renal Inflammation and Fibrosis in Porcine Model Studies

Background: Defects in NO-soluble guanylate cyclase (sGC)-cGMP signaling are implicated in several cardiovascular diseases. IW-1973, a novel sGC stimulator has been shown to reduce blood pressure and preserve kidney function in the Dahl-s rat model (Dxs) of hypertension. Mechanically IW-1973 demonstrates direct anti-fibrotic effects through blocking TGFβ-mediated signaling in human renal proximal tubular cells. This study evaluated the effect of IW-1973 on renal inflammation and fibrosis in Dxs and unilateral ureteral obstruction (UUO) rat models.

Methods: In Dxs rats, IW-1973 treatment (1, 3 and 10 mg/kg) started 2 weeks after rats began a high salt diet and continued for 6 weeks (total 8 weeks). For the UUO model, rats underwent surgery then received IW-1973 in chow for 2 weeks.

Results: Analysis of kidneys from IW-1973-treated Dxs rats demonstrated a dose-dependent reduction in the expression of inflammatory genes TNFα, NFκB-1, ICAM-1 and VCAM-1. Acute administration of IW-1973 (1 and 10 mg/kg) significantly reduced LPS-induced increases in IL-6 and TNFα (p<0.01), and increased IL-10 levels (p<0.01) in C57BL/6 mice, supporting the anti-inflammatory activity observed in the Dxs rat model. In the UUO model, rats had statistically significant increases in renal inflammation (p<0.01), and PGC-1αO/E mice underwent surgery then received IW-1973 in chow for 2 weeks.

Conclusions: These preclinical data suggest that sGC stimulation represents a mechanism that warrants investigation for the treatment of renal inflammatory and fibrotic diseases.

Funding: Pharmaceutical Company Support - Ironwood Pharmaceuticals, Inc.

FR-PO197

PGC-1α Protects TGF-β Induced Fibrosis by Suppressing TGFβRI Expression Affected to Smad2/3 Activation

Background: Renal fibrosis results from aberrant accumulation of extracellular matrix mainly driven by transforming growth factor β (TGF-β). This process is initiated by binding of active TGF-β1 to TGF-β type I and type II receptor (TGFβRI and II) complex, which is transduced to intracellular signals for pro-fibrotic gene expression through Smad2/3 activation. Peroxisome proliferator-activated receptor (PPAR) ligands such as α-GC, are known to regulate renal fibrosis.

Methods: As in vivo and in vitro model of renal fibrosis, Left kidneys of C57BL/6J mice were subjected to unilateral ureteral obstruction (UUO) for 7 or 14 days. Human proximal tubule (HK-2) cells were stable transduced with human PGC-1α expression vector, constitutive GFP (PGC-1αg) or empty vector (Mock). PGC-1αg and PGC-1αrii-ir HK-2 cells were assessed by western blotting and immunofluorescence.

Results: The level of PGC-1α was diminished throughout the course of ureteral obstruction and was associated with increased levels of fibrotic cytokine and fibrotic markers, such as TGF-β, fibronectin, vimentin, and alpha-smooth muscle actin (α-SMA).

Consistent with in vivo data, the level of PGC-1α were reduced in TGF-β treated HK-2 cells. Stable expression of PGC-1α (PGC-1αg) in HK-2 cells attenuated the TGF-β induced upregulation of fibrotic markers (fibronectin, vimentin, and α-SMA) and downregulation of epithelial marker (E-cadherin), compared to PGC-1αrii-ir. Overexpression of PGC-1α significantly suppressed TGFβRII expression, and subsequently phosphorylation of Smad2/3 was reduced.

Conclusions: PGC-1α regulates canonical TGF-β/Smad signal pathway by targeting TGFβRII expression, resulting in anti-fibrotic effect.

Funding: Government Support - Non-U.S.

FR-PO198

Indoxyl Sulfate Triggers Increased Oxidative Stress and Eryptosis

Background: Uremic toxins increase oxidative stress and red blood cell (RBC) death (eryptosis). We explore the effect of indoxyl sulfate (IS) on reactive oxygen species (ROS) production and eryptosis, and its effect on the RBC antioxidant system.

Methods: RBC from 6 healthy subjects were incubated for 6, 12 and 24h with buffer (negative control – NC) or IS (4.49, 23.1; and 44.5mM/L) in the presence or absence of diphenylenediamine (DIPI, 10µM). Flow cytometry was used to determine eryptosis (by Annexin-V/PE staining) and ROS production (by DCFH-DA probe). Levels of reduced glutathione (GSH) were measured by spectrophotometry using tert-Butyl hydroperoxide (TBHP) as positive control. Data are presented as mean±SD.

Results: IS increased ROS in a time- and dose-dependent manner (Table 1) between 6 and 12h, and stabilized after 24h. Eryptosis increased in a dose- and time-dependent manner (Figure 1). Results indicated that IS does not affect GSH concentration (Table 1).

Table 1. ROS production, Eryptosis and GSH levels

<table>
<thead>
<tr>
<th>IS (mM/L)</th>
<th>ROS (Mean Fluorescence Intensity (MFI); µmol GSH/µg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6h</td>
<td>2.9±0.9±1.0***</td>
</tr>
<tr>
<td>12h</td>
<td>2.1±0.1±1.0***</td>
</tr>
<tr>
<td>24h</td>
<td>2.1±0.2±1.0***</td>
</tr>
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</table>

Conclusions: These findings suggest that APE1/Ref-1 inhibitor attenuates H2O2 mediated renal tubular apoptosis. APE1/Ref-1 is a multipotent protein that plays an essential role in the cellular response to oxidative stress. In the present study, we investigated the role of APE1/Ref-1 in ischemia-refusion (IR) injury in rat kidney and hydrogen peroxide (H2O2) induced renal tubular apoptosis.

Funding: Government Support - Non-U.S.

FR-PO199

Role of APE1/Ref-1 in Hydrogen Peroxide-Induced Apoptosis in Human Renal HK-2 Cells

Background: Apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) is a key metabolic regulator that stimulates mitochondrial biogenesis, and may play a role in renal fibrosis. We investigated whether PGC-1α may regulate TGF-β/Smad signal pathways in the pathogenesis of renal fibrosis.

Methods: APE1/Ref-1 siRNA was transiently localized in the nucleus in the kidney tubule cell, while there was lack of APE1/Ref-1 in the glomerulus. The fluorescence of APE1/Ref-1 was most prominent in the proximal tubule. Consistent with the expression of APE1/Ref-1, the level of APE1/Ref-1 protein also was highest in the cortex, modest in the outer medulla, and lowest in the inner medulla. In rat model of renal IR injury, the level of APE1/Ref-1 protein was increased compared with that in kidneys subjected to sham operation. We found that over-expression of APE1/Ref-1 in HK-2 cell enhanced the ratio of Bax/Bcl-2. The suppression of APE1/Ref-1 by the pharmacologic inhibitors E3330 in HK-2 cell with ROS production, resulted in decreased ratio of Bax/Bcl-2 and altered phosphorylation of ERK1/2, p38, JNK1/2, and NF-kB.

Conclusions: These findings suggest that APE1/Ref-1 inhibitor attenuates HO2- induced apoptosis in HK-2 cells by modulating the ERK/p38 signaling pathways.

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

410A
FR-PO200
Novel Non-Coding RNA Regulated by HIF-1 Suppresses Apoptosis in Renal Tubular Epithelial Cells

Jumai Mimura, 1 Yosuke Hirakawa, 1 Natsuki Kushida, 1 Yasuharu Kanji, 2 Yutaka Suzuki, 1 Hiroko Aburatani, 3 Massaomi Nagakura. 1

1 Div of Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan; 2 Div of GenomeScience, Research Center for Advanced Science and Technology, Japan.

Background: We have reported that chronic tubulointerstitial hypoxia plays an important role as the final common pathway to end-stage renal disease. HIF-1 (hypoxia inducible factor-1) is a master transcriptional factor under hypoxia, regulating downstream target genes. Genome-wide analysis of HIF-1 binding sites using high throughput sequencers has clarified various kinds of downstream targets and made it possible to demonstrate the novel effects of HIF-1, such as histone modifications. Our current study is to identify novel HIF-1 downstream epigenetic factors which may play important roles in different contexts.

Methods: HK2 (human kidney-2) and primary cultured tubular cells (RPTEC: renal proximal tubular epithelial cells) are exposed to 1% hypoxia. We performed genome-wide analysis of RNA-seq to clarify the expressions of mRNA and long intergenic non-coding RNA (lincRNA). We also examined ChIP-seq using HIF-1 antibody to identify HIF-1 binding sites under hypoxia.

Results: RNA-seq identified 580 lincRNAs which are up-regulated under hypoxic condition in both cells. ChIP-seq analysis demonstrated that HIF-1 also binds to the lincRNAs under hypoxia. The expression of novel lincRNA, DARS-AS1 (aspartyl-tRNA synthetase antisense-1), is up-regulated only under hypoxia and HIF-1 binds to its promoter region, which includes two HREs (hypoxia responsive elements). Its expression is also up-regulated with cobalt chloride exposure, while it is not under hypoxia when HIF-1 is knocked down by siRNA. To clarify the biological roles of DARS-AS1, we measured the activity of caspase 3/7 using anti-sense oligo of DARS-AS1. As a result, apoptotic cell death was significantly inhibited by knockdown of DARS-AS1.

Conclusions: We firstly identified the novel lincRNA regulated by HIF-1 under hypoxia and clarified that DARS-AS1 plays important roles in inhibiting apoptotic cell death in renal tubular cells.

Funding: Government Support - Non-U.S.

FR-PO201
Dimethyl Fumarate Treatment Regulates Macrophage Polarization upon Oxidative Stress in Renal Inflammation

Yi Li, Li Wang. Renal Dis and Inst of Nephrology, Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: Characterized by macrophage polarization, renal inflammation represents a ubiquitous human health problem, effective therapies with limited side effects are still lacking. In this study, we examine the role of Dimethyl Fumarate (DMF) in macrophage polarization induced by oxidative stress of renal inflammation.

Methods: Balb/c mice (n=10) were administrated by 50 mg/kg DMF then injected with 10 μg/kg LPS. After tested renal dysfunction and histological features upon LPS nephritis, RT-PCR detected the level of IL-6, MCP-1, TNF-α, IFN-γ, IL-10 and CD206 in murine kidney. Before stimulated with LPS, the Raw264.7 macrophage cells were respectively pre-treated with DMF, Nrf-2 agonist SNR or ROS inhibitor NAC. The results of mi-tracker staining were observed by confocal. Flow cytometry measured the production of ROS by DCF-DA and the expression of M1 macrophage marker iNOS. Western blot detected the expression of Nrf-2 and Sirt-1 in vivo and in vitro.

Results: DMF ameliorated murine LPS nephritis on renal dysfunction by reducing blood urea nitrogen and serum creatinine, then decreased the histological features following renal injury. DMF reduced TNF-α level in IL-6, MCP-1, TNF-α and IFN-γ after LPS injection, whereas it did not decrease the level of IL-10 and CD206. Compared with LPS induced Raw264.7 cells, DMF significantly inhibited the expression of iNOS and reduced the production of Nitrite. Current study also revealed the role of DMF in protecting against intracellular ROS accumulation and mitochondria dysfunction upon LPS induced nephritis. DMF increased the level of Nrf-2 and Sirt-1 following in vivo and in vitro LPS treatment.

Conclusions: This study showed that DMF augmented LPS-induced acute nephritis and related cellular malfunction, indicating protective effects of DMF on regulating macrophage polarization upon oxidative stress in LPS induced acute renal inflammation via Nrf-2-mediated pathway.

FR-PO202
Following Site-Selective Endothelial Injury, Endothelial Cells Die from Necrosis and Apoptosis, but Not from Necroptosis

Jan Sradnick, 1 Anika Ludemann, 1 Kathleen Fischer, 1 Andreas Linkermann, 2 Bernd Hohenstein, 2 Christian Hugo. 1

1 Div of Nephrology, Dept of Internal Medicine III, Univ Hospital CGC, Dresden; 2 Clinic for Nephrology and Hypertension, Univesity Hospital, Kiel, Germany.

Background: Since the introduction of our site-selective endothelial injury model in murine kidneys, we have shown that particular cell types do (platelets) or do not (extrarenal progenitor cells) play a role for the occurrence or repair of endothelial cell (EC) lesions. With respect to the initiation of disease and cellular response, the mechanisms of EC death might be relevant. We here aimed to investigate EC death following EC injury (ECI) in mice.

Methods: Using renal-arterial perfusion of ConcanavalinA (ConA)-anti-ConA, selective ECI was induced in C57Bl/6 mice. Kidneys were harvested after 24h (n=5) and 72h (n=6), 5 mice served as controls. Flow cytometry was used to analyze inflammatory cells and the expression of markers then performing them with flow cytometry. Our study is to identify novel HIF-1 downstream epigenetic factors which may play important roles in different contexts.

Results: Kidneys demonstrated EC lesions reflected by a EC reduction of 25% measured after 24h and 72h (sham 10%±2 vs d1: 7%±1; d3: 7%±1 FACS). As described previously neutrophils were increased 24h, T-cells and macrophages 72h after ECI. The amount of 7AAD+ EC was raised after 24h (14%±5; p<0.01) and 72h (16%±2; p<0.01) compared to controls (8%±1). More apoptotic EC were found after 24h (1.9±1 vs. sham 0.3±0.1; p<0.01). In contrast, less necrototic EC were found and stayed unchanged over time (contr.: 0.16%±0.1; 24h: 0.15%±0.2; 72h: 0.3%±0.2). Similar data were found in Tie2 transgenic mice injured with ECI and I/R.

Conclusions: Necrosis and apoptosis represent the dominant EC death mechanisms during the initial time course of our disease model, while necroptosis is no major cell death mechanism in EC in this disease model. These findings will now have to undergo further validation using interventional strategies blocking the individual mechanisms.

Funding: Government Support - Non-U.S.

FR-PO203
Tumor Necrosis Factor (TNF) α-Converting Enzyme Inhibitors Attenuate Lipopolysaccharide-Induced Reactive Oxygen Species and Mitogen-Activated Protein Kinase Kinase in HK 2 Cells

Yun Hui Bae, 1 Seong Kwon Ma, 1 Jong Un Lee, 1 Soo Wan Kim. 1 Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea.

Background: Lipopolysaccharide (LPS) induces acute kidney injury (AKI), which key is the development of tumor necrosis factor-1 (TNFα). TNFα-converting enzyme (TACE) is responsible for the shedding of cell surface TNF. It is also associated with ACE2 shedding. We hypothesize that LPS suppresses ACE2 by increasing TACE and TACE inhibitors attenuate LPS injury in HK 2 cells.

Methods: Intravenous LPS (10mg/kg) in male mice induced increased serum creatinine, TNFα, and urinary neutrophil gelat (NGAL).

Results: LPS increased Angiotensin II, angiotensin II type 1 receptor, mitogen activated protein kinase (MAPK), TACE expression and TACE activity, while decreased ACE2 expression in LPS induced AKI mice model and LPS-treated HK2 cell. LPS induced reactive oxygen species (ROS) and down-regulation of ACE2 expression were prevented by TACE inhibitors in HK 2 cells. Cell viability also increased by TACE inhibitor treatment in LPS treated in HK2 cells. TACE inhibition also attenuated mitogen activated protein kinase (MAPK), cytochrome oxygenase 2 (COX2), and hemodynamics-1 (HO-1) which is oxidative stress markers.

Conclusions: Our findings indicate that LPS-induced TACE activation partially contribute to ACE2 shedding and TACE inhibitors attenuate LPS-induced ROS and MAPK pathway in HK 2 cells.

Funding: Government Support - Non-U.S.

FR-PO204
Enhanced Oxidation of HDL in a Rabbit Model of Chronic Kidney Disease

Florens Eun, 1,2 Caroline C. Pelletier, 3 Sandrine Lemoinne, 1 Laurent Juillard, 1,2 Christoph Soulage, 1,2 Nephrology, Hospices Civils de Lyon, Lyon, France; 3 INSERM U1060 - CarMeN, Villeurbanne, France; 1 INSERM, Villeurbanne, France.

Background: Recent studies have shown modified proprieties for HDL in chronic kidney disease (CKD). As the cardiovascular mortality remains the major cause of death in CKD and as oxidative stress is raised in CKD, we aimed to explore the specific role of renal dysfunction, on lipoproteins modifications in a rabbit model of CKD.

Methods: Rabbits were nephrectomized with a surgical 5/6-fold reduction technique. Lipoproteins were isolated from plasma by potassium bromide stepwise density gradient ultracentrifugation. Malondialdehyde (MDA) was measured by high performance liquid chromatography (HPLC), 4-hydroxy-nonenal (HNE) and 4-hydroxy-2-hexenal (HHE) adducts were assayed by dot-blot. Copper-induced oxidation of lipidoprotein was performed with addition of CuSO4 and formation of conjugated dienes were monitored.

Results: 8 CKD rabbits were compared with 9 Sham operated. Creatinine levels were significantly higher in CKD group (93 vs 214 μM, p<0.001) as well as plasmatic level of MDA (0.98 vs 0.83 mM, p<0.05). MDA levels in LDL were not altered in the CKD group while increased in the HDL from CKD rabbits (0.89 vs 2.64 nmol/mg of proteins, p<0.05). HNE-adducts were also raised in the HDL of CKD group (p<0.05) while HHE-adducts were only raised in LDL of CKD group (p<0.05). Copper-induced oxidation showed higher production of conjugated dienes in LDL and HDL from CKD animals.

Conclusions: CKD rabbits exhibited extensive oxidative modifications in HDL, even if LDL seemed to be more sensitive to oxidation. This observation is consistent with the modified functions of HDL in CKD reported in the literature.

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

Underline represents presenting author.

411A
FR-PO205
Antioxidant Modulates Diabetes Induced Cardiorenal Injury in an Experimental Model of Cardiorenal Syndrome
Firoozeh Farahmand, Internal Medicine, Div of Nephrology, Saint Louis Univ, Saint Louis, MO.

Background: There is growing evidence that oxidative stress is one of the key mediators of cardiorenal syndrome (CRS), and has a role in pathological processes in diabetic nephropathy, as well as diabetic cardiomyopathy. Therefore, an understanding of the role of oxidative stress in both renal and cardiac oxidative stress is essential in the development of novel and effective therapeutic strategies to improve the survival and prognosis in CRS patients.

Methods: Diabetes was induced in rats with single injection of streptozocin (STZ). Animals were randomly divided into 4 groups: CONT, CONT+Lysosan, Diabetics Control, and Diabetics+Lysosan. At 4 weeks left ventricle (LV) systolic pressure (LVSP), aortic systolic (AS)pressure, LV diastolic pressure, LV hypertrophy (LVH), and LV function were measured, and the slope of the LV end-diastolic P-V relationship (EDPVR) as index of LV stiffness were calculated. After sacrificing the animals, the renal cortex and the heart were removed for histology, antioxidant enzymes, and lipid peroxidation measurement.

Results: In STZ-induced diabetic group at 4 weeks there was a significant drop in LVSP and AS pressure, and increased renal and myocardial lipid peroxidation, and decreased in antioxidants enzymes. These effects were inhibited by lysosan. In Diabetics+Lysosan group lysosan also significantly reduced renal and myocardial histopathological alterations.

Conclusions: Our results indicate diabetic nephropathy and diabetic cardiomyopathy are associated with antioxidant deficit that can be reversed with lysosan. Improved cardiac function with lysosan may be due to the recovery of the antioxidant in the heart. In the oxidative stress condition, diabetes control offer a unique therapeutic option for the treatment of cardiorenal injury in diabetes, and benefit reducing diabetes-induced renal damage.

FR-PO206
Assessing the Impact of Primary Cilia Loss on Epithelial Phenotype and Function in a Human Renal Proximal Tubular Epithelial Cell Line
Michael Higgins, Tara McMorrow. School of Biomolecular and Biomedical Science, Conway Inst, Univ College Dublin, Dublin, Ireland.

Background: The primary cilium is a hair-like microtubule based structure, protruding from nearly all mammalian cells. The primary cilium is well established as a crucial signalling hub with receptors for Wnt and hedgehog localized to the primary cilium. Primary cilia have been found to be implicated in a range of diseases collectively called ciliopathies. In recent years there has been increased interest in the link between the primary cilium and the development and progression of cancer, with several cilia associated genes dysregulated in numerous cancers. The primary cilium has been found to be absent in renal cell carcinomas, breast and pancreatic cancers. The aim of this study was to assess the impact of cilia loss on epithelial and mesenchymal marker expression and to investigate the effects on epithelial function by assessing epithelial barrier function.

Methods: A number of known deciliating chemicals were used to induce primary cilia loss. The immunofluorescent labelling of ciliary markers ARL13b and acetylated alpha tubulin were employed to confirm the absence or presence of a primary cilium in human renal cells. Western blotting and Real Time PCR were used to assess the effect of HG on caveolin-1/RhoA and Src kinases. Interference with Src/caveolin-1/RhoA signaling may provide a new therapeutic option for the treatment of renal cell carcinoma.

Results: HG-induced FN upregulation require caveolae and caveolin-1 interaction between passages 7 and 15. We then examined the influence of HG on cavin-1/RhoA signaling and FN secretion in mouse MCs.

Conclusions: We show that high levels of glucose time and dose dependently increased citrate and isocitrate, TCA cycle intermediates, in HG-treated Hcb-19 compared to C3H. As well, a 2-fold increase in malonyl CoA was observed in Hcb-19 cells suggesting that acetylCoA was driven towards lipogenesis. This data was supported by a lower PDH1ε and citrate synthase activity and protein expression in these cells. As well, the downregulation of, SeahoxF analyzer revealed that the cavin-1/RhoA cells displayed lower mitochondrial oxygen consumption and a reduced respiratory capacity. Furthermore, Hcb-19 cells displaying a markedly lower protein expression of electron transport chain complexes (ETC) I, II, and III, the key components of mitochondrial electron transport pathway mediating DN.

Funding: Government Support - Non-U.S.

FR-PO207
Reactive Oxygen Species Control Primary Cilia Length in Kidney Tubule Cells
Sang Jun Han, Jee In Kim, Kwon Moo Park. 1Dept of Anatomy and BK 21 Project, Kyungkook National Univ School of Medicine, Daegu, Republic of Korea; 2Dept of Molecular Medicine and MRC, Keimyung Univ School of Medicine, Daegu, Republic of Korea.

Background: Primary cilia is involved in kidney function. Recent studies have demonstrated that primary cilia length changes are associated with acute kidney injury, suggesting that primary cilia may play an important role the progression of various kidney diseases. Here, we investigated whether reactive oxygen mass reductions induced by unilateral nephrectomy (UNx) and transient unilateral ischemia (UI) affect primary cilia length and its molecular mechanisms.

Methods: MCs were exposed to either unilateral nephrectomy (UNx) or unilateral ischemia for 30 min (UI). Some mice were administered Mn(III) Tetrakis (1-methyl-4- pyridyl) porphyrin (MnTMPyP, a ROS scavenger) for 8 days daily beginning on 1 day after those operations. Primary cilia was visualized by immunofluorescence staining using anti-acetylated-a-tubulin antibody and its length was measured under microscope.

Results: UNx increased primary cilia length in all tubular segments including proximal tubule, Henle's loop and collecting duct, and papillic cells of the remaining kidney 9 days later. UI also increased primary cilia length in tubule cells and papillic cells of the UI-exposed kidneys. UNx and UI increased reactive oxygen species (ROS) levels in the remaining kidneys and UI-induced kidneys, respectively. Treatments of MnTMPyP prevented those elongations of primary cilia and increases of ROS production. UNx results in the hypertrophy of the remaining kidneys 9 days later. UI induced tubular cell damage and fibrosis in the UI-induced kidneys 9 days after the operation. Treatments of MnTMPyP prevented the hypertrophy of the remaining kidney after UNx and post-UI treatment.

Conclusions: ROS-induced changes of primary cilia length may play an important role for compensatory response to UNx- or UI-induced renal mass reductions.

Funding: Government Support - Non-U.S.

FR-PO208
High Glucose Stimulation of Mitochondrial Metabolism and Superoxide Generation Is Mediated by Thioredoxin Interacting Protein (TXNIP)
Anu Shah, Ling Xia, Lemuix Lua, Michael B. Wheeler, James W. Dennis, James McMorrow. 1Dept of Physiology, Univ of Toronto, Toronto, ON, Canada; 2Lunenfeld Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, ON, Canada.

Background: Thioredoxin-interacting protein (TXNIP) is an endogenous inhibitor of thioredoxin (Trx), a third protein that regulates cellular redox status. TXNIP is upregulated by high glucose (HG) and augments reactive oxygen species (ROS). We recently showed that a reduction of TXNIP inhibits HG-induced mitochondrial membrane potential and superoxide production in cultured renal mesangial cells (MCS) and that TXNIP - mice are protected from diabetic nephropathy (DN) (JASN 2015).

Methods: To investigate mechanisms, metabolic profiling and bioenergetics of HG-treated CHI (wild type) and Hcb-19 (TXNIP deficient) MCS were assessed.

Results: Metabolic analysis revealed higher glycolytic, but significantly reduced citrate and ascorbate, TCA cycle intermediates, in HG-treated Hcb-19 compared to CHI. As well, a 2-fold increase in malonyl CoA was observed in Hcb-19 cells suggesting that acetylCoA was driven towards lipogenesis. These data were supported by a lower PDH1ε and citrate synthase activity and protein expression in these cells. As well, the downregulation of, SeahoxFS analyzer revealed that HG cells displayed lower mitochondrial oxygen consumption and a reduced respiratory capacity. Further, Hcb-19 cells displayed a markedly lower protein expression of electron transport chain complexes (ETC) I, II, and III, the key components of mitochondrial electron transport pathway mediating DN.

Funding: Government Support - Non-U.S.

FR-PO209
High Glucose Induced Fibronectin Upregulation in Cultured Mesangial Cells Involves Caveolin-1-Dependent RhoA-GTP Activation via Src Kinase
Yinqiao Li, Juan Jin. Zhejiang Province People's Hospital, Dept of Nephrology, Hangzhou, China.

Background: Increasing evidence indicates that diabetic-mediated renal interstitial fibrosis through extracellular matrix protein (ECM) accumulation is a key event in the development of diabetic kidney disease (DKD). High glucose (HG) promotes excessive accumulation of ECM proteins and expression of fibrotic factors in mesangial cells (MCs), which leads to subsequent diabetic renal dysfunction. The activation of RhoA and its downstream mediator Rho kinase act as crucial mediators of strain-induced the matrix protein fibronectin (FN) secretion in MCs, which depend on intact caveolae. However, the involvement of caveolae/caveolin-1 in HG-induced dysfunction of MCs has not been assessed.

Methods: Primary MCs were obtained from Sprague-Dawley rat glomeruli by differential sieving and cultured in DMEM supplemented with supplemented with 20% fetal calf serum, streptomycin, and penicillin. Experiments were carried out using cells between passages 6 and 15. We then examined the influence of HG on cavin-1/RhoA signaling and FN secretion in mouse MCs.

Results: We show that high levels of glucose time and dose dependently increased citrate and isocitrate, TCA cycle intermediates, in HG-treated Hcb-19 compared to C3H. As well, a 2-fold increase in malonyl CoA was observed in Hcb-19 cells suggesting that acetylCoA was driven towards lipogenesis. These data were supported by a lower PDH1ε and citrate synthase activity and protein expression in these cells. As well, the downregulation of, SeahoxFS analyzer revealed that HG cells displayed lower mitochondrial oxygen consumption and a reduced respiratory capacity. Further, Hcb-19 cells displayed a markedly lower protein expression of electron transport chain complexes (ETC) I, II, and III, the key components of mitochondrial electron transport pathway mediating DN.

Funding: Government Support - Non-U.S.
**FR-PO210**

**Activation of PDGF Receptor beta (PDGFRb) by High Glucose (HG) Forces mTORC1 Signaling to Induce Proximal Tubular Epithelial Cell (PTEC) Hypertrophy and Matrix Expansion**

_Falguni Das,1,2 Nandini Ghosh-Choudhury,1 Meenalakshmi M. MARIAPPAN,1 Balakumtalam S. KASINATH,1 Goutam Ghosh-Choudhury,1,3 Medicine, UTHSCSA, San Antonio, Texas; 2Pathology, UTHSCSA, San Antonio, Texas._

**Background:** Increased expression of PDGF BB and PDGFRb has been reported in both glomerular and proximal tubular compartments in humans and rodent diabetic nephropathy. Whether hyperglycemia activates PDGF-mediated signaling in renal cells has not been investigated.

**Methods:** Human PTEC, immunoblotting, siRNA transfection, protein synthesis and cell hypertrophy assays, and mouse model of Type 1 diabetes were used.

**Results:** High glucose (HG) significantly increased phosphorylation of PDGFRb at the autophosphorylation site Tyr-857 and PI 3 kinase binding site Tyr-751 in a time-dependent manner. A PDGFRb-specific inhibitor JNJ-10198409 (JNJ) blocked these phosphorylations, resulting in inhibition of association of PI 3 kinase with the PDGFRb leading to suppression of Akt activation in response to HG. Similarly, siRNAs against PDGFRb abolished HG-induced Akt activation. Both JNJ and siPDGFRb inhibited HG-induced phosphorylation of two mTORC1 endogenous inhibitors PRAS40 and tuberin and, consequently, suppressed mTORC1 activation, as judged by phosphorylation of S6 kinase, rp65 and 4EBP-1. Interestingly, JNJ and siPDGFRb did not have any effect on HG-stimulated MEK/Erk1/2 activation and phosphorylation of their downstream target eIF4E.

**Conclusions:** These results provide the first direct evidence for the requirement of PDGFRb activation in HG-induced PTEC injury found in diabetic nephropathy. Furthermore, we uncover a specific role of mTORC1 signaling downstream of PDGFRb in hyperglycemia-induced stimulation of PTEC hypertrophy and matrix protein synthesis.

_Funding: NIDDK Support, VA Support_

**FR-PO211**

**mTORC2/PKCβ II Node Contributes to TGFB (TGFβ)-Induced Twist1 Expression and Proximal Tubular Epithelial Cell (PTEC) Injury**

_Falguni Das,1,2 Nandini Ghosh-Choudhury,1 Balakumtalam S. KASINATH,1 Goutam Ghosh-Choudhury,1,3 Medicine, UTHSCSA, San Antonio, Texas; 2Pathology, UTHSCSA, San Antonio, Texas._

**Background:** TGFB contributes to renal fibrosis via the master regulator Twist1, which regulates epithelial-mesenchymal transition (EMT) in the proximal tubular epithelial cells. But the mechanistic basis by which TGFB increases Twist1 and fibrotic marker expression remains elusive.

**Methods:** Human PTEC, immunoblotting, siRNA transfection, plasmid-derived overexpression, protein synthesis and cell hypertrophy assays were used.

**Results:** TGFB-induced expression of Twist1 in PTEC. Both PI 3 kinase inhibitor I294002 and mTOR inhibitor rapamycin blocked TGFB-induced twist1 by phosphorylation. Similarly, inhibition of PDGFRb and its complex formation with PI 3 kinase in the renal cortex of OVE26 mice with type 1 diabetes. The renal cortical PDGFRb activation was associated with phosphorylation of Akt and mTORC1 activation, and expression of fibronectin and collagen I (a2) in the diabetic mice.

**Conclusions:** These results provide the first direct evidence for the requirement of PDGFRβ activation in HG-induced Twist1 expression in proximal tubular epithelial cells.

**Funding: NIDDK Support, VA Support**

**FR-PO212**

**Investigating the Role of the PAR-1 Receptor and Th17 Cells in Idiopathic Nephrotic Syndrome**

_Carl J. May,1 Gavin Ian Welsh,2 Moin Saleem,1,2 Bristol Renal, Univ of Bristol, Bristol, Avon, United Kingdom; Bristol Royal Children’s Hospital, Bristol, Avon, United Kingdom._

**Background:** There is increasing evidence that a subset of T helper (Th17) cells can survive steroid treatment and may be driving complex insulin resistant conditions such as diabetic nephropathy, CRF, and rheumatic colitis and asthma. Additionally there is evidence to suggest a role for a circulating factor(s) released by T cells in idiopathic nephrotic syndrome. Work published previously by our group demonstrated that nephritic plasma is capable of increasing podocyte motility. This factor signals via the PAR-1 receptor. We hypothesised that Th17 cells are capable of signaling to the podocyte and that this signaling occurs via the PAR-1 receptor.

**Methods:** Th17 cells were cultured and their culture supernatants were retrieved and applied to conditionally immortalised wild-type human podocytes. Protein was extracted and used in western blotting experiments to investigate intracellular signalling. Such assays were performed to look at podocyte motility. A PAR-1 agonist containing the sequence of the tethered ligand was used to look at the effect of PAR-1 stimulation on the podocyte.

**Results:** Th17 cell culture supernatant treatment of the podocytes stimulated p38 MAPK and PAR-1 signaling pathway(s). Only the INK target site (S178) of paxillin was also phosphorylated. Th17 cell culture treatment also significantly increased podocyte motility. This effect was blocked by both JNK inhibition and Protease inhibition. Suggesting that the effector molecule in the Th17 cell culture supernatant is a protease that acts via JNK. PAR-1 agonist treatment of podocytes stimulated the same signalling events. The PAR-1 agonist treatment had such a large effect on adhesion that motility could not be measured.

**Conclusions:** This work suggests that there is a hitherto unknown protease present in Th17 cell culture supernatant that signals via the PAR-1 receptor on the podocyte and via JNK and Paxillin phosphorylation affects podocyte motility and or adhesion. Further inhibitor studies are required to confirm this pathway. However, if shown to be correct, this work provide multiple therapeutic targets that could be used to protect the podocyte against the circulating factor.

_Funding: Government Support - Non-U.S._

**FR-PO213**

**p70S6K Cross Talk with p66ShcA Modulates Progression of HIV-Associated Nephropathy (HIVAN)**

_Manoj K. Tembhe,1 Partab Rai,1 Vinod Sharma,1 Hanan K. Tawadrous,2 Anil K. Mongia,2 Seyedeh Shadafarin Marashi Shoshihari,3 Goutam Ghosh-Choudhury,1,3 Medicine, UTHSCSA, San Antonio, TX; 2Pathology, UTHSCSA, San Antonio, TX._

**Background:** Down regulation of p66ShcA has been demonstrated to provide protection against HIV mediated kidney cell injury. At present there is no effective tool to inhibit p66ShcA pathway. We observed a cross talk between p66ShcA and p70S6K. On that account we hypothesize that inhibition of p70S6K would also down regulate p66ShcA pathway and would prevent progression of HIVAN.

**Methods:** Renal tissue lysates of sex and age matched control, Tg26/p66+/- and Tg26/p66-/- mice were evaluated for phospho-p70S6K and downstream signaling. Control and Tg26 mice were administered either normal saline or PF47 (an inhibitor of p70S6K, 5mg/Kg every other day, intraperitoneally) for 4 weeks. Urinary protein analysis was carried out and renal tissue were evaluated for severity of renal lesions. Renal tissue lysates were probed for phospho-p66Shc and total p66ShcA. For in vitro studies, mouse proximal tubular cells (MT) were transduced with either empty vector (EV-MTC) or NL4-3 (HIV/MTC) and transfected with siRNAp66, siRNAp70S6K, and scrambled siRNA. Subsequently, protein blots were probed for p66ShcA, p70S6K and actin. To study molecular binding, EV/MTC and HIV/MTC lysates were immunoprecipitated with anti-p66ShcA antibody and probed for p70S6K.

**Results:** Tg26/p66+/- mice displayed attenuated renal tissue expression of phospho-p70S6K, whereas, Tg26/PF47 mice were administered either normal saline or PF47 (an inhibitor of p70S6K, 5mg/Kg every other day, intraperitoneally) for 4 weeks. Urinary protein analysis was carried out and renal tissue were evaluated for severity of renal lesions. Renal tissue lysates were probed for phospho-p66ShcA and total p66ShcA. For in vitro studies, mouse proximal tubular cells (MT) were transduced with either empty vector (EV-MTC) or NL4-3 (HIV/MTC) and transfected with siRNAp66, siRNAp70S6K, and scrambled siRNA. Subsequently, protein blots were probed for p66ShcA, p70S6K and actin. To study molecular binding, EV/MTC and HIV/MTC lysates were immunoprecipitated with anti-p66ShcA antibody and probed for p70S6K.

**Conclusions:** Cross talk between p66ShcA and p70S6K plays a role in the progression of renal lesions in HIVAN models.

_Funding: NIDDK Support_
Kidney Risk Variants Apolipoprotein L1 Increase Efflux of Rubidium in Human Embryonic Kidney Cells Opeyemi A. Obahia,1 Jayue Zhang,2 David J. Friedman,3 Martin R. Pollak.4 Internal Medicine, Massachusetts General Hospital, Boston, MA; Internal Medicine, Beth Israel Deaconess Medical Center, Boston, MA.

Background: The proposed mechanism of trypanosome lysis by human Apolipoprotein L1 (APOL1) includes APOL1-mediated ion transport across trypanosome membranes. It is unknown if pathomechanism of APOL1 mediated kidney disease also involves aberrant ion transport by kidney risk variants APOL1 (G1 or G2). We recently reported that expression of G1 or G2 APOL1 in human embryonic kidney (HEK) cells increased efflux of cellular potassium which ultimately led to cell death via induction of stress activated protein kinase signaling. To further characterize this initial finding that G1 or G2 APOL1 or their surrogates act as potassium channels in mammalian cells, we investigate if the expression of G1 or G2 APOL1 would increase the efflux of rubidium (Rb+)—a well-established tracer of potassium movement across cell membrane.

Methods: Stably transfected HEK cells were induced to express APOL1 (G0, G1, or G2) for 5 or 9Hr. The cells were loaded with Rb+ for 3Hr, then washed, and incubated for 9 Hr. Results in significant increase of extracellular, but decrease of intracellular Rb+.

Results: Compared with IgAN model group, the expression quantity of TIM1,TLR4,MyD88,TIM1 bp65,IL-4mRNA was lower (P<0.01).

Conclusions: These results corroborate our prior findings and raise the possibility that aberrant depletions of cellular potassium by G1 or G2 APOL1 may be integral to APOL1 nephropathy in individuals of recent African Ancestry.

FR-PO216
Effect of a Novel Pan-NOX Inhibitor on Phenotype Transition of Mesothelial Cells and Peritoneal Fibrosis Jiveon Ko,1 Eun Sun Ryu,1 Dal-Ah Kim,1 Sun-Hee Park,2 Yong-Lim Kim,2 Duk-Hee Kang.1 Divs of Nephrology, Ewha Womans Univ School of Medicine, Seoul, Republic of Korea; Divs of Nephrology, Kyung-Pook National Univ School of Medicine, Daegu, Republic of Korea.

Background: Oxidative stress plays a key role in the development of peritoneal fibrosis, and NADPH oxidases (NOX) substantially contribute to generation of ROS in peritoneum. However, it is not known whether each isoforms of NOX (NOX-1, -2, -4) play a different role in peritoneal damage. Recent data suggested epithelial-to-mesenchymal transition (EMT) of peritoneal mesothelial cells is an early process of fibrotic progression. Anti-oxidant effect of a novel pyrazole derivative pan-NOX inhibitor Ewha-18278 was recently reported in animal model of osteoporosis.

Methods: EMT was evaluated by an alteration of morphology and the expressions of E-cadherin and α-SMA. ROS generation & the expression of NOX isoforms were measured in TGFβ1-exposed human peritoneal mesothelial cells (HPMCs). We investigated the effect of Ewha-18278 on EMT, the expression of antioxidant [reduced/oxidized glutathione ratio (GSH/GSSG), superoxide dismutase (SOD)] and peritoneal fibrosis in animal model of peritoneal dialysis (PD) by 8-week infusion of dialysate via intraperitoneal catheter.

Results: TGFβ1 enhanced NOX activity and ROS generation. NOX-1 was the major NOX detected in HPMCs, however TGFβ1 upregulated only NOX-4 mRNA expression. Despite an absence of NOX-1 up-regulation by TGFβ1, both siNOX-1 and siNOX-4 ameliorated TGFβ1-induced EMT. Ewha-18278 decreased TGFβ1-induced ROS generation and EMT of HPMCs. In animal model of PD, intraperitoneal administration of Ewha-18278 decreased the peritoneal fibrosis with an increase in GSH/GSSG and SOD activity in peritoneal dialysate whereas it decreased the expression of nitrotyrosine in peritoneum and 8-hydroxy-2′-deoxyguanosine in dialysate.

Conclusions: Increased NOX-1/2 activity with an enhanced NOX-4 expression plays a major role in ROS generation & EMT of peritoneum. Our result indicates a novel pan-NOX inhibitor as a new therapeutic agent for treatmen of peritoneal fibrosis.

FR-PO217
Glyocolytic Sheding as a Novel Mechanism of Uric Acid-Induced Endothelial Dysfunction Jiveon Ko,1 Eun Sun Ryu,1 Dal-Ah Kim,2 Richard J. Johnson,3 Duk-Hee Kang.1 Divs of Nephrology, Ewha Womans Univ School of Medicine, Seoul, Republic of Korea; Divs of Nephrology, Univ of Colorado.

Background: Recent data suggested a causative role of uric acid (UA) in the development renal disease. Endothelial dysfunction is regarded as one of the key mechanisms of UA-induced renal disease. Endothelial-to-mesenchymal transition (EndoMT) is an early process of endothelial dysfunction, and is known to play a role in the progression of renal fibrosis. Glycolysis is a structure covering endothelium composed of membrane-bound proteoglycans and glycoproteins with adsorbed plasma components, which can cause endothelial dysfunction via intraluminal shedding.

Methods: EndoMT was evaluated by cell morphology and a comparison of the expression of VE-cadherin or CD31 and α-SMA in HUVECs and animal model of hyperuricemia (Sprague-Dawley rats fed with 2% oxonic acid for 6 weeks). NAPDH oxidase (NOX) activity, ROS generation, endothelial permeability and markers of glycocalyx shedding were assessed. To investigate the role of glycocalyx shedding in EndoMT, the effect of GM6001 (matrix metalloproteinase inhibitor) on UA-induced endo-EMT was examined.

Results: UA induced endoEMT (48 hours) and ROS generation via NOX (15 min) and mitochondrial activation (6 hours) with an increase in glycolycalx shedding (6 hours). UA-induced EndoMT, glycocalyx shedding and increase in vascular permeability were blocked by probenecid (500 μM). Anti-oxidant treatment ameliorated endoEMT; however did not change glycocalyx shedding in HUVECs. GM6001 (10 μM) also alleviated UA-induced endoMT. In the kidney of hyperuricemic rats, endothelial staining in peritubular capillaries (PTC) was decreased with de-novo expression of α-SMA in PTC. Plasma levels of syndecan-1 & harpin sulfate were increased in hyperuricemic rats, which were ameliorated by allopurinol.

Conclusions: UA per se induced a phenotypic transition of endothelial cells via oxidative stress and glyocalyx shedding, which could be one of the mechanisms of uric acid-induced endothelial dysfunction and nephropathy.

FR-PO218
Non-Canonical Regulation of Heterotrimeric G-Protein Subunits by Accessory Proteins in the Collecting Duct Taketsugu Hama,1,2 Jeffrey D. Pressly,1 Frank Park.1 1Pharmaceutical Sciences, The Univ of Tennessee Health Science Center, Memphis, TN; 2Pediatrics, Wakayama Univ, Wakayama, Japan.

Background: Heterotrimeric G-proteins are known to play a fundamentally central role in the biological homeostasis of renal tubular epithelial cells. Recent studies have shown that renal tubular epithelial cells can exhibit atypical modes of regulation on G-protein subunits through the actions of intracellular accessory proteins. Accessory proteins can bind to distinct G-protein α or βγ subunits to control a multitude of biological functions, including the repertoire of intracellular signaling, modulation of signaling amplitude, and alteration in protein mobilization within the cell.
Results: In this study, our group describes the ability of a novel accessory protein, thyroglobulin-interacting protein 13 (TRIP13), to control MAPK signalling networks by interacting with various combinations of Gβγ dimers, most notably Gβ7γγ. Of the 5 known β and 12 γ isoforms, we demonstrated that only 4 β (β1, β2, β4, and β5) and 5 γ (γ5, γ7, γ10, γ11 and γ12) isoforms were expressed in collecting duct mRNA from two different mouse lines by RT-PCR analysis. Transient over-expression of Gβγ with either Gγ1, Gγ4, or Gγ5 subunits promoted MAPK activity for ERK1/2, p38 MAPK, and SADPJK/NK, but not ERK5. In the presence of TRIP13, however, Gβγ signaling was found to selectively regulate the phosphorylation of ERK1/2 and p38 MAPK, with no observable change in the activating Gγ1Gγ5 complex. The Gγ1 Gβγ dimer combinations, Gγ1γ7 and Gγ1γ7γ12 were observed to either partially or completely lose their ability to activate ERK1/2 and p38 MAPK in the presence of TRIP13. Genetic knockdown of Gγ1 using 2 distinct short hairpin RNA constructs or over-expression of TRIP13 in collecting duct cells demonstrated accelerated wound closure by 21-47% compared to control cells, which could be partially blocked by the selective p38 MAPK inhibitor, SB203580.

Conclusions: In conclusion, TRIP13 is a newly identified accessory protein, which can selectively sequester Gγ1, and accelerate cell migration following tissue damage, and may be a future therapeutic target to control wound healing of tubular epithelial cells in the kidney.

Funding: NIDDK Support

FR-PO219

Ergothioneine Plays a Key Role in Kidney-Intestinal Interaction of CKD through Organic Cation Transporter 1 Dysfunction Yauyuki Shimozaki, Kengo Furutuchi, Shinji Kitajima, Tadashi Toyama, Akimori Hara, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Takashi Wada. Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan.

Background: Chronic kidney disease (CKD) affects other organ damages. We hypothesized that ergothioneine (ERGO), which is the anti-oxidant derived from diet, was related to the progression of CKD and kidney-intestinal interaction. We focused on organic cation transporter 1 (OCTN1) and PDZ domain containing 1 (PDZK1). OCTN1 is a specific transporter for organic cations and PDZK1 is involved in the transporter stabilization on apical cellular membrane and modulates transporter function.

Methods: To evaluate the effects of intestinal OCTN1 function in CKD, everted sac method was used in CKD model or control mice. Furthermore, the pathological changes and oxidative stress in the kidney of OCTN1−/− or OCTN1+/+ were evaluated in the CKD model mice. Moreover, the expression of OCTN1 and PDZK1 in small intestine were confirmed by RT-PCR, Western blot and immunohistochemistry.

Results: The uptake of ERGO in everted sac significantly decreased in CKD mice than that of control mice. Kidney interstitial fibrosis, muscle interstitial fibrosis, azotemia, and the content of hydroxyproline of injured kidney, was significantly advanced in OCTN1−/− mice. Moreover, oxidative stress, as assessed by 4-HNE stain and carbonyl protein ELISA, was exaggerated in OCTN1−/− mice. The mRNA and protein level of intestinal OCTN1 were not different in CKD mice, however, the localization on apical cellular membrane decreased in CKD mice intestine. The expression level of PDZK1 decreased in CKD mice.

Conclusions: The reduction of OCTN1 function and ERGO uptake may participate in oxidative stress and progression of kidney injury. The decreased PDZK1 expression may disturb OCTN1 function and stabilization on cellular membrane, which may correlate the mechanism of kidney-intestinal-network in CKD.

Funding: Government Support - Non-U.S.

FR-PO220

Indoxyl Sulfate Up-Regulates P-Glycoprotein Transporter through an Aryl Hydrocarbon Receptor Pathway Takayuki Shigesawa, 1, 2 Nathalie Mc Kay, 1, 3 Bertrand Paul, 1, 4 Bertrand Durssol, 1, 4 Philippe Brunet, 1, 5 Stephane Buruty, 1, 5 Claire Cerini, 1, 5 YRCM, INSERM UMR-S 1076, Air-Marseille Univ, Marseille, France; 2CAPES, Foundation, Ministry of Education of Brazil, 70040-020, Brasilia, DF, Brazil; 3APHM, Hôpital de la Conception, Centre de Néphrologie et Transplantation Réinale, Marseille, France; 4APHM, Hôpital de la Conception, Service d’Hématologie et de Biologie Vasculaire, Marseille, France.

Background: Chronic kidney disease (CKD) is associated with profound changes in drug metabolism. Reduction of drug renal clearances is a major reason, but some drugs with only hepatic metabolism have modified half life during CKD. CKD induces an accumulation of interstitial solutes called uricogenic toxins. Aryl hydrocarbon receptor (AhR) is a transcription factor which is activated by uricogenic toxins and mediates their toxic effects. It has been shown that urea can inhibit the function and expression of hepatic drug metabolizing enzymes and drug transporters. The objective of this work is to study the effects of the indoxyl uronic soluble indoxyl sulfate (IS), on the expression and activity of the efflux cellular transporter, P-glycoprotein (P-gp) which is encoded by ABCB1.

Methods: Levels of ABCB1 mRNA were studied by RT-PCR, the P-gp levels by flow cytometry and by western blotting. The activity of P-gp was measured with rhodamine 123 in the presence or absence of an inhibitor, verapamil. The role of AhR was studied using small interfering RNA. Transplant patients were recruited from APHM.

Results: In a human hepatocellular liver carcinoma cell line, IS increased both the mRNA and protein levels of P-gp. IS increased the efflux activity of P-gp, an effect that was partially inhibited after incubation with verapamil. The effects of IS on P-gp are AhR-dependent. Dioxin, a well known agonist of AhR, also increased the expression and activity of P-gp. In heart and kidney transplant recipients receiving cyclosporine A (n=109), a substitute for P-gp, a lower serum levels of IS need higher doses of cyclosporine to achieve the target blood level.

Conclusions: In conclusion, IS acting through AhR activates the xenobiotic efflux transporter P-gp and could modify the hepatic clearance of drugs such as cyclosporine.

Funding: Government Support - Non-U.S.

FR-PO221

Urinary Exosomes Contain MicroRNAs Capable of Paracrine Modulation of Tubular Transporters Fiona E. Karet, 1 Tannia Gracia, 1 Xiaonian Wang, 2 Ya Su, 1 Elizabeth Norgert, 1 Pablo Moreno, 3 Gos Micklem, 1 Medical Genetics, Univ of Cambridge, Cambridge, United Kingdom; 2Pathology, Univ of Cambridge, Cambridge, United Kingdom; 3Genetics, Univ of Cambridge, Cambridge, United Kingdom.

Background: Exosomes derived from all nephron segments are present in human urine, where their full functionality is poorly understood, but is known to include direct antimicrobial activity. Although one report has suggested in vitro uptake of exosomes by renal cortical collecting duct cells, most studies of human urinary exosomes have focused on biomarker discovery rather than exosome function. Exosomes from other sources have been demonstrated to contain microRNA (miRNA) species.

Methods: Urinary exosomes were isolated from healthy volunteers. The miRNA repertoire of these exosomes was identified using deep sequencing of miRNA-enriched fractions. Targets for the identified miRNAs were predicted using 5 different algorithms and a selection was validated by exposing renal tubular epithelial cells to fresh urinary exosomes and measuring their protein levels. Live cell microscopy examined cellular uptake of exosomes.

Results: 276 mature miRNAs were identified in urinary exosomes, together with some miRNA precursors, mRNA and other non-coding RNAs. For the top 10 miRNAs we found an enrichment of target genes encoding a variety of channels and transporters (eg of organic molecules and mono- and divalent ions). DAVID enrichment analysis highlighted the possibility of these identified miRNAs exerting effects on regulators of key functions such as sodium reabsorption and potassium secretion in the kidney in a paracrine manner. Selected targets were validated by qRT-PCR, and to provide proof of concept, cultured renal epithelial cells were exposed to pools of urinary exosomes, cellular exosomal uptake was confirmed and downregulation of SNAT2 and ROMK protein expression levels was observed.

Conclusions: The significant presence of miRNAs in urinary exosomes demonstrated the potential regulatory roles that these noncoding RNAs could play in the kidney. These data suggest that exosomes could be suitable for biomarker development and therapeutic options for kidney diseases, which will require further in vivo studies.

FR-PO222

PDLIM5 Is Required for Membrane Targeting of AE1 in Kidney Fiona E. Karet, 1 Ya Su, 1 Thomas F. Henrietta, 1 Yahui Yan, 1 Nathaniel, 1 Pablo Moreno, 1 Univ of Cambridge, United Kingdom; 2Univ College London, United Kingdom.

Background: Anion exchanger 1 mediates Cl/HCO3 exchange across the plasma membranes of erythrocytes and kidney epithelial cells (kAE1). In kidney, AE1’s main activity is basolaterally in type A intercalated cells. Kidney interstitial fibrosis, muscle interstitial fibrosis, azotemia and the content of hydroxyproline of injured kidney, was significantly advanced in OCTN1−/− mice. Moreover, oxidative stress, assessed by 4-HNE stain and carbonyl protein ELISA, was exaggerated in OCTN1−/− mice. The mRNA and protein level of intestinal OCTN1 were not different in CKD mice, whereas, however, the localization on apical cellular membrane decreased in CKD mice intestine. The expression level of PDZK1 decreased in CKD mice.

Conclusions: The reduction of OCTN1 function and ERGO uptake may participate in oxidative stress and progression of kidney injury. The decreased PDZK1 expression may disturb OCTN1 function and stabilization on cellular membrane, which may correlate the mechanism of kidney-intestinal-network in CKD.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO223

Calcineurin Inhibitor-Induced Endothelial Cell Injury and Dysfunction – A Role for Complement? Chia Wei Teoh,1 Magdalena Riedl,1 Lisa Robinson,2 Christoph Licht.1,2 Div of Nephrology, The Hospital for Sick Children, Toronto, Toronto, ON, Canada; 1Dept of Paediatrics, Univ of Toronto, Toronto, ON, Canada.

Background: Calcineurin inhibitors (CNIs) are widely used immunosuppressive agents which are in up to 14% of renal graft biopsies associated with thrombotic microangiopathy (TMA) (in up to 90% subclinical). Evidencing evidence suggests a central role for complement dysregulation in the pathogenesis of CNI-induced TMA. It has recently been shown that CNIs can induce endothelial cell (EC) release of complement-activating microparticles that lead to bystander EC injury. However, the exact mechanism of CNI-induced complement-mediated injury and possibly resulting EC dysfunction remains unknown.

Methods: EC cytotoxicity was assessed via LDH assay. Complement activation regulation were assessed by flow cytometry for C3c and surface bound complement regulators CD46, CD55 and CD59. EC repair was assessed by scratch wound assay. Blood outgrowth endothelial cells (BOECs) were incubated with various concentrations/durations of cyclosporine (CsA) 10 microgram/ml for 24 hours and subsequently exposed to 50% normal human serum (complement active) or heat inactivated serum (complement inactive).

Results: CsA cytotoxicity was dose and duration-dependent. An optimal balance of EC proinflammatory and CNI effect was achieved with CsA 5 microgram/ml for 24 hours. The sequence of CsA incubation (above) and 50% NHS resulted in enhanced EC complement (C3c) deposition and cell death. In addition, scratch wound healing was also significantly impaired. Of note, CsAled to upregulation of CD46, CD55 and CD59. CsA cytotoxicity is dose and duration dependent. CsA causes complement activation on EC with increased cell death and impaired endothelial repair. Unexpectedly, we found that CsA led to upregulation of surface-bound complement regulators CD46, CD55 and CD59. Further experiments are ongoing to unravel the mechanism of CsA induced complement activation and its effects on EC injury and dysfunction.

FR-PO224

TLR4 Links Uric Acid with the Innate Immune System to Mediate Injury in Proximal Tubule Cells Giacomo Guzzottol,1 Danielle Verzola,1 Samantha Milanesi,1 Barbara Bonino,1 Francesca Cappadona,1 Emanuele L. Parodi,1 Abitha Murugavel,1 Francesca Viazzi,1 Roberto Pontemoli,1 1IRCCS AOI San Martino-IST; 2IRCCS AOI San Martino-IST; 3IRCCS AOI San Martino-IST; 4IRCCS AOI San Martino-IST; 5IRCCS AOI San Martino-IST; 6IRCCS AOI San Martino-IST; 7IRCCS AOI San Martino-IST.

Background: Hyperuricaemia has been linked to the development of inflammation and proinflammatory and CNI effects. However the mechanism by which uric acid (UA) may cause these effects are poorly explored. Tubular cells (tPTCs) possess both the afferent and efferent limbs of the innate immune system, involving Toll like receptors (TLRs) and both early and late-phase cytokines. TLR4 signals through a pathway that includes a cytosolic innate immune receptor, Toll-like receptor4 (TLR4) recognize pathogen-associated danger signals but is also activated via endogenous ligands. The aim of the present study was to examine the immune activation induced by UA in TPTCs.

Methods: Human tPTCs line (HK-2) was exposed for 0-5 hours to UA (12 mg/dL). Cells were pretreated with 1 µM TLR4 antagonist (Tak242) or valasartan (5 µm) or losartan (10 µm). TLR4 ligand and protein expression were evaluated by immunofluorescence and western blots. Unstimulated and stimulated tPTCs with UA were assessed by flow cytometry for C3c and surface bound complement regulators CD46, CD55 and CD59. Further experiments are ongoing to unravel the mechanism of TLR4 induced complement activation and its effects on EC injury. Each experiment was performed in triplicate and the data were analyzed by Student’s t-test. Data were expressed as mean ± SEM.

Results: Exposure of HK-2 to UA resulted in increased gene and protein expression of TLR4 (p<0.05) and in upregulation of proinflammatory cytokine MCP-1 (p<0.05). Oxidized and/or carboxylated NOx (p<0.01). UA induced NF-κB signaling (phosphorylated-pep5) and p65 inhibition blunted the upregulation of TLR4 mRNA (p<0.001). Pretreatment with Tak242 attenuated the UA induced expression of both MCP-1 and NOx mRNA (p<0.001). While preincubation with valasartan did not affect the effects investigated, U-73122 treatment inhibited by losartan blocked both MCP-1 and NOx mRNAs.

Conclusions: Our results show that TLR4 links UA with the innate immune system to mediate injury in TPTCs. These effects are prevented by inhibition of UA intracellular transport. These results might explain the chronic tubulointerstitial damage observed in hyperuricaemic states and suggest that UA transport in pTCs is necessary for urate-mediated effects. These effects are prevented by inhibition of UA intracellular transport. These results might explain the chronic tubulointerstitial damage observed in hyperuricaemic states and suggest that UA transport in pTCs is necessary for urate-mediated effects.
3'-UTR was not affected. Transfection of LLC-PK1 cells with mir-148b mimicked reduced endogenous mortalin mRNA and protein levels, while transfection with mir-148b inhibitor resulted in an increase.

**Conclusions:** Mir-148b directly suppresses mortalin expression in LLC-PK1 cells. This indicates that mir-148b may negatively regulate mortalin expression in UUO-induced kidney injury leading to tubular proteinuria. Thus, mir-148b may be a potential therapeutic target for modulation of tubular protein reabsorption in obstructive kidney injury. Further studies should examine if mir-148b is important for mortalin expression in other conditions.

**FR-PO228**

Loss of Mitochondrial Heat Shock Protein, Mortalin during Renal Cold Storage and Transplantation

Nirmala Parajuli, Lee Ann MacMillan-Crow. Pharmacology/Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR.

**Background:** Long-term graft viability continues to be problematic after transplantation, especially in kidneys that require cold storage (CS). Our prior study reported that renal CS leads to increased mitochondrial injury and renal damage following transplantation (J. Kidney, 2: 114, 2016). Hence, studies are needed to understand the loss of mitochondrial function during kidney transplantation. Mortalin is a heat-uninducible mitochondrial chaperone within the heat shock protein 70 (Hsp70) family that maintains proper folding of mitochondrial proteins. Reduction in mortalin expression in normal cells leads to mitochondrial fragmentation and dysfunction. The goal of this study is to evaluate if mortalin is altered during renal CS and transplantation.

**Methods:** Male Lewis rat kidneys exposed to CS (18 hr) followed by transplantation (in vivo), or a rat kidney proximal tubular cells (NRK) exposed to CS (0-18 hr) followed by rewarming (in vitro) models were used. MKT-077 (a rhodacyanine dye) was used to inhibit mortalin function in NRK cells. Mitochondrial function was assessed via high resolution respirometry.

**Results:** Mortalin expression was decreased after CS plus transplantation (in vivo) or rewarming (in vitro), NRK cells treated with the mortalin inhibitor, MKT-077 (without CS) showed a dose dependent increase in mitochondrial reactive oxygen species, cell death, and impaired mitochondrial respiration. These studies suggest that inhibition of mortalin function contributes to renal mitochondrial dysfunction.

**Conclusions:** These data suggest, for the first time, that renal CS leads to altered mortalin expression/activity leading to mitochondrial dysfunction, oxidative stress, and renal cell death. New studies designed to preserve the mortalin function may have promising therapeutic implications for better outcomes after renal transplantation.

**Funding:** NIDDK Support

**FR-PO229**

Mass Spectrometry and Cellular Bioenergetics Analysis Reveals Altered Mitochondrial Function in the Kidneys of Na-H Exchanger Regulatory Factor Isoform 1 (NHERF1) Deficient Mice

Amanda R. Sherwood, 1 Syed J. Khandmiri, 2 Caryl Conklin, 1 Kenneth Gagnon, 2 Michelle T. Barati, 3 Adrienne M. Bushau, 1 Michael Merchant, 1 Eleanor D. Lederer. 11 Dept of Medicine, Univ of Louisville School of Medicine, Louisville, KY; 2 Dept of Physiology, Howard Univ, Washington, DC; 3 Nephrology, Robley Rex VA Medical Center, Louisville, KY.

**Background:** NHERF1 is a protein that plays a critical role in both defining the renal BBM but membranes of cellular organelles such as the mitochondria, leading to a lower respiration rate, 40% in mitochondrial reserve capacity. As the role of NHERF1 in total BBM protein composition has not previously been explored in the kidney cortex of 2-month old wild-type and NHERF1 KO mice, we hypothesized that LL syntheses resulting in enhanced neutrophil activation and are potentially an indicator of disease state.

**Funding:** NIDDK Support

**FR-PO230**

Organization of the Leukotriene Synthetic Complex in Neutrophils as an Indicator of Disease State

Angela Bair Schmider, 1 Matthew Godin, 1 Hunter Elliott, 1 Roy J. Soberman. 1 Medicine, Massachusetts General Hospital, Charlestown, MA; 2 Cell Biology, Harvard Medical School, Boston, MA.

**Background:** The recruitment and activation of neutrophils is a prominent component of tissue injury in anti-neutrophil cytoplasmic autoantibody-vasculitis (AAV). The chemotactic lipid, leukotriene (LTJβ), plays a role in the initial recruitment of neutrophils from the vasculature. We previously identified the LT synthetic complex to involve multiple steps in its organization on the nuclear envelope resulting in LTβ synthesis. We hypothesized that organization of the core members of this structure, 5-lipoxygenase (5-LO) and 5-lipoxygenase-activating protein (FLAP), form supramolecular structures as an additional regulatory step in LTβ synthesis resulting in enhanced neutrophil recruitment and activation.

**Methods:** We paired Static Optical Reconstruction Microscopy (STORM) with cluster analysis and Fluorescence Lifetime Imaging Microscopy (FLIM) to show the reorganization of 5-LO/FLAP into supramolecular clusters on the nuclear envelope in response to priming and activation from neutrophils of patients with AAV and healthy controls. Primary antibodies against 5-LO/FLAP were used for all microscopy experiments. STORM required secondary antibodies Cy3b and AlexaFluor647. To test the hypothesis that LT synthetic complexes were organized into larger groups, we developed unbiased automated cluster analysis algorithms to analyze primary STORM data. FLIM required AlexaFluor488 and 594 secondary antibodies.

**Results:** The priming and activation of neutrophils results in reorganization of 5-LO and FLAP into supramolecular clusters.

**Conclusion:** Using a novel approach we have identified novel supramolecular complexes of LT synthetic enzymes that play a major regulatory role in neutrophil activation and are potentially an indicator of disease state.

**Funding:** NIDDK Support

**FR-PO231**

Attenuation of Na,K-ATPase Mediated Oxidant Amplification with pNaKtide Partially Reverses PNX-Induced Experimental Uremic Cardiomyopathy

Jiang Liu, 1 Muhammad A. Chaudhry, 1 Kyle D. Maxwell, 1 Yanling Yan, 1 Xiaoliang Wang, 1 Precya Tushar Shah, 1 Asad A. Khawaja, 1 Rebecca Martin, 1 Christopher A. Drummond, 2 Steven T. Haller, 1 David J. Kennedy, 1 Jiangu Tien, 1 Zi-Jan Xie, 1 Joseph I. Shapiro. 1 Marshall Univ JCE School of Medicine; 2 Univ of Toledo College of Medicine.

**Background:** In C57BL/6 mice, Na,K-ATPase mediated oxidant amplification is involved in 5/6 renal partial nephrectomy (PNX) induced cardiac fibrosis with week 4 of post-surgery. Here we report that attenuation of Na,K-ATPase mediated oxidant amplification with pNaKtide ameliorates experimental uremic cardiomyopathy.**

**Methods:** PNX was performed and C57BL/6 mice, Na,K-ATPase mediated oxidant amplification is involved in 5/6 renal partial nephrectomy (PNX) induced cardiac fibrosis with week 4 of post-surgery. Here we report that attenuation of Na,K-ATPase mediated oxidant amplification with pNaKtide ameliorates experimental uremic cardiomyopathy.**

**Results:** Comparing with PNX group 5 weeks post-surgery, pNaKtide appeared to reverse PNX-induced anemia and cardiac hypertrophy based on heart weight/body weight ratio. Many (but not all) of the echocardiographic features of uremic cardiomyopathy were reversed by pNaKtide in a dose dependent fashion after one week administration. Specifically, left ventricular wall thickness (anterior, posterior and relative wall thickness) as well as left ventricular mass index (LVMI) were ameliorated by pNaKtide at the higher doses. The myocardial performance index (MPI) changes were not reversed by pNaKtide. At higher doses, pNaKtide also reversed the fibrosis as assessed by histology and collagen-I expression. Administration of pNaKtide also attenuated left ventricular wall thickening and ERK1/2 activation as well as oxidant stress as assessed by protein carbonylation. pNaKtide at higher doses reversed PNX-mediated increases in plasma creatinine and BUN, but not plasma cystatin C.

**Conclusions:** Attenuation of Na,K-ATPase mediated oxidant amplification with pNaKtide is able to partially reverse PNX-induced experimental uremic cardiomyopathy.

**Funding:** Other NIH Support - HL109015; HL071556; HL105649
Activation of Gβγ-Akt Signaling Mediates the Differential Effects of β2 Adrenoceptor Agonists on Mitochondrial Biogenesis

Results: 

Adrenoceptor agonist clenbuterol does not induce MB. We sought to determine the differences in signaling between formoterol and clenbuterol in renal MB. We used here hydrostatic filtration-dialysis (HFD) to enrich UEVs followed by screening their RNA content. We identified the SIRPα mutants (SIRPα Mt) that have impaired insulin signaling. This is a model of CKD. We hypothesized that SIRPα mediates organ crosstalk in CKD.

Methods: We used here hydrostatic filtration-dialysis (HFD) to enrich UEVs followed by screening their RNA content. We identified the SIRPα mutants (SIRPα Mt) that have impaired insulin signaling. This is a model of CKD. We hypothesized that SIRPα mediates organ crosstalk in CKD.

Results: Activation of ERK induces Nrf2 while p38 MAPK deactivates Nrf2 and overexpression of MCM3 in PTCs transiently increased phosphorylation of ERK1/2 followed by decreased p38 MAPK phosphorylation. Overexpression or knockdown of MCM3 in PTCs did not alter phospho-S6K/GSK3β, a kinase known to deactivate Nrf2. Overexpression of MCM3 increased expression of p21, a cyclin kinase inhibitor that stabilizes Nrf2 and is upregulated in DN. Alternatively, knockdown of MCM3 in tubule cells decreased p21. Unlike MCM3, neither member of the MCM2-7 helicase, MCM7, was not increased in renal tubules of diabetic mice, but was down-regulated in PTC following knockdown of MCM3.

Conclusions: In conclusion, regulation of ERK and p38 MAP kinase are likely mechanisms by which SIRPα stabilizes TGF-β signaling and may also serve to protect Nrf2 and p21-associated with DN. Regulation of p21 in PTC by MCM3 may also serve to stabilize Nrf2, as well as, regulating tubule cell cycle arrest and/or cell death associated with DN or other renal pathologies. Lack of MCM7 regulation in tubules of diabetic mice suggests that MCM3 induction during diabetes may have roles independent of the MCM2-7 helicase.

Funding: NIDDK Support

FR-PO246

Urinary Vesicles and Differential Centrifugation: Failure of Full Vesicle Content Recover

Lucas Musante,1 Dorota Ewa Tatarach,1 Harry B. Holthofer,1 2 Centre for BioAnalytical Sciences, Dublin City Univ, Dublin, County, Ireland; 2Freiburg Inst for Advanced Studies, Albert-Ludwigs Univ, Freiburg, Germany.

Background: Urinary extracellular vesicles (UEVs), especially the exosome fraction, are an ideal, uninvasive source of biomarkers. The bulk of protocols designed for their isolation are based on differential centrifugations at relative centrifugation force (RCF) of 20000g (P2), 40.000g (P40) and 200.000g (P200) respectively. However, a fraction of EVs sediments already at P40 and yet another fraction is in the final supernatant (SN200) to be disregarded. This means loss of diagnostic EVs throughout the process.

Methods: We used here hydrostatic filtration-dialysis (HFD) to enrich UEVs followed by differential centrifugation. Western blot (WB), ELISA and Tunable Resistive Pulse Sensing (TRSP) were used to characterize and quantify UEVs. Additionally, transmission electron microscopy (TEM) and scanning electron microscopy (SEM) were used to characterize UEVs. A major complication of chronic kidney disease (CKD) is insulin resistance, causing metabolic dysregulation of carbohydrate, protein, and lipid metabolism.

Results: Suppression of SIRPα signaling impairs insulin signaling by interfering with intracellular insulin signaling. Suppression of SIRPα improves insulin signaling, promotes lean mass and increases burning of WAT. We conclude that in CKD, SIRPα mediates cross talk between muscle and adipose tissue promoting dysregulation of protein and lipid metabolism likely exacerbating mortality.

Funding: VA Support, Private Foundation Support

FR-PO234

Minichromosome Maintenance Protein 3 Regulates Renal Tubule Cell Signaling Associated with Nrf2 Activation


Background: Altered tubule cell function contributes to progression of diabetic nephropathy (DN). Previous studies in our lab showed upregulation of minichromosome maintenance protein 3 (MCM3), a member of MCM2-7 DNA helicase, in renal tubules of diabetic mice. In addition, MCM3 protein associated with and stabilized Nrf2 in cultured tubule cells, suggesting their association and accumulation of a novel, MnSOD augmented caspase-3 cleavage. This study addressed the hypothesis that MCM3 regulates cell signaling pathways involved in Nrf2 stabilization and DN.

Methods: HK-1 human proximal tubule cells (PTCs) were transfected with MCM3 DNA or MCM3 siRNA to overexpress or knockdown MCM3, respectively. Total and phosphorylated-ERK and p38 MAP Kinases and glycogen synthase kinase 3β (GSK3β), Nrf2, p21 were analyzed by western blotting. Kidney sections of OVE26 diabetic and FVB control mice were immunostained for MCM3.

Results: Activation of ERK induces Nrf2 while p38 MAPK deactivates Nrf2 and overexpression of MCM3 in PTCs transiently increased phosphorylation of ERK1/2 followed by decreased p38 MAPK phosphorylation. Overexpression or knockdown of MCM3 in PTCs did not alter phospho-S6K/GSK3β, a kinase known to deactivate Nrf2. Overexpression of MCM3 increased expression of p21, a cyclin kinase inhibitor that stabilizes Nrf2 and is upregulated in DN. Alternatively, knockdown of MCM3 in tubule cells decreased p21. Unlike MCM3, neither member of the MCM2-7 helicase, MCM7, was not increased in renal tubules of diabetic mice, but was down-regulated in PTC following knockdown of MCM3.

Conclusions: In conclusion, regulation of ERK and p38 MAP kinase are likely mechanisms by which MCM3 stabilizes TGF-β signaling and may also serve to protect Nrf2 and p21-associated with DN. Regulation of p21 in PTC by MCM3 may also serve to stabilize Nrf2, as well as, regulating tubule cell cycle arrest and/or cell death associated with DN or other renal pathologies. Lack of MCM7 regulation in tubules of diabetic mice suggests that MCM3 induction during diabetes may have roles independent of the MCM2-7 helicase.

Funding: NIDDK Support

FR-PO235

Suppression of SIRPα Signaling Affecting Adipose Tissue and Muscle Metabolism: Evidence of Organ Cross-Talk in Chronic Kidney Disease

Jingdong Dong,1 Jian Wu,2 Zhaoxong Hu,2 William E. Mitch,1 Sandhya S. Thomas,1,2 Medicine, Baylor College of Medicine, Houston, TX; 2Medicine, Michael E. DeBakey Veteran Affairs Medical Center, Houston, TX.

Background: A major complication of chronic kidney disease (CKD) is insulin resistance, causing metabolic dysregulation of carbohydrate, protein, and lipid metabolism. The large scope of metabolic interrelationships between fat and muscle tissues in CKD suggest there is organ crosstalk between fat and skeletal muscle tissues that worsens insulin resistance, signal regulatory Protein alpha (SIRPα), regulates muscle metabolism, we hypothesized that SIRPα mediates organ crosstalk in CKD.

Methods: SIRPα whole body mutant (Mi) mice and wildtype mice (WT) were compared after inducing subtotal nephrectomy. DEXA was used to assess body composition. Skeletal muscles and adipose tissues were evaluated by western blot analysis.

Results: Compared to WT CKD mice, SIRPα Mt mice with CKD had improved insulin sensitivity signified as increased tyrosine phosphorylation of IRS1 and pAkt in skeletal muscles and adipose tissues; there also were increased markers of white adipose tissue (WAT) browning (i.e., UCP-1), 2-3 fold plus significant increases in mitochondrial activity (acytetyl-CoA carboxylase, PGC-1α --5 fold) SIRPα Mt mice also had increased lean mass vs. responses of wild type mice (WT) with CKD.

Conclusions: SIRPα mediates impaired insulin signaling by interfering with intracellular insulin signaling. Suppression of SIRPα improves insulin signaling, promotes lean mass and increases burning of WAT. We conclude that in CKD, SIRPα mediates cross talk between muscle and adipose tissue promoting dysregulation of protein and lipid metabolism likely exacerbating mortality.

Funding: VA Support, Private Foundation Support

FR-PO232

Cell Signaling, Oxidative Stress

Michelle Cell Signaling Associated with Nrf2 Activation

Robert Bruce Cameron, Craig Cano Beeson, Rick G. Schnellmann. Drug Discovery and Biomedical Sciences, Medical University of South Carolina, Charleston, SC.

Background: AKI is associated with suppression of mitochondrial function, and drugs that induce mitochondrial biogenesis (MB) are effective in preclinical models of AKI. Formoterol, a β2 adrenoceptor agonist, induces MB and stimulates recovery of renal function following AKI in mice, but the β2AR agonist clenbuterol does not induce MB. We sought to determine the differences in signaling between formoterol and clenbuterol in renal MB.

Methods: For in vitro studies, renal proximal tubule cells (RPTC) were treated with 30nM formoterol or 30nM clenbuterol. RPTC were also pretreated with 100nM gallicin, 1µM L-NAME, or 5µM ODQ. For in vivo studies, C57BL/6 mice received 0.3mg/kg formoterol or 0.3mg/kg clenbuterol (i.p.). MB was assessed by FCPP-uncoupled oxygen consumption rate using a Seahorse instrument and by mRNA expression of renalin and NDUFS1. Results: In both RPTC and mice, formoterol, but not clenbuterol, increased AKI phosphorylation after 30 min. Pretreatment with the Gβγ-inhibitor gallicin blocked formoterol-induced increases in AKI phosphorylation in RPTC. At 1h, formoterol, but not clenbuterol, increased eNOS phosphorylation, which was prevented by pretreatment with gallicin or the Akt inhibitor MK2206 in RPTC. Both formoterol and clenbuterol increased cGMP in RPTC. Formoterol-induced MB was attenuated by pretreatment with gallicin, MK2206, the NOS inhibitor L-NAME, and the sGC inhibitor ODQ in RPTC.

Conclusions: Formoterol induced MB by activating the Gβγ-Akt-eNOS-cGMP pathway, leading to increased MB gene transcription and oxidative metabolism. In contrast, clenbuterol did not activate AKI or induce MB. Formoterol and clenbuterol increased cGMP production, cGMP is necessary but not sufficient for β2AR-dependent MB. We propose that structural differences between formoterol and clenbuterol result in distinct receptor interactions that cause differential activation of the Gβγ-Akt pathway. Compound(s) that selectively activate the Gβγ-Akt pathway are efficacious inducers of MB and potential therapeutics for renal MB and injury.

Funding: NIDDK Support, Other NIH Support - R01 GM084147, VA Support
FR-PO237
Identification of Differentially Regulated Pathways in Cellular Models of Mutant Uromodulin Expression Celine Schaeffer, Matteo Trudu, Elena Pasqualotto, Stefania Merella, Dejan Lazarevic, Davide Cittaro, Luca Rampoldi. San Raffaele Scientific Inst, Milan, Italy.

Background: Uromodulin is the most abundant urinary protein. It is exclusively produced and released in the urine by renal epithelial cells lining the thick ascending limb of Henle’s loop (TAL). Mutations in UMOD, the gene encoding uromodulin, cause autosomal dominant hereditary kidney disease uromodulin-associated (ADTKD-UMOD). While the primary effect of all mutations, retention in the endoplasmic reticulum (ER), is well established, its downstream effects are still unknown.

Methods: To gain insight into ADTKD-UMOD pathogenesis, we performed transcriptional profiling and biochemical characterization of cellular models (immortalized mouse TAL cells) of robust wild-type or mutant (C150S) GFP-tagged uromodulin expression.

Results: Similar to previous studies, mutant uromodulin is ER retained, but its expression does not impact on cell viability and proliferation. Transcriptional profiling identified 45 up- and 20 down-regulated (fold change >1.5, adjusted p-value<0.05) genes in mutant cells relative to wild type ones. Up-regulated genes include several ER resident chaperones and protein disulfide isomerases. Consistently, pathway enrichment analysis indicates that mutant uromodulin expression affects ER function, protein homeostasis and calcium signaling. Interestingly, among the three branches of the Unfolded Protein Response (UPR), i.e ATF6, PERK and IRE1, only the one driven by IRE1 is induced, as shown by an increased splicing of XBP1. Treatment with specific IRE1 inhibitor Response (UPR), i.e ATF6, PERK and IRE1, only the one driven by IRE1 is induced, and calcium signalling. Interestingly, among the three branches of the Unfolded Protein Response (UPR), i.e ATF6, PERK and IRE1, only the one driven by IRE1 is induced, as shown by an increased splicing of XBP1. Treatment with specific IRE1 inhibitor.

Conclusions: Our work shows that ER stress is the main effect induced by mutant uromodulin expression. This cell model will be an interesting tool where to further dissect the molecular pathways of ADTKD-UMOD pathogenesis.

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

FR-PO238

Background: Clinical studies have identified patients with nephrotic syndrome (NS) caused by mutations in genes involved in the biosynthesis of Coenzyme Q10 (CoQ10), a lipid component of the mitochondrial electron transport chain and an important antioxidant. However, the cellular mechanisms through which these mutations induce podocyte injury remain obscure.

Methods: We developed Drosophila models of CoQ-related renal diseases by exploiting the striking similarities between Drosophila nephrocytes and human podocytes. We performed the first systematic in vivo analysis for each of the 10 COQ genes using nephrocyte-specific gene silencing, with various functions of assays, as well as electron microscopy.

Results: We found that silencing each of these COQ genes specifically in nephrocytes shortened the life span of flies. Moreover, nephrocyte-specific silencing of Coq2, Coq6, and Coq8, which are genes involved in the CoQ pathway that have been associated with genetic NS, causes juvenile lethality. Dramatic adaptive changes in these cells, resembling Coq2-silencing led to an abnormal localization of silt diaphragms, collapse of lacunar channels, and increased number of dysmorphic mitochondria. In addition, Coq2 deficient nephrocytes showed elevated levels of reactive oxygen species, and increased sensitivity to oxidative stress. These phenotypes were rescued by expressing the wild-type human COQ2 gene specifically in nephrocytes, but not the mutant allele derived from a patient with COQ2 nephropathy. Furthermore, dietary supplementation with Coenzyme Q10 reversed this phenotype.

Conclusions: We conclude that transgenic Drosophila lines carrying mutations in the CoQ pathway genes are a relevant model to explore the pathogenesis of podocyte injury, and could serve as a new drug-testing platform for novel therapeutic approaches.

Funding: NIDDK Support

FR-PO239
Mesenchymal Stromal Cells Accelerate Epithelial Tight Junction Assembly via the AMP-Activated Protein Kinase Pathway, Independently of Liver Kinase b1 Pascal Rowart,1 Pauline Ericpin,1 Jean-Marie H. Krzinski,1 Michael Sebbagh,2 Francois Jouret.1 1Univ of Liège, Belgium; 2Centre de Recherche en Cancérologie de Marseille, France.

Background: Disruption of epithelial tight junctions (TJ) is one of the earliest hallmarks of acute kidney injury (AKI). Mesenchymal stromal cells (MSC) represent a potentially useful tool to ameliorate insult-induced injury and facilitate protection, repair, and functional recovery following AKI. Hence, we hypothesized that MSC may modulate TJ. We focused on the AMP-activated protein kinase (AMPK) pathway since it participates both in energy salvage and TJ maintenance.

Methods: Madin-Darby canine kidney (MDCK) cells were cultured alone or in direct contact with rat bone marrow derived MSC (upon a 3:1 ratio) for 5 days. Next, a Ca2+ switch, i.e. switching cells from [5μM Ca2+] (for 48h) to [1.8mM Ca2+] (up to 2h), was assessed upon ZO-1 relocation by immunofluorescence, and AMPK phosphorylation was quantified by immunoblotting. Experiments were repeated using MDCK stably expressing ShRNA against the AMPK kinase, Liver kinase b1 (Lkb1), or against Luciferase (LUC, used as control).

Results: Following Ca2+ switch, ZO-1 relocation occurred significantly faster in MDCK/MSC versus MDCK. Correspondingly, phospho-AMPK total AMPK ratio was 1.7-fold increased in MDCK/MSC versus MDCK alone (n=4, p<0.001). Of note, AMPK was not detectable in MSC alone. As previously reported, Ca2+-induced ZO-1 relocation to the Lkb1 gene deletion in Lkb1-/-ShRNA versus LUC-ShRNA MDCK. However, after 48-hour Ca2+ deprivation, ZO-1 associated ZO-1 was significantly more abundant in MSC co-culture systems of either ShRNA in comparison to corresponding ShRNA MDCK alone. Following Ca2+ switch, ZO-1 relocation occurred twice faster in ShRNA MDCK/ MSC versus ShRNA MDCK alone (n=4, p<0.001). Phospho-AMPK total AMPK ratio was 1.5-fold increased following Ca2+ switch in ShRNA MDCK/MSC versus ShRNA MDCK alone (n=4, p<0.001). No difference in phospho-AMPK total AMPK ratio was observed between Lkb1-ShRNA versus LUC-ShRNA MDCK following Ca2+ switch.

Conclusions: Our results suggest that MSC may modulate AMPK activation in epithelial cells at the time of Ca2+-induced TJ assembly, independently of Lkb1

FR-PO240
nrip2 Is Required for Megalin-Dependent Endocytosis via Retinoic Acid Pathway in Zebrafish Proximal Tubule, Qing Hua, Wei-Bin, Le, Xiao-Dong Zhu, Ling Wang, Wei-Song Qin, Zhao-Hong Chen, ZhiHong Liu. National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.

Background: Nuclear receptors are transcription factors which require multiple protein-protein interactions to stimulate or repress target gene expression. Nuclear Receptor Interacting Protein 2 (Nrip2) can down-regulate transcriptional activation by binding to retinoic acid receptor in the mouse brain. Retinoic acid (RA) is essential for directing the patterning of the proximodistal nephron segmentation in zebrafish. However, the role of nrip2 and its association with RA are still unknown in zebrafish kidney.

Methods: We investigated the expression pattern of nrip2 in zebrafish by in situ hybridization. To examine the role of nrip2, we generated nrip2 knock-out (KO) zebrafish using CRIPSR/Cas9 system. Transmission Electron Microscope (TEM) and zebrafish proximal tubule uptake were carried out. We also detected the expression of megalin by immunostaining and analyzed the promoter region of megalin.

Results: nrip2 is expressed predominately and dynamically in zebrafish proximal tubule during embryogenesis. We introduced a double-strand DNA break in exon2 of nrip2 and established nrip2 KO zebrafish. TEM images show nrip2 deficiency results in reduced amount of endocytic apparatus and cilia in the proximal tubule. Endocytosis is impaired in the nrip2 deficiency embryos, the tracer 10KD FITC-Dextran were injected into the cardinal vein of embryos, which are efficiently taken up by the renal tubular cells of control embryos, in contrast, uptake is severely impaired in the nrip2 deficiency embryos. The expression of megalin is reduced in nrip2 deficiency embryos compared with wild-type embryos. There are two RA response elements are contained in the promoter region of megalin, indicating the expression of megalin could be altered by RA.

Conclusions: These results suggest that loss of nrip2 results in impaired megalin-dependent endocytosis in zebrafish proximal tubule and indicate that nrip2 acts upstream regulator of megalin via RA pathway, which will be investigated furthermore.

FR-PO241
Glomerular Endothelial Cells Exposed to Salt-Stress and Aldosterone Loose Key Components from their Glycocalyx Resulting in Functional Damage Matthew J. Butler, Simon C. Satchell. Bristol Renal, Univ of Bristol, United Kingdom.

Background: Aldosterone and salt excess exacerbate proteinuria and may contribute to the progression of kidney disease. We investigated the effects of aldosterone and salt on conditionally immortalised glomerular endothelial cell (CoGeNC) glycocalyx; a protective glycoprotein layer on cells’ luminal surface which forms part of the glomerular protein barrier and contributes to laminar shear stress (LSS) detection, as a potential mechanism of damage.

Methods: CoGeNCs were exposed to standard media (125mmol NaCl, 0 aldobsterone) or supplemented media (145mmol NaCl, 0.1mm aldosterone). Glyocalyx damage was assessed using immunofluorescence. Functional damage was assessed using cells reaction to LSS; studying up-regulation of Krupple like factor 2 (KLF2) mRNA as an index of LSS Results: 145 mmol NaCl and 0.1 nM aldosterone for 5 days resulted in significant up-regulation of matrix metalloproteinases (MMP2) and 9 mRNA, but not heparanase mRNA, and significantly reduced surface expression of heparan sulphate (HS) and syndecan 4 (Synd 4). Reduced expression was associated with a functional impairment in cells ability to up-regulate KLF2 in response to LSS.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Inhibition of MMPs using the broad spectrum inhibitor Batimastat (5µm) partially restored cells surface expression of HS and Synd 4 and maintained cells ability to up-regulate KL2f in response to LSS. 

Conclusions: Physiologically relevant levels of aldosterone, when combined with elevated salt concentrations, damage CICGECN glycocalyx. Synd 4 is a LSS sensitive molecule within the glycocalyx. MMP 2 and 9 are known to cleave Synd 4 from the glycocalyx. Inhibition of MMP 2 and 9 prevents HS and Synd 4 loss from the glycocalyx and restores the physiological response to LSS. This work suggests MMP inhibitors may protect the glycocalyx from the damaging effects of aldosterone and salt exposure.

Funding: Government Support - Non-U.S.

FR-PO242

Drug Repositioning Screening for the Discovery of Inhibitors of Keap1–Nrf2 Interaction Using Fluorescent Correlation Spectroscopy Yuki Yoshizaki, Eisie Sohara, Takayasu Mor, Eriko Kikuchi, Daiei Takahashi, Moko Zeniya, Yuya Araki, Yutaro Nomura, Tatemitsu Rai, Shinichi Uchida. Nephrology, Tokyo Medical and Dental Univ, Bunkyo-ku, Tokyo, Japan.

Background: The Keap1-Nrf2-ARE pathway signal is the major regulator of cyto-protective responses to oxidant and electrophilic stress. Recently, activation of the Nrf2 defense response has been shown to protect against several kinds of diseases, such as diabetes, cardiovascular disease, inflammation and cancer. Moreover, the Nrf2 activator Bardoxolone methyl is now clinically evaluated for the treatment of chronic kidney disease. In this study, we focused on the disruption Keap1–Nrf2 interaction, in order to up-regulate the expression of ARE-controlled cyto-protective oxidative stress response, enzyme, such as HO-1. We screened the inhibitors of Keap1-Nrf2 protein-protein interaction, in terms of drug repositioning, using Fluorescent Correlation Spectroscopy (FCS).

Methods: FCS is a method capable of measuring the fluctuation rate of a fluorescently labelled single peptide as output of the diffusion times. For this screening, we used FCS to detect the inhibition of Keap1-Nrf2 binding by drugs.

Results: We succeeded to detect the protein interaction between fluorescent TAMRA-labeled small peptides of Nrf2 and GST-Keap1, and performed drug screening using chemical screening library for drug repositioning, arranged by Tokyo Medical and Dental University chemical library center. We judged that the compound had an inhibitory effect on the binding when the measured diffusion time was not increased, compared to the sample without Keap1 protein. As a result of screening 1633 drugs, we extracted 13 drugs that reproducibly disrupted the binding of Nrf2 to Keap1 in FCS. In HepG2 cells, protein level of Nrf2 was actually increased by administration of 11 of the 13 screened drugs. Furthermore, we detected the up-regulation of ARE gene promoter activity and increasing HO-1 mRNA by 2 drugs.

Conclusions: We screened the inhibitors of Keap1-Nrf2 interaction using FCS. These two compounds could be the promising drug candidates for activation of Nrf2-ARE pathway.

Funding: Government Support - Non-U.S.

FR-PO243

The Adaptor Protein CD2AP and L-type Lectin LAM2A Regulate GPRC5B Trafficking for Its Exosome Release Kenneth Kwon, Sekyung Oh, Marisa Nacke, Keith Mostov, Joshua H. Lipschutz. 1 Medicine, Medical Univ of South Carolina - MUSC, Charleston, SC; 2Anatomy and Biochemistry/ Biophysics, Univ of Cal University School of Medicine — UCSF, San Francisco, CA; 3Cancer Research UK Beatson Inst, Glasgow, United Kingdom; 4Stanford Univ, Palo Alto, CA.

Background: Exosomes, 40-100 nm extracellular vesicles, transport biological macromolecules that mediate intercellular communications. While exosomes are known to originate from maturation of endosomes into multivesicular bodies (MVBs) with subsequent fusion of the MVBs with the plasma membrane, it remains unclear how cargos are selected for exosomal release. Previously we have shown that GPRC5B, an orphan G protein coupled receptor is induced during in vitro renal tubulogenesis and loaded on exosomes released from renal tubule cells in culture and in human kidneys. Interestingly, intercellular transfer of GPRC5B via exosomes can drive in vivo renal tubule growth.

Methods: Using an inducible expression system for the exosome cargo protein GPRC5B and following its trafficking trajectory, combined with CRISPR/Cas9 technology.

Results: we show here that CD2AP is required for internalization of GPRC5B for exosomal release, while LAM2A (also known as VIP36) inhibits exosome release of GPRC5B. LMAN2 appears to be specifically required for the accumulation in the trans Golgi network (TGN), thereby restricting GPRC5B movement along the exosomal pathway by interfering with TGN-to-endosome transport of GPRC5B.

Conclusions: We propose that GPRC5B is released into exosomes through a TGN-traversing pathway in which LAM2A critically impedes the flux of exosomes.

FR-PO244

Combination of Omega-3 Fatty Acids and Vitamin D Has Synergistic Effect on Up-Regulation of NRF-2 Expression and Down-Regulation of SREBP-1 in 5/6 Nephrectomy Rats Young Ki Son,1 Kitae Kim,1 Su Mi Lee,1 Sung Hyun Son,2 Won Suk An,1 Seong Eun Kim,1 Internal Medicine, Dong-A Univ Hospital, Busan, Korea; ‘Nephrology, BHS Han Sea Hospital, Busan, Korea.

Background: The Nrf-2 regulates antioxidant and anti-inflammatory process in kidney injury model. Recent study showed that SREBP-1 mediates angiotensin II-induced pro-inflammatory responses. The present study aimed to investigate whether omega-3 FA and vitamin D which were related with anti-inflammatory process affects the Nrf-2 and SREBP-1 expression and has anti-inflammatory, anti-apoptotic, and anti-fibrotic processes in 5/6 nephrectomy rats.

Methods: Male Sprague Dawley rats were divided into five groups: sham control (0.97% saline), 5/6 nephrectomy rats (NX) (0.9% saline), 5/6 NX treated with vitamin D (cholecalciferol 3000 IU/kg/week) group, 5/6 NX treated with omega-3 FA (300 mg/kg/day by gastric gavage) group, 5/6 NX treated with vitamin D and omega-3 FA groups. The expression of Ik-b, transforming growth factor (TGF-β1), o-smooth muscle actin (α-SMA), E-cadherin, Smads for inflammation and fibrosis, caspase-3, caspase-7, BAX, and Bcl-2 for apoptosis, and Nrf2 and SREBP-1 were examined. The expression levels of apoptosis-associated factors were examined by western blot analysis.

Results: Serum BUN and creatinine was the lowest in 5/6 NX treated with omega-3 FA and vitamin D group among 5/6 Nx rats. Compared with control, 5/6 NX group significantly up-regulated caspase 3, 3caspase, Ikβ, a-SMA, E-cadherin, SREBP-1, TGF β and Smad2/3 expression and down-regulated Smad6 and Nrf2 expression. We found that omega-3 FA prevented these up and down regulations related with apoptosis, inflammation, and fibrosis. There were no significant differences on expression of these factors between 5/6 Nx with untreated group and 5/6 Nx with vitamin D group. However, increased expression of Nrf2 and decreased SREBP-1 expression was distinguished by omega-3 FA and vitamin D combination in 5/6 Nx rats.

Conclusions: Nrf-2 activator combination of omega-3 FA and SREBP-1 reduction are potential mechanism induced by omega-3 FA supplementation attenuating pro-inflammatory pathway, fibrotic processes and apoptosis. These mechanisms may be reinforced by additional vitamin D supplementation.

FR-PO245

Molecular Insights into the Program of Proximal Tubules Surviving a Resolving Acute Kidney Injury Aurélien Batallie,1 Pierre Galichon,1,2 David Legous,3 Eric Rondeau,4,5 Alexandre Hertig,4,6 Inserm UMR S 1155, Paris, France; 7Sorbonne Univ, UPMC Université Paris 06, Paris, France; 8NérophysioLOGie et Transplantation Rénale, Hôpital Ténon, Assistance Publique - Hôpitaux de Paris, Paris, France.

Background: In human beings, even a reversible episode of acute kidney injury (AKI) increases the risk of chronic kidney disease. “Maladaptive repair” was coined to name the pro-fibrotic epithelial changes observed in the aftermath of an AKI. Our aim was to interrogate the effect of a history of a reversible AKI on the transcriptomic pattern of tubular epithelial cells facing a second aggression.

Methods: Adult C57BL6/J wild-type mice were subjected to a left nephrectomy with (AKI group) or without (Sham group) 20 minutes clamping of the right renal vascular pedicle. Histological recovery was assessed at day 28. At this time point, all mice were subjected to a second hit: angiotensin 2 was continuously administered via subcutaneous pump (1 µg/kg/min). Renal fibrosis was assessed by Sirius red coloration. Ex vivo isolation of proximal tubular cells at day 0, 28 and 56 was performed to access total mRNA for high-throughput sequencing.

Results: At day 2, AKI mice displayed acute tubular necrosis at the cortico-medullary junction, and impaired renal function. At day 28, histological recovery was complete, and indistinguishable from sham-operated mice. Arterial pressure and heart rate response to angiotensin 2 was similar in both groups. At day 56, mice with a previous history of AKI displayed significantly more renal fibrosis (p<0.001). Investigating the transcriptome of isolated tubular cells, a principal component analysis and clustering individualizes specialized transcriptomes within experimental groups. Up-regulation of metabolic pathways (oxidative phosphorylation, fatty acid metabolism, glycolysis, PPAR signalling pathway) was found in the AKI group compared to the Sham group at day 56.

Conclusions: A resolving episode of AKI poised for activation genes involved in metabolic pathways and durably sensitizes differentiated epithelial cells in a way that promotes energetic hyperactivity concurrently to organ fibrogenesis.

Funding: Pharmaceutical Company Support - Astellas Pharma; Behring, Private Foundation Support
FR-PO246

GDF11 Improves Tubule Regeneration after AKI in Elderly Mice
Xiang-Mei Chen, Lingling Wu. Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing.

Background: The effects of GDF11 on organ regeneration and repair after injury in elderly mice are highly controversial questions. However, this does not imply the autocrine and paracrine GDF11 is without effect. GDF11 is necessary in metamorphic development, and its expression level is highest in the adult kidney. The function of GDF11 on kidney regeneration and its molecular mechanism were explored in this study.

Methods: Firstly, GDF11 was restored in the kidney of old mice aged 23-24 months by four dose of intraperitoneal (i.p.) injection of recombinant GDF11 (30 mg/kg/d) 48h before bilateral kidney ischemia-reperfusion injury (IRI), and the control group was given an equal volume of vehicle. Renal function, tubular injury scores, tubule cells dedifferentiation and proliferation were assessed at IRI 72h. Next, Tgf-β Pathway Phosphorylation Antibody Array was used to analyze phosphorylation events at specific sites in human primary proximal tubule cells (HPTCs) treated by GDF11 or equal volume of 0.1% BSA. Finally, tubule cells dedifferentiation, proliferation and migration were assessed in HPTCs treated by rGDF11 in the presence or absence of the ERK1/2 inhibitor U0126 (10 μM).

Results: Firstly, GDF11 supplementation in the kidneys of aged mice increased decreased marker vimentin and Pax2 expression and the percentage of S6 phosphorylated deoxyuridine (EdU) positive proximal tubular epithelial cells. GDF11 improved the renal repair, kidney functional recovery and survival of elderly mice at IRI 72 h. Next, GDF11 upregulated Abl1, e-Myc, ERK1/2, Smad1 and Akt phosphorylation by above 1.5 fold in IRI kidneys. Finally, GDF11 promoted TNC mRNA and protein expression in vivo and in vitro after GDF11 treatment, and GDF11 regulated dedifferentiation and proliferation in proximal tubule cells via an ERK1/2-dependent pathway in vitro.

Conclusions: Our study indicated that GDF11 could increase tubule cell dedifferentiation and proliferation and improve tubule regeneration after AKI in old mice though ERK1/2 signaling pathway.

FR-PO247

Mesenchymal Stromal Cell-Elaborated Stromal Cell Derived Factor-1 (CXCL12) Is a Potency Marker, Essential for Their Migration and Renoprotective Efficacy in AKI
Anna Guo,1 Ping Zhang,2 Zhuna Hu,1 Christof Westenfelder.1,2 Medicine, U of Utah and VA Medical Centers, SLC, UT; 1Physiology, U of Utah, SLC, UT.

Background: We and others showed in preclinical and clinical studies that Mesenchymal Stem Cells (MSCs) are renoprotective when administered within hours of an acute kidney injury (AKI), due largely to (1) MSCs homing to kidneys in response to increased renal expression of SDF-1 and (2) MSC release of protective and reparative cytokines. While renal SDF-1 is upregulated in response to AKI, MSCs also express SDF-1. As SDF-1 expression decreases with passaging of MSCs, and as off-the-shelf MSCs are currently the only cell therapy available for AKI, we investigated the role of MSC-expressed SDF-1 in MSC (1) homing and (2) renoprotection.

Methods: 1) The ability of P2 wild type (wt) MSCs vs. MSCs in which SDF-1 was knocked down by siRNA (siMSCs) to migrate toward normal or injured (ATP depleted) NRK cells was assessed in a transwell system. 2) IRI AKI was induced by a renal pedicle clamp in 3 groups of 6 Fischer344 rats. Post reflow, rats were infused i.a. with saline, vehicle or siMSCs. Renal function, tubular injury scores, tubule cells dedifferentiation and proliferation were assessed in AKI 24h. 3) Normal Rat Kidney (NRK) cells was assessed in a transwell system. 2) IRI AKI was induced by a renal pedicle clamp in 3 groups of 6 Fischer344 rats. Post reflow, rats were infused i.a. with saline, vehicle or siMSCs. Renal function, tubular injury scores, tubule cells dedifferentiation and proliferation were assessed in AKI 24h. Finally, ERK1/2 signaling pathway was investigated in NRK cells treated with saline, P2 MSCs or siMSCs.

Results: Firstly, SDF-1. As SDF-1 expression decreases with passaging of MSCs, and as off-the-shelf MSCs are currently the only cell therapy available for AKI, we investigated the role of MSC-expressed SDF-1 in MSC (1) homing and (2) renoprotection. As SDF-1 expression decreases with passaging of MSCs, and as off-the-shelf MSCs are currently the only cell therapy available for AKI, we investigated the role of MSC-expressed SDF-1 in MSC (1) homing and (2) renoprotection.

Conclusions: SDF-1 is a known renal cell survival factor and distress signal. Increased expression of pro-inflammatory cytokines and homeostatic chemokines, suggesting that SDF-1 in injured kidney is detrimental and contribute to sustained inflammation and maladaptive repair after AKI. Notably, lineage tracing analysis demonstrated that resident fibroblasts diversified into fibroblasts with distinct phenotypes, including p75 neurotrophin receptor expressing fibroblasts, retinoic acid producing fibroblasts and homeostatic fibroblasts producing fibroblast growth factor 21 with anti-Cd4 monoclonal antibody as well as dexamethasone abolished TLTs and improved renal outcomes. TLTs were also observed in aged human kidneys, whose cellular and molecular components were similar to those of mouse TLTs.

Conclusions: TLTs represent a novel therapeutic target of AKI in the elderly.

Funding: Pharmaceutical Company Support - Mitsubishi Tanabe Pharma Corporation, Government Support - Non-U.S.

FR-PO250

Kidney Damage Triggers a PGC1α-to-c-MYC Warburg Shift Perpetuating the Activation of Fibrogenic Progenitor Cells
Dario R. Lemos,1 Gamze Karaca,1 Ivan G. Gomez,1 Graham Marsh,1 Bryce Gordon Johnson,1 Benjamin D. Humphreys,2 Jeremy Stuart Duffield,1 Biogen, Cambridge, MA; 1Div of Nephrology, Washington Univ, St. Louis, MO.

Background: CKD is characterized by fibrosis & inflammation, two major factors impairing tissue regeneration. This inflammatory milieu is deleterious to epithelial cells. In the same environment, however, mesenchymal progenitor cells proliferate and differentiate into myofibroblasts, suggesting inflammatory signals have a positive impact on fibroblast metabolism.

Results: Whole genome analysis of kidney from patients with CKD & fibrosis revealed a unique metabolic signature characterized by reduced expression of genes involved in oxidative phosphorylation (Ox Phos), mitochondrial (mito) activity, and elevated glycolysis and autophagy. Using the kidney ischaemia reperfusion model, we found a similar metabolic shift within 72hs after damage. The injured kidney displays increased autophagy, reduced levels of the autophagy cargo protein P62/SQSTM1, loss of the mito biogenesis regulator PGC1α, and the concomitant upregulation of the glycolysis master regulator c-MYC and downstream targets. Nuclear localization of c-MYC in interstitial fibrogenic cells, indicated c-MYC is active 72hs after damage. Stimulation of PDGFRβ+ fibrogenic progenitors from young and mouse kidneys in vitro with IL1, TNFα and LPS, induced autophagy, loss of P62, reduced mTORS signaling, and triggered the PGC1α-to-c-MYC switch. This transcriptional shift resulted in a metabolic phenotype characterized by lower Ox Phos. capacity and increased aerobic glycolysis. The latter driven by c-MYC as indicated by the blockade of the effect of JQ1 on PGC1α, a two previously characterized c-MYC inhibitors. Similar to observations in cancer cells, the inflammatory signals induce proliferation of PDGFRβ+ progenitor cells in a c-MYC-dependent manner. Direct interaction with P62 regulates c-MYC levels in human PDGFRβ+ progenitors.

Conclusions: We have identified a novel molecular mechanism driving the activation of mesenchymal fibrogenic progenitors in response to damage. The mechanism relies on a metabolic switch that resembles the Reverse Warburg effect observed in cancer associated fibroblasts.

Funding: Pharmaceutical Company Support - Biogen
Myeloid Cell Heme Oxygenase-1 Expression Regulates the AKI to CKD Transition

Jeremy M. Lever,1 Ravindra Boddula,1 Orelouwa O. Adeyomi,1 James George,2 Anupam Agarwal,1,3 1Div of Nephrology, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL; 2Div of Cardiothoracic Surgery, Dept of Surgery, Univ of Alabama at Birmingham, Birmingham, Birmingham, AL; 3Birmingham VA Medical Center, Birmingham, AL.

Background: Acute kidney injury (AKI) is a major public health concern, accounting for up to 3% of hospitalized patients. Those who experience AKI requiring dialysis are at a 28-fold increased risk of chronic kidney disease (CKD). Heme oxygenase-1 (HO-1) is an inducible, ubiquitous, cytoprotective enzyme that catalyzes the heme. Its induction is protective in animal models of AKI. We have demonstrated that myeloid cell HO-1 deficiency results in worse ischemia-reperfusion injury (IRI) in the acute setting.

Methods: For this study, we modeled the AKI to CKD transition in mice using unilateral IRI, leaving the contralateral kidney intact, and followed the animals for 3 weeks. Given the importance of macrophages (MΦs) in regulating kidney damage after AKI, we hypothesized that HO-1 deficiency in myeloid cells would lead to worse outcomes in this model. We used cre-lox mice in which HO-1 is deleted in myeloid cell populations (LySO-MOH-1-/-).

Results: Surprisingly, we found LysM-HO-1-/- mice exhibited less proteinuria and renal fibrosis, when compared with fixed control mice (LysM-HO-1+/+) (urinary ACR: 0.13 ± 0.02 vs 0.188 ± 0.02 in LysMO-H1-/- and LysMO-HO-1+/+, respectively, p<0.05). In addition, greater absolute numbers of bone marrow-derived MΦs (F4/80+/CD11b+) 7.22x10^4 vs 4.9x10^4 vs 6x10^4 (p<0.03) and NK cells (NK1.1. 4.5x10^4 vs 6x10^4 vs 2.4x10^4 vs 5x10^4, p=0.02) were observed in injured kidneys from LysM-HO-1-/- mice, indicating these cell types may play a protective role in this model. Further, myeloid cell HO-1 deficiency resulted in a trend toward lower proportions of pro-fibrotic tissue-resident MΦs (F4/80+/CD11b+), 12.14 ± 1.3% versus 15.66 ± 1.6%, p=0.07).

Conclusions: These studies demonstrate that HO-1 expression in myeloid cells regulates progression in the AKI to CKD model, having potential implications for developing cell-based therapies or strategies involving modulation of HO-1 expression in the AKI to CKD transition.

Funding: NIDDK Support, Other NIH Support - NIGMS Medical Scientist Training Program

FR-PO254

Umbilical Cord-Derived Cells Protect against Maladaptive Repair in Renal Ischemia-Reperfusion Injury

Camila Eleuterio Rodrigues, Jose Manuel Condor Capcha, Ana C. de Bragança, Talita S. Ranches, Priscila Queiroz Gouveia, Denise M. Malheiros, Patricia Ferreira Oliveira, Mirela Santinido, Rildo A. Volpini, Irene L. Noronha, Lucia Andrade. Univ of Sao Paulo, Brazil.

Background: Human umbilical cord-derived mesenchymal stromal cells (huMSCs) are a treatment option in ischemia/reperfusion injury (IRI)-induced AKI, but their role in slow progression to CKD is unclear.

Methods: Male rats were induced to renal IRI, i.e. injected 6h later with saline or 1x10^6 huMSCs suspended in saline. On day 2 (D2), D7 or D49, we evaluated plasma and urinary parameters. In kidney tissue, we performed western blotting (AQP2, β-gal, p21, p16, TGFβ, miRNA expression). Data are mean±SEM.

Results: On D2, renal filtration and tubular function were better in treated rats. Recovery was similar on D7, but treated rats showed less dysfunction on D49.

Conclusions: Treatment with huMSCs might slow progression from AKI to CKD. (Supported by FAPESP).

Funding: Government Support - Non-U.S.

FR-PO255

Tenascin-C Expressing Stromal Cell Is a Potential Niche for the Injury Repairing of the Kidney following Ischemia-Reperfusion Injury

Qionghong Xie, Min Zhang, Xiaoyi Mao, Da Shang, Chuanming Mao. Div of Nephrology, Huashan Hospital, Shanghai, China.

Background: Tenascin-C (TNC), a non-structural extracellular matrix glycoprotein, is involved in creating a specific microenvironment for cell survival, proliferation and migration. The study examined the role of tenascin-C in ischemic reperfusion (IR) induced acute kidney injury (AKI).

Methods: A TNC promoter driven inducible CreER2 knock-in mouse line with an EGFP was generated and IR was used as an AKI model. Homozygous TNCcreER2+/+ (TNCCre2) was used to examine the role of TNC in AKI. The cellular distribution of TNC in the kidney was determined using immunohorrorcense and TNC reporter transgenic mice. The double-transgenic TNC-CreER2 Rosa26TdTmice were used for cell lineage tracing.

Results: TNC is normally expressed in renal medullar interstitial cells (RCMC) and markedly induced in the whole kidney, especially in the outer medulla and the cortex.

Inhibition of TGF-β Activity by a RGD Small Molecule Alpha V Integrin Inhibitor Reduces Fibrosis in a Mouse Model of Nephrotic Inulin Diet

Rosa-tdTomato mice, 1,3 Subhashini Ferreira,1,3 Malheiros, Patricia O. Eleuterio, Jose Manuel Condor Capcha, Ana C. de Bragança, Talita S. Ranches, Priscila Queiroz Gouveia, Denise M. Malheiros, Patricia Ferreira Oliveira, Mirela Santinido, Rildo A. Volpini, Irene L. Noronha, Lucia Andrade. Univ of Sao Paulo, Brazil.

Background: Targeting TGF-β activity is an attractive strategy for anti-fibrotic therapy. However, clinical trials have shown that global targeting of TGF-β signaling has serious adverse effects. A more promising approach is to disrupt TGF-β activation specifically in the injured tissue. TGF-β is held in an inactive state by binding of the Latency Associated Peptide (LAP) to the extracellular matrix (ECM). Binding of alpha v integrins to the arginine-glycine-aspartic acid (RGD) LAP motif is a major mechanism that releases biologically active TGF-β. Inhibition of integrin binding to the RGD motif prevents TGF-β activation.

Methods: CWHM-12 is novel highly potent peptidomimetic that inhibits all RGD integrins. CWHM-12 potently blocked TGF-β activation by LTC-14 myofibroblasts with a mean IC50 value of 1.5 nM (SD 0.78 – n=4). To determine if inhibition of RGD integrins could prevent kidney fibrosis, we tested CWHM-12 in mice exposed to the nephrotoxin Aristolochic Acid-I (AA). Active drug was infused by osmotic mini-pumps at a rate of 1 mg/kg body weight per day. Kidney injury was induced by a single intra-peritoneal injection of AA (5 mg/kg body weight) 1 day after drug infusion.

Results: 28 days after injury, serum creatinine was significantly less (0.15 ± 0.02 mg/dl, P<0.01) in animals treated with CWHM-12 compared with vehicle, indicating partial renal protection. CWHM-12 significantly attenuated upregulation of TGFβ1 mRNA (32 ± 7-fold), a major component of ECM deposition in injured kidneys; this was confirmed by Sirius red staining. Smooth muscle actin staining revealed a significant decrease (26% area) in drug treated kidneys versus vehicle (n=3, P<0.001). RNA-seq analysis revealed a significant decrease in many predicted (Col1a1, Mmp2, Fln1, Cigl) and activated myofibroblast genes (Rgs6, Crif1, Gli1, Pdgfrb) in injured kidneys treated with CWHM-12.

Conclusions: Inhibition of RGD integrins is a promising novel therapeutic approach to slow progressive CKD by limiting fibrosis.

FR-PO251

Proximal Tubule-Specific Heme Oxygenase-1 Modulates the Progression of AKI to CKD

Laurence Marie Black,1 James George,2 Anupam Agarwal,1,3 Subhashini Bolitsy,1 1Nephrology Research and Training Center, Div of Nephrology, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL; 2Dept of Surgery, Univ of Alabama at Birmingham, Birmingham, Birmingham, AL; 3Birmingham VA Medical Center, Birmingham, AL.

Background: Acute kidney injury (AKI) is associated with high morbidity and mortality, and can lead to chronic kidney disease (CKD), though the mechanism(s) are unclear. AKI is ameliorated by the induction of heme oxygenase-1 (HO-1), a cytoprotective enzyme that catalyzes the breakdown of pro-oxidant heme, into pro-survival by-products. Such induction of HO-1 occurs predominately in renal proximal tubules (PT), which are important for fluid, nutrient, and electrolyte homeostasis and thus consume significant energy.

Methods: To evaluate the role of PT-specific HO-1 in the transition from AKI to CKD, we used transgenic mice generated using the cre-lox system, to manipulate HO-1 expression specifically in the PT. We examined the progression to CKD using unilateral kidney ischemic injury (30 minutes) followed by reperfusion and leaving the contralateral kidney intact.

Results: We demonstrate that select PT-specific HO-1 deletion lessens the severity of fibrotic remodeling in the injured kidney, as evident by decreased expression of fibronectin, α-smooth muscle actin, and reduced collagen deposition. PT deletion of HO-1 also led to significantly reduced expression of inflammatory markers, such as TNF-α, in the injured kidneys compared to wild-type littermates. Interestingly, HO-1 led to decreased levels of urinary neutrophil gelatinase-associated lipocalin (NGAL), a biomarker of AKI, at 24h post-injury and reduced NOGAL gene expression in the injured kidneys at day 21.

Conclusions: These results suggest a role of PT-specific HO-1 in modulating fibrotic remodeling post-ischemic injury and may provide insight into the generation of therapies for preventing progression from AKI to CKD.

Funding: NIDDK Support, VA Support
Kidney injury.

Par polarity protein family, first found to be important in establishing embryonic polarity in C. elegans. Par1a and Par1b are functionally redundant mammalian homologues that are highly expressed basolaterally in the developing kidney and regulate cell adhesion and polarity. Mice with 1 of 4 copies of Par1a or Par1b deletion had severe adhesion defects are hallmarks of acute kidney injury which lead to transport defects and back-leak of toxins. We hypothesize that Par1 proteins play an important role in acute kidney injury recovery by regulating polarity and adhesion.

To test the effect of Par1a and 1b deletion on development of renal tubular injury,
cisplatin treated mice were significantly lighter than that of vehicle with cisplatin treated mice (p<0.05). In microscopy, Par1-/- Par1b-/- Par1a Par1b deletion mice showed regenerative tubules and cell adhesion.

Partitioning defective (Par)1 is a serine threonine kinase member of Par polarity protein family, first found to be important in establishing embryonic polarity in C. elegans. Par1a and Par1b are functionally redundant mammalian homologues that are highly expressed basolaterally in the developing kidney and regulate cell adhesion and polarity. Mice with 1 of 4 copies of Par1a or Par1b die after birth and have hypoplastic kidneys with abnormal proximal tubular cell-cell adhesion. Increased expression of Par1a and Par1b is noted in acute kidney injury in mice and humans. Apico-basolateral adhesion defects are hallmarks of acute kidney injury which lead to transport defects and back-leak of toxins. We hypothesize that Par1 proteins play an important role in acute kidney injury recovery by regulating polarity and adhesion.

Methods: To test the effect of Par1a and 1b deletion on development of renal tubular injury, cisplatin treated mice were significantly lighter than that of vehicle with cisplatin treated mice (p<0.05). In microscopy, Par1-/- Par1b-/- Par1a Par1b deletion mice showed regenerative tubules and cell adhesion.

Conclusions: Mice with loss of Par1a or 1b exhibited more severe tubular injury following cisplatin injection in mice. This was associated with severe mis-localization of cell-cell adhesion proteins and increased apoptosis. This experimental model suggests that Par1b in contributes to cellular polarity and renal regeneration in the setting of acute kidney injury.

Funding: NIDDK Support, Other NIH Support - NIH RO3 DK105242, Clinical Research Support

FR-PO255

Persistent Kidney Injury Molecule-1 (Kim-1) Promotes AKI to CKD Transition after Severe Renal Ischemia-Reperfusion Injury (IRI)

Xiaoying Gu,1 Xizhong Zhang,2 Aaron R. Haig,1 Lakshman Gunaratnam,2
1West China School of Medicine, Chengdu, Sichuan, China; 2Schluch School of Medicine and Dentistry, Western Un, London, ON, Canada.

Background: Maladaptive repair after acute kidney injury (AKI) driven by renal tubular epithelial cell (TEC) secretion of profibrotic factors results in tubulointerstitial fibrosis and chronic kidney disease (CKD). Kim-1 is a phosphatidylinerse receptor upregulated on proximal TECs during AKI. We showed Kim-1 mediates phagocytic clearance of apoptotic and necrotic cells and protects against renal damage acutely after bilateral renal IRI. However, transgenic overexpression of Kim-1 in TECs promotes spontaneous kidney fibrosis. We thus investigated whether Kim-1 can promote AKI to CKD transition.

Methods: We subjected Kim-1 deficient (KO) and wild-type (WT) mice to unilateral renal pedicle clamping for 35 min (moderate) or 45 min (severe) (n=3-5/group/ experiment). Mice were euthanized at 3 and 28 days. Renal damage and fibrosis were assessed by a pathologist blinded to mouse genotype using standard scales. Quantitative RT-PCR was used to detects expression of profibrotic factors (Collagen-1&4) and inflammatory cytokines (MCP-1, IL-1β, IL-6, TNF-α) and Kim-1.

Results: As expected, KO mice exhibited worse renal injury (median injury score 4.5 vs 3.5, p<0.05) and greater MCP-1, IL-1β and IL-6 mRNA expression (p<0.05 for each) than WT mice 3 days after moderate UIRI. Surprisingly, these differences were not present 3 days after severe UIRI. At 28 days, renal fibrosis, profibrotic factors, and inflammatory cytokines were not different between KO and WT mice after moderate UIRI, but after severe UIRI, KO mice had less fibrosis (p<0.05). In microscopy, KO mice exhibited increased tubular epithelial cell necrosis and fibrosis (p<0.05 vs each).

Conclusions: Our data suggest that Kim-1’s protective role during the acute phase of AKI is overwhelmed if the injury is severe, and that persistent Kim-1 expression after severe injury can promote long-term renal fibrosis. These results have implications when considering potential therapeutic options that target Kim-1 during AKI.

Funding: Government Support - Non-U.S.

FR-PO256

NecroX-7, Necroptosis Inhibitor, Attenuates Cisplatin Nephropathy

Abhijeet Pal1,2,1 Jong Jeong Young,1,2 Hong Jin Bae,1,2 Young Rok Bae,1,2 Kang Wook Du,1 Kimberly Pal1,2,1
1Pediatric Nephrology, Children Hospital of Montefiore and Albert Einstein Medical College, Bronx, NY; 2Emergency and Critical Center, The Univ of Tokyo, Bunkyou, Tokyo, Japan; 3Emergency and Critical Care Medicine, The Univ of Tokyo, Bunkyo, Tokyo, Japan.

Background: Reactive oxygen species (ROS) generation and necrosis play a important role in cisplatin nephrotoxicity. There have been developed NecroX series that can attenuate necroptosis pathway. Especially, NecroX-7 showed anti-necroptotic and anti-oxidative feature. We investigated the effect of NecroX-7 on cisplatin nephrotoxicity in mice.

Methods: C57BL/6 mice were divided into 4 groups; normal control group (n=7), NecroX-7 treated control group (n=7), vehicle with cisplatin (20mg/kg, intraperitoneal injection) treated group (n=9), and NecroX-7 (2mg/kg, intraperitoneal injection) with cisplatin treated group (n=9). NecroX-7 with cisplatin injected mice were euthanized at 1 day or 7 day. We examined histologic findings (H&E and PAS stain). We examined for oxidative stress and necroptosis.

Results: The levels of BUN and serum creatinine in NecroX-7 with cisplatin treated mice were significantly lower than that of vehicle with cisplatin treated mice (p<0.05). In microscopy, NecroX-7 significantly reduced renal tubular epithelial cell necrosis and detachment in cisplatin treated mice kidney. NecroX-7 significantly reduced RIP1, RIP3, MLKL, and PARP in cisplatin treated mice kidney. Also it reduced p22phox expression and 4-40I deoxyoxynasine positive cells in cisplatin treated mice kidney. Rileved UCP2 expression in cisplatin treated mice kidney.

Conclusions: NecroX-7 attenuates oxidative and necrotic renal injury in cisplatin induced nephrotoxicity.

FR-PO257

NecroX-7, Necroptosis Inhibitor, Attenuates Cisplatin Nephropathy

Abhijeet Pal1,2,1 Jong Jeong Young,1,2 Hong Jin Bae,1,2 Young Rok Bae,1,2 Kang Wook Du,1 Kimberly Pal1,2,1
1Pediatric Nephrology, Children Hospital of Montefiore and Albert Einstein Medical College, Bronx, NY; 2Emergency and Critical Center, The Univ of Tokyo, Bunkyou, Tokyo, Japan; 3Emergency and Critical Care Medicine, The Univ of Tokyo, Bunkyo, Tokyo, Japan.

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Conclusions: NecroX-7 attenuates oxidative and necrotic renal injury in cisplatin induced nephrotoxicity.

FR-PO258

NecroX-7, Necroptosis Inhibitor, Attenuates Cisplatin Nephropathy

Abhijeet Pal1,2,1 Jong Jeong Young,1,2 Hong Jin Bae,1,2 Young Rok Bae,1,2 Kang Wook Du,1 Kimberly Pal1,2,1
1Pediatric Nephrology, Children Hospital of Montefiore and Albert Einstein Medical College, Bronx, NY; 2Emergency and Critical Center, The Univ of Tokyo, Bunkyou, Tokyo, Japan; 3Emergency and Critical Care Medicine, The Univ of Tokyo, Bunkyo, Tokyo, Japan.

Background: Reactive oxygen species (ROS) generation and necrosis play a important role in cisplatin nephrotoxicity. There have been developed NecroX series that can attenuate necroptosis pathway. Especially, NecroX-7 showed anti-necroptotic and anti-oxidative feature. We investigated the effect of NecroX-7 on cisplatin nephrotoxicity in mice.

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Conclusions: NecroX-7 attenuates oxidative and necrotic renal injury in cisplatin induced nephrotoxicity.
Glomerular abnormalities including sclerosis were not found in the both groups. Orally administration of telmisartan, an angiotensin II receptor blocker, improved interstitial fibrosis not in the URI+UNx group, but in the URI group. In addition, telmisartan administration inhibited mRNA expression of profibrotic factors (oSMa, TGF-β1, and Galectin-3) only in the URI group. After induction of anemia by hemolysis with phoma hydrolysate administration, serum erythropoietin concentration was significantly higher in the URI group than in the URI+UNx group, but renal EPO mRNA expression in the ischemic kidney is higher in URI+UNx group than in URI group.

Conclusions: We found the differences in post-ischemic fibrosis, an anti-fibrotic effect of telmisartan and erythropoietin producing ability in response to anemia between the two AKI-to-CKD models. These differences will suggest that careful interpretation is necessary for animal experiments that evaluate AKI to CKD progression.

FR-PO261
Human Mesenchymal Stromal Cells Derived Extracellular Vesicles Alleviate Renal Ischemic Reperfusion Injury and Enhance Angiogenesis in Rats

Xiangyu Ren

Background: Mesenchymal stromal cells (MSCs) derived extracellular vesicles (EVs) were regarded as a potent medium for kidney injury repair and angiogenesis plays an important role in tissue repair. However, MSC-EVs’ pro-angiogenesis effect in ischemia-reperfusion induced kidney injury and its potential mechanisms has yet to be determined.

Methods: EVs were isolated from the conditioned medium of human Wharton-Jelly mesenchymal stromal cells (hWJMSCs) (treated with RNAse or not) were injected in rats intravenously after unilateral kidney ischemia. Animals were sacrificed at 24h and 2 weeks after injury resorption. Next, we examined the renal functions and histology to assess the therapeutic effect of the EVs. Moreover, we investigated the pro-angiogenesis effects and the probable mechanisms.

Results: It was observed that human MSC-EVs could reduce cell apoptosis and enhances cell proliferation 24h after kidney injury, meanwhile renal function was improved and histological lesion was mitigated. Moreover, at this time point we found VEGF up-regulated in EVs group and HIF-1α was down-regulated. Further, the capillary vessel density was increased in EVs group after 2 weeks and the renal fibrosis was reduced as well. In vitro, EVs could both deliver human VEGF directly to renal tubular epithelial cells (TECs) and induced rats VEGF synthesis in TECs under hypoxic conditions. Most importantly, all the beneficial effects of MSC-EVs were abrogated by RNAse treated except for the delivery of human VEGF.

Conclusions: MSC-EVs could protect against IRI kidney injury through pro-angiogenesis effects, and both the delivery of pro-angiogenesis related proteins and RNAVs involve in this process. This provides the direction for future clinical applications.

Funding: Government Support - Non-U.S.

FR-PO262
FTY720 Reduced Acute Kidney Injury in a Sepsis Rat Model via Spk1 Pathway

Jun Yan Fang,1 Lei Zhang,2 Xin Li,2 Feng Ding.1 1Dept of Nephrology, The 9th People’s Hospital of Shanghai The Medicine College of Shanghai JiaoTong Univ, Shanghai, China; 2Dept of Nephrology, Shanghai Jiaotong Univ Affiliated First People’s Hospital Baoshan Branch, Shanghai, China.

Background: Sphingosine kinase-1 (Spk1-1), an enzyme which is active in neutrophils and macrophages, regulates proinflammatory responses that are important in endotoxemia and sepsis. Recent study shows that Spk-1 and its product sphingosine-1-phosphate(SIP) promote inflammation via TNF-αsignalling and the canonical NF-B activation pathway.

Methods: FTY720, a Spk1 inhibitor, is a FDA approved sphingosine-1-phosphate (SIP) receptor agonist. Recent evidences demonstrate that FTY720 offers therapeutic potential against lung injuries in murine sepsis models. We therefore hypothesized that treatment with FTY720, could promote inflammation via TNF-αsignalling and the canonical NF-B activation pathway.

Results: FTY720 reduced acute kidney injury by induced cell apoptosis and enhanced cell proliferation 24h after kidney injury, meanwhile renal function was improved and histological lesion was mitigated. Moreover, at this time point we found VEGF up-regulated in EVs group and HIF-1α was down-regulated. Further, the capillary vessel density was increased in EVs group after 2 weeks and the renal fibrosis was reduced as well. In vitro, EVs could both deliver human VEGF directly to renal tubular epithelial cells (TECs) and induced rats VEGF synthesis in TECs under hypoxic conditions. Most importantly, all the beneficial effects of MSC-EVs were abrogated by RNAse treated except for the delivery of human VEGF.

Conclusions: MSC-EVs could protect against IRI kidney injury through pro-angiogenesis effects, and both the delivery of pro-angiogenesis related proteins and RNAVs involve in this process. This provides the direction for future clinical applications.

Funding: Government Support - Non-U.S.

FR-PO263
Endothelial Colony Forming Cells (ECFCs) in Murine AKI: Implications for Future Cell-Based Therapies

Daniel Patschan, Susann Patschan, Gerhard A. Mueller. Clinic of Nephrology and Rheumatology, Univ Hospital of Göttingen, Göttingen, Niedersachsen, Germany.

Background: Early Endothelial Progenitor Cells (eEPCs) have been proven as effective tool in murine ischemic AKI and in diabetic nephropathy. Only few data in contrast have been published about the role of so-called Endothelial Colony Forming Cells (ECFCs - late EPCs) and their potential in ischemic AKI. We therefore aimed to investigate ECFC effects on postischemic kidney function and structure over several weeks. Our special interest focused on endothelial-to-mesenchymal transition (EndoMT), peritubular capillary density (PTCD), endothelial alpha-Tubulin (α-T - cytoskeletal integrity), and endothelial p62 (marker of autophagocytic flux).

Methods: C57Bl/6 12 weeks were subjected to unilateral renal ischemia for 45 minutes followed by 45 minutes of reperfusion induced kidney injury and its potential mechanisms has yet to be determined.

Results: Cell therapy improved kidney function exclusively at week 1 (35 and 45 min). Ischemia-induced fibrosis was diminished in all experimental groups by ECFCs, while PTCD loss remained unaffected. Significant EndoMT was detected in only two of 6 groups (35 min, week 4 and 45 min, week 6). ECFCs reduced EndoMT only in the latter. Endothelial α-T declined under almost all experimental conditions and these effects were further aggravated by ECFCs. p62 was elevated in endothelial cells, more so after 45 than after 35 minutes of ischemia. Cell therapy did not modulate p62 abundances at any timepoint.

Conclusions: ECFCs act AKI-protective in the mid- to long-term. There are certain differences in renal outcome parameters between eEPCs and ECFC. The latter do not prevent animals from peri-tubular capillary loss and they also do not further elevate endothelial p62. We conclude that differences between eEPCs and ECFCs result from certain mechanisms by which the cells act around and within vessels. Overall, ECFC treatment was not as efficient in preventing mice from ischemic mid- to long-term damage as eEPC therapy.

FR-PO264
The Role of C1q in Apoptotic Cells Phagocytosis In Vitro and Obstructive/ Ischemic Renal Injury In Vivo

D. O. Sullivan, Jeremy Hughes, David A. Ferenbach. MRC Centre for Inflammation Research, Univ of Edinburgh, Edinburgh, United Kingdom.

Background: C1q initiates classical complement activation and is implicated in glomerular disease pathology. C1q binds to antibodies/surface proteins, activates C3 binding, mediates apoptotic cell (AC) clearance and modulates macrophage phenotype. Recent studies demonstrate that C1q levels increase in aging rodents and man, and via intracellular Mr1 signaling inhibits skeletal muscle regeneration in aged mice. We tested the hypothesis that increased C1q may augment fibrosis and worsen AKI/inflammation via complement-mediated injury.

Methods: Serum was obtained and used for in vitro studies of primary murine bone marrow derived macrophage (BMDM) phagocytosis. C57Bl6 and C1q KO animals underwent unilateral ureteric obstruction and ischaemia-reperfusion injury.

Results: In vitro, serum from aged mice had higher C1q levels (170.5±7.5 vs 92.7±14.8ng/mL; p<0.05 O vs Y), and augmented AC phagocytosis by BMDM (%phagoc 45.1±0.9 vs 27.8±1.8; p<0.05 O vs Y). AC treated with C1q depleted serum showed absent C3 labeling, which was fully restored by addition of recombinant C1q. BMDM phagocytosis of ACs was assessed with C1q replete and C1q depleted human serum. Compared to serum free the addition of C1q alone had little effect on phagocytosis (%phagoc 31.8±1.3 vs 34.0±1.1), the addition of human serum augmented phagocytosis (%phagoc 55.1±0.1 vs 0.01 vs serum free), with C1q depleted serum ineffective (%phagoc 29.3±0.8 vs 0.01 vs normal serum). The addition of C1q to C1q depleted serum phagocytosis (%phagoc 51.6±2.1) demonstrating that serum is essential for propagation of the C1q phagocytosis signal. In vivo, baseline renal collagen expression in C1KO and wild-type mice was comparable. C1qKO animals showed no protected phenotype (equal creatinine and ATN) after acute IRI and worse fibrosis after d7 unilateral ureteric obstruction (%collagen deposition 14.2±2.1 vs 8.5±1.3, C1qKO vs WT, p<0.04).

Conclusions: We found no improvement in injury levels in C1qKO mice with worsened scattering after UO or in vivo. In vitro experiments showed major defects in AC clearance in the absence of C1q. Inadequate labeling and uptake of ACs may lead to increased tissue injury and fibrosis.

Funding: Private Foundation Support

FR-PO265
Ischemic Rats Kidneys: Alive, Dead or in Suspended Animation?

Jesus H. Dominguez,1 James M. Dominguez,2 Katherine J. Kelly.2 Medicine, FAMC, Indianapolis, IN; 1Medicine, IUMC, Indianapolis, IN.

Background: Severe acute kidney injury (AKI) from ischemia/reperfusion (IR) destroys nephrons. There is no cure, and recovery is uncertain.

Methods: Rats with 50 min of bilateral renal IR were treated with intravenous renal exosomes (exo) from normoxic (Norex) or ischemic preconditioned (IPex) renal cells, 24 and 48 hrs post IR.

Results: ICAM1 protein ratio (n = 5) on IPexo/Norex was 1.85 fold (p < 0.002). IPexo fused with renal cells. There were 312 mRNA in exos, and 25 differentially expressed with mRNA in IR, e.g. higher for Drd4 (78 fold), TMEPAI (80 fold) Put5b2 (8 fold) among others. There were 4 rat groups, Sham, untreated IR (IRun), IR given Norex, and IR given IPexo (n = 5). Renal function was negligible 24 hrs post-IR, and it

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
recovered in IRIPCexo by 24 hrs, but not in IRUn. Rats were terminated 6 days post IR and renal phenotypes and RNAseq genes obtained. Kidneys from IRUn group had severe lipid peroxidation, inflammation, fibrosis, proliferation, and loss of microvasculature, but IRIPCexo group did not, p < 0.05 for all. Genotypes included 12,159 genes in each group, and were compared with each other. MDS plots of log-fold changes for each transcriptome pair showed a clear separation between Sham and IRNorex (3141 altered genes), a midrange between Sham and IRNorex (71 altered genes), and p < 0.05 for all. Gene pathways activated in IRUn, but not in IRIPCexo, included metabolic, proliferation, DNA replication, cell cycle, phagosome, protein digestion and absorption, and biological regulation. IRIPCexo gene cargo contains repair mRNAs in the form of enzymes, receptors, or structural proteins.

**Funding:** NIDDK Support, VA Support, Private Foundation Support

**FR-PO266**

**Early Inhibition of p53 Leads to Renoprotection and Attenuation of Senescence**

**Ariena Baisapua,** 1,2 Birgit Berkenkamp, 1 Raj Bhayadia, 1 Inga Soerensen-Zender, 2 Herrmann G. Hallet, 2 Anette Melk, 2 Roland Schmitt, 2

1Kidney, Liver and Metabolic Diseases, Children’s Hospital, Hannover Medical School (MHH), Hannover, Germany, 2Nephrology, MHH, Hannover, Germany.

**Background:** Early inhibition of p53 has been reported to be renoprotective during acute kidney injury (AKI). These positive effects were mainly attributed to a reduction in apoptosis. Since p53 through its main transactivational target p21 is also involved in the development of senescence of senescent-associated-β-galactosidase and p21 expression, we aimed to investigate the short- and long-term effects of early targeting of p53 targeting siRNA in a mouse model of renal ischemia reperfusion (IR) injury.

**Methods:** Mice undergoing IR injury received 6 injections of p53 specific or scrambled siRNA until D10 and were harvested at Day 14 or Day 30 (early treatment groups). In an additional continuous treatment group mice received 11 doses of p53 specific or scrambled siRNA until Day 26 and were harvested at Day 30.

**Results:** At D14, we found that p53 siRNA treatment protected against IR injury and significantly ameliorated the development of senescence (fewer senescent-associated-β-galactosidase and p21 expression). The beneficial effects (less acute injury and chronic tubular atrophy, reduced inflammation, less fibrosis and better preservation of peritubular capillaries) persisted even with a prolonged observation period of D30. However, most of these positive effects were lost when p53 siRNA treatment was continued until D30.

**Conclusions:** Our results showing attenuated senescence through early p53 inhibition are in line with the known dual function of p53. The reversal of the renoprotective effects in the group of continuously treated animals suggests that the function of p53 differs between the early and later phase after IR and that latent expression of p53 is essential for long-term recovery. These data are important in the light of therapeutic approaches using p53 targeting siRNA to prevent AKI and delayed graft function.

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

**FR-PO267**

**ERK1/2 Rapidly Downregulates PGC-1α Expression in Renal Physiological and Pathological Conditions**

Jasmin B. Collig, Ryan Whitaker, Rick G. Schnellmann, Drug Discovery and Biomedical Sciences, Medical University of South Carolina, Charleston, SC.

**Background:** Previous studies demonstrated that suppression of mitochondrial biogenesis (MB) through decreased peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) is an important contributor to renal ischemia reperfusion (IR) injury and repair. While ERK1/2 regulates numerous cell signaling pathways, the role of physiological and after renal IR remains limited.

**Methods:** Transtam and gelatin exposure blocked ERK1/2 phosphorylation and increased PGC-1α mRNA in RPTC after 1 and 4 hr. The mRNA levels of PGC-1α targets NDUFs1, NRF1, and TFAM increased at 1, 4, and/or 24 hr after ERK1/2 inhibition. Transtamod and gelatinod administered to naïve mice increased PGC-1α mRNA 4h in the cortex and transtamod upregulated EGF and subsequent FOXP3α/mRNA nuclear pFOXP3α by 60% in 30 min and in rTC and in vivo nuclear pFOXP3α decreased 60% in the cortex, leading to increased expression of downstream FOXP3α genes, including PGC-1α. In the IR AKI model, pERK1/2 increased 4-fold in 1 and 3 post IR and was linked to aldosterone mRNA and protein. In a model of ischaemia-reperfusion injury (IR), mineralocorticoid receptor (MR) antagonism has shown beneficial effects against renal IR consequences. The potential benefit of non-steroidal MR antagonists such as finerenone has not been explored. Therefore, we evaluated the efficacy of finerenone to prevent the acute and chronic consequences of ischemic AKI.

**Results:** For the acute study (24 hours), 18 rats were divided in: sham, rats subjected to bilateral renal ischemia of 25 min and rats that received three doses of finerenone at -48 h, -24 h and 1 h before the ischemia. For the chronic study (4 months), 21 rats were divided in: sham, rats 45 min of bilateral ischemia and rats treated with Fierenone at 24 h, 1, 7, and 14 days post IR. The left kidney was used for histology and the right kidney for molecular analysis.

**Conclusions:** After 24 hr of reperfusion, the untreated IR rats presented a 3-fold increase in plasma creatinine, accompanied by 40% of tubules presenting cell detachment and casts. ProBNP-1 and NGAL mRNA levels were induced by 30-fold. In contrast, the rats that received finerenone presented normal creatinine and significantly fewer injured tubules (11%) and a less pronounced induction of kim-1 and NGAL (8-fold). After 4 months, the untreated IR rats developed chronic kidney disease (CKD), evidenced by kidney dysfunction, increased proteinuria (121.6 vs 14.3 mg/24h in sham) and renal vascular resistance (16.8 vs 11.4 mmHg/ml in sham). Tubule dilation, extensive tubule-Interstitial fibrosis and an increase in kidney TGF-β and Collagen-I mRNA levels also characterized CKD. The transition from AKI to CKD was fully prevented by finerenone administration at the time of IR.

**Funding:** BAYER Pharma AG, Government Support - Non-U.S.

**FR-PO270**

**Kidney Injury Molecule-1 Overexpression Promotes Healing of Injured Kidney Epithelial Cells and Induces Alternative Activated Macrophage Polarization**

Joseph C.K. Leung, 1 Loretta Y.Y. Chan, 1 Kar Neng Lai, 2 Sydney C.W. Tang. 1 'Dept of Medicine, The University of Hong Kong, Hong Kong; Hong Kong Sanatorium & Hospital, Hong Kong.

**Background:** Kidney injury molecule-1 (KIM-1) acts as a double-edged sword in injured kidney. We aim to study the effects and mechanism of KIM-1 overexpression on the healing of injured kidney proximal tubular epithelial cells (PTEC) and macrophage polarization.

**Methods:** Oxidative injury model by H2O2 was established in murine PTEC with KIM-1 overexpression (KIM-1-PTEC). Cell viability, proliferation and apoptosis were
FR-PO271

Disruption of Hypoxia-Inducible Factor-1 Alpha Deteriorates Renal Ischemia-Reperfusion Injury through Reduction of v-KLF-2-Induced Apoptosis in Tubules Kazuma Ota, Yoshitaka Kiihira, Yuki Iizawa-Ishizawa, Yuya Horinouchi, Yasumasa Ikeda, Chiaki Ikeda, Kazuma Watanabe.

Background: Hypoxia-inducible factor (Hif)-1α is upregulated during renal ischemia-reperfusion (IR) and is involved in induction of apoptosis and the following process in renal proximal tubular cells (PTCs). The intracellular ion homeostasis is disrupted before the IR-induced apoptosis; increase in intracellular Ca2+ concentration, [Ca2+]; and decrease in [K-]. It is known that the voltage-gated potassium channel Kv2 activated by Ca2+ influx is involved in induction of neuronal apoptosis. In this study, we explored the role of Kv2 in renal IR injury (IRI) and its relationship to Hif-1α.

Methods: Hif-1α heterozygous knockout mice (HKO) and their wild type littermates (WT) were used. For induction of IRI, the right kidney was removed and the left renal vessels were clamped for 45 min followed by reperfusion.

Results: HKO showed severer renal dysfunction and reduced expression of Kv2.2 compared with WT. The preadministration of 4-aminopyridine (4AP), an inhibitor of Kv2 channels, exacerbated renal dysfunction in C57BL/6 mice after I/R. In addition, the treatment of dimethylxaloylglycine, a Hif-1α activator, with human PTC line HK2 increased Kv2.2 channels, exacerbated renal dysfunction in C57BL/6 mice after IR. Moreover, the delayed induction of apoptosis in PTCs was observed in HKO mice. 4AP inhibited Ca2+ ionophore ionomycin-induced apoptosis in HK2 cells. Therefore, Kv2.2 is probably responsible for apoptosis induction in PTCs. Localization and molecular weight of Kv2.2 were changed by I/R in the kidney of C57BL/6 mice and the changes were mimicked by the treatment of siomycin with HK2, indicating that Ca2+ activates Kv2.2 in renal I/R.

Conclusions: The present study shows that Hif-1α plays an important role in recovery from IRI through induction of Kv2.2 which leads to PTC apoptosis. PTC apoptosis mediated by Hif-1α-Kv2.2 pathway is considered a key event for recovery from IRI.

FR-PO274

Laser-Irradiation in a Closed Microcirculation System to Study Endothelial Regeneration Meinhard Roessler, Florian Schmiede, Jan S radnick, Udo Klotzbach, Vladimir T. Todorov, Frank Sonntag, Christian Hugo, Bernd Hohenstein. 1

Background: Microfluidic systems are small, chip-sized platforms, which can be used as cellularized organoid systems to study cell processes and cell-cell interactions. To investigate regeneration, the generation of specific cell damage in the channels is necessary but difficult due to limited accessibility. The present project aimed to establish a well-defined lesion in a human endothelial cell (EC) layer without removing dead cells and signaling molecules.

Methods: Microfluidic platforms were produced by Fraunhofer IWS by layer lamination manufacturing according to the system's needs, containing reservoirs, chambers, valves and an integrated micropump. Human umbilical vein EC (HUCEC) and outgrowth EC (OEC) were used. Laser ablation was performed using an Olympus Spinning Disc Microscope with a laser diode at a wavelength of 405nm for 5 to 15 minutes with a power of 2 - 2.4mW. EC injury was observed by phase contrast microscopy and LIVE/DEAD Viability/Cytotoxicity Kit whereas Time-lapse recording was used to visualize the regeneration of the injured EC layer.

Results: Following an initial attachment phase (4 hours), the fibronectin-coated channel was covered with fibronectin, cells/cm² within 3 to 6 days under pulsatile flow. Laser irradiation of 10 minutes minimum
created a selective destruction of the EC-monolayer in areas of approximately 200x200µm or 400 µm (stochastic, respectively). EC density showed an influence on the time needed to induce cell death. Time-lapse recordings indicate that surrounding EC start movement and proliferation towards the damaged site and are able to fill the gap within two to three days.

**Conclusions:** Pro-defined EC lesions in channels of microfluidic systems can be created by laser-irradiation reproducibly. This method in combination with kidney-specific EC will allow to further understand central mechanisms of EC triggering and signaling upon injury.

**FR-PO275**

The Role of IL-6 Signaling on the Transition of Acute Kidney Injury to Chronic Kidney Disease

Yuyu Yao, Zixiao Qian, Huichen Wang, Xijie Zhao, Xinyu Zhao, Xuefeng Li, Xiaoyang Han, Shiyi Zeng, Yachun Wang, Feng Li, Jie Wang, Xinmin Wu, Xiaolin Yang, Yuanyuan Chen, Qi Pan, Jiaping He, Xiaoxuan Li, Hong He, Hongbo Li, Guangyu Guo, Xiangpeng Wang, Qiong Sun, Yuxin Liu, Zizheng Zong, Deyou Wang, Xianan Zhu, Shaohui Zhai, Weiping Li, Zhiqiang Wu, and Xizheng Zong

**Background:** IL-6 is a multifaceted cytokine and a novel molecular target in several inflammatory diseases (rheumatoid arthritis, asthma, colitis). Recent studies showed that trans-signaling by an IL-6/IL-6 receptor complex (which then binds cell-attached gp130) can protect against acute kidney injury (AKI); however, the role of IL-6 signaling in renal disease remains largely unexamined. Here, we studied the role of IL-6 signaling during the AKI to chronic kidney disease (CKD) transition.

**Methods:** C57BL/6 mice were subjected to ischemia reperfusion injury (IRI, 28°, 4 h)-CD-1 mice were treated with folate acid (250mg/kg). 14 days later, glomerulat filtration rate (GFR) was measured using FITC-labeled sinistrin, and renal fibrosis was evaluated by Masson’s Trichrome. IL-6 mRNA and sIL-6 levels significantly increased on day 1 following IRI and remained higher than sham group through day 5, whereas serum soluble gp130 level did not change. These data suggest persistent IL-6 trans-signal activation during the post-AKI recovery phase. To investigate the effect of exogenous IL-6 during recovery from IRI, rmIL-6 or PBS was administered by osmotic mini pump (0.1 µg/h). Renal tubule cells were also tested.

**Results:** Trans-signal activation by IL-6/sIL-6 receptor complex (which then binds cell-attached gp130) prevents renal cell death following severe IR. Decreased AKI: Basic Repair, Regeneration

**FR-PO276**

Rat and Human Renal Exosomes Protect Ischemic Rat Kidneys and Cells

Jinho Park, Byoung-Koo Park, and Hyoung-Chan Park

**Background:** Acute kidney injury (AKI) from ischemia/reperfusion (IR) can result in renal cell death, loss of kidney structure and function. There is no available therapy that prevents renal cell death following severe IR.

We hypothesized that rat renal exosomes (rExo) from normal tubule cells (rNKC) limit cell death in IR rats. In order to evaluate clinical use, human renal exosomes (hExo) from hypoxia-resistant immortalized proximal tubule cells (hNKC, gift of Dr. R Bocale) were also tested.

**Methods:** rNKC (4 hrs) and hNKC (24-48 hrs) were cultured in normoxia or 1% O2 hypoxia, and normoxic or ischemia pre-conditioned (ICP), rExo or hExo, were harvested for 72 more hours while back in normoxia. rExo had higher levels of ICAM-1 protein than normoxic rExo (1.85 fold ± 0.02). rExo fuses with targeted cells. Results: rExo had higher mRNA encoding Catalase, SOD1, HSP72, and HIF (fold increase over normoxic rExo: 1.3, 1.5, 1.7, 1.6; p < 0.05). rExo prevented rat renal cell injury given intravenously 24 hours after 50 minutes of IR. These effects included reduced renal injury and genotypes comparable to sham controls, while untreated IR rats had very advanced renal damage: damaged microvasculature, severe inflammation, scarring, and proliferation. Lipid peroxidation and cell proliferation were also elevated, p < 0.05.

We fused hExo from hNKC which were resistant to 48 h hypoxia. Hexo were added to rat NRK-52 cells, and HLA mRNA transfer from hexo to rat cells confirmed fusion. NKR52E cells were subjected to 24 hrs of hypoxia and 24 hrs of re-oxygenation. Cell viability was unaffected by hypoxia, and increased 5.3 fold after re-oxygenation (p < 0.05). Hexo lowered mortality of hypoxic/re-oxygenated NKR52E cells by 55 %, p < 0.05. Results: rExo and hExo carry the protective effect of hypoxia inducible factor-1α and attenuated renal ischemia/reperfusion injury in mice, accompanied by up-regulation of miR-21 and increased angiogenesis. Thrombomodulin 1 expression was down-regulated. These effects of cell pretreatment were attenuated by inhibition of miR-21.

**Conclusions:** Hypoxia inducible factor-1α induced angiogenesis by increasing not only vascular endothelial growth factor but also miR-21 via inhibiting a novel target gene thrombomodulin 1. Both of them may contribute to the protective effect of hypoxia inducible factor-1α on renal ischemia/reperfusion injury.

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

**FR-PO278**

Rosuvastatin Treatment Ameliorated Renal Tubulointerstitial Fibrosis in Murine Model of Chronic Kidney Disease

Taeyeon Kim, Hyung Jin Kim, Seung-Woo Kim, Min-Na Kim, Dong-Su Park, Ji-Woo Kim, Eun-Young Choi, Ji-Hyun Shin, and Hyung Jong Kim

**Background:** Tubulointerstitial fibrosis plays an important role in progressive chronic kidney disease (CKD). Lysyl oxidase like-2 (LOXL2), a member of the lysyl oxidase (LOX) family, promotes crosslinking of collagen and elastin that has been implicated in liver and lung fibrosis. Rosuvastatin (ROS)’s pleiotropic actions include anti-fibrotic effects. Aim of the study was to investigate the effect of ROS on renal LOXL2 activity and tubulointerstitial fibrosis in a murine CKD model.

**Methods:** Male FVB mice were subjected to 42 minutes of unilateral ischemic acute kidney injury and after 2 weeks the mice underwent contralateral nephrectomy to induce a murine model of CKD. Animals were divided into 2 groups: vehicle (methylcellulose) or rosuvastatin (10mg/kg/day) by gavage. After 4 weeks, mice were sacrificed and kidneys were harvested for analysis.

**Results:** Our murine CKD model showed increased BUN (47.8 ± 4.7 vs. normal 24.3 ± 3.6 mg/dL, p<0.01) and renal anemia (hemoglobin level: 11.0 ± 1.0 g/dL vs. normal 13.2 ± 0.4 g/dL, p<0.01) and overt proteinuria compared to age-matched control mice. F4/80-positive inflammatory cell infiltration in the interstitium was significantly reduced by ROS treatment (2.8 ± 1.2 vs. 39.8 ± 8.3 HPF, p<0.01). The mRNA expression of TGFß1, LOXL2 was higher in ROS vs. vehicle (3.61 ± 1.21 vs. 7.72 ± 3.46, p<0.03, ROS vs. vehicle ). Furthermore, tubulointerstitial fibrosis assessed by Sirius Red staining, was significantly attenuated with ROS treatment (2.08 ± 0.49 vs. 7.75 ± 3.16, p<0.03, ROS vs. vehicle).

**Conclusions:** Rosuvastatin treatment showed significant anti-fibrotic effects via down regulation of renal LOXL2 expression.

**Funding:** National Institutes of Health - Non-U.S.

**FR-PO279**

Hypoxia Inducible Factor-1α Activation Attenuates Renal Ischemia/Reperfusion Injury by the miR-21, Thrombomodulin 1, and Angiogenesis Pathway

Xiaobing Xiang, Nana Song, Xiaoyan Jiao, Jianchu Han, Mingyu Liang, Xiaojing Ding, and Nephrology, Zhongshan Hospital, Shanghai, China; Physiology and Center of Systems Molecular Medicine, Medical College of Wisconsin, Milwaukee, WI.

**Background:** Angiogenesis contributes to the repair process after renal ischemia/reperfusion injury. In the present study, we tested the hypothesis that miR-21 induced angiogenesis by inhibiting a novel target gene thrombomodulin 1.

**Methods:** Cobalt chloride was administered intraperitoneally 24h prior to renal ischemia/reperfusion injury. Human umbilical vein endothelial cells were treated by 1% O2 for 24h. Locked nucleic acid modified anti-miR-21 or scrambled anti-miR was transfected into hypoxic cells or delivered into the mice via tail vein injection less than 1h prior to cobalt chloride treatment. Morphologic and functional parameters, vascular density, miR-21 and thrombomodulin 1 expression in vivo and in vitro were assessed 24h after reperfusion or hypoxia.

**Results:** Hypoxia up-regulated hypoxia inducible factor-1α, vascular endothelial growth factor and miR-21, down-regulated predicted miR-21 target gene thrombomodulin 1, and increased tube formation in endothelial cells. Inhibition of miR-21 led to increased thrombomodulin 1 abundance and decreased tube formation in hypoxia endothelial cells. Cobalt chloride activated hypoxia inducible factor-1α and attenuated renal ischemia/reperfusion injury in mice, accompanied by up-regulation of miR-21 and increased angiogenesis. Thrombomodulin 1 expression was down-regulated. These effects of cobalt pre-treatment were attenuated by inhibition of miR-21.

**Conclusions:** Hypoxia inducible factor-1α induced angiogenesis by increasing not only vascular endothelial growth factor but also miR-21 via inhibiting a novel target gene thrombomodulin 1. Both of them may contribute to the protective effect of hypoxia inducible factor-1α on renal ischemia/reperfusion injury.

**Funding:** Government Support - Non-U.S.
Hepcidin-Dependent Dynamic Regulation of Renal and Splenic Iron Balance

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Exosome Production and Its Regulation of EGFR during Wound Healing in Renal Tubular Cells

Xiaoguang Zhou, Qi Sheng Yao, Zheng Dong, Dept of Urology, Taihe Hospital, Huabei Univ of Medicine, Shizhu, Hubei, China; 2 Dept of Cellular Biology and Anatomy, Medical College of Georgia at Augusta Univ and Charle Norwood VA Medical Center, Augusta, GA.

Background: Kidney repair following injury involves the reconstitution of a structurally and functionally intact tubular epithelium. Growth factors and their receptors, such as epidermal growth factor receptor (EGFR), are important to the repair of renal tubules. Exosomes are cell-produced small (~100nm in diameter) vesicles that contain and transfer proteins, RNAs and DNAs between cells. In this study, we examined exosomes production in a scratch wound healing model of renal tubular cells. We further examined the relationship between exosomes production and EGFR activation.

Methods: A scratch wound healing model was established by using renal proximal tubular cells (RPTC) cells. Rate of wound healing and EGFR activation after scratch wounding were analyzed with and without application of an EGFR inhibitor, gefitinib. Exosomes were isolated from the culture media of RPTC cells after wound with and without treatment of gefitinib. The expression of EGFR in exosomes was investigated by testing the effect of the gefitinib and the exosomes production inhibitor, GW4869.

Results: EGFR activation occurred shortly after scratch wounding. Wound repair after injury was significantly inhibited by Gefitinib. Interestingly, scratch wounding induced a significant increase of exosomes production, which was not affected by gefitinib. EGFR was observed in exosomes and EGFR expression in exosomes increased after injury. Nonetheless, inhibition of exosome release by GW4869 did not decrease the expression of EGFR in exosomes.

Conclusions: Scratch wounding in renal tubular cells leads to EGFR activation, which is critical to wound healing. Wound healing is associated with exosome production. Exosome production does not depend on EGFR, but the release of exosome may be favor to increases the rate of wound healing in renal tubular cells.

Exosome Production and Its Regulation of EGFR during Wound Healing in Renal Tubular Cells

Xiaoguang Zhou, Qi Sheng Yao, Zheng Dong, Dept of Urology, Taihe Hospital, Huabei Univ of Medicine, Shizhu, Hubei, China; 2 Dept of Cellular Biology and Anatomy, Medical College of Georgia at Augusta Univ and Charle Norwood VA Medical Center, Augusta, GA.

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Establishment of Scanning Electron Microscopic (SEM) Analysis at Various Stages of Renal Tubular Epithelium Subculture

Kikoyo Inou, Hiroyuki Morita, Yoshihiko Inoue, Tadahide Mazumi, Tomohito Mizuno, Fumihiko Kojima, Asahi Yoshizuma, Dept of Nephrology, Showa Univ Fujigaoka Hospital, Yokohama, Kanagawa, Japan; 2 Dept of Endocrinology and Metabolism, Aichi Medical Univ School of Medicine, Nagakute, Aichi, Japan; 3 Yokohama Dai-iich Hospital, Yokohama, Kanagawa, Japan.

Background: Renal tubular epithelium (RTE) are capable of regenerating themselves after a severe injury seen, for example, in acute kidney injury (AKI) where cell migration plays a pivotal role. RTE subculture serves as a tool to study cell migration in vitro. However, little is known about ultrastructure of cell migration in vitro. In the present study, we established an experimental protocol for scanning electron microscopy (SEM) in RTE subculture to study fine ultrastructural changes.

Methods: Rattus norvegicus kidney tubular epithelial cells, NRK-52E (ATCC CRL-1571) were subcultured. Early floating cells and subsequent adherent ones were fixed, and subjected to SEM examinations. Minor modifications were made to the original SEM protocol. In separate experiments, small interfering RNA (siRNA) for actin related protein 3 (Arp3) was added to culture medium.

Results: We optimized SEM protocol (figure), and found that there were 2 types of floating cells: one with small sphere structures and the other with microvilli on a cell surface, and that further study may contribute to find a clue for constructing a new therapeutic strategy for AKI.

Conclusions: Ultrastructural findings were new, to the best of our knowledge. We claim that we obtained a tool to study how a known gene playing an important role in actin assembly influences ultrastructure in cell migration, and that further study may contribute to find a clue for constructing a new therapeutic strategy for AKI.
emphasized. MIOX, an enzyme expressed in proximal tubules, is up-regulated under high glucose (HG) ambience. It channels distal intermediaries of glycolytic pathway into glucuronate-xylulose pathway with the generation of reactive oxygen species (ROS).

Methods: We investigated epigenetic regulation of MIOX to delineate various mechanism(s) that lead up to its upregulation, generation of ROS and relevant downstream events contributing to high osmolarity hypertrophy.

Results: Kidneys of mice with STZ-induced diabetes had increased expression of MIOX with hypermethylation of its promoter spanning up to ~750 bp, as assessed by bisulfite sequencing. Likewise hypermethylation was observed in HK-2 cells under HG ambience. In silico program analysis of the promoter region revealed putative binding site for Sp-1 transcription factor, the region enriched with GC dinucleotides. EMSA studies indicated markedly increased binding of Sp-1 to MIOX promoter under HG ambience, which was significantly reduced by the selective Sp-1 inhibitor, mithramycin. A smaller 26 base pair (bp) DNA fragment spanning region of Sp-1 was used for luciferase reporter assay. Activity was increased under HG ambience, while it was reduced when combined with losartan. Both nephrin and VDR displayed more than 70% cytosine methylation (CpG islands). HG/HF treated cell lines had marked deacetylation of VDR and neddylation via ubiquitination. ChIP assays revealed binding of Snail at VDR and nephrin promoters.

Conclusions: Reversal of epigenetic alterations in renal tissues contributed to decrease in proteinuria in diabetic mice.

Funding: NIDDK Support

FR-PO291

Hyperglycemia-Dependent Epigenetic and Gene Expression Profiles in Human Mesangial Cells

Ae Seo Deok,1 Katalin K. Gluck,2 Abheepsa Pal,2 Amit Verma,2 Qiu,3 Ioannis Mantzaris,2 Vinay V. Meggs,2 Noelynne Oliver,2 Gilbert W. Moeckel,1 1Dept of Pathology, Yale Univ School of Medicine; 2Boehringer Ingelheim Pharmaceuticals, Inc.

Background: Hyperglycemia induces gene expression changes in glomeruli. Epigenetic modifications have been implicated as a mechanism contributing to dysregulated gene expression by hyperglycemia. We investigated the effects of hyperglycemia on histone and DNA methylation status in human mesangial cells (HMCs). We performed comprehensive RNA-seq analysis to assess changes in gene expression and identify candidate genes that may be affected by epigenetic modifications.

Methods: We isolated RNA, DNA and histones from cultured HMCs in osmolality-adjusted high glucose (HG, 25mM) or normal glucose (NG, 5.6mM) medium for 10 or 20 days. We compared histone and DNA methylation changes by using Epigenet ELISA plates. DNA methylation status was evaluated by Yale Center for Genome Analysis using Infinium HumanMethylation450 DNA analysis BeadChip kit. We determined gene expression by RNA-seq analysis.

Results: Most lysine residues showed increased histone methylation at the moni, di and tri modification level in HG condition. Especially, H3K4me3, H3K9me1, H3K36me2, H3K79me1 and H3K79me3 were strongly hypermethylated; only H3K36me1 was hemimethylated. DNA methylation analysis showed that 2279 CpG islands were hypermethylated and 959 CpG islands were hypomethylated in HG condition at day10. RNA-seq analysis showed that a total 941 mRNAs were changed in HG condition at day20. Combining results of our epigenetic and gene expression analyses identified candidate genes for epigenetic changes due to hyperglycemia. Included among them are: CCL2, a known marker of renal disease; CDKN1a, which has a role in mesangial cell hypertrophy; and TXNIP, known to be upregulated by hyperglycemia, thought to play a critical role in diabetic nephropathy (DN). For all of these genes, mRNA expression was strongly upregulated.

Conclusions: Hyperglycemia affects the histone and DNA methylation status, and changes expression levels of many genes in HMCs. Further analysis will clarify the precise mechanisms of these epigenetic changes and relationships among the affected genes in DN progression.

Funding: NIDDK Support

FR-PO292

ERK/MAPK Signaling-Depended Cytosolic Translocation of Dnmt3a Plays a Role in High Glucose-Induced CTGF Hypo-Methylation in Mesangial Cells

Bin Yi, Aimei Li, Wei Zhang, Hao Zhang. Dept of Nephrology, The Third Xiangya Hospital, Central South Univ, Changsha, Hunan, China.

Background: Diabetic nephropathy (DN) has become a major cause of end stage renal disease. Connective tissue growth factor (CTGF), a fibrogenic factor, played an important role in the pathogenesis of DN. We have previously identified that high glucose induces the expression of CTGF by decreasing DNA methylation. Researches in tumor cells have confirmed that ERK/MAPK signaling pathway were involved in regulation of DNA methyltransferases (Dnmts), while no relevant research were reported in human mesangial cells (HMCs). The aim of this study was to investigate the mechanisms of the CTGF hypomethylation in an ERK/MAPK signaling involved way in HMCs.

Methods: Human mesangial cells are treated with normal glucose (5mM) or high glucose (30mM) respectively. Immunoﬂuorescence staining, real-time PCR or western blotting was performed to determine the cellular distribution and expression of CTGF and Dnmt3a. CHIP-PCR assay was applied to investigate the capability of Dnmt3a binding the CpG island of CTGF. Methylation speciﬁc PCR was used to detect the methylation state of CTGF promoter. ERK/MAPK signaling inhibitor was used to verify ERK/MAPK signaling in high glucose-induced Dnmt3a cytosolic translocation.

Results: High glucose induces cytosolic translocation of Dnmt3a (p<0.05). Although the protein expression of total Dnmt3a were not altered, nuclear Dnmt3a was significantly reduced and cytosolic Dnmt3a were elevated after high glucose treatment. No changes of total Dnmt3a were observed. We have conﬁrmed that ERK/MAPK signaling pathway were involved in regulation of DNA methyltransferases (Dnmts), while no relevant research were reported in human mesangial cells (HMCs). The aim of this study was to investigate the mechanisms of the CTGF hypomethylation in an ERK/MAPK signaling involved way in HMCs.

Conclusions: High glucose induces cytosolic translocation of Dnmt3a via activating ERK/MAPK signaling pathway, which contributes to decrease the binding of Dnmt3a on CTGF promoter and subsequently CTGF hypomethylation in mesangial cells.

Funding: NIDDK Support
FR-PO293

Activated Protein C Reverses Sustained Tubular p21-expression and Senescence via a Methylation Dependent Mechanism


Background: The importance of tubular damage in diabetic nephropathy (dNP) is increasingly recognized. Tubular damage in dNP is characterized by tubular hypertrophy and senescence, but the pathophysiological mechanism relevance, the underlying mechanisms, and therapeutic strategies allowing targeting such mechanisms are lacking. Furthermore, it is not known whether these changes are related to the hyperglycemic memory in diabetes. Interestingly, (pAC) ameliorates glomerular damage epigenetically. We hypothesized that tubular damage is epigenetically controlled and that pAC may target the underlying mechanism.

Methods: Type-1 (streptozotocin) diabetic mice were analyzed. DNp was validated based on albuminuria. A subset of mice was treated with SGLT2 inhibitor, pAC, or Saza-deoxycytidine alone or in combination for 6 weeks.

Results: Gene-expression analyses identified p21 as the prominently induced gene in dNP (STZ model). Expression of p21 was further increased in mice with low pAC levels. In-vitro study showed that glucose induced p21 expression remains high after normalization of glucose concentration, suggesting that p21 is epigenetically controlled. Intriguingly, exposure of p21 at time of glucose normalization (25 to 5.5 mm) reversed p21 expression. In parallel, glucose reduced DNMTs activity and DNMT1/3b expression, which remained low despite glucose normalization. These glucose-induced persistent changes were reversed by pAC. Likewise, in diabetic mice (16 weeks of DM) p21 expression in renal tubular compartment remained high despite blood glucose normalization for the last 6 weeks using SGLT2 inhibitor. pAC treatment during the last 6 weeks abolished hyperglycemia induced sustained p21 expression and protected from tubular damage (histological damage, KIM-1) and senescence (SA β-gal). Concomitant treatment with Saza-deoxycytidine abolished pAC’s protective effect.

Conclusions: This suggests that p21 induces tubular senescence in dNP, which is sustained despite normalization of glucose level. Importantly, persistent p21 expression and tubular senescence can be reversed by pAC.

Funding: Private Foundation Support

FR-PO294

Transcriptome Analysis of Kidneys Identifies Novel Pathogenic Canonical Pathways in Experimental Diabetic Nephropathy

Sharma S. Prabhakar, Aumyot Prongdong, E Chepchumba K. Yego. Internal Medicine, Texas Tech Univ Health Sciences Center, Lubbock, TX.

Background: Diabetic nephropathy (DN) is the most common cause of end-stage renal disease worldwide and its current therapy remains ineffective as the pathogenesis remains unclear. In this study we examined genomic profile of kidneys from an experimental DN model to obtain better insights into pathogenesis.

Methods: We used obese ZSF rats, an established model of DN, and maintained from 8-26 weeks to harvest kidneys at sacrifice. Lean ZSF, littermates, which do not develop DN served as controls. RNA was isolated from the kidneys and processed for transcriptome analysis using Illumina HiSeq 2500. RNA from obese and lean ZSF, rats was compared. The differential gene list from this analysis was imported into Ingenuity Pathway Analysis (IPA) for global transcriptome analysis and pathway mapping.

Results: The top canonical pathways with a significant Z score include Wnt-β catenin and anti-oxidant pathway, Endothelin-1, AMP kinase, complement system, cytokine signaling, eNOS signaling, CAM, IL-1, NF-kB, leptin signaling, RAS and aldosterone pathways. Significantly expressed but not hitherto reported pathways include G-protein coupled receptor, hepatic fibrosis, Ca+ transport signaling and hepatic fibrosis and synthesis. The molecules significantly upregulated (fold change in parenthesis) include D4, zinc and double PHO finger family (x79), PG E receptor 2 (x28)cholinergic receptor CHRNA5 (x12), Phospholipase A PLA2GA (x16), PLA 2GF (x15), adrenoreceptor α1D (x10) LPS binding proteins and HMG co A. Significantly negatively regulated molecules include Cyt P450 2c8 (x359), Acyl coA synthase ACS 6 (x39) and chondroitin 6 (x51).

Conclusions: Next Gen sequencing of kidneys with DN revealed pathways which regulate inflammation, oxidative stress, cell cycle and fibrosis. The pathogenic significance of these proteins particularly cyt P450, FABP-1, zinc finger proteins, HS3ST3 proteins adrenergic and cholinergic receptors in DN warrant more systematic investigation.

Funding: Private Foundation Support

FR-PO295

Heterogeneous Nuclear Ribonucleoprotein F Overexpression Stimulates Sirtuin 1 and Ameliorates Kidney Injury in Mice with Type 2 Diabetes Induced by High Fat-Diet/Streptozotocin Chao-Sheng Lo, Anindyah Ghosh, Chin-Han Wu, Shuiling Zhao, Isabelle Chemier, Janos G. Filep, Julie R. Ingelfinger, Shao-Ling Zhang, John S.D. Chan. CRCHUM, Univ of Montreal, Montreal, QC, Canada; Ren Ctr, Maisonneuve-Rosemont Hosp., Montreal, QC, Canada; Pediatric Nephrol Unit, Mass Gen Hosp, Boston, MA.

Background: We investigated the impact of overexpression of heterogeneous nuclear ribonucleoprotein F (hnRNPF, a transcription factor) on the expression and signaling of the NAD+-dependent deacetylase sirtuin 1 (SIRT1) and the development of renal proximal tubular cell (RPTC) inflammation and tubulointerstitial fibrosis in mice with type 2 diabetes induced by high fat-diet (HFD) and streptozotocin (STZ).

Methods: 4-week old hnRNPF-transgenic (hnRNPF-Tg) mice overexpressing hnRNPF F in their RPTCs and non-transgenic littermates (C57BL/6 strain) were fed a normal diet (ND) or a HFD for 16 weeks and received a single STZ injection (45 mg/kg, i.p.) at week 8. Body weight and blood glucose were monitored weekly. Glucose tolerance and insulin sensitivity were assessed at week 19. At week 20, kidneys were processed for histology. Renal proximal tubular (RPT) gene and protein expression were evaluated by real time-qPCR and Western blotting, respectively. In vitro studies were performed on immortalized rat RPTCs (IRPTCs) stably transfected with hnRNPF F cDNA or Sirt1 gene promoter.

Results: HFD/STZ-treated mice developed obesity, hyperglycemia, hyperinsulinemia, insulin resistance and tubulointerstitial fibrosis parallel with markedly increased expression of pro-inflammatory (TNF-α, MCP-1 and PAI-1) and pro-fibrotic (TGF-β1, Col IV and FN1) markers and decreased expression of SIRT1 in RPTCs. These changes were attenuated in HFD/STZ-hnRNPF F-Tg mice. In vitro, hnRNPF F overexpression in IRPTCs stimulated Sirt1 gene promoter activity via a DNA responsive element (nucleotides N-973 to N-962 upstream of the transcriptional start site).

Conclusions: Our findings indicate that hnRNPF F overexpression can attenuate RPTC inflammation and fibrosis in type 2 diabetes induced by HFD/STZ via up-regulation of Sirt1 gene expression and signaling.

Funding: Government Support - Non-U.S.

FR-PO296

MicroRNA-27a Promotes Podocyte Injury via Suppression of PPAR gamma/b-Catenin Signaling in Diabetic Nephropathy Xiaowan Bai, Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China; National Clinical Research Center for Kidney Disease, State Key Laboratory of Organ Failure Research, Guangdong Provincial Inst of Nephrology.

Background: Podocyte injury plays a pivotal role in diabetic nephropathy (DN). MicroRNA-27a (miR-27a) upregulation has been identified in diabetes. We asked whether miR-27a mediates podocyte injury through PPAR gamma/beta-Catenin signaling in DN.

Methods: The expression and functional relevance of miR-27a, PPAR gamma, and beta-Catenin were investigated in cultured podocytes and glomeruli of diabetic rats and patients using in vitro and in vivo approaches. Biological parameters were analyzed using enzyme linked immunosorbent assay (ELISA).

Results: High glucose stimulated miR-27a expression and promoted podocyte injury via repression of PPAR gamma/beta-Catenin signaling. Plasma miR-27a downregulation improved renal function and attenuated podocyte injury in diabetic rats (table 1) and DN patients.

Conclusions: We propose a novel role of the miR-27a/PPAR gamma/b-Catenin axis in fostering podocyte injury in DN. Targeting miR-27a could be evaluated as a potential therapeutic approach for DN.

Variables | DM_miR-iNC (n=7) | DM_miR-27a (n=7) | P
--- | --- | --- | ---
Scr (umol/L) | 114.3±7.56 | 67.2±2.28* | .001
Serum BUN (mmol/L) | 15.6±4.24 | 11.0±1.52* | .001
Blood glucose (mmol/L) | 26.31±1.36 | 25.70±2.15 | .77
UAER (μg/min) | 1.45±0.21 | 0.67±0.06* | .001
UACR (μg/mmol) | 27.32±2.32 | 15.35±1.16* | .001
Ccr (ml·min^-1·Kg^-1) | 3.48±0.45 | 7.37±0.82* | .001

Funding: Government Support - Non-U.S.

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

431A
FR-PO297
The miR-21/PDCD4/JNK Circuit Plays a Key Role in the Pathogenesis of Diabetic Nephropathy. Hao Wu,¹ Yonggang Wang,¹ Yunfeng Qiao,² Tie Li,¹ Fuchun Wang.¹ ¹China-Japan Union Hospital of Jilin Univ, China; ²Jilin Province People’s Hospital, China; ³The Second Hospital of Jilin Univ, China; ⁴Changchun Univ of Chinese Medicine, China. Background: c-Jun N-terminal kinase (JNK) and microRNA-21 (miR-21) play key roles in the pathogenesis of diabetic nephropathy (DN). However, it is unknown whether the two factors have reciprocal interactions which may form a positive feedback circuit that contributes to the pathogenesis of DN. Methods: 8-week-old male C57BL/6J mice were induced to diabetes by injection of streptozotocin. A specific JNK inhibitor, SP600125, was administered to diabetic mice in the presence or absence of a specific miR-21 mimic (miR-21-M). In addition, a specific miR-21 inhibitor (miR-21-I) was administered to diabetic mice to determine its effect on JNK. To determine whether programmed cell death protein 4 (PDCD4), a known target of miR-21, was the key factor through which miR-21-I inhibited JNK function, the PDCD4 siRNA was transfected into mouse mesangial cells under high glucose condition. Results: Both SP600125 and miR-21-M markedly inhibited JNK function. Furthermore, the inhibitors decreased renal miR-21 along with increased mRNA and protein levels of PDCD4. As a result, they both produced similar defenses against diabetes-induced renal inflammation, fibrosis and albuminuria. Interestingly, co-administration of miR-21-M abolished the inhibitory effect of SP600125 on JNK function, indicating miR-21 as the upstream of JNK. Finally, PDCD4 siRNA abolished the inhibitory effect of miR-21-I on JNK function in high glucose cultured mouse mesangial cells. Conclusions: The present study indicates a positive feedback loop between JNK and miR-21, which may play a key role in the pathogenesis of DN. Funding: Government Support - Non-U.S.

FR-PO298
Screening miRNAs in Urine Exosomes as New Biomarkers for Diabetic Kidney Disease Jing Zhang, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ. Nanjing, Jiangsu, China. Background: Diabetic kidney disease (DKD) is the main cause of chronic renal failure, while the diagnosis of DKD is still based on proteinuria, serum creatinine, et al, which has some limitations. In this study, we would like to detect the miRNAs in urine exosomes of patients with type 2 diabetes mellitus (T2DM), to explore its correlation with proteinuria and renal function. Methods: Thirty inpatients with T2DM were enrolled in this study. According to the presence of microalbuminuria or clinical proteinuria, patients were randomly divided into three groups: group one is the patients without microalbuminuria or clinical proteinuria, group two is with microalbuminuria but without clinical proteinuria, and group three is with clinical proteinuria. Another ten healthy people were enrolled as control. Morning urine samples were collected from those patients, and urine exosomes were isolated by the kit and observed by transmission electron microscopy. Quantifications of urinary miRNAs were performed using stem-loop qRT-PCR followed by TaqMan PCR, and the correlations between miRNAs and proteinuria and renal function were analyzed. Results: The exosomes isolated by the kit from 2ml of urine samples appeared as clusters of vesicles of 30-100nm in diameter under electron microscope. Compared with healthy controls, the levels of miR-21, miR-192 and miR-377 in urine exosomes of patients with T2DM were significantly increased, while the levels of miR-29a were significantly decreased (P < 0.05). And between each two of the three groups of T2DM, the levels of miR-21, miR-192 and miR-29a changed significantly (P < 0.05). Moreover, the level of miR-192 was significantly correlated with estimated glomerular filtration rate (eGFR), while positive correlations with blood urea nitrogen, serum creatinine and proteinuria (P < 0.05). Conclusions: Compared with healthy control, the levels of miRNAs in urine exosomes of patients with T2DM change significantly, and have some correlations with proteinuria and renal function, which may be use as the new biomarkers of DKD. Funding: Government Support - Non-U.S.

FR-PO299
miRNAs and Epigenetic Regulation of Genes in Diabetic Nephropathy Beina Teng, Janina Müller-Delie, Hermann G. Haller, Mario Schiffer. Nephrology, Medical School Hannover, Hannover, Germany. Background: DNA methylation and microRNAs has been identified as two key mechanisms that underlie the evolutionarily conserved phenomenon associated with developmental and pathological gene regulation, thus may cause different pathological conditions in humans. Increasing evidence suggested that dysregulation of the epigenome and microRNAs are involved in the progression of nephropathy, which is a serious complication of diabetes mellitus and is associated with high mortality. Methods: We examined the expression profiling of miRNAs by performing a screening with urin from patient with diabetic nephropathy and healthy human, or human podocytes under diabetic conditions. A genome-wide methylation was screened in human podocytes stressed for 7 days with 30 mM glucose and mannitol as osmotic control. Samples for RNA expression microarrays were isolated from glomeruli of type 1 diabetic mice or human podocytes treated with high glucose for no less than seven days. Results: We found that expression of 25 miRNAs were stastically significantly different not only in the patient with diabetic nephropathy but also human podocytes under diabetic conditions. Using prediction tool, we identified top 20 targets for all the 25 miRNAs and compared the candidates with RNA expression profiling. Furthermore we analyzed miRNA expression changes and DNA methylation in a cross-sectional study of diabetic nephropathy and was able to identify the changes in miRNA expression under diabetic conditions that are regulated by aberrant DNA methylation. Conclusions: Diabetic nephropathy is always associated with dysregulation of several genes that are epigenetically and by microRNAs regulated which could be useful as biomarkers for diagnosis of diabetic nephropathy. Using an antagonist or mimics of miRNAs could be potential therapeutic strategy for diabetic nephropathy.

FR-PO300
miRNA Expression Correlates with Fibrosis in Diabetic Nephropathy Francesca Conserva,¹,² Mariagrazia Barozzino,² Paola Pontrelli,² Annarita Oranger,³ Francesco Pesce,² Federica Giannattasio,² Matteo Accetturo,² Massimo Papale,² Maria Teresa Rocchetti,² Giuseppe Castellano,² Simona Simone,¹ Salvatore Di Paolo,¹ Giovanni B. Pertosa,¹ Loreto Gesuludo,¹ ¹IRCSS, Maugeri Foundation, Cassano Murge (BA), Italy; ²Nephrology Unit, Dept of Emergency and Organ Transplant, Univ of Bari, Italy; ³Nephrology Unit, Dimiccoli Hospital, Barletta (BA), Italy. Background: Diabetic Nephropathy (DN) is the primary cause of End Stage Renal Disease. We discovered that urine of DN patients (pts) are enriched in free ubiquitin and accumulation of lysine63-ubiquitinated (K63Ub) proteins at tubular level is involved in epithelial-to-mesenchymal transition (EMT). By microarray, we identified a set of miRNAs deregulated in DN kidneys. Aim of our study was to identify miRNAs regulating the increased expression of K63Ub proteins and involved in the progression of fibrosis in DN. Methods: Total RNA was extracted from cell free urine of 10 biopsy-proven DN pts with type 2 diabetes (T2D), 10 pts with T2D and membranous nephropathy (MN) and 10 pts with T2D and normal renal function. miRNA expression was assessed by qPCR. Results: Among deregulated miRNAs, 9 miRNAs were selected for validation on DN pts (FC >1.5) compared to controls and T2D-MN. In silico we found 3 miRNAs with a predicted interaction withUBE2V1, an ubiquitin-conjugating E2 enzyme variant that mediates the formation of K63Ub chains. These miRNAs downregulation was further validated on both kidney biopsies (p<0.01, DN vs CTRL, p<0.03 T2D-MN vs CTRL, p<.05 DN vs T2D-MN) and in vitro on tubular cells in a model of hyperglycemia (FC~2.3). Since those miRNAs were described as correlated to EMT, we tested their prognostic strength in the progression of kidney damage by matching urinary expression with the degree of fibrosis at the tissue level. Interestingly, miR-21 was significantly downregulated in urine of DN pts compared to other groups. Moreover, this miRNA urinary levels were independent predictors of the degree of renal fibrosis in DN (p<0.03). Conclusions: In conclusion we confirm the role of ubiquitination as a pathogenic mechanism in the progression of kidney damage and suggest the validation of this miRNA as diagnostic biomarker of tubular fibrosis progression in DN.

FR-PO301
Altered Distribution of HDL, Extracellular Vesicle and Argonaute-2 Associated Circulating microRNAs in Diabetic Nephropathy and Systemic Microvascular Damage Barend W. Florijn,¹,² Jacques Duijs,¹,² Greeso M. Dallinga-Thie,³ Anita N. Böng,⁴ Wendy Stam,⁴ Ton J. Rabelink,¹,² Marlies Reinders,¹ Roel Bijkerk,¹,² Anton Jan Zonneveld,³,⁴,¹ Dept of Internal Medicine, Leiden Univ Medical Center, Leiden, Netherlands; ²Einhoven Laboratory for Experimental Vascular Research, Leiden Univ Medical Center, Leiden, Netherlands; ³Dept of Vascular Biology, Amsterdam Medical Center, Amsterdam, Netherlands; ⁴Dept of Clinical Chemistry, Amsterdam Medical Center, Leiden, Netherlands. Background: We previously demonstrated an association between total plasma levels of specific microRNAs (miRNAs) and microvascular injury in patients with diabetic nephropathy (DN). Circulating miRNAs are carried by extracellular vesicles (EVs), RNA-binding protein Argonaute2 (Ago2) or high-density lipoprotein (HDL). Identification of the carrier specificity of these miRNAs can enhance the biomarker potential of miRNAs. In addition, carrier-specific transfer of miRNAs to vascular cells may play a causal role in vascular injury. Methods: Here we assessed the plasma carrier distribution of miRNAs in DN (n=21), diabetes mellitus (DM; n=15; eGFR ≥ 30 mL/min) patients and healthy controls (n=15). EVs, HDL and Ago2 were isolated using size exclusion chromatography, KBr density gradient ultracentrifugation and immunoprecipitation respectively. MiRNA expression was determined using TaqMan miRNA Arrays and correlated to markers of vascular injury, including angptiopetin-1 (Ang1), angptiopetin-2 (Ang2),solute trombomulin (sTM) and capillary density. Results: Specific miRNA-carrier complexes were identified to be associated with DN and vascular injury. EV-miR-21 and Ago2-miR-660 levels displayed a significant increase in both DM and DN groups compared to healthy controls and correlated with capillary density in vivo. sTM expression was increased in DN and correlated with levels of Ang2, while both HDL-miR-152 and Ago-miR-152 levels displayed a significant increase in DN. Interestingly, only Ago-miR-152 levels correlated with levels of Ang2 and sTM. Conclusions: Our data suggest that miRNAs in specific carriers may contribute to vascular injury and could improve selectivity and sensitivity of biomarkers for microvascular injury in DN.
FR-PO302
Characterizing the Urinary Peptidome of Early Type 1 Diabetes to Infer Protease Activity in the Kidneys
Julie Anh Dung Van, Ashley Di Mceo, Eleftherios P Diamandis, James W. Scholey, Ana Konvalinka. Medicine, Univ of Toronto, Toronto, ON, Canada.

Background: Proteolytic activity in the kidney may induce early functional and structural changes in type 1 diabetes. Evidence suggests that this activity may be specific to some proteases and their protein substrates, and that resulting peptides generated within kidneys may be excreted into the urine and provide a footprint of intrarenal proteolysis. We aim to compare urinary peptides of adolescents with uncomplicated type 1 diabetes and healthy peers and to infer protease activity in the kidney by using differentially excreted peptides.

Methods: We collected second-morning, midstream urines from 15 cases with type 1 diabetes and 15 age- and sex-matched controls from the observational arm of the Adolescent Diabetes Cardio-Renal Intervention Trial at The Hospital for Sick Children in Toronto. Urine volumes normalized to 90 ml of creatinine were subjected to 10Ka filter centrifugation to isolate naturally occurring peptides. Filtered peptides were then fractionated by strong cation exchange liquid chromatography and analyzed on Q-Exactive Mass spectrometer. MaxQuan software was used for peptide/protein identification and label-free quantification. Peptide Extractor and Proteasix were used to infer protease activity based on the amino acid sequence of peptides.

Results: While our study is currently ongoing, our preliminary data revealed promising results. A total of 1098 peptides from 307 unique proteins were identified in a healthy volunteer urine sample. The coefficients of variation were 35% for samples processed on the same day and 40% for samples processed on different days. Uromodulin, collagens and clustrein fragments were among the most abundant kidney-derived peptides. Bioinformatic analyses showed that proteolysis occurred near the C-terminus of the proteins and that it was perhaps carried out by plasmin and trypsin.

Conclusions: Our preliminary findings suggest that we can identify urine peptides with good reproducibility. Furthermore, we computationally predicted endogenous protease activity by examining the urinary peptidome. Future work will be conducted in a cross-sectional study of patients with diabetes and healthy controls.

FR-PO303
Global Proteomic Analysis of Insulin Action in Glomerular Podocytes
Salman Hosawi,1 Richard Coward,2 Martin J. Humphries,1 Rachel Lennon,1,11
1Wellcome Trust Centre for Cell-Matrix Research, Univ of Manchester, United Kingdom; 2Academic Renal Uni, Univ of Bristol, United Kingdom; Inst of Human Development, Univ of Manchester, United Kingdom.

Background: Diabetic nephropathy (DN) is a leading cause of kidney failure worldwide. In DN, there is progressive glomerular dysfunction and recent studies have demonstrated that the podocyte is a direct target for insulin action. Furthermore, deletion of the insulin receptor (IR) from podocytes leads to progressive kidney damage and eventual kidney failure. This study utilized a global unbiased proteomic approach to examine insulin signaling in podocytes under normal and resistant conditions, with the aim of identifying key molecules that could be targeted for diagnostic or therapeutic purposes.

Methods: Mouse and human immortalised podocyte cell lines were used under normal or resistant conditions (induced by the free fatty acid palmitate). The IR was isolated following whole cell immunoprecipitation (IP) or plasma membrane immunoprecipitation (PM-IP) and label-free mass spectrometry (MS) was used to detect alterations in insulin signaling. Western blotting was used for candidate validation and glucose uptake assays were employed to assess functional responses to insulin stimulation.

Results: Both human and mouse podocytes responded to insulin stimulation, and this response was abolished in the presence of 50μM palmitate. The conditions for isolating the IR using (IP) from whole cell lysates and (PM-IP) were optimised. 23 of the previously described IR interactors were detected by MS in addition to a number of potentially novel or podocyte-specific interactors. Furthermore, palmitate-induced insulin resistance altered the IR interactome in podocytes.

Conclusions: This study provides insight into the complexity and specificity of insulin signaling in podocytes, and may explain how insulin resistance can affect the integrity of the glomerular filtration barrier in diseases such as DN. The different methods of isolating the IR provided a better view on the level of disruption of the insulin signaling pathway. Selected candidates from the MS data could be targeted for therapeutic purposes, or could be used as diagnostic markers for podocyte injury.

Funding: Government Support - Non-U.S.

FR-PO304
Silic-Based Proteomics of Primary Human Kidney Cells Reveals a Novel Link between Male Sex Hormones and Impaired Energy Metabolism in Diabetic Kidney Disease
Sergi Clotet-Frixeras,1 Maria Jose Soler,1 Maria Gubern,1 Malgorzata P Flanagan,1 Eleftherios P Diamandis,1 James W. Scholey,1 Ana Konvalinka.1,11 1Univ Health Network, Toronto, ON, Canada; 2Nephrology, UAMS and John L McClellan VA Hospital, Little Rock, AR; 3Nephropath, Little Rock, AR.

Background: Male sex predisposes to many kidney diseases. We hypothesized that dihydrotestosterone(DHT) would alter the biology of the renal tubular cell by inducing changes in the proteome.

Methods: We employed spike-in SILAC to accurately quantify the proteome in DHT-treated and control human proximal tubular epithelial cells(PTEC). Top candidate proteins were verified in vitro and in vivo by Western Blot.Renal oxidative stress(OS) was assessed by nitrotyrosine immunostaining.

Results: Of the 5043 quantified proteins, 104 were differentially regulated. Biological processes related to energy metabolism were significantly enriched among DHT-regulated proteins.SILAC ratios of 3 candidates representing glycolysis,N-acetylglucosamine metabolism and fatty acid β-oxidation, namely glucose-6-phosphate isomerase(GPI),glucosamine-6-phosphate-N-acetyltransferase 1(GPNPT1) and mitochondrial trifunctional protein subunit a alpha(HADHA),were validated in vitro and in vivo.Males showed significantly higher renal GPNPT1 and HADHA in 2 models of diabetes. Enrichment analysis revealed a link between our DHT-regulated proteins and OS in the diabetic kidney,which was validated in vivo.

Conclusions: This is the most in depth quantitative proteomic study of human primary PTEC response to sex hormones. We suggest for the first time that male sex hormones perturbed energy metabolism in kidney cells,resulting in increased oxidative stress in the cortex. We propose a novel link that may help to understand the more rapid kidney disease progression ascribed to male sex.

FR-PO305
Id1 Expression in Kidney Endothelial Cells Protects against Diabetes Induced Microvascular Injury
Matthew D. Ploekin,1 Shree G. Sharma,2
1Nephrology, UAMS and John L McClellan VA Hospital, Little Rock, AR; 2Nephropath, Little Rock, AR.

Background: The inhibitor of differentiation (Id) family of transcription regulators are induced in response to growth factors and oxidative stress and have an important role in promoting cell proliferation and inhibiting senescence. Id1 expression in endothelial cells (EC) is required for a normal response to injury. Id1 expression is limited to EC in the normal kidney. Because endothelial dysfunction is an important mechanism in the development of diabetic nephropathy, we determined if endothelial Id1 expression prevents microvascular injury and nephropathy in response to hyperglycemia.

Methods: Streptozotocin treated Id1 knockout and WT B6;129 littermates were examined at 3 and 6 months. EC were isolated from these mice by FACs and used for whole genome microarray analysis.

Results: Id1 expression was increased up to 15-fold in WT diabetic kidney EC. Id1 diabetic KO mice developed mesangial and peritubular and glomerular myofibroblast proliferation and matrix deposition. Electron microscopy demonstrated peritubular capillary endothelial cell injury and lumen narrowing. EC damage in KO mice was associated with increased albuminuria compared with WT mice. Fluorescence microangiography showed a 45% reduction in capillary perfusion area despite no significant reduction in CD31 stained areas. Gene expression microarray analysis of EC isolated from WT and KO control and diabetic mice demonstrated upregulation of type 1 collagen transcription factors and activation of cell senescence pathways in KO cells. Kidneys from KO diabetic mice showed increased EC macroH2A.1 expression, a senescence associated heterochromatin marker. Examination of cultured EC showed that Id1 expression was induced by low level oxidative stress and KO resulted in decreased cell proliferation, increased p53 expression and expression of DNA damage markers compared with WT cells.

Conclusions: These results suggest that endothelial Id1 upregulation in response to hyperglycemia is an adaptive response that protects against microvascular injury and senescence and the development of nephropathy.

Funding: VA Support
FR-PO306
Heparanase-2 Antagonizes Heparanase-1-Induced Shedding of Endothelial Glycocalyx and Prevents Endothelial Dysfunction and Albuminuria in Zebrasfish
Hermann G. Haller, Yulja Kiyan, Sergey Tkachuk, Klaus Stahl, Anna Bertram, Sarah Berger, Mario Schiffer. Clinic of Hypertension and Nephrology, Hannover Medical School, Hannover, Germany.

Background: Heparanase-1 is induced by hyperglycemia and mediates the deleterious effects of hyperglycaemia on the endothelium. Heparanase-2, a homologue of heparanase-1, associates physically with heparanase-1 and inhibits heparanase enzymatic activity. Using (1) cultured endothelial cells in a microfluidity chamber and (2) a zebrafish model of glomerular albuminuria we have tested the hypothesis that heparanase-2 prevents heparanase-1-induced downregulation of endothelial glycocalyx and exerts anti-inflammatory effects.

Methods: Endothelial glycocalyx was assessed by confocal microscopy and dot-blot analysis in cultured microvascular endothelial cells (MEC). Gene expression was analysed by RT-PCR and microarray. Heparanase-2 was down-regulated by morpholino in transgenic zebrasfish Tg(fabp1-DHFR.TGF) and proteinuria assessed by the Fabp-eye-assay. Glomerular endothelial cells were assessed by EM. Gene and protein expression was analysed by real-time qPCR and western blot analysis.

Results: High glucose induced expression of heparanase-1 and shedding of glycocalyx. Overexpression of heparanase-2 prevented the loss of glycocalyx, while silencing of heparanase-2 exacerbated glycocalyx loss. In addition, heparanase-2 overexpression reduced monocyte adhesion, reduced NFκB signalling and led to an anti-inflammatory cytokine pattern. In zebrafish silencing of heparanase-2 induced edema, endothelial cell swelling and massive proteinuria in the zebrafish. Rescue experiments with different heparanase-2 constructs demonstrated that the C-terminus is responsible for the protective effects on the glomerular endothelial cells.

Conclusions: Heparanase-2 stabilizes the endothelial glycocalyx and prevents heparanase-1-induced endothelial damage and dysfunction. It is the first endogenous heparanase-1 inhibitor and induction of heparanase-2 may be a therapeutic strategy in diabetic nephropathy and other glomerulopathies.

FR-PO307
Soluble Nogo-B Improves Altered Angiogenesis: Implication for Diabetic Kidney Disease
Anthea Solan, Luigi Grudi, Iaqi Pan, Xiaoyan Bai, Anthea Elaine Hayward, Kathryn E. White, Fan Fan Hou, David A. Long.

1Cardiovascular Div, King’s College London, London, United Kingdom; 2Nanjung Hospital, Southern Medical Univ, Guangzhou, China; 3Electron Microscopy Unit, Univ of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom; 4Inst of Child Health, Univ London, London, United Kingdom.

Background: Abnormal angiogenesis is involved in the pathogenesis of diabetic nephropathy (DN). Neurite outgrowth inhibitor (Nogo-B) is expressed in endothelial cells (EC) and vascular smooth muscle cells. A soluble form of Nogo-B (sNogo-B) has been identified in the circulation and promotes angiogenesis by binding to the Nogo-B receptor NgBr on EC. We asked whether Nogo-B is expressed in glomeruli and whether its expression is modulated by diabetes, further we explored whether sNogo-B could ameliorate abnormal angiogenesis as an experimental model of DN with human cells incubated with patients’ serum.

Methods: Nogo-B expression in glomeruli of control and diabetic mice was assessed with immunogold and western immunoblotting. Kidney biopsies from patients with type 1 diabetes and thin basement membrane nephropathy (as controls) were used for Nogo-B expression analysis with immunohistochemistry. Angiogenesis assay was conducted with human umbilical vein endothelial cells (HUVEC) on matrigel; HUVEC were incubated with serum from T1DM/DN- or T1DM/DN+ patients. T1DM/DN- patients had similar clinical characteristics. sNogo-B was overexpressed by viral vector.

Results: Full length Nogo-B was expressed in glomerular EC and podocytes; Nogo-B was downregulated in glomeruli of diabetic mice and of patients with DN (p<0.04). Overexpression of soluble Nogo-B rescued the altered angiogenesis (reduced tube length/number) observed in HUVEC incubated with T1DM/DN+ serum (p<0.002), while no effect was observed in the angiogenesis of HUVEC incubated with serum from T1DM/DN- patients. Overexpression of sNogo-B in HUVEC was paralleled by a decrease in AKT phosphorylation. The release of Platelet microparticles(PMPs) is considered to be proinflammatory and elicit cytokine responses. This study was undertaken to investigate the role of PMPs in glomerular endothelial injury in diabetic nephropathy (DN).

Methods: Eight-week old male Sprague-Dawley rats were divided into three groups: normoglycemic control (control), streptozotocin-induced diabetic rats (DM), and diabetic rats treated with Aspirin (DM+ Aspirin). The determination of PMPs was used by flow cytometry and confocal microscopy. The inflammatory cytokines released from PMPs was checked by protein microarray contain a variety of inflammatory cytokines, immunohistochemical staining, or Western blot. The glomerular endothelial injury was evaluated through measuring the change of endothelial surface layer (ESL), endothelial fenestration, cellular junction, and glomerular permeability by electron microscope, immunofluorescence staining and Western blot. The ratio of urinary microalbumin to creatinine (ACR) was detected by enzyme-linked immunosorbent assay.

Results: Compared to the control, the serum level of PMPs was significantly increased in DM rats, while it was reduced by Aspirin. Aspirin treatment decreased the production of inflammatory cytokines in PMPs suspension, blood serum and glomerulus. Using confocal microscopy, the enhanced interaction between PMPs and glomerular endothelium was observed in DM rat, which was inhibited by Aspirin. Interestingly, the elevated PMPs and production of inflammatory cytokines from PMPs were correlated with the glomerular endothelial injury by decreasing the ESL thickness and endothelial fenestration, destroying cellular junction and reducing permeability and ESL level in DM rats. Decrease of serum PMPs and production of inflammatory cytokines by Aspirin ameliorated the glomerular endothelial injury compared to the DM group.

Conclusions: Elevated serum PMPs contributes to glomerular endothelial injury in diabetic nephropathy through the release of inflammatory cytokines from PMPs.

FR-PO310
The Progression of Diabetic Nephropathy in CSE-/-, eNOS-/-, db/db, CSE/-/ db/db, and eNOS-/- db/db Murine Models: A Comparative Study
Claudia J. McCarthy, Christopher G. Kevil, Kevin J. McCarthy, Dept of Pathology and Translational Pathobiology, LSU Health Sciences Center, Shreveport, LA.

Background: Targeted deletion of eNOS (eNOS-/-) in mice is associated enhanced development of glomerulosclerosis. However, the role of another gasotransmitter, hydrogen sulfide, (H2S) in the onset and progression of diabetic nephropathy is still not entirely clear. The purpose of this study was to compare the development of diabetic nephropathy between CSE-/-, eNOS-/-, (CSE/-/eNOS-/-) and db/db mice.

Methods: Age matched (16 wks) CSE-/-, eNOS-/- and eNOS-/- db/db, CSE-/- db/db mice were used. Prior to sacrifice, blood was drawn for H2S measurement. After sacrifice, the kidneys were removed, and processed for light and electron microscopy, a segment of the kidney used for sulfide measurement. Morphology readouts included measurement of glomerular areas (AT), mesangial areas (AM), and calculation of the AM:AT ratio. Pedicel areas followed a similar trend, except that AM was less in eNOS-/- mice compared to the former groups. There was no difference in AT between the CSE-/-, eNOS-/- glomeruli; however an increase (p<0.0001) in AT was seen in CSE-/-db/db and eNOS-/-db/db glomeruli when compared to the former groups. There was no difference in AT between the db/db, and eNOS-/-db/db glomeruli, but AT was less (p<0.0001) in the eNOS-/-db/db glomeruli. Mesangial areas (AM) followed a similar trend, except that AM increased (p<0.0001) in the eNOS-/- db/db

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glomerulonephritis over all groups. The AM/AT ratio, an indicator of mesangial expansion, was not different among the diabetic animal models. There were no differences in the ultrastructural morphology among the diabetic models. H2S metabolites were significantly reduced in plasma and kidneys of db/db mice. Measurement of discrete biochemical sulfide forms revealed that bound sulfane sulfur was blunted in CSE-/- and db/db mice, with CSE: db/db mice showing the greatest reduction in bound sulfane sulfur in the kidney.

Conclusions: These reductions suggest a potential difference in sulfide dependent signaling responses, the mesangial cells appear to be most affected by changes in H2S.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO311

Altered Hemodynamic Responses to Infused Insulin in TALLYHO/Jng Obese Mice
Carolyn M. Ecelbarger,1 Swasti Tiwari,2 Hwal Lee,1 Lijun Li,3 1Dept of Medicine, Georgetown Univ, Washington, DC; 2Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, India.

Background: Insulin resistance blunts glucose uptake in the major metabolic tissues; however, the impact of ‘insulin-resistance’ within the cardiovascular-renal system remains unclear. Previously we showed reduced protein expression for the insulin receptor (IR) in different regions of the kidney in obese, relative to lean rats; however, the main metabolic factors driving IR expression in kidney were unclear, as well as, whether these changes were associated with altered hemodynamics.

Methods: We infused young, adult lean (C57Bl6) and obese (TALLYHO/Jng) male mice (n = 6/group) with insulin (40 U/kg bw) for 2 weeks while monitoring blood pressure (BP) and heart rate (HR) by radiotelemetry. In additional mice (F2 cross, 75% TALLYHO/25% C57Bl6) we correlated metabolic factors with IR protein in different regions of the kidney to determine which factors were best correlated with IR.

Results: Obese mice had significantly higher basal BP (10-12 mm Hg) with a slight fall in BP (mean 4 mm Hg) in the first 3 days of insulin infusion, which returned to basal levels by day 14. In contrast, lean mice demonstrated a mean 7 mm Hg fall in the first 3 days, followed by a fairly substantial rise (15 mm Hg). Basal HR was significantly higher in the obese mice (mean 650 versus 540 beats per minute); however, HR rose in the lean mice sharply in the first 2 days then stabilized at a higher level. This rise was not seen in obese mice. At two weeks, no significant differences existed between lean and obese mice for HR or BP. Body weight was significantly negatively correlated with IR protein in kidney cortex and outer medulla. Glucose peak during a glucose tolerance test was also negatively correlated with IR protein in the outer medulla.

Conclusions: Hemodynamic responses to insulin infusion are attenuated in obese mice indicating ‘insulin resistance’ of these cardiovascular responses. Chronic insulin infusion abrogated differences between lean and obese mice suggesting insulin, per se was the direct cause of these differences. Reduced renal IR expression may partially explain attenuated responses to insulin infusion in obese mice.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO312

Deficient Endothelial Heparan Sulfate Prevents Renal Inflammation and Fibrosis in Murine Diabetic Nephropathy
Ditmir Talisma,1 Kirankumar Katta,1 Marierce A. Ettema,2 Berna Kei,1 Marion Kusche-Gullberg,2 Coen C. Kusche3 1Dept of Medicine, Georgetown Univ, Washington, DC; 2Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, India; 3Dept of Biomed., Univ of Bergen, Norway.

Background: Recent findings suggest a role for inflammation in the development of diabetic nephropathy (DN). Endothelial heparan sulfate (HS) is known for its cytokine/chemokine binding capacities and subsequent presentation to high affinity receptors on leukocytes. For the sulfation and function of HS the enzyme N-deacetylase N-sulfotransferase-1 (NDST-1) is essential. In this study we aim to assess the role of endothelial HS in renal inflammation and fibrosis in a mouse DN model.

Methods: To induce diabetes, age matched C57Bl6/J WT and C57Bl6/J Cre' NDST-1 mice were intraperitoneally injected with streptozocin (50 mg/kg). Control mice received citrate buffer (n=8-10/group). At baseline, two and eight weeks follow up urine and plasma was collected and plasma glucose, urinary creatinine and albuminuria were measured. Two months after diabetes induction the animals were sacrificed and kidneys were isolated. Immunohistochemically stained for macrophages, collagen III and sSMA. Expression of VCAM-1, collagen III, IV, TGF-b1 and fibronectin was measured using qRT-PCR.

Results: Diabetes induction was evidenced by significant increased values of blood glucose and albuminuria, without differences between WT and KO animals. Compared to WT, NDST-1 KO animals showed decreased interstitial macropages (p<0.05). The reduction in inflammation was confirmed by a reduced mRNA expression of VCAM-1 (p<0.001). KO animals also showed a reduced interstitial collagen III deposition (p<0.001) and myofibroblast shown by a reduction interstitial sSMA staining (p<0.01). The reduction in fibrosis was confirmed a reduced mRNA expression of collagen I (p<0.001), III (p<0.005), IV (p<0.001), TGF-b1 (p<0.001) and fibronectin (p<0.001). Furthermore, glomerulosclerosis was reduced in the NDST-1 KO animals (p<0.001).

Conclusions: Our results show the role of endothelial HS in the development of renal inflammation and subsequent fibrosis in DN in mice. These results suggest that HS can be a potential target for therapy in DN.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO313

Delivery of Murine Recombinant ACE2 in Different Mouse Models of Albuminuria
Jan A Wysocki,1 Minhao Ye,2 Daniel Battle.1 Northwestern Univ; Chicago, IL.

Background: Targeting RAS is the mainstay of therapy for CKD. New approaches, based on fostering the degradation of Ang II, rather than blocking or the formation or action of AngII could be complementary or even better. ACE2, the main enzyme that degrades Ang II, is a large 100kD protein that normally is not filterable by glomeruli. This study examined whether murine recombinant rACE2 can increase urinary and kidney ACE2 in three models of kidney disease with different degrees of albuminuria.

Methods: db/db mice, mice with STZ-induced diabetes and Alport model of CKD due to col4A3 gene deficiency that results in advanced alterations in the glomerular basement membrane and robust proteinuria were used. Serum ACE2 was overexpressed chronically using ACE2 minicircle (MC) in STZ mice or acutely via i.p. injection of rACE2 to db/db and Col4A3-/- mice. ACR was 534±70, 87±23 and 3902±495 ug/mg in db/db, STZ and Alport mice, respectively.

Results: In MaCACE2-treated STZ mice, serum ACE2 activity was markedly augmented, but urine ACE2 activity did not increase (Figure). In db/db, infusion of rACE2 increased serum ACE2 activity markedly without any increase in urine ACE2 activity (Figure). By contrast, in maRACE2-treated Col4A3/- mice, the increase in serum ACE2 activity was associated with a marked increase in kidney (5.5 vs. 13.5±3.6 RU/ml prote) and urinary ACE2 activity (Figure).

Conclusions: A large enzyme such as ACE2 cannot be filtered in mouse models of diabetes-induced moderate glomerular injury such as in STZ and db/db with modest albuminuria. When glomerular permeability is sufficiently altered, as in the Col4A3-/- model of CKD with robust proteinuria, an increase in serum ACE2 results in an increase in both kidney and urinary ACE2 activity. The potential renoprotective action of this enzyme will likely depend on local kidney delivery rather than systemic levels in the circulation.

Funding: NIDDK Support, Private Foundation Support

FR-PO314

Effect of ACE2 Deletion on Circulating and Renal ACE in Non-Obese Diabetic (NOD) Mice
Vanesa Palau,1 Heleia Roca Ho, Marta Riera,1 Marta Rebull, Javier Gimeno, Julio Pascual, Maria Jose Soler. Nephrology, Hospital del Mar Medical Research Inst (IMIM), Barcelona, Spain.

Background: ACE2 is altered in diabetic nephropathy(DN). Downregulation of ACE2 either by gene deletion or by pharmacological inhibition worsens DN in STZ and Akita model of type 1 diabetes. We demonstrated that loss of ACE2 contributes to an increase in renal injury and proteinuria in the non-obese diabetic (NOD) mice. We hypothesized that ACE2 is altered in ACE2KO mice under NOD and NOR background.

Methods: NOD and non-obese resistant(NOR) mice with a deletion on ACE2 gene compared to NOD and NOR WT mice after 30 days of diabetes were studied. Systolic blood pressure(SBP), glucose and urinary albumin excretion(UAE) were measured. ACE enzymatic activity in serum and renal cortex were assessed by a fluorometric method. Renal cortex protein expression was studied by western-blots.

Results: NOD diabetic mice present significant increase in blood glucose, SBP and UAE as compared to NOR mice. However, no differences were observed between WT and KO mice. NODACE2 KO mice showed higher serum ACE activity compared with NORACE2 KO. NODACE2 KO mice showed a decreased circulating ACE activity as compared to NODACE2 WT. Renal ACE activity was increased in NORACE2 KO as compared to NORACE2 WT.

Conclusions: Diabetes increases blood glucose, SBP, UAE and serum ACE activity. Interestingly, ACE2 deletion decreases serum ACE activity in NOD mice and increases renal cortex ACE activity in NOR mice. These results suggested that ACE2 deletion exerts a different effect on circulating and renal ACE activity in diabetic and non-diabetic mice.

Funding: NIDDK Support, Other NIH Support - NHLBI

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

435A
FR-PO315
Effects of Angiotensin 1-7 on Klotho, mTOR and Podocyte Proteins Expression in Zucker Diabetic Fatty Rats. Jorge E. Toblli, 1 Maria Maselli, 1 Gabriel Cao, 1 Margarita Angerosa, 1 Fernando Pablo Dominici, 2 Lab. of Exp. Medicine, Hospital Alremen. UBA, Buenos Aires, Argentina; 2Biochemistry, UBA, Buenos Aires, Argentina.

Background: Current information indicates a link between Klotho deficiency and increased mTOR signaling which is associated with oxidative stress and inflammation/renal fibrosis in diabetic nephropathy. The RAAS blockade modulates Klotho, however, the role of angiotensin 1-7(ANG1-7) on Klotho and mTOR is still unclear. This study evaluates the effect of (ANG1-7)on Klotho, mTOR and podocyte expression proteins in kidney of Zucker Diabetic Fatty (ZDF) Rats.

Methods: ZDF and controls lean Zucker rats (LZr) were used: 1) ZDF saline,2) ZDF+ANG1-7, 3) LZr+saline. For 4 wks, animals received either saline or ANG1-7 (100 ng/kg/min) by subcutaneous osmotic pumps. Kidneys were removed at the end of the experiment.

Results: Ang 1-7 infusion increased Klotho expression and modified favorably mTOR in kidney of ZDF rat. Furthermore, podocyte protein expression was also improved. These changes were associated with reduction in HSP27 and GBM thickness.

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FR-PO316
Podocyte rearrangement as compared to the non-silenced cells. No differences were observed when

FR-PO317
Vascular Actions of AT1 Angiotensin Receptors Do Not Contribute to Albuminuria or Hyperfiltration in Diabetic Kidney Disease

Background: Blockade of the renin angiotensin system (RAS) reduces albuminuria, attenuates hyperfiltration, and slows the progression of diabetic nephropathy (DN) by preventing vasocastion and subsequent increases in glomerular hydrostatic pressure. Since RAS blockade disrupts Ang II signaling in all tissues, the specific contribution of vascular AT1R in DN has been difficult to delineate.

Methods: We generated 129Sv/Ev mice with cell-specific loss of AT1A from VSMCs (SMKOs) using Cre-lox. To remove AT1R from VSMCs, we crossed the SMKOs with AT1B-/- mice, lacking the minor AT1B isoform. To study the impact of vascular AT1R in DN, we crossed AT1B-/-/SMKO mice with mice having the Ins2(−/−) AKITA mutation, which lack a develop DM1 early. To enhance kidney injury, mice underwent uninephrectomy (UNX) at 11wks.

Results: Glucose levels were elevated (~500mg/dL) and similar at 10, 16 and 24wks between the groups. Prior to UNX, albuminuria was similar between Control AKITA and AT1B-/- (307±27 µg/24hrs, P=NS). Albuminuria increased with age but with no significant differences between the groups at 16wks (307±106 Control AKITA vs 313±117 AT1B-/-/SMKO AKITA µg/24hrs; P=NS) or 24wks (494±236 versus 730±217 µg/24hrs; P=NS), despite a trend toward higher albuminuria in AT1B-/-/SMKO ATIKAs. There was no significant difference in GFR (via FITC-inulin) between non-diabetic Control and AT1B-/-/SMKO AKITAs. There was no significant difference in GFR between Control AKITA and AT1B-/-/SMKO AKITAs (P=NS). We measured mRNA levels by qPCR of putative kidney injury markers and found no differences in Col1A1, NGAL, or TGFβ1 between Control AKITA and AT1B-/-/SMKO AKITA.

Conclusions: Our studies indicate that the absence of vascular AT1R responses is not sufficient to reduce albuminuria and prevent hyperfiltration in a mouse model of DN. This suggests that blockade of AT1R in other cell lineages may contribute to beneficial actions of ARBs in DN.

Funding: NIDDK Support, VA Support

FR-PO318
Altered Expression of Urate Transporters URAT1 and ABCG2 in Diabetic Rats and Their Response to Hypoglycemic Agents
Daiso Tovoku, Shigeru Shibata, Emiko Kuriyabashi-Oomu, Shin-Ichiro Asakawa, Kenichi Ishizawa, Shunya Uchida. Dept of Intern Med, Teikyo Univ School of Medicine, Tokyo, Japan.

Background: Co-incidence of hyperuricemia is a common finding in diabetic patients, and previous studies suggest that insulin resistance is associated with the decreased renal clearance of uric acid (UA). Recent data also demonstrated that a Na+-glucose co-transporter 2 (SGLT2) inhibitor can reduce serum UA in type 2 diabetes (Zinn et al. NEJM 2015). However, the detailed regulation of urate transporters in diabetes has remained unclear. Using rat models, we evaluated the changes in renal UA handling and urate transporters in diabetes, as well as their response to hypoglycemic agents. Podocytes key cells in glomerular filtration barrier with their own RAS. In the puromycin model of podocyte damage, an increased mTOR signaling which is associated with oxidative stress and inflammation/renal fibrosis in diabetic nephropathy (DN).

Methods: Daily UA excretion was markedly increased in STZ rats as compared with controls (5.8±1.5 12.5±2.4† 18.6±2.6§). Albuminuria significantly decreased, whereas ABCG2 (ATP-binding cassette sub-family G member 2) was increased, consistent with the increased renal UA clearance. Moreover, treatment with insulin but not Ipragliflozin (Ipra) (an SGLT2 inhibitor; 15 mg/kg chow) showed no differences in their response to hypoglycemic agents. Podocytes key cells in glomerular filtration barrier with their own RAS. In the puromycin model of podocyte damage, an increased mTOR signaling which is associated with oxidative stress and inflammation/renal fibrosis in diabetic nephropathy (DN).

Results: ACE2 gene silenced-podocytes showed a differentially cytoskeletal rearrangement as compared to the non-silenced cells. No differences were observed when InsR were silenced. This effect was correlated with a different pattern of growing after 17h.

FR-PO318
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Results: ACE2 gene silenced-podocytes showed a differentially cytoskeletal rearrangement as compared to the non-silenced cells. No differences were observed when InsR were silenced. This effect was correlated with a different pattern of growing after 17h.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
436A
Conclusions: These data show that insulin decreases renal UA clearance via modulation of ABCG2, consistent with a mechanism for the inverse association between hyperinsulinemia and hyperuricemia. The data also indicate that renal urate handling in diabetic patients is influenced by the types of hypoglycemic agents.

FR-PO319
Basolateral High Glucose Induces Sodium Glucose Transporter Expression via GLUT2/Importin 1 alpha/HNF1 alpha: Pathway in Renal Tubular Cell
Hiroyuki Umino, Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. Internal Medicine, Keio Univ, Tokyo, Japan.

Background: We recently reported the nephroprotective effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors through the maintenance of renal sirtuin 1 expression, although, the mechanism underlying increased SGLT2 expression in diabetic nephropathy remains unknown.

Methods: We constructed a 2-chamber culture system, with the upper layer representing the renal tubular cells of the lumen and the lower layer representing the vascular lumen. Normal glucose (NG) and high glucose (HG) culture media were used for the upper layer. By using cultured primary proximal renal tubular cells, we investigated the presence of polarity, i.e., whether SGLT2 expression was dependent on glycemic stimulus from an upper or lower layer.

Results: SGLT2 expression increased in HG medium in the lower chamber, indicating that hyperglycemic stimulus from vascular lumen is responsible. Using small interfering RNA to inhibit the expression of membrane proteins localized to the basolateral side of the cells, we found that decreased glucose transporter 2 (GLUT2) expression led to decreased SGLT2 expression. GLUT2 was bound to importin α1, an intracellular transport protein, in cells maintained in NG. Reportedly, when GLUT2 sensed retrograde glucose flow which is in the opposite direction of normal glucose flow in HG, GLUT2 dissociated from importin α1, which translocated from the cytoplasm to the nucleus. We used MEGA® alignment software to predict protein binding and identified a DNA motif for HNF1α transcription factor for GLUT2 binding.

Conclusions: These findings suggested that detection of hyperglycemia on the basolateral side by GLUT2 during early stage diabetes mellitus leads to retrograde signal transduction which is in a direction opposite to that of the normal glucose flow via the GLUT2-importin α1-HNF1α pathway, with subsequent upregulation of SGLT2 expression. We propose this pathway interception as a new therapeutic target.

FR-PO320
The Role of TLR4/NF-κB Signaling Pathway on Mitochondria-Related Apoptosis in Tubular Cells in Diabetic Kidney Disease
Xuejia Xu, Zhongqiu Yuan, Xuemei Liu, Lin Sun, Fu-You Liu. Dept of Nephrology, The Second Xiangya Hospital of Central South Univ, ChangSha, Hunan, China.

Background: The role and precise mechanism of TLR4 in mitochondria-related oxidative damage and apoptosis of renal tubular in diabetic kidney disease (DKD) remains unknown.

Methods: We examined the expression of TLR4 in renal biopsy tissues and analyzed its correlation with tubulointerstitial damage of DKD patients. In HK-2 cells, we detected the expression of TLR4, NF-κB and cleaved Caspase-3 by quantitative real-time PCR and western blotting, and analyzed mitochondrial function and apoptosis by flow cytometry and immunofluorescence. PGC-1α plasmids were used for the overexpression of PGC-1α in HK-2 cells.

Results: Results showed that TLR4 was extensively expressed in the renal tubular of DKD patients, coexistent with mitochondria swelling and deformation. The level of TLR4 was positively related to the tubulointerstitial damage reflecting by tubular interstitial damage score and urinary β-NAG levels. In vitro, the expression of TLR4 increased in HK-2 cells treated with high glucose (HG), leading to activation of NF-κB, decreased expression of PGC-1α, mitochondrial deformation, cytochrome C redistribution, increased expression of cleaved caspase-3 and even apoptosis, while TLR4/NF-κB blockers and PGC-1α over-expression reversed these trends.

Conclusions: Data indicated that TLR4/NF-κB signaling may be the upstream of PGC-1α and promote the tubular damage of DKD by modulating the mitochondria-related oxidative damage and apoptosis.

Funding: Government Support - Non-U.S.

FR-PO321
RhoA Activation Contributes to Hyperplastic Phenotype of Proximal Tubular Cells in the Initiation of Obesity-Related Kidney Damages
Makiko Naitoh, Hirobumi Tokuyama, Shu Wakino, Hiroshi Itoh. Internal Medicine, Keio Univ, Shinjuku, Tokyo, Japan.

Background: Hyperplastic phenotype is supposed to trigger the initiation of obesity-induced renal damages. A small GTP-binding protein, RhoA, and its effector, Rho-kinase, have several pathological functions including cell motility, proliferation and inflammatory response. We have previously demonstrated that excess fat intake causes obesity-induced renal injuries, which proceeds by an increased RhoA/Rho-kinase pathway in proximal tubules and inflammatory process. In the present study we examined whether Rho/Rho-kinase contributes to the hyperplastic phenotypes in obesity-induced renal injury.

Methods: We created mice that overexpressed dominant negative RhoA genes specifically in a proximal tubules (PT) under the control of promoter of sodium-phosphate co-transporter (PT-DN-RhoA) in C57BL/6J backgrounds. PT-DN-RhoA mice and their wild-type littermates (WT) were fed a high fat (HF) or low fat diet (LFD) for 12 weeks.

Results: WT on HFD (WT-HFD) not only developed obesity but also manifested renal histological changes, tubulointerstitial changes, and inflammation in proximal tubules, tubulointerstitial fibrosis, and a marked increase in the number of PCNA and Ki-67 positive tubulipalial epithelial cells compared with WT on LFD as early as 2 weeks after the HFD feeding, which paralleled the increase in urinary excretion of NGAL (neutrophil gelatinase-associated lipocalin). These hyperplastic phenotypes were ameliorated in HFD-fed PT-DN-RhoA mice. Among cell cycle regulators, cyclin-dependent kinase inhibitors p27 was remarkably reduced in WT-HFD, which were restored in DN-RhoA TG mice with HFD.

Conclusions: Excess fat intake causes the hyperplastic phenotype of obesity-induced renal injury, which is mediated by an RhoA activation and subsequent downregulation of p27 pathway in proximal tubules. The intervention of Rho/p27 pathway may constitute a novel strategy blocking the initiation process of obesity-induced renal damages. Urinary NGAL can be useful markers for the detection of this hyperplastic phenotype.

FR-PO322
Subclinical Lithium Dose Attenuates Glomerulosclerosis but Causes Tubular Injury in Diabetic BTBR ob/ob Mice
Thuein de Groot, 1,2 Leanne Kosse, 1,2 Lars Damen, 1,2 Susan Marie Sheehan, 1,2 Peter M.T. Deen, 1,2 Ron Korstanje, 1,2 The Jackson Laboratory; Bar Harbor; "Radboud Univ Med. Center, Nijmegen, Netherlands.

Background: Type 2 diabetes mellitus (T2DM) is the most important risk factor to develop chronic kidney disease (CKD). Glycogen synthase kinase 3 (GSK3) plays an important role in the development of DM and renal injury. GSK3 activation increases glucose uptake in insulin-insensitive muscle and adipose tissue, while in acute kidney injury it reduces albuminuria and glomerulosclerosis. The only clinically available GSK3 inhibitor is lithium, however in bipolar patients chronic lithium administration (0.6-1 mg/kg) increases the risk of developing tubulointerstitial nephropathy. Therefore, our aim was to investigate the effect of subclinical lithium doses on the development of DM and kidney injury in a mouse model of diabetic nephropathy.

Methods: Twelve-week old female BTBR ob/ob mice were treated with 12 weeks with 0, 10 and 40 mmol LiCl/kg after which DM parameters, urine albumin-creatinine ratio (ACR), FITC-insulin clearance, and renal histology were analyzed and compared to wild type (w) BTBR mice on regular chow.

Results: In contrast to wild type BTBR mice, ob/ob mice demonstrated elevated blood pressure, increased blood glucose levels, which metformin ameliorates peripheral insulin resistance. This highlights the potential of SHIP2 as a potential therapeutic target to treat insulin resistance. To date only a few chemical compounds possessing an inhibitory effect on TLR4 are known. All of them have poor bioavailability and none have reached clinical use.

Methods: To identify novel small molecules that inhibit SHIP2 we performed virtual screening of chemical libraries followed by validation using cultured cells, diabetic db/db mice and kidney tissue from patients with T2DM.

Results: Virtual screening of chemical libraries containing 88680 molecules revealed metformin as a potential SHIP2 inhibitor. Although metformin has been used to treat T2DM in vivo, the exact molecular mechanism by which it enhances peripheral insulin sensitivity has remained elusive. We found that metformin inhibits the catalytic activity of the in vitro produced and purified SHIP2 phosphatase domain. Metformin also inhibited the catalytic activity of SHIP2 in cultured rat skeletal muscle cells and human podocytes, and protected podocytes against high glucose overexpression of SHIP2. Metformin also enhanced glucose uptake, which was reduced by SHIP2 overexpression in these cells. In vivo, metformin reduced the activity of SHIP2 in skeletal muscle and kidney tissue of metformin-treated diabetic db/db mice. Furthermore, we observed that T2DM patients on insulin medication showed decreased activity in SHIP2 in cultured human podocytes. These results suggest that metformin receiving metformin the activity of SHIP2 in the kidney was similar to that observed in patients without T2DM.

Conclusions: Metformin inhibits the activity of SHIP2, providing a mechanism by which metformin ameliorates peripheral insulin resistance. This highlights the potential of
Changes of DPP-4 and DPP-4 Substrates According to Aging in Kidney

Eun Nam Kim, Ji-Yeun Chang, In-Ae Jang, Ji Hee Lim, Min Young Kim, Tae Hyun Ban, Hye Eun Yoon, Cheol Whee Park, Bumsoon Choi. Div of Nephrology, Dept of Internal Medicine, Dept of Internal Medicine, The Catholic Univ of Korea, Republic of Korea.

Background: The incretin-based agents such as dipeptidyl peptidase IV (DPP-IV) inhibitor and glucagon-like peptide-1 (GLP-1) agonist was associated with diverse protective effect including renoprotective effect except lowering glucose. Aging kidney was characterized by decreased glomerular filtration rate, impaired electrolyte balance, decreased plasma renin activity and histological changes such as glomerulosclerosis and tubular atrophy. We investigated the renal function, albuminuria, the concentration and activity of DPP-4 and DPP-4 substrates in serum and urine, and expression of incretin hormone in renal tissue with aging in mice model.

Methods: C57BL/6 mice were divided into three groups according to age differences; 2-months-old (N=8), 12-months-old (N=8), and 24-months-old (N=8). We measured renal function, histological change in aging mice. Also, the concentrations and expressions of DPP-4 and DPP-4 substrates were measured in serum and renal tissue in aging mice.

Results: According to aging, albuminuria (16.5 ± 1.1 ng/24hr vs. 41.5 ± 8.4 ng/24hr, 65.5 ± 10.4 ng/24hr; p < 0.05 vs. 2M) was increased and Creatinine clearance (p > 0.05 vs. 12M) was decreased. There were increases in mesangial volume and tubulointerstitial fibrosis in 24-month-old mice (p < 0.01). There were also increases in F4/80 expression (0.4 ± 0.01%, 2.8 ± 0.3%, 19 ± 1.9%; p < 0.01) and in apoptosis detected by TUNEL (positive mesangial cells, 0.2% ± 0.06% vs. 0.5% ± 0.03%), 2.6% ± 0.6%; glomerulus and cortical tubular areas, 0.27 ± 0.09% vs. 0.53 ± 0.12%, 2.8 ± 0.67%). Urine isoprostane (7.4 ± 0.3% vs. 19.4 ± 0.78%, 21.9 ± 1.9%) excretion increased with aging. DPP-IV concentrations in serum and DPP-IV activities in renal tissue were gradually increased (p < 0.001 and p < 0.05, respectively). GLP-1 receptor and DPP-4-IV protein levels in renal tissue were significantly increased with aging in western blot (p < 0.001 and 0.05, respectively).

Conclusions: It is suggested that incretin based treatment is a possible strategy for preventing an aging process in the kidney.
Methods: To define the mechanism of LJ-2698, we performed in vitro experiments using human glomerular mesangial cells (HGCMCs), type I diabetic model (streptozotocin (STZ)-induced type 1-diabetic mice (HSR/NDmcr-cp (SHR/ND)) and a type 2-diabetic model (forehead obese (OBF) mice). In both models, we evaluated the effect of LJ-2698 on PAR-1 and PAR-2 signaling, gene expression, and protein expression in HGCMCs. We also examined the proteinuria and inflammation in male SHR/NDmcr-cp (SHR/ND) rats, rodent model of metabolic syndrome/type 2 diabetes, and sacrificed them at 3 weeks, serum and 24-hour urine samples were collected for biomedical studies. The level of urinary albumin and creatinine was also measured at every 6 weeks.

Results: The levels of urinary albumin, creatinine, and albumin-creatinine ratio were significantly decreased in the SHR/NDmcr-cp (SHR/ND) rats treated with LJ-2698 compared to the SHR/NDmcr-cp (SHR/ND) rats treated with vehicle. In addition, the levels of urinary albumin and creatinine were also decreased in the SHR/NDmcr-cp (SHR/ND) rats treated with LJ-2698 compared to the SHR/NDmcr-cp (SHR/ND) rats treated with vehicle. In contrast, the levels of urinary albumin and creatinine were not significantly different in the SHR/NDmcr-cp (SHR/ND) rats treated with vehicle and the SHR/NDmcr-cp (SHR/ND) rats treated with LJ-2698.

Conclusions: Our results showed that LJ-2698 had a protective effect on the reduction of renal function in the SHR/NDmcr-cp (SHR/ND) rats.

Funding: This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Numbers 15H04406 and 15H04407.

FR-PO333
Cyanoate Increases Glucose Homeostasis and Hepatic Steatosis in Normal and High Fat-Fed Mice

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: In the current study, we explored the in vivo and in vitro metabolic effects of cyanate in normal chow diet (NCD)- and high fat diet (HFD)-fed mice.

Results: Contrary to our expectations, we found that cyanate treatment improved glucose tolerance, increased insulin sensitivity and alleviated hepatic steatosis in both NCD- and HFD-fed mice compared with corresponding control groups. Histological analyses of liver tissue and serum levels of blood urea nitrogen and creatinine revealed no significant differences between cyanate-treated and control mice groups. Interestingly, we found that cyanate treatment decreased appetite and body weight in both diet groups. And we also found that cyanate treatment decreased lipid peroxidation levels in the sera and kidney, attenuated reactive oxygen species (ROS) levels in the kidney. Thus we examined in vitro carboxylated albumin (cAlb) in Caki-2 kidney cell lines for antioxidant effects of cyanate. We found that cAlb significantly reduced ROS generation compared with Alb.

Conclusions: Taken together, the results in this study may indicate that cyanate improves glucose tolerance and hepatic steatosis possibly via exerting anorexic and antioxidative effects.

FR-PO334
Iron Chelation Ameliorates Fibrotic Pathways in ZSF1 Obese Rat
A. Bilal Malik,1 Chhanda Bose,2 Sudhir V. Shah.2 1Univ of Washington, Seattle, WA; 2Univ of Arkansas for Medical Sciences, Little Rock, AR.

Background: Labile iron, by virtue of its ability to participate in free-radical reactions, plays an important role in diabetic nephropathy. Chelating catalytic iron would provide beneficial effects including amelioration of oxidative and consequently fibrotic pathways involved in progression.

Methods: The oral iron chelator deferiprone was administered to ZSF1 obese rats beginning age 8 weeks over a 24 week treatment period at a dose of 125mg/kg of body weight, dissolved in drinking water. A lean and obese ZSF1 rat group was also followed simultaneously without intervention and served as control groups. Real time quantitative PCR in rat kidneys was done to determine the activity of the oxidative and fibrotic pathways. cDNA was synthesized from RNA, isolated post treatment from control and treated kidneys. Taqman PCR Gene Expression reagents were used to detect eNOS, TGF-β, Smad3 and Collagen 1A1 chain (Cola5A1) and reference genes. cDNA and relative gene expression were calculated from Cq values using a ΔΔCq. Statistical significance relative to control is shown.

Results: 

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<th>eNOS</th>
<th>TGF-β</th>
<th>Smad3</th>
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<td>Lean Control [10]</td>
<td>0.08</td>
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<td>0.006</td>
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<tr>
<td>Obese [10]</td>
<td>0.235</td>
<td>0.138</td>
<td>0.009</td>
<td>0.194</td>
</tr>
<tr>
<td>Obese Treated [10]</td>
<td>0.511</td>
<td>0.076</td>
<td>0.022</td>
<td>0.092</td>
</tr>
</tbody>
</table>

Conclusions: Treatment with oral iron chelator deferiprone down regulated the oxidative and fibrotic pathways in the ZSF1 obese rat, an F1 hybrid model of type 2 diabetic nephropathy. The relative gene and messenger RNA expression levels of eNOS, TGF-β, Smad3 and Cola5A1 in treated obese rats returned to the levels expressed in non-diabetic lean rats with significant improvement compared with the obese non-treated group. Iron chelation may provide a new therapeutic modality for halting progression of diabetic nephropathy.

FR-PO335
An Immunomodulatory Device Improves Insulin Resistance in an Obese Porcine Model of Metabolic Syndrome A. Westover, K. Johnston, D. Buffington,1 H. David Humes.1,2 \*Innovative BioTherapies, Ann Arbor, MI; 1\*Internal Medicine, Univ of Michigan Medical School, Ann Arbor, MI.

Background: Obesity is associated with tissue inflammation which is a crucial etiology of insulin resistance (IR). This inflammation centers around circulating monocytes (MO) which form pro-inflammatory adipose tissue macrophages (ATM). Specific approaches targeting MO/ATM may improve IR without the adverse side effects of generalized immunosuppression.

Methods: An extracorporeal based biomimetic membrane leukocyte processing device, called the Selective Cytophoretic Device (SCD), was evaluated to assess the therapeutic impact in an Ossabaw miniature swine model of IR with metabolic syndrome (MetS). Pigs received 36 6 hour SCD therapy (Rx) sessions over a 1 week period, with measurements for assessing changes in IR via IV glucose tolerance test (GTT) and homeostatic model assessment (HOMA)-IR scores followed up to 2 weeks post Rx. Leukocyte parameters were assessed to determine impact of SCD Rx on the inflammatory state associated with MetS. Circulating neutrophil (NE) activation was measured by CD11R3 and Ne apoptosis rates were assessed via Annexin V assay. Systemic MO numbers were determined by manual white blood cell counts.

Results: SCD Rx in this porcine model demonstrated a significant (p=0.033) effect on decreasing circulating NE activation levels as measured by CD11R3 and on returning Ne apoptotic rates toward naive, non-inflammatory rates (p=0.023). For MO, a reduction in the absolute circulating MO counts was observed pre to post SCD Rx (p=0.007). These changes were associated with improvements in IR as determined by GTT. These improvements were also reflected in lowering of HOMA-IR scores for up to 2 weeks post SCD Rx. A decrease in TNFα was also consistently observed post SCD Rx, achieving significance at p=0.0022.

Conclusions: The above study provides strong evidence that SCD Rx reduced the chronic systemic inflammation associated with MetS as presented in this model. These results allow for the planning of first in man studies in obese type 2 diabetic patients.

Funding: Other NIH Support - NIH RR013223 and HL062552 to M. Sturek and the Comparative Medicine Center of the Indiana School of Medicine and Purdue University in developing the Ossabaw Swine Resource, Other U.S. Government Support

FR-PO336
Low Admission Serum Cyanate Concentration Predicts Mortality in Hospitalized Patients Independent of Body Mass Index
Wisit Thongprayoon, Charat Kianoush Banaei-Kashani, Kunio Humes.

Background: Low serum cyanate was associated with poor outcomes in critically ill and dialysis patients. The association between low admission serum cyanate and risk of in-hospital mortality is limited. The aim of this study is to assess the independent association between low admission cyanate and in-hospital mortality in hospitalized patients.

Methods: This is a single-center cohort study conducted at a tertiary referral hospital. All hospitalized adult patients who had admission cyanate available from January 2011 to December 2013 were included. Admission cyanate was categorized into 7 groups (<0.4, 0.4-0.5, 0.5-0.6, 0.6-0.7, 0.7-0.8, 0.9-1.0, 1.1-1.2, 1.3-1.4 and ≥1.5 mg/dL). The primary outcome was in-hospital mortality. Logistic regression analysis was performed to obtain the odds ratio of in-hospital mortality of various admission cyanate levels using cyanate 0.7-0.8 mg/dL as the reference group.

Results: Of 73,994 patients included, 973 (1.3%) died in the hospital. The association between different categories of admission cyanate and in-hospital mortality assumed a U-shaped curve, with both low and high cyanate associated with higher in-hospital mortality.

When adjusting for age, sex, ethnicity, principal diagnosis and comorbidities, very low cyanate (<0.4 mg/dL) was significantly associated with increased mortality (OR 3.29; 95% CI 2.08-5.00), exceeding the risk related with markedly elevated creatinine (OR 2.65; 95% CI 2.11-3.35 for cyanate ≥1.5 mg/dL). The association remained statistically significant following adjustment for body mass index.

Conclusions: Low admission cyanate was independently associated with increased in-hospital mortality in hospitalized patients. Low serum cyanate might be a better surrogate marker of low muscle mass than a low body mass index.

FR-PO337
Free and Bound Serum Sialic Acid Profiling of End Stage Renal Disease Patients
Kunio Kawajishi,1 Sandra Diaz,1 Biswa Choudhury,2 David Herold,2 Robyn A. Cunard,3,4 Kumar Sharma,4 Ajit Varki.1,2 \*Cellular & Molecular Medicine; 3Pathology; 4Medicine; \*VANDS; 4Inst of Metabolomic Medicine, UC San Diego, La Jolla, CA.

Background: Sialic acids (Sias) are a diverse family of molecules found at the outer tips of the glycan forest that covers all vertebrate cells. Previous studies reported increased serum total Sia associated with atherosclerosis in the general population and in patients with end stage renal disease (ESRD) undergoing hemodialysis (HD) therapy. However, there has been no profiling of the types of sialic acids in ESRD patients. The aim of this study was to analyze which types of free Sias and Sia-containing glycans accumulate in the sera of ESRD patients. Analysis focused on N-Acetylsialaminic acid (Neu5Ac), N-glycolylneuraminic acid and Cola5A1 in treated obese rats returned to the levels expressed in non-diabetic lean rats with significant improvement compared with the obese non-treated group. Iron chelation may provide a new therapeutic modality for halting progression of diabetic nephropathy.

Funding: Private Foundation Support
acid (Neu5Gc, which is not naturally made by humans), and the common lower vertebrate Sia 3-deoxy-D-glycero-D-galacto-nonulosonic acid (Kdn). Kdn is almost undetectable in normal human tissues except in some cancer.

Methods: Serum samples from HD patients (N=60) and normal controls (N=20) were analyzed for free and protein bound Sias by DMB derivatization, high performance liquid chromatography (HPLC) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). Bound Sias were released by mild acid. Sialylated N-glycans were released by PNGase F followed by 2-aminobenzamide (2-AB) labeling. The fluorescently tagged sialylglycans were analyzed with or without sialidase pretreatment. Bound Sias were released by mild acid. Sialylated neutral losses were analyzed only in ESRD patients, as well as much higher levels of free Neu5Ac and Kdn. No free form of Neu5Gc was detected. However, small amounts of peak corresponding to bound Neu5Gc were detected in both HD and normal control samples. N-glycan profiling using 2-AB labeling showed no sialidase resistant anomics were detected only in HD serum.

Conclusions: We show accumulation of free Neu5Ac and Kdn in HD patients, and possible bound Neu5Gc (presumably of dietary origin from red meat) in HD patients and in normal controls. These findings suggest that human and non-human Sias can accumulate in HD patients and may be potentially used by human cells. We are currently studying the sialidase-resistant peaks.

Funding: Other NIH support - NIGMS

FR-PO338
Bioimpedance Vectorial Analysis as a Tool for Early Diagnosis of Acute Kidney Injury
Luis Ignacio Bonilla,1 Sara Samoni,2,3 Allina Primavera Flores Mendoza,1 Jesus Cruz Valdez,1 Claudio Ronco.3 1Nephrology Dept, Hospital Univ, Monterrey, Mexico; 2Inst of Life Sciences, S. Anna School of Advanced Studies, Pisa, Italy; 3International Renal Research Inst, San Bortolo Hospital, Vicenza, Italy.

Background: Fluid overload(FO) is a frequent condition in critically ill patients. FO increases the volume of distribution of creatinine, thus decreasing serum creatinine (sCr) concentration, which may contribute to delay the diagnosis of Acute Kidney Injury (AKI) and underestimation of its severity. Our aim was to assess the incidence of AKI based on corrected creatinine according to a formula using total body water(TBW) estimated by bioimpedance.

Methods: This is a prospective, double-center study.Body fluid status was assessed in 40 adult patients during the first 24 hours after admission to ICU. Total body Bioelectric Impedance Analysis (BIA) was performed to evaluate TBW(kg) and the hydration scale with vectorial analysis (BIVA).Patients were eligible if: i) baseline SCr levels were available and ii) BIVA hydration level was more than 81% of lean body mass, indicating moderate to severe hydramia. We applied the following correction formula measuredScr × TBW/ (0.65 ×Body Weight).Acute Kidney Injury was diagnosed from Scr increase, according to KDIGO criteria, before and after creatinine correction.

Results: 26 pts. (61.5% male; median age 76.75 years) were considered eligible for the study. The average baseline value of sCr was 0.93±0.36. 24 hours after admission, sCr was 1.18±0.85. The average increase of uncorrected sCr value was 0.24±0.63. After correcting sCr for fluid overload, the average value of was 1.33±0.89 with an increase of 0.40±0.66. The incidence of AKI was 38.4% and 43.2%, respectively before and after correction. Taking into account measured sCr, 34.6%, 0% and 3.8% of patients developed AKI stage I, II and III. After correction for TBW overload, the percentages of pts. with stage I, II and III of AKI were 26.9%, 11.5% and 3.85%.

Conclusions: We suggest the utilization of TBW estimated by BIA to early diagnose AKI, and in hyperhydrated patients. Further studies, including more patients, are needed to assess the correlation of AKI diagnosed with our formula with major outcomes.

FR-PO339
Bioimpedance Spectroscopy for Assessment of Volume Changes during Intravenous Fluid Therapy: A Crossover Study in Healthy Volunteers
Manfred Hecking,1 Matthias Ernstrümmner,2 Peter Wabel.1 1Nephrology, Medical Univ of Vienna, Austria; 2Anesthesiology, Medical Univ of Vienna, Austria; 3Fresenius Medical Care Germany.

Background: Intravenous (iv) fluid therapy is among the most common medical tasks, but its immediate and intermediate effects on the fluid compartments and hemodynamics of the human body remain enigmatic to the majority of clinicians. We therefore tested bioimpedance spectroscopy (BIS) for assessment of volume changes in healthy volunteers.

Methods: After an overnight fast, 15 males received isotonic fluid therapy (Elo-mel®, 441A) for 113 mol/l and Uosm – 137mOsm/kg. She was treated with 2.4 liters of 0.9% Normal Saline over 48 hours, with improvement of Pna to 117mol/l. However over the next 24 (Day 3) hours she developed Polyuria of 5.4 liters, which was approximately 3 liters in excess of the total infused fluids with a concomitant rise in Pna to 124 mmol/l. The patient’s polyuria was attributed to loss of RWP mechanism, caused by increased solute delivery in the absence of ADH secretion.

Conclusions: BIS-based assessment revealed a clinically meaningful and sustained increase in ECV after iv fluid therapy, up to 50% of the infused volume. Similar studies in subjects with illness are needed to quantify the OH cut-off for worse outcomes.

FR-PO340
Residual Water Permeability: A Novel Concept Challenging Current Diagnosis of Syndrome of Inappropriate ADH
Hormuz Daro Dustoore,1 Chandra Mauli Jha,2 Ken J. Donaldson,3 Thalakunte Thathiah,1 Hatem Mohyeldin Ebeid,1 Samra Abouachacra. 1Div of Nephrology, Rahba Hospital- Johns Hopkins International, United Arab Emirates; 2Div of Nephrology, Burjeel Hospital, United Arab Emirates; 3Div of Nephrology, Dunfries and Galloway Royal Infirmary, United Arab Emirates; 4Div of Nephrology, Al Noor Hospital, United Arab Emirates; 5Div of Medicine, Tawam Hospital, United Arab Emirates.

Background: Residual Water Permeability (RWP) is a mechanism by which up to 5 liters of water can absorb down the osmolar gradient between Tubular and Medullary Intertistium, and is active only in the complete absence of ADH activity. We describe a case of a patient labeled as Syndrome of Inappropriate ADH (SIADH), however by showing an active RWP system, we challenged the diagnosis of SIADH and labelled this as a case of Resist Osmostat with concomitant Primary Polydipsia.

Methods: A 71-year-old lady presented with nausea, vomiting, Plasma Sodium (Pna)- 113 mol/l and Uosm = 137mOsm/kg. She was treated with 2.4 liters of 0.9% Normal Saline over 48 hours, with improvement of Pna to 117mol/l. However over the next 24 (Day 3) hours she developed Polyuria of 5.4 liters, which was approximately 3 liters in excess of the total infused fluids with a concomitant rise in Pna to 124 mmol/l. The patient’s polyuria was attributed to loss of RWP mechanism, caused by increased solute delivery in the absence of ADH secretion.

Conclusions: This is a prospective, dual-center study. Body fluid status was assessed in 40 adult patients during the first 24 hours after admission to ICU. Total body Bioelectric Impedance Analysis (BIA) was performed to evaluate TBW(kg) and the hydration scale with vectorial analysis (BIVA). Patients were eligible if: i) baseline SCr levels were available and ii) BIVA hydration level was more than 81% of lean body mass, indicating moderate to severe hydramia. We applied the following correction formula measuredScr × TBW/ (0.65 ×Body Weight). Acute Kidney Injury was diagnosed from Scr increase, according to KDIGO criteria, before and after creatinine correction.

Results: 26 pts. (61.5% male; median age 76.75 years) were considered eligible for the study. The average baseline value of sCr was 0.93±0.36. 24 hours after admission, sCr was 1.18±0.85. The average increase of uncorrected sCr value was 0.24±0.63. After correcting sCr for fluid overload, the average value of was 1.33±0.89 with an increase of 0.40±0.66. The incidence of AKI was 38.4% and 43.2%, respectively before and after correction. Taking into account measured sCr, 34.6%, 0% and 3.8% of patients developed AKI stage I, II and III. After correction for TBW overload, the percentages of pts. with stage I, II and III of AKI were 26.9%, 11.5% and 3.85%.

Conclusions: We suggest the utilization of TBW estimated by BIA to early diagnose AKI, and in hyperhydrated patients. Further studies, including more patients, are needed to assess the correlation of AKI diagnosed with our formula with major outcomes.

Residual Water Permeability and Polyuria
Conclusions: The case highlights that an RWP system implies complete absence of ADH activity and rules out SIADH as a diagnosis despite Uosm> 100mOsm/kg. We describe a case of a patient labeled as Syndrome of Inappropriate ADH (SIADH), however by showing an active RWP system, we challenged the diagnosis of SIADH and labelled this as a case of Resist Osmostat with concomitant Primary Polydipsia.

Methods: A 71-year-old lady presented with nausea, vomiting, Plasma Sodium (Pna)- 113 mol/l and Uosm = 137mOsm/kg. She was treated with 2.4 liters of 0.9% Normal Saline over 48 hours, with improvement of Pna to 117mol/l. However over the next 24 (Day 3) hours she developed Polyuria of 5.4 liters, which was approximately 3 liters in excess of the total infused fluids with a concomitant rise in Pna to 124 mmol/l. The patient’s polyuria was attributed to loss of RWP mechanism, caused by increased solute delivery in the absence of ADH secretion.
Background: Nitric Oxide (NO) has an effect on renal water and sodium excretion, but the effect is unknown in the principal cells of the nephron. In a dose-response study, we measured the effect of tolvaptan on renal handling of water and sodium and systemic hemodynamics during baseline and NO-inhibition with L-NMMA.

Methods: In a randomized, placebo-controlled double-blind, cross over study, 15 healthy subjects received tolvaptan 15, 30 and 45mg or placebo. L-NMMA was given as a bolus followed by continuous infusion during 60 min. We measured GFR, urinary flow (UO), free water clearance (C_H2O), fractional excretion of sodium (FE_{NaCl}), plasma vasopressin (p-AVP), and central blood pressure (cBP).

Results: During baseline, tolvaptan increased UO and C_H2O, whereas GFR and FE_{NaCl} were unchanged. P-AVP increased three fold. After NO inhibition, UO and C_H2O decreased, but to a lesser extent during tolvaptan. FE_{NaCl} decreased only after placebo. U-AQP2 decreased to the same extent during all tolvaptan doses. U-ENaCγ decreased only after placebo. Central BP increased after NO-inhibition.

Conclusions: During baseline conditions, tolvaptan increased renal water excretion in a dose dependent way. NO-inhibition antagonized the increases in renal water and sodium excretion by tolvaptan. The lack of decrease in u-AQP2 by tolvaptan could be due to a counteracting effect of elevated P-AVP.

**FR-P0342**

Evidence of Early Enhanced Effects of Vasopressin Type 2-Receptor Antagonist on Urinary Sodium and Potassium Excretion

Sawaya Ishigaki, Taiki Yamada, Naroo Hashai, Akiko Kato, Hideo Yasuda. Internal Medicine 1, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan; Blood Purification Unit, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan.

Background: Vasopressin type-2 receptor antagonist (V2-R antagonist) is well known to promote water diuresis by blocking the permeability to water of the collecting ducts. However, the possible effects of V2-R antagonist on sodium and potassium handling remain unknown. One of the experimental models that V2-R antagonist is known to increase natriuresis by inhibiting V2-R mediated stimulation of epithelial sodium channel in the collecting duct, and also increase potassium excretion by a flow-dependent mechanism. This study evaluated whether the V2-R antagonist influence the sodium and potassium excretion in humans.

Methods: Five patients with autosomal dominant polycystic kidney disease (ADPKD) were administered 45mg oral nonpeptide V2-R antagonist, tolvaptan (TiV). Urine flow, sodium and potassium excretion in the next 3 hours were compared with basal values obtained 2 hours prior administration of TiV.

Results: Urine flow increased upon TiV administration (p=0.01), sodium and potassium excretion rate (sodium 8.2±1.812±2.38 mEq/l, p<0.01, potassium 2.2±1.92±7.11 mEq/l, p<0.01) significantly increased in the first 3 hours after TiV administration. Subjects significantly lost weight (-0.49±0.30kg, p=0.02) without altering their serum sodium concentration (143.0±2.4 143±2.0 mEq/l, p=0.96) and plasma osmolality (289.8±4.7 299.1±6.2 mOsm/kgH2O, p=0.45).

Conclusions: TiV rapidly increases urinary sodium and potassium excretion in patients with ADPKD.

**FR-P0343**

Role of Vasopressin in Dehydration-Associated Kidney Disease

I. Gabriela Sanchez-Lozada, 1 Fernando E. Garcia-Arroyo, 1 Monica Gabriela Bias-Martoon, 2 Guillermo Gonzaga, 1 Octaviano Silverio, 1 Maria Cecilia Cristobal, 1 Virgilia Soto, 1 Richard J. Johnson, 1 Edilia Tapia. 1 Renal Physiopathology, INC Ignacio Chavez, Mexico City, Mexico; 2 Pathology, INC Ignacio Chavez, Mexico City, Mexico; 1 Renal Diseases, U of Colorado, Aurora, CO.

Background: The role of vasopressin in rats undergoing mild thermal dehydration followed by 2 h rehydration with fructose or water, by administering conivaptan, a V1a and V2 antagonist was studied.

Methods: Four groups of male Wistar rats were exposed to hyperthermia (37°C ± 1°C) for 2 h and rehydrated with water (W), or 10% fructose (F) during 2 h for 30 days. Two groups received vehicle (W-Veh and F-Veh), and two received Conivaptan (C, 3 mg/kg BW, W-C and F-C). After rehydration rats received tap water and food ad libitum. A group of normal control (NC) rats was also included. At the end of the study, plasma and urine osmolality and plasma copeptin were evaluated. In renal cortex homogenates sorbitol, fructose, uric acid, oxidative stress as well as the expression of aldose reductase, fructokinase, xanthine oxidase, Nox4, p22phox, gp91phox and vasopressin receptors V1a and V2 were assessed.

Results: Chronic recurrent heat stress was associated with mild renal functional changes (decreased CrCl, and tubular injury with systemic inflammation and renal oxidative stress as well as mitochondrial dysfunction) that were markedly exacerbated by rehydration with

**FR-P0344**

A Serine Protease Inhibitor Increases Osmotic Free Water Excretion Together with Inhibition of Urinary AQP2 Excretion Yutaka Kakizoe, 1 Terumasa Nakagawa, 1 Yoshikazu Miyasato, 1 Yuichi Izumi, 1 Takashige Kuwabara, 1 Masatake Adachi, 1 Kenichi Kitamura, 2 Masashi Mukoyama. 1 Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; 2 Internal Medicine III, Univ of Yamanashi Faculty of Medicine, Japan.

Background: Serine proteases (SPs) have pivotal physiological roles in our body. In the kidney, it is reported that the epithelial sodium channel (ENaC) is activated via the proteolytic cleavage of α and γ subunits by SPs. We reported that a synthetic SP inhibitor (SPI) could inhibit the cleavage of ENaC and increased urinary sodium excretion in aldosterone-infused rats. These results suggest the important roles of SPs within the kidney in the regulation of sodium homeostasis and blood pressure. However, physiological roles of SPs in the kidney still remain unclear. In this study, we administrated CM to normal rats in order to explore novel physiological roles of SPs in renal tubule and water homeostasis.

Methods: Six-week-old male Sprague-Dawley rats were divided into control and CM groups. CM group rats were subcutaneously implanted with sustained-release pellets of CM (14 mg/day). After 24 h urine collection was performed, rats were sacrificed at day 7 to obtain blood and kidney samples. In another experiment, desmopressin (20ng/h) was infused subcutaneously to rats which were treated with CM.

Results: CM significantly increased urinary volume in about two-fold throughout the experimental period independently of sodium and osmolyte excretion, indicating that CM increased osmotic free water excretion. The levels of vasopressin, potassium and calcium in blood as well as osmolality in the inner medulla, that is important for urine concentration, were not changed by CM. Urinary exosomal aquaporin-2 (AQP2) excretion was downregulated by CM, indicating that CM suppressed vasopressin signal in collecting duct. The infusion of desmopressin recovered urinary AQP2 excretion and diminished poluria caused by CM.

Conclusions: Our results suggest that SPs are associated with water homeostasis in the kidney and that SPI could be the new class of diuretics.
Inhibition of Mitochondrial Oxidative Stress Attenuates the Downregulation of AQP2 in Obstructive Kidney Disease: Role of COX-2/PGE2/V2 Receptor Pathway.

Shanjun Fu, Mi Liu, Yue Zhang, Guixia Ding, Songming Huang, Aihua Zhang.
1Dept of Nephrology, Nanjing Children’s Hospital affiliated to Nanjing Medical University, Nanjing, China; 2Nanjing Key Lab of Pediatrics, Nanjing, China.

Background: Downregulation of aquaporins (AQPs) in obstructive kidney disease has been demonstrated with elusive mechanisms. Our previous study indicated that mitochondrial dysfunction played crucial role in this process (ASN abstract, 103A, 2014). However, it is still uncertain how that mitochondrial dysfunction affected the AQPs in obstructive kidney disease. This study was undertaken to investigate the role of mitochondrial-derived oxidative stress in mediating obstruction-induced downregulation of AQPs.

Methods: Mice with unilateral ureteral obstruction (UUO) or sham surgery were subjected to MnTBAP (a SOD mimic) or vehicle treatment by osmotic minipumps.

Results: After UUO, renal SOD-specific SOD was reduced by 50% accompanied by a 2.2-fold increase of oxidative stress marker TBARs. Meanwhile, AQP1, AQP2, and AQP4 were remarkably downregulated by 70-90% as determined by Western blotting and qRT-PCR. Administration of MnTBAP significantly attenuated AQP2 downregulation by 40% (p<0.05) in line with complete blockade of TBARs elevation, while BSA and MnSO4 downregulated by 50% accompanied by a 2.2-fold increase of oxidative stress marker TBARs.

Conclusions: The findings suggested an important role of mitochondrial oxidative stress in mediating AQP2 downregulation in obstructed kidney disease possibly via modulating COX-2/PGE2/V2 receptor pathway.

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

Underline represents presenting author.
inhibited by chloroquine (a blocker of the lysosomal pathway) treatment, but not by MG132 (a proteasome inhibitor). Immunochemistry demonstrated that internalized AQP2 was more associated with lysosomal marker (LAMP-1) in the primary cultured IMCD cells under the Vps35 knockdown.

**Conclusions:** Vps35 is an interacting protein with AQP2 and depletion of Vps35 is likely to be associated with increased lysosomal degradation of AQP2 protein.

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

### FR-PO354

**Gain-Of-Function Mutations in the Vasopressin Type 2 Receptor Causing Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD): Evidence for Vasopressin-Independent Increase in AQP2 Trafficking and Osmotic Water Permeability**

**Background:** Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) results from gain-of-function mutations in the AQP2 gene coding for vasopressin receptor 2 (V2R) and is characterized by spontaneous antidiuresis and undetectable vasopressin circulating levels. Here, we investigate the effects of two mutations, R137C and F229V, on receptor-mediated intracellular signaling controlling AQP2 trafficking and function.

**Methods:** M1 cells were stably co-transfected with human AQP2 and wild type (WT) V2R or its mutants V2-R137C and V2R-F229V, AQP2 phosphorylation was evaluated by confocal studies and western blotting experiments. Osmotic water transport was evaluated by a calcium-based method. Intracellular cAMP was measured by cAMP ELISA kit.

**Results:** Confocal studies revealed that in cells expressing V2R-R137C, AQP2 was in part localized to the plasma membrane while a clear plasma membrane localization was found for cell expressing V2R-F229V. Functional experiments revealed a slight though significant increase in temporal osmotic response in cells expressing V2R-R137C whereas expression of V2R-F229V strongly increased the osmotic water permeability compared to cells expressing the WT receptors. Since AQP2 trafficking can be regulated by phosphorylation, we next evaluated AQP2 phosphorylation state in cells expressing the receptors. A significant increase in AQP2-S256 and AQP2-T269 phosphorylation, associated with significantly higher cAMP levels, was found in cells expressing V2R-F229V. Interestingly, in cells expressing V2R-R137C significantly lower levels of AQP2-S261 phosphorylation paralleled by decreased phosphorylation of p38 MAPK, the kinase committed to phosphorylate S261, were observed likely resulting in lower extent of AQP2 degradation.

**Conclusions:** These findings suggest that the constitutive activity of the V2R-R137C and V2R-F229V mutants upregulates AQP2 trafficking through two different signaling pathways. Whereas, V2R-F229V induces a cAMP-dependent increase of AQP2 phosphorylation, V2R-R137C seems to increase AQP2 abundance in cells.

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

### FR-PO353

**Acute Activation of AMPK Inhibits Aquaporin-2**

**Background:** Aquaporin-2 (AQP2) maintains water homeostasis and traffics from intracellular vesicles to the apical membrane of principal cells in response to vasopressin (AVP), which is released with low intravascular volume. Decreased kidney perfusion or its loss is associated with AKD, a metabolic sensor that inhibits several transport proteins. We hypothesized that AMPK inhibits AQP2 possibly to protect the interstitial gradient required for urine concentration during metabolic stress when low intravascular volume induces AVP release and there is decreased distal nephron permeation.

**Methods:** We used ex vivo kidney slices, hypoxic lysin for AQP2 expression Xenopus oocytes, surface biotinylation of mpCD2 ceil, phosphorylation assays, and mass spectrometry.

**Results:** Acute AMPK activation with 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (AIAR, 75 min) in kidney slices prevented baseline AQP2 apical accumulation in principal cells but did not prevent AQP2 apical accumulation in response to the AVP analog desmopressin (dDAVP). Prolonged AMPK activation prevented AQP2 cell membrane accumulation in response to forskolin in mouse collecting duct cells. Moreover, AMPK inhibition accelerated hypotonic lysis of Xenopus oocytes expressing AQP2. AMPK promoted Ser-261 phosphorylation and antagonized dDAVP-dependent phosphorylation of other AQP2 COOH-terminal sites. Although AMPK weakly phosphorylated immunoprecipitated AQP2 in vitro, no direct AMPK phosphorylation of AQP2 terminus was detected by mass spectrometry.

**Conclusions:** Our findings suggest an increasing, time-dependent antagonism of AMPK on AQP2, as AICAR inhibits cAMP-dependent apical accumulation and AVP-dependent phosphorylation of AQP2. AMPK inhibition of AQP2 likely does not involve direct AQP2 phosphorylation by AMPK.

**Funding:** NIDDK Support, Pharmaceutical Company Support - DCL, Private Foundation Support

### FR-PO356

**Effects of Nephrotoxins on Claudin 2 Expression and Paracellular Water Transport**

**Background:** Tight junction proteins are important for the selective permeability of the paracellular route and thus tissue specific function. In the proximal tubulus the pore forming Claudins, claudin 2 and 10 are highly expressed, contributing to the high permeability within this part of the nephron. Recently it has been shown that claudin 2 is not only permeable to...
Regulated Ser-261 Dephosphorylation Combined with Ser-256 and Ser-269 Phosphorylation in the C-Terminal of Aquaporin-2 Water Channel Naofumi Yui, Sei Sasaki, Shinichi Uchida. Nephrology, Tokyo Medical and Dental Univ, Bunkyo-ku, Tokyo, Japan.

Results: AQP2 has multiple vasopressin-sensitive serine-serine sites in its C-terminal that need to be dephosphorylated before it can be trafficked to the cell membrane. It is known that pS269 decreases and pS269 increases stimulated by vasopressin with a constant Ser-256 phosphorylation, however; how these phosphorylation and dephosphorylation is regulated in combination remains to be clarified.

Methods: In this study, we performed combinatorial analysis of AQP2 phosphorylation in the acute phase of forskolin (FK) stimulation. AQP2-MDCK cells were either treated or not treated with FK (20 µM) and then subjected to phospho-specific immunoprecipitation assays.

Results: First, we performed time-series analysis of phosphorylation in the initial phase of FK stimulation. A significant increase of pS269 was detectable within 1 min. A significant decrease of pS261 was detectable at 10 min, however; it was not occurred at 1 min. During the stimulation, pS256 status was constant. This demonstrated that Ser-269 phosphorylation preceded Ser-261 dephosphorylation. Next, pS269-positive AQP2 was isolated by the phospho-specific immunoprecipitation. In the steady state, pS256-positve AQP2 was strongly phosphorylated at Ser-261. After 10 min of FK treatment, pS269 signal significantly increased (1.00±0.05 to 5.62±0.25, P<0.01, n=4) and pS261 signal strongly decreased (1.00±0.05 to 0.30±0.13, P<0.01, n=4) in the pS256-positive AQP2 population. Further, pS269-positive AQP2 was isolated after 1 min or 10 min of FK treatment. At 1 min, pS261 signal was strongly dephosphorylated in the pS269-positive AQP2. After 10 min of the treatment, pS261 signal in the pS269-positive AQP2 population strikingly decreased (1.00±0.07 to 0.30±0.12, P<0.01, n=4).

Conclusions: Ser-269 and Ser-256 phosphorylation combined with Ser-269 dephosphorylation is regulated in combination. However, how these phosphorylation and dephosphorylation is regulated in combination remains to be clarified.

Funding: Government Support - Non-U.S.

FR-P0357

Protein Phosphatase 2c Is Responsible for S261 De-Phosphorylation, but Did Not Affect Aquaporin-2 Trafficking Pui Wen Cheung, Lars Ueberdiek, Richard Bouley, Dennis Brown. Medicine/Nephrology, Massachusetts General Hospital, Boston, MA.

Background: Aquaporin-2 (AQP2) trafficking and degradation are regulated by phosphorylation and dephosphorylation of 4 essential serine sites on the AQP2 c-terminus. Upon vasopressin (VP) stimulation, it is thought that S261 needs to be dephosphorylated first for other serine residues (S256 and S269) to be phosphorylated or dephosphorylated. However, another study identified that S256 and S269 dephosphorylation occurred before S261 dephosphorylation and determining whether this process is dependent on S256, the major regulator of AQP2 trafficking.

Methods: We pretreated LLC-PK1 cells stably expressing AQP2 (LLC-AQP2) with protein phosphatase (PP) inhibitors including okadaic acid, an inhibitor of PP1, PP2a, PP2b, and PP5; cyclosporine, an inhibitor of PP2b and PP5, and sodium orthovanadate, which inhibits PP2c. After 10 min VP treatment, we used immunocytochemistry to determine AQP2 localization, and western blot and specific phospho-antibodies against S256 and S261 to measure phosphorylation. We also treated rat kidney tissue slices to confirm AQP2 localization in situ by pre-treating tissues with PP inhibitors before VP.

Results: Inhibition of protein phosphatases (PPs) with okadaic acid, cyclosporine or sanguinarine did not lead to a noticeable alteration of AQP2 trafficking in LLC-AQP2 cells, and they also did not induce a significant change in S256 phosphorylation or S261 dephosphorylation on their own. Interestingly, we found that VP-induced de-phosphorylation of S261 occurred not only in LLC-AQP2 cells, but also in S256A mutant cells. Importantly, VP induced S261 dephosphorylation was almost completely prevented by inhibiting PP2c with sanguinarine but not the other PP inhibitors. Blocking S261 dephosphorylation with sanguinarine did not, however, affect VP-induced AQP2 membrane accumulation in either cultured cells or kidney tissue.

Conclusions: Our results show that S261 de-phosphorylation is dependent on protein phosphatase 2c (PP2c) activity, and is independent of S256 phosphorylation. These findings suggest an independent pattern of phosphorylation of some AQP2 C-terminal serine residues that will allow more detailed study of their physiological functions.

Funding: NIDDK Support, Private Foundation Support

FR-P0359

Protein Phosphatase 2c is Responsible for S261 Dephosphorylation, but Did Not Affect Aquaporin-2 Trafficking Pui Wen Cheung, Lars Ueberdiek, Richard Bouley, Dennis Brown. Medicine/Nephrology, Massachusetts General Hospital, Boston, MA.

Background: Protein phosphatase (PP) inhibitors, including okadaic acid, sodium orthovanadate, and sodium 4-(2-aminoethylbenzenesulfonyl)fluoride (AEBSF), were all found to be effective in de-phosphorylating all phospho-serine sites of AQP2 in both cultured cells and kidney tissue. However, it is unknown what mechanism regulates this process. Here we investigated the relationship between oxidative stress, claudin-2 regulation and paracellular water transport.

Methods: We pretreated LLC-PK1 cells stably expressing AQP2 (LLC-AQP2) with protein phosphatase (PP) inhibitors including, okadaic acid, an inhibitor of PP1, PP2a, PP3 and sodium 4-(2-aminoethylbenzenesulfonyl)fluoride (AEBSF), and exposed to 10 of exposure to 10 min of exogenous VP exposure to 10 min of exogenous VP.

Results: AQP2 has multiple vasopressin-sensitive serine-serine sites in its C-terminal that need to be dephosphorylated before it can be trafficked to the cell membrane. It is known that pS269 decreases and pS269 increases stimulated by vasopressin with a constant Ser-256 phosphorylation, however; how these phosphorylation and dephosphorylation is regulated in combination remains to be clarified.

Methods: In this study, we performed combinatorial analysis of AQP2 phosphorylation in the acute phase of forskolin (FK) stimulation. AQP2-MDCK cells were either treated or not treated with FK (20 µM) and then subjected to phospho-specific immunoprecipitation assays.

Results: First, we performed time-series analysis of phosphorylation in the initial phase of FK stimulation. A significant increase of pS269 was detectable within 1 min. A significant decrease of pS261 was detectable at 10 min, however; it was not occurred at 1 min. During the stimulation, pS256 status was constant. This demonstrated that Ser-269 phosphorylation preceded Ser-261 dephosphorylation. Next, pS269-positive AQP2 was isolated by the phospho-specific immunoprecipitation. In the steady state, pS256-positive AQP2 was strongly phosphorylated at Ser-261. After 10 min of FK treatment, pS269 signal significantly increased (1.00±0.05 to 5.62±0.25, P<0.01, n=4) and pS261 signal strongly decreased (1.00±0.05 to 0.30±0.13, P<0.01, n=4) in the pS256-positive AQP2 population. Further, pS269-positive AQP2 was isolated after 1 min or 10 min of FK treatment. At 1 min, pS261 signal was strongly dephosphorylated in the pS269-positive AQP2. After 10 min of the treatment, pS261 signal in the pS269-positive AQP2 population strikingly decreased (1.00±0.07 to 0.30±0.12, P<0.01, n=4).

Conclusions: Ser-269 and Ser-256 phosphorylation combined with Ser-269 dephosphorylation is regulated in combination. However, how these phosphorylation and dephosphorylation is regulated in combination remains to be clarified.

Funding: Government Support - Non-U.S.

FR-P0360

Gender Comparison of Volume Regulating Hormones and Aquaporin-2 Excretion following Graded Central Hypovolemia Nandu Goswami,1 Johannes Reichmuth,2 Amnaniya Russo,1 Marialtina Centore,3 Irhad Trozic,2 Rebecca Ruedl,1 Andreas Roessler,3 Marianna Rianieri,2 Annarita Di Masc,3 Catia Femia Carbuttì,2 Ferdinando Sassò,3 Natale Gaspare Di Mise,3 Grazia Tamma,1 Giovanna Valenti.2 1Medical Univ, 2Univers of Bari, 3Second Univ of Naples.

Background: Central hypovolemia induced by orthostatic loading induces reno-vascular changes that can lead to syncope. In this study we investigated volume regulating hormonal responses and reno-vascular changes in male and female subjects as they underwent central hypovolemia, induced by graded lower body negative pressure (LBNP).

Methods: 37 subjects (n = 19 males; n = 18 females. ages: 18 - 30 yrs) were subjected to graded LBNP until LBNP of 40 mmHg. Blood and urine samples were collected at rest and after 10 min recovery. The volume regulating hormones Vasopressin (measured as coetinin); Brain natriuretic peptide (BNP), ACTH and adrenomedullin (ADM) were measured in the plasma using standard methods. Urinary-AQP2 excretion was measured by ELISA as biomarker for the renal system response to vasopressin.

Results: Under basal conditions, males had significantly higher vasopressin levels compared with females. However both sexes responded to the central hypovolemia with a significant reduction of vasopressin levels, as measured at 10 min of recovery. BNP, secreted by the ventricles of the heart in response to excessive stretching of heart, was higher in males than in female under basal conditions and increased significantly after the orthostatic stress only in female. Conversely, ADM, a vasodilator peptide hormone, increased significantly after orthostatic loading only in males. u-AQP2 excretion was significantly higher in females than in males at rest and did not change significantly after 10 min recovery.

Conclusions: Analysis of volume regulating hormones indicate that soon after returning to the supine position at the end of the central hypovolemia, the expected sudden volume loading should stimulate different inputs to the brain, leading to inhibition of vasopressin release in females and stimulating a preferential adaptive vascular response in males as shown by the increases in ADM, whereas females showed a preferential renal response as shown by the increases in BNP.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Sex-Different Differences in Water Homeostasis in Wild-Type and V-ATPase B1 Knockout Mice

**Methods:** We performed a prospective cohort study among 1460 women and 1480 men in the Tromso Study 2009-2013. Endpoints were all-cause mortality, incident myocardial infarction and incident stroke. We analyzed hazard ratios (HR) for these endpoints per 59 µmol/L increase in baseline uric acid. We stratified the analyses by echocardiographic markers of diastolic dysfunction.

**Results:** Multivariable adjusted Cox regression analyses showed that uric acid predicted all-cause mortality in subjects with E/A ratio < 0.75 (HR 1.12, 95% confidence interval [CI] 1.00-1.25, p = 0.04) or E/A ratio > 1.5 (HR 1.51, 95% CI 1.09-2.09, p = 0.01, p for interaction between E/A ratio and uric acid = 0.02). Uric acid also increased in persons with severely enlarged left atria (HR 2.20, 95% CI 1.01-2.12, p = 0.04 and HR 1.13, 95% CI 1.02-1.26, p = 0.02, respectively; p for interaction = 0.04). Furthermore, in participants with isovolumic relaxation time ≤ 60 ms, mortality risk was far higher with increasing uric acid (HR 4.98, 95% CI 2.02-12.26, p < 0.001 for interaction < 0.001). Finally, uric acid predicted ischemic stroke risk in subjects with severely enlarged left atria (HR 1.62, 95% CI 1.03-2.53, p = 0.04, p for interaction = 0.04).

**Conclusions:** Uric acid was a predictor of all-cause mortality in subjects with echocardiographic indices of diastolic dysfunction, and was associated with increased ischemic stroke risk in persons with severely enlarged left atria.

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

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**Sex-specific Relationship of Serum Uric Acid with All-cause Mortality in Adults with Normal Kidney Function—An Observational Study**

**Background:** Elevated serum uric acid is associated with cardiovascular and protective roles in human disease, with protective effects of hyperuricemia in neurodegenerative diseases. Of the multiple genes associated in genome-wide association studies with SUA, variation in the SLC2A9 gene encoding the urate transporter GLUT9 is a primary determinant; baseshifted GLUT9 functions as the exit pathway for urate in the proximal tubule, with enhanced expression including in acute kidney injury. In this study, we examined the relationship between SUA and all-cause mortality in the Tromso Study 1994-2013.

**Methods:** The Tromso Study is an ongoing population-based cohort study established in 1972 in Tromsø, Norway. Participants aged over 40 years who underwent routine health check-ups from 1994 to 2013 were included. Endpoints were all-cause mortality, incident myocardial infarction and incident ischemic stroke. We analyzed hazard ratios (HR) for these endpoints per 59 µmol/L increase in baseline uric acid. We stratified the analyses by echocardiographic markers of diastolic dysfunction.

**Results:** Mortality risk was far higher with increasing uric acid (HR 4.98, 95% CI 2.02-12.26, p < 0.001 for interaction < 0.001). Finally, uric acid predicted ischemic stroke risk in subjects with severely enlarged left atria (HR 1.62, 95% CI 1.03-2.53, p = 0.04, p for interaction = 0.04).

**Conclusions:** Uric acid was a predictor of all-cause mortality in subjects with echocardiographic indices of diastolic dysfunction, and was associated with increased ischemic stroke risk in persons with severely enlarged left atria.

**Funding:** Government Support - Non-U.S.
FR-PO366
Evidence of Phospho-Regulated Expression of Urate Secretory Transporter ABCG2
Owen M. Woodward,² Alexis Holherr,² Meng Li,² Michael Kottgen.¹ ¹Physiology, Univ of Maryland School of Medicine, Baltimore, MD; ²Nephrology, Univ Medical Centre Freiburg, Freiburg, Germany

Background: ABCG2 is a high capacity urate secretory transporter of the renal proximal tubule. The common Q141K ABCG2 mutation causes gout in humans through an increased instability of the nucleotide-binding domain leading to enhanced degradation and reduced function.

Results: Here, we found ABCG2 protein rescued from degradation with the proteasome inhibitor MG-132 is phosphorylated; raising the possibility that a phospho-degron regulates ABCG2 trafficking and expression. An in silico analysis of ABCG2 revealed a limited number of predicted phosphorylation sites, including S195, a serine conserved in the mammalian lineage. The upstream RNKX5 represents a target motif for AKT1 and PDK, which both co-immunoprecipitated with ABCG2. Specifically, endogenous AKT1 pulled down both over expressed ABCG2 in HEK293 cells as well as endogenous ABCG2 in mouse kidney lysate. AKT1 and ABCG2 transcript co-localize in the proximal S2 segment of the mammalian nephron and inhibiting the AKT1 kinase cascade with PI3K inhibitor LY294002, or with growth factor receptor (RTK) inhibitor Vandetanib, dramatically up-regulated ABCG2 expression. Conversely, activating the AKT1 cascade with FBS down-regulated ABCG2 expression. Replacement of the S195 residue with a phosphomimetic aspartic acid resulted in significant reduction in ABCG2 expression, localization of ABCG2 to perinuclear compartments, and significant sensitivity to MG-132, confirming the S195 residue as a phospho-degron. Finally, a non-phosphorylatable S195A substitution led to the complete rescue of the Q141K gout mutant protein expression and trafficking.

Conclusions: Modulated ABCG2 structure indicates phosphorylation of the S195 residue may only be possible when the nucleotide-binding domains are separated, suggesting the S195 phospho-degron may be part of a novel regulatory mechanism for function and trafficking in ABCG2 transporters. American Heart Association: 14SD18860004 & Ardea Biosciences.

Funding: Pharmaceutical Company Support - Ardea Biosciences, Private Foundation Support

FR-PO367
Aldosterone and Vasopressin Are Erythropoietic Hormones
Hiroshi Nonoguchi,¹ Yuichiro Izumi,² Yukiko Yasukouchi,² Yasushi Nakayama,² Takanori Nagai,³ Masayoshi Nanami,² Takeshi Nakashishi,² Masashi Mukoyama,² Katsumasa Kawahara.¹ Internal Medicine, Kitasato Univ Medical Center, Kitamoto, Saitama, Japan; ²Nephrology, Kumamoto Univ, Kumamoto, Japan; ³Physiology, Kitasato Univ, Sagamihara, Kanagawa, Japan; ⁴Kidney and Dialysis, Hyogo Medical College, Nishinomiya, Hyogo, Japan

Background: Erythropoietin (Epo) is produced by the renal tubules in response to hypoxia and/or anemia (Nagai T, et al. BBRC 2014). We investigated the effects of aldosterone and vasopressin on mRNA expression of Epo in distal nephron segments.

Methods: Tubule suspensions (TS) of cortex (CX), outer medulla (OM) and inner medulla (IM) were prepared from 5-7 week-old rats. Nephron segments were microdissected after the incubation of kidney slices in solution containing collagenase and VRC. TS or nephron segments were incubated with 10⁻⁶ M and 10⁻⁸ M aldosterone, vasopressin or vehicle for 2 hrs at 37°C. After the RNA extraction, the expressions of GAPDH, Epo, EpoR, HIF2α, HIF1α, PHD2, mineralocorticoid receptor (MR), glucocorticoid receptor, EGFR, vasopressin V2 and V1α receptors (V2R and V1αR, respectively), GATA2 and GATA3 mRNAs were examined using real time PCR.

Results: Epo mRNA expression was detected in TS of CX, OM and IM (CX>OM>IM) and was time-dependently decreased. Aldosterone and vasopressin increased Epo mRNA expression in TS of CX and OM and vasopressin increased Epo mRNA in TS of IM. In microdissected nephron segments, Epo mRNA was decreased with time. After 2-hr incubation with vehicle, Epo mRNA expression was not observed in CAL and MAL, while its expression was remained at detectable level in the collecting ducts. Aldosterone and vasopressin stimulated the expression of Epo mRNA in CAL, MAL, CCD, OMCD and IMCD. Aldosterone and vasopressin stimulated mRNA expression of MR and V2R/V1αR, respectively. Aldosterone stimulated the expression of Epo mRNA along with the increase of HIF2α, GATA 2 and GATA 3 mRNAs but not with HIF1α. Aldosterone and vasopressin also stimulated EpoR mRNA expression in IMCD.

Conclusions: Epo is produced by the distal nephrons in normal condition. Aldosterone and vasopressin are erythropoietic hormones that are possibly under the control of HIF2α and GATA3 pathways in the distal nephrons.


FR-PO368
Aldosterone-Regulated miRNAs and Their Target Genes in Mouse Cortical Collecting Duct Cells
Tae-Hwan Kwon.¹,² Hyun Jun Jung,² Hye-Jung Choi,¹ Tae-Hwan Kwon.¹,² ¹Biochemistry and Cell Biology, Sch of Med, Kyungpook Natl Univ, Taegu, Republic of Korea; ²NHLBI/NIH, Bethesda, MD; ³BK21 Plus KNU Biomedical Convergence Program, Sch of Med, Kyungpook Natl Univ, Taegu, Republic of Korea

Background: Mature microRNA (miRNA) is a modulator in the post-transcriptional regulation. The present study aimed to identify the aldosterone-regulated miRNAs and their target genes in mpkCCDc14 cells. Target genes of the selected miRNAs and their biological functions and processes were predicted.

Methods: Microarray chip assay (Affymetrix GeneChip miRNA 4.0 array) was done in the mpkCCDc14 cells in the absence or the presence of aldosterone treatment (10⁻⁸ M) for 3 d. The candidate miRNAs were selected by 1) more or less than 30% of significant fold-changes (protocol 1), or 2) differential expression analysis carried out using the R package ‘bridge’ (Gottardo R. bridge: Bayesian Robust Inference for Differential Gene Expression, R package version 1.34.0., protocol 2). To predict putative target genes of identified miRNAs and miRNAs-enriched pathways, DIANA-miRPath program was employed.

Results: In protocol 1, 29 miRNAs were significantly up-regulated more than 1.3 fold-change and 27 miRNAs were markedly down-regulated less than 0.7 fold-change in mpkCCDc14 cells after aldosterone treatment. In protocol 2, 5 up-regulated and 7 down-regulated miRNAs (more than 1.2 fold-change and less than 0.8 fold-change) were selected with high posterior probabilities (> 0.95). According to DIANA-miRPath program, 55 KEGG pathways (protocol 1) and 29 KEGG pathways (protocol 2) were profiled. In particular, Wnt signaling pathway, which was the most highly ranked, was selected. The quantitative changes of 7 up- and 8 down-regulated mature miRNAs enriched in the Wnt signaling pathways were further examined by qPCR and particularly miR-130b-3p was significantly increased. Six target genes (Rock1, skp1a, Tbl1x1p, Ppp2rc, Wnt2b, Pdch1) of miR-130b-3p were identified, which need to be further evaluated for the aldosterone-induced pathophysiology.

Conclusions: Aldosterone induces significant changes in miRNA expression in mpkCCDc14 cells, which could be involved in a number of pathways including Wnt signaling.

Funding: Government Support - Non-U.S.

FR-PO369
Elevated Polymorphonuclear Myeloid Deprived Suppressor Cell in Patients with End-Stage Renal Disease associated with Infectious Events
Yan-Fang Xing,¹ Xing Li.² ¹Dept of Nephrology, The Third Affiliated Hospital of Guangzhou Medical Univ; ²Dept of Medical Oncology, The Third Affiliated Hospital of Sun Yat-sen Univ.

Background: Infectious disease is one of the common complications in patients with end-stage renal disease (ESRD) due to systemic immuno-suppression and inflammation without clear mechanism. The present study was aimed to determine the Myeloid Deprived Suppressor Cells (MDSCs) level in ESRD patients and its association with infectious events.

Methods: A total of 29 ESRD patients and 30 matched health control were tested the MDSC in peripheral blood mononuclear cells (PBMC) by Flow cytometry. PMN-MDSC was defined as HLA-DR⁺/CD11b⁺/CD33⁺CD14⁺CD15⁻ with M-ESRD defined as HLA-DR⁺/CD11b⁺/CD33⁺CD14⁺CD15⁻ [figure1A]. MDSC depleted (A MDSC), or undepleted PBMCs were stimulated with anti-CD3/anti-CD28 for 3 days to test T cell responses by intracellular IFN-γ production. The association of MDSC with infectious events including respiratory tract infection, catheter related bloodstream infection and infection of digestive canal within 1 year before testing was analyzed retrospectively.

Results: The frequency of PMN-MDSC was higher in ESRD patients as compared to healthy controls (p<0.001) with M-ESRD unchanged [figure1B]. Removal of PMN-MDSCs increased the expansion of antigen non-specific IFN-γ+ T cells, which indicated that PMN-MDSC suppressed immune responses. M-ESRD and immature myeloid cells (IMC) in health control were not suppressive [figure1C]. The ESRD patients were classified into two subsidiary sets according to PMN-MDSC levels. ESRD patients with higher level of PMN-MDSC >6.41845% displayed increased infectious events within 1 year before this study (p<0.01) [figure1D].
Conclusions: In summary, the present study firstly indentified increased PMN-MDSC in ESRD patients and its association with infectious events.

FR-PO370

Effect of Omega-3 Fatty Acids on STAMP2 Expression in 5/6 Nephrectomized Rat Model

Su Mi Lee, Yun Jung Oh, Sung Hyun Son, Young Ki Son, Seong Eun Kim, Won Suk Ah. Dong-A Univ, Busan, Republic of Korea; Cheju Halma General Hospital, Jeju, Republic of Korea; BHS Han Sea Hospital, Busan, Republic of Korea.

Background: Six transmembrane protein of prostate 2 (STAMP2) is known as critical modulator of inflammation and metabolism in adipose tissue. In recent study, STAMP2 had an important role in hepatic steatosis, but there is no data about the expression of STAMP2 in chronic kidney disease which is inflammatory status and related with metabolic disorder. This study aimed to investigate the STAMP2 expression of heart and kidney in 5/6 nephrectomy (Nx) rats. In addition, we evaluated the effect of omega-3 fatty acid (FA) and vitamin D which are related with inflammation and metabolic disorder on STAMP2 expression.

Methods: Sprague Dawley rats were divided into four groups: sham control (0.9% saline), 5/6 Nx treated with omega-3 FA (300 mg/kg/day by gastric gavage) group, 5/6 Nx treated with vitamin D (cholecalciferol 3000 IU/kg/week) and omega-3 FA groups. The expression of ICib, NF-kB, AMPK, SREBP1, Nosx, LXRα and STAMP2 were examined by western blot analysis.

Results: BUN and creatinine were the lowest in 5/6 Nx treated with omega-3 FA and vitamin D group among 5/6 Nx rat model. Compared with control, there was significant up-regulation of ICib, NF-kB, AMPK, SREBP1, Nosx, and LXRα expression and a down-regulation of STAMP2 and phosphorylated AMPK expression in kidney and heart in 5/6 Nex model. We found that omega-3 FA prevented these up and down regulations related with inflammation and metabolic disorder of lipid. The STAMP2 expression was significantly up-regulated by omega-3 FA supplementation in both kidney and heart. In particular, STAMP2 expression was much more up-regulated in 5/6 Nx rats treated with omega-3 FA and vitamin D.

Conclusions: The STAMP2 suppression of heart and kidney was found in 5/6 Nx rats. STAMP2 activation induced by omega-3 FA supplementation may be one of potential mechanisms attenuating inflammation and metabolic disorder.

FR-PO371

Targeted Metabolomic Analysis of Kidney from the Subtotal Nephrectomy Mouse Model of Chronic Kidney Disease

Hiroyuki Kituchi,1 Naohiro Nomura,1 Yoji Andrew Minaminishima,2 Tatemuji Raı,1 Shinichi Uchida,1 Eisie Sohara,1 Nephrology, Tokyo Medical and Dental Univ; Molecular and Cellular Biology, Medical Inst of Bioregulation, Kyushu Univ.

Background: Metabolome analysis is a powerful tool for the identification and the quantification of the critical metabolites closely related to diseases. Little is known about the changes of metabolite profile in chronic kidney disease (CKD). We applied a global targeted metabolome profiling approach to kidney samples obtained from C57BL/6J mice performed with subtotal nephrectomy (STN) which is the most common model of non-diabetic CKD.

Methods: Using capillary electrophoresis-time-of-flight mass spectrometry (CE-TOF-MS), we analyzed low molecular weight metabolites of kidney in the CKD mice (n=4) and sham control mice (n=4). The acquired data were analyzed using principal component analysis (PCA) followed by Kruskal-Wallis test and Dunn’s post-test to assess the statistical significance.

Results: CE-TOF-MS analysis showed metabolically significant profiles of kidney comprised of 278 metabolites. We found that 78 metabolites were significantly increased, and 13 metabolites were significantly decreased in kidney samples from CKD model mice. In the STN kidney, well-known uremic toxin such as 3-indoxylsulfuric acid, creatinine, and hippuric acid were significantly increased, indicating that our disease mouse model properly developed CKD. Interestingly, energy-related metabolites such as ATP, UTP, CTP were significantly decreased, compared with sham control.

Conclusions: Metabolomic analysis of kidney from CKD mice provided the useful information for identifying novel markers and elucidating the pathophysiology of CKD. The results suggested that some renal ATP-generating pathways were apparently impaired in CKD.

Funding: Government Support - Non-U.S.

FR-PO372

Calciprotein Particle Ripening Induces Mitochondrial Damage and Activates the NLRP3 Inflammasome

Edward R. Smith,1 Timothy D. Hewitson,1 Parisa Aghagolzadeh,2 Matthias Bachtler,2 Andreas Pasch,2 Stephen G. Holt,1 1Royal Melbourne Hospital, Australia; 2Univ of Bern, Switzerland.

Background: Calciprotein particles (CPP) accumulate and ripen from an amorphous (CPPi) to crystalline (CPPii) state in uremia and are associated with inflammation, vascular dysfunction and mortality. In vitro studies implicates NLRP3 inflammasome activation, but the mechanism and evidence of in vivo effects remains unknown.

Methods: NLRP3 priming/activation was evaluated in human monocyte-derived macrophage and in differentiated THP-1 cells. Uptake and effects on lysosomal/mitochondrial function/cell fate were assessed by flow cytometry. Live-cell imaging and particle localisation were assessed by laser-scanning confocal and super-resolution microscopy. For in vivo studies, CPPii or vehicle were administered to 12 week-old uremic or non-uremic Wistar rats via tail vein injection (twice daily for 5 days). Some animals received additional treatment with an NLRP1 inhibitor (MC950) via subcutaneous minipump, or a mitochondria-targeted antioxidant (MitoQ10) via intraperitoneal injection or vehicle controls (n=6 for each treatment). Serum was collected after 6 days to assess inflammation/oxidative stress.

Results: In vitro, CPPi failed to prime or activate the NLRP3 inflammasome. In contrast, CPP-II primed inflammatory cytokine synthesis via Toll-like receptor-4/6/NF-κB-signalling. Binding and endocytosis of CPPii resulted in marked changes in intracellular calcium that were not apparent with CPPi. CPPii induced lysosomal destabilisation, loss of mitochondrial (mt) membrane potential, increased mtROS production and a release of mtDNA. NLRP3 activation, as well as sustained excursions in intracellular calcium, amplified mitochondrial damage via mitochondrial transition pore opening and induced interleukin (IL)-1β secretion. In uremic rats, intravenous administration of CPPii, but not CPPi, resulted in elevations in IL-1β, IL-6 and oxidative stress over 6 days, which were attenuated by concurrent treatment with MC950 or MitoQ10 compared to vehicle controls.

Conclusions: CPP ripening drives inflammation via NLRP3 activation and effects on mitochondrial function. Targeting these pathways may have therapeutic potential in patients with CKD.

Funding: Pharmaceutical Company Support - Amgen Australia, Private Foundation Support

FR-PO373

Exercise Improves Skeletal Muscle, but Does Not Alter Disease Progression in a Rat Model of Chronic Kidney Disease

Keith Avin,2 Neal X. Chen,3 Sharon M. Moe,2,3 Matthew R. Allen,2,3 Jason M. Organ,2,3 1Physical Therapy, Indiana Univ, Indianapolis, IN; 2Nephrology, Indiana Univ, Indianapolis, IN; 3Anatomy and Cell Biology, Indiana Univ, Indianapolis, IN; 4Veterans Affairs Medical Center, Indianapolis, IN.

Background: Chronic kidney disease (CKD) is associated with musculoskeletal deterioration characterized by decreased skeletal muscle size (i.e. atrophy) and impaired muscle function. Currently, exercise interventions have experienced tempered success which may be the result of a lack of understanding of the pathogenesis of muscle dysfunction.

Methods: We used a slowly, progressive, naturally occurring, CKD rat model (Cy+/− rat) and its normal littermate (NL). A graded 10-week treadmill exercise protocol began at 25 weeks of age (~CKD stage 2/3) and concluded at 35 weeks. At 35 weeks, we tested muscle strength in vivo, sacrificed and collected tissues and prepared for histology or RNA analysis using real time qPCR.

Results: Sarcopenia was first demonstrated in CKD rats (compared to NL) by reduced muscle fiber cross sectional area (p<0.05) and impaired strength (p<0.05). As the force produced during maximal, electrically stimulated dorsiflexion. CKD rats demonstrated altered gene expression responses in muscle regeneration (Pax-7, MyoD and myogenin (p<0.05) and proteolysis (Atrogin-1 and MuRF-1 (p<0.05). CKD rats who performed 10 weeks of treadmill training restored gene expression markers of skeletal muscle regeneration and muscle proteolysis similar to NL levels (p<0.001; CKD vs CKD exercise). At 30 weeks of age maximal torque production (20%, p=0.05) and power (27%, p<0.01) were higher, when comparing CKD to CKD-exercise although there were no differences at 35 weeks of age.

Conclusions: In a progressive rat model of CKD, exercise restored the regenerative and proteolytic profile to that normal littermates with improved strength at 30 weeks of age (stage 4/5 CKD). However, exercise did not alter the disease progression or end-stage disease muscle strength.

Funding: Private Foundation Support
The Role of microRNA-26 on Muscle-Heart Crosstalk in Mice with Chronic Kidney Disease

Bin Wang,1,2 Aiqing Zhang,1 Faten Hasounah,1 Xiaoan H. Wang,1 Renal Div, Emory Univ, Atlanta, GA; 1Dept of Nephrology, Huashan Hospital of Fudan Univ, Changzhou, Jiangsu, China.

Background: Uremic cardiomyopathy and muscle atrophy contribute to CKD-induced morbidity and mortality. Exosomes, natural carriers of many signal molecules including microRNA (miR), mediate organ to organ communication. We hypothesized that miR-26 would benefit both CKD-induced muscle wasting and cardiomyopathy through exosome-mediated muscle-heart crosstalk.

Methods: CKD model in mice: 5/6 subtotal nephrectomy for 10 weeks. NanoSight instrument was used to quantify exosomes. A miR deep sequencing assay and qPCR were used to examine miR-26a expression in CKD muscle and cardiac muscle. Adiposectomy, which reduces fat mass in mice, was performed to determine if adipose tissue is a potential source of miR-26a. Exosome-mediated muscle-heart crosstalk was investigated by western blot.

Results: We found that serum-derived exosomes from CKD mice are larger than sham using NanoSight. MiR-26a was increased in CKD muscle and also increased in visceral adipose tissue (p<0.05). We observed increased cardiac miR-26a expression in CKD mice and also increased circulating miR-26a in CKD mice. We further confirmed that FoxO1, a-SMA, GSK-3β, and CTGF were increased in CKD mice. Cardiac sonography also showed that the percentage of ejection fraction was reduced in CKD mice treated with miR-26a. In a cell culture model, we showed that exosomes containing miR-26a from skeletal muscle cells can transfer miR-26a to H9C2 cardiac cells and attenuate uremic serum-induced upregulation of FoxO1 in H9C2 cell, providing evidence that skeletal muscle is a source of miR-26a for CKD-induced muscle wasting. We observed increased miR-26a expression in the heart following TA muscle injection. Interestingly, cardiac fibrosis was partially depressed in miR-26a overexpressing CKD mice. We further confirmed that FoxO1, a-SMA, GSK-3β, and CTGF were increased in CKD mice. Cardiac sonography also showed that the percentage of ejection fraction was reduced in CKD mice treated with miR-26a. In a cell culture model, we showed that exosomes containing miR-26a from skeletal muscle cells can transfer miR-26a to H9C2 cardiac cells and attenuate uremic serum-induced upregulation of FoxO1 in H9C2 cell, providing evidence that skeletal muscle is a source of miR-26a for CKD-induced muscle wasting.

Conclusions: Exogenous miR-26a not only attenuated skeletal muscle atrophy but also ameliorated uremic cardiomyopathy by targeting multiple mRNAs, possibly through exosome-mediated muscle-heart crosstalk.

Funding: Other NIH Support - NIH R01 AR060268

Mitochondrial Dysfunction in Uremic Muscle

Maria P. Martinez Cantarin, Zhao Lin,2 Bonita E. Falkner.1 Medicine, Thomas Jefferson Univ Hospital, Philadelphia, PA; 1Kimmel Cancer Center; Thomas Jefferson Univ, Philadelphia, PA.

Background: Muscle wasting is associated with uremia leading to increased mortality. Different factors have been associated with increased muscle wasting in chronic kidney disease models. Mitochondrial biogenesis is a key component of skeletal muscle function and structure. We set up to determine if inflammation and or reactive oxygen species (ROS) play a role in the uremic muscle’s metabolic dysfunction.

Methods: We studied mitochondrial function in muscle of ESRD patients using the protein expression of TOMM20 by western blot. We exposed a myoblast cell line (C2C12) to uremic and normal human serum (2%, 5%, and 10% serum for 24h) with and without N-acetylcysteine (NAC) 10mM and then studied mitochondrial function by mitotracker orange. We also observed C2C12 cells toascending concentrations of TNFα (0.1, 0.1 ng/ml) and IL6 (0.1, 1 ng/ml) with and without adiponectin (1 ug/ml) on mitochondrial mitochondrial function by mitotracker orange. We also assessed TOMM20 protein expression of C2C12 exposed to TNFα.

Results: We demonstrate lower TOMM20 protein expression in ESRD patients compared to controls but western blot analysis consistent with reduced mitochondrial function. C2C12 cells exposed to uremia show a decrease in mitochondrial activity with increasing uremic serum concentrations compared to cells exposed to normal serum (p<0.01 for 2% and 5% serum and p<0.05 for 10% serum). When NAC was added to uremic serum, cells exposed to urremia and NAC were able to rescue mitotracker activity to similar levels of cells exposed to normal serum (p<0.05). Mitochondrial activity in C2C12 cells decreases with increasing concentrations of TNFα and IL6 (p<0.01 for both cytokines). Exposure to TNFα and the anti-inflammatory adiponectin results in an increase in mitochondrial function compared to cells exposed to TNFα alone although only at low TNFα doses (1 ng/ml) p<0.05. Similar to human muscle exposed to uremia, we demonstrated that TOMM20 protein expression decreases in C2C12 exposed to high concentrations of TNFα.

Conclusions: In summary, our data suggest that inflammation and oxidative stress promote mitochondrial dysfunction in ESRD.

Funding: Private Foundation Support

Adipose Tissue Inflammation in ESRD

Maria P. Martinez Cantarin,1 Diana Whitaker Meneses,2 Bonita E. Falkner.1 Medicine, Div of Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA; 1Medical Oncology, Kimmel Cancer Center, Thomas Jefferson Univ, Philadelphia, PA.

Background: ESRD patients have increased inflammation with high levels of circulating inflammatory markers. Systemic inflammation is associated with poor outcomes in patients with ESRD. Multiple mechanisms have been proposed to explain how ESRD is a chronic inflammatory state but each one’s contribution is unknown. Adipose tissue is a major source of cytokine-producing adipocytes and we set up to study if the adipose tissue of ESRD could contribute to systemic inflammation in ESRD.

Methods: Participants were recruited from the Thomas Jefferson University Hospital (TJUH) transplant program. Criteria for inclusion in the study included having ESRD and undergoing kidney transplantation at our institution. The control group consisted of kidney donors with normal kidney function. While the participants were under general anesthesia for kidney donation or kidney transplantation, 250 mg of omental visceral fat and 250 mg of subcutaneous fat were obtained. Fixed adipose tissue samples were processed and Paraffin-embedded sections of visceral and subcutaneous adipose tissue were immunostained for the macrophage marker CD163. Adipose tissue macrophage infiltration was measured as the number of CD163+ cells in 10 randomly chosen 40x areas (high power field) by 2 independent pathologists. Number of CD163+ cells was normalized by 100 adipocytes.

Results: Compared to controls, ESRD patients have increased macrophage infiltration in visceral and subcutaneous adipose tissue, as determined by the quantification of CD163+ cells (n=10 for both adipose tissues). After participants were stratified by BMI as obese (BMI >30) versus non-obese (BMI <30), non-ESRD patients continue to present higher macrophage infiltration in subcutaneous and visceral adipose tissue compared to controls (p<0.01 for both tissues).

Conclusions: Our study demonstrates that the adipose tissue of uremic patients has increased macrophage infiltration in non-obese individuals. We propose that adipose tissue is a potential source of inflammation in ESRD that is not related to increased adiposity.

Funding: Private Foundation Support

Mitochondrial Fragmentation in Patients on Maintenance Hemodialysis

Jorge Gamboa,1 Theodore F. Towece,2 Emily C. Bush,2 Baback Roshanravan,2 Serpl Muge Dege,1 Talat Alp Ikizler.1 Medicine, Vanderbilt Univ Medical Center, Nashville, TN; 2Medical and Rehabilitation, Vanderbilt Univ Medical Center, Nashville, TN; 1Medicine, Univ of Washington, Seattle, WA.

Background: Fasting and sarcopenia, defined as a reduction in muscle mass and/ or muscle strength, are common in patients on maintenance hemodialysis (MHD). Mitochondria are important for proper muscle function. Mitochondria are organelles that are constantly undergoing either fusion, to become larger structures, or fission, a process of mitochondrial division. A balance between mitochondrial fusion and fission is essential for proper mitochondrial function. Increased mitochondrial fission will result in mitochondrial fragmentation and smaller mitochondria. Thus, we evaluated the hypothesis that mitochondrial fragmentation is increased in patients on MHD.

Methods: We measure mitochondrial size using electron microscopy. We evaluated 10 patients on MHD and 15 controls with no CKD that were matched by age, gender, race, and BMI. We also measured OPA-1 and Fis-1, markers of mitochondrial fission and fusion respectively, by western blot.

Results: Controls and patients on MHD were similar in terms of age (52.8±8.7 vs. 59.3±7.3, p<0.01) and BMI (27.0±6.2 vs. 29.0±5.1, p<0.01) and OPA-1 and Fis-1 expression. Frequency distribution of individual areas showed a shift to the left in patients on MHD (Figure 1C). We did not find any difference in the abundance of either OPA-1 or Fis-1 between the groups.

Conclusions: Smaller mitochondria in skeletal muscle of patients on MHD may be the consequence of increased mitochondrial fission for segregation and elimination of damaged mitochondrial. Future studies are required to study how changes in mitochondrial dynamic and function may impact frailty and sarcopenia in patients on MHD.

Funding: NIDDK Support

Renoprotective Effect of Shen-Yan-Fang-Shuai Formula in Type 2 Diabetic Kidney Disease Rats Model by Inhibiting the TNF-α/NF-κB Signaling Pathway

Jie Lv, Zhen Wang, Jingwei Zhou, Yaoxian Wang. Nephrology, Dongchimen Hospital Affiliated to Beijing Univ of Chinese Medicine, Beijing, China.

Background: Diabetic Kidney Disease (DKD) is the leading cause of end stage kidney disease and satisfactory therapeutic strategies have not yet been established. Shen-Yan-Fang-Shuai Formula (SYFSF), a traditional Chinese Formula composed of Astragalus, Angelica, Rhubarb and four other herbs, has been widely used as an effective treatment for DKD patients in China. Studies have shown that SYFSF components including emodin or flavonoids inhibit renal inflammation. However little is known about the underlying molecular mechanisms of SYFSF protection. In this study, we compared the renoprotective effect of SYFSF to ARB in a type 2 DKD rat model.

Methods: The male Wistar rats were divided into four groups: control group (n=10), DKD model group (vehicle treated, n=9), DKD model with SYFSF (DKD+SYFSF) group (n=10) and DKD model with Irbesartan (DKD+I) group (n=10). DKD model was induced by high-fat diet, low-dose intraperitoneal injection of streptozotocin (STZ) and...
uninephrectomy. Blood glucose level >16.7 mmol/l was defined as Highglucose. Rats were treated for 8 weeks with SYFSF once daily by oral gavage. The kidneys were harvested for histology, immunohistochemistry, western-blot, and real-time quantitative PCR analysis. Results: SYFSF significantly decreases 24 hour albuminuria (10.12± 3.7 VS 40.41± 16.72 mg, p<0.01) and serum Creatinine levels, with no changes in glucose levels compared to the NP group. In addition, SYFSF ameliorates the glomerulosclerosis and interstitial fibrosis induced by DKD (p<0.01). These renoprotective effects were associated with reduced kidney cortex expression of TNF-α,NF-κB p65, TGF-β1 and Col-I (p<0.05).

Conclusions: SYFSF provides significant renoprotective effects in type-2 DKD rats independently of glucose levels compared to Irsbeatan treatment. This is associated with the inhibition of TNF-α/eNOS+Kb inflammatory pathway. Therefore, SYFSF may be a beneficial treatment for DKD patients.

Funding: Government Support - Non-U.S.

FR-PO379

Hyperphosphate Increases the Expression of Inflammatory Factors in Monocytes via Sodium-Dependent Phosphate Cotransporter Pit-1

Method: SIRT3+/+ and SIRT3–/– mice that were fed ethanol liquid diet. More importantly, the ACR was significantly higher in SIRT3–/– and ethanol fed mice, suggesting that acetylation modification impairs mitochondrial oxidative phosphorylation. Indeed, the western blot analyses showed a significant increase of the acetylation status of mitochondrial proteins involved in energy metabolism and ROS production, SIRT3

Conclusions: SYFSF provides significant renoprotective effects in type-2 DKD rats independently of glucose levels compared to Irsbeatan treatment. This is associated with the inhibition of TNF-α/eNOS+Kb inflammatory pathway. Therefore, SYFSF may be a beneficial treatment for DKD patients.

Funding: Government Support - Non-U.S.

FR-PO381

Evaluation of the Impact of Gut Microbiota on Uremic Solute Accumulation by CE-TOFMS-Based Metabolomics Approach

Methods: To clarify this issue, we compared adenine-induced chronic kidney disease (KD) mice and control mice under germ-free (GF) or specific pathogen-free (SPF) conditions, and examined their metabolic profiles of plasma, feces and urine using CE-TOFMS-based approach.

Results: We found that GF condition demonstrated profound changes in the plasma metabolites of the KD mice. Among 57 uremic solutes that accumulated in plasma of SPF-KD, plasma levels of 11 solutes were significantly lower in GF-KD than that in SPF-KD, suggesting that these solutes were considered to be “gut microbiota-derived uremic solutes” (GM-US), including indoxyl sulfate, cholate, hippurate, p-cresyl sulfate, phenyl sulfate, trimethylamine N-oxide, phenacetate, dimethylglycine, γ-glutamino butyrate, glutarate, and 2,3-dihydroxyepoate. Metabolic pathway profiling also suggested that microbiota are involved in the metabolism of GM-US. Thus, GF condition attenuated the accumulation of the harmful uremic solutes in CKD condition: however, we revealed that renal damage was unexpectedly more severe in GF-KD than in SPF-KD, suggesting that gut microbial action such as production of colonic short-chain fatty acids played renoprotective roles and that loss of beneficial microbial effects exacerbated renal damage in GF-KD.

Conclusions: Collectively, our findings indicated that gut microbiota largely contributes to the production of harmful uremic solutes and, meanwhile, microbiota has potential beneficial effects against CKD progression. Gut microbiota therefore would represent dual roles in the pathophysiology of CKD.

Funding: Government Support - Non-U.S.

FR-PO382

25 (OH)D Treatment Improve Inflammatory Pathway on Monocytes Lineage (U937) in Uremic Environment

Results: We observed a high expression of TLR4 in monocytes incubated with uremic serum (US) and lower expression after 25(OH)D treatment (US ~ 4010±518 vs HS ~ 778±403 and US+D ~ 3113±316 vs HS+D ~ 1121±221; p < 0.004) and lower expression of VDR in monocytes+ US compared with HS (US ~ 7812±618 vs HS ~ 9659±908; p = 0.01). The CYP24 were higher in monocytes+ US than monocytes+ HS (p < 0.008). CYP27 and ROS not showed differences.

Conclusions: These preliminary results shown that uremic environment induce inflammation, mainly for presence of uremic toxins in plasma from uremic patients. This inflammation state in these patients is associated with a high risk for cardiovascular disease and infections. The aim of this study was evaluated the effect of 25(OH)D on inflammatory pathway as: toll-like receptor 4 (TLR4), oxidative stress (ROS) and expression of vitamin D receptor (VDR), 24 hydroxylase (CYP24) and hidroxilase 1-α (CYP27) on monocytes cells in uremic environment.

Methods: The human monocytes (U937) lineage were pre-treatment with and without of 25(OH)D (30 ng/ml) (D) for 24 hours and after that these were incubated with 50% of healthy serum (HS) or uremic serum (US) for 24 hours at 37°C and 5% CO2. The monocytes were characterized by CD14+ expression. The TLR-4, VDR, CYP24, CYP27 were evaluated. The culture media human monocyte antibody conjugated with different fluorescence and ROS were evaluated by DCFH-DA. The flow cytometer was used to detect the expression of these markers.

Results: We observed a high expression of TLR4 in monocytes incubated with uremic serum (US) and low expression after 25(OH)D treatment (US ~ 4010±518 vs HS ~ 778±403). The 25(OH)D has been associated as a modulator of inflammatory response. It has been recognized that the uremic environment induce inflammation, mainly for presence of uremic toxins in plasma from uremic patients. This inflammation state in these patients is associated with a high risk for cardiovascular disease and infections. The aim of this study was evaluated the effect of 25(OH)D on inflammatory pathway as: toll-like receptor 4 (TLR4), oxidative stress (ROS) and expression of vitamin D receptor (VDR), 24 hydroxylase (CYP24) and hidroxilase 1-α (CYP27) on monocytes cells in uremic environment.

Conclusions: We observed a high expression of TLR4 in monocytes incubated with uremic serum (US) and low expression after 25(OH)D treatment (US ~ 4010±518 vs HS ~ 778±403). The 25(OH)D has been associated as a modulator of inflammatory response. It has been recognized that the uremic environment induce inflammation, mainly for presence of uremic toxins in plasma from uremic patients. This inflammation state in these patients is associated with a high risk for cardiovascular disease and infections. The aim of this study was evaluated the effect of 25(OH)D on inflammatory pathway as: toll-like receptor 4 (TLR4), oxidative stress (ROS) and expression of vitamin D receptor (VDR), 24 hydroxylase (CYP24) and hidroxilase 1-α (CYP27) on monocytes cells in uremic environment.

Funding: Medical Affairs Medical Center, Washington, DC.

Background: Studies have shown that sirtuins (SIRTs) are beneficial in kidney injury. In particular, SIRT3, a NAD-dependent deacetylase, protects renal tubular cells through antagonizing and anti-inflammatory effects, especially in proximal tubular cells. Chronic alcohol exposure is known to cause protein hyperacetylation in the mitochondria that may play a critical role in the pathogenesis of alcoholic liver disease, but the mechanism through which chronic ethanol consumption damages the kidney has not been studied. We hypothesize that hyperacetylation of kidney mitochondrial proteins may be responsible for renal dysfunction during chronic alcohol consumption.

Methods: SIRT3+/+ and SIRT3–/– mice were pair-fed 6% ethanol or Control diet (CD) for 8 weeks. CD fed mice served as controls. At the end of the 6 weeks, the animals were sacrificed and kidneys harvested for western-blot analysis.

Results: Chronic Alcohol Mediated Hyper-Acetylation of Kidney Mitochondrial Proteins Causes Renal Dysfunction Caroline Panco,1 Zhongping Lu,1 Raj Lakschman,2 The George Washington Univ; 2Veterans Affairs Medical Center, Washington, DC.

Conferences: Chronic alcohol-induced hyperacetylation of kidney mitochondrial proteins contributes to renal dysfunction. This study can use therapeutic strategies to reverse and/or delay renal damage during chronic alcohol consumption.

Funding: Other NIH Support - NIH K22 Award

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

Underline represents presenting author.

450A
FR-PO384
The Influence of Acute Aerobic Exercise on Immune Cell Subsets in Renal Transplant Recipients

Patrick J. Highton, Jill Neale, Darren R. Churchward, Charlotte E. Grantham, Nicollete C. Bishopp, Alice C. Smith, Leicesther Kidney Exercise Team, Univ of Leicester, Leicester, Leicester, United Kingdom; School of Sport, Exercise and Health Sciences, Loughborough Univ, Leicester, Leicester, United Kingdom.

Background: Renal Transplant Recipients (RTRs) are immunologically vulnerable due to immunosuppression and systemic inflammation. In health, moderate exercise reduces systemic inflammation and is anti-inflammatory and immunomodulatory, but intense exercise can elicit inflammatory cytokine release and transiently suppress immunity leaving an “open window” for infection. Physical activity has many potential benefits for RTRs, but guidelines for safe and effective exercise for this unique population are lacking. In this study, we investigated the effects of exercise on immune and inflammatory cells in RTRs.

Methods: 15 RTRs (13 male; age 53±15 years) completed 20 minutes of continuous walking at 85% of individual maximum speed defined at a previous visit. Blood samples were obtained before, immediately after and 1 hour after this standardised walk. T cell and monocyte subsets were analysed by flow cytometry.

Results: Intermediate monocytes (CD14+++) decreased immediately following exercise (3.80±0.31% vs 3.10±0.21%, p=.012), whilst non-classical monocytes (CD14−) increased (5.99±0.82% vs 7.25±1.03%, p=.022). There was no change in CD14+ classical monocytes. Number and % of CD8+ T cells decreased during the hour of recovery (0.60±0.12±/μL vs 0.51±0.11±/μL, p=.049; 31.6±2.97% vs 28.8±4.17%, p=.025). Regulatory T cells (TRegs) were increased by exercise (5.59±0.54% vs 6.55±0.73%, p=.005).

Conclusions: A bout of exercise exerts significant effects on monocyte and T cell populations in RTRs. Anti-inflammatory classical monocytes were unaffected, but intermediate monocytes decreased and non-classical monocytes increased. Both of these subsets are considered pro-inflammatory and elucidation of the overall inflammatory significance requires further investigation. The reduction in circulating CD8+ T cells may represent an “open window” for infection after exercise. TRegs are anti-inflammatory and critical for graft tolerance: their increase after exercise is reassuring and may be beneficial.

FR-PO385
Loss of CD127 Expression on Circulating CD8+ T Cells in Patients with End-Stage Renal Disease and Its Association with Resistance to Erythropoiesis-Stimulating Agents

Kenichiro Iio, Yutaka Ando, Nephrology, National Hospital Organization, Osaka Minami Medical Center, Kawachinagano, Osaka, Japan.

Background: IL-7 is important for T cell homeostasis. In response to an infection, IL-7 enhances CD8+ T-cell proliferation and cytolytic activity. Decreased CD127 (IL-7Rα) expression on CD8+ T cells may contribute to the loss of CD8+ cytotoxic T lymphocyte activity, thereby increasing susceptibility to infection. Resistance to erythropoiesis-stimulating agents (ESAs) is associated with cardiovascular disease and increased mortality in end-stage renal disease (ESRD) patients. Immune disorders such as chronic inflammation are also involved.

Methods: The present study compared the T cell phenotypes between 53 patients with stage 5 or 5D chronic kidney disease (CKD) and 16 control patients with stage 1 to 3a CKD. Furthermore, multivariate regression analysis was performed to detect the association between T cell phenotypes and the erythropoietin resistance index (ERI; μg/kg/Hb/week). Flow cytometric analysis was performed to detect CD127+ CD8+ T cells, CD3+ T cells, CD4+ T cells, and CD8+ T cells among the peripheral blood mononuclear cells.

Results: The proportion of CD127+ expressing CD8+ cells and the numbers of CD3+ and CD4+ cells were significantly lower in ESRD patients than in the controls. Based on multivariate linear regression analysis, the proportion of CD127+ CD8+ T cells, but not the numbers of CD3+ cells or CD4+ cells, was associated with the ERI (β = −0.0006; p = 0.02). A decrease in the proportion of CD127+ CD8+ T cells and the numbers of CD3+ and CD4+ T cells may contribute to the loss of CD8+ T-cell function in patients with ESRD. Immunochemical changes that increase susceptibility to infection may indicate resistance to ESAs.

Conclusions: Measurement of CD127 expression may provide valuable information in assessing the risk of infectious complications and chronic inflammation. Further studies are needed to determine the clinical significance of CD127 expression in patients with end-stage renal disease and to establish the optimal strategies for the management of infectious complications and chronic inflammation.

FR-PO386
Subjective Global Assessment Is Linked to Nuclear Factor-xB Expression in Hemodialysis Patients

Denise Mafra, Viviane Oliveira Leal, Najia Elias Farage, Ludmila F.M.F. Cardozo, Milena Barca Stockler-Pinto, José Carlos Carraro-Eduardo, Denis Fouque, Federal Univ Fluminense; State Univ de Rio de Janeiro; Univ Claude Bernard, Lyon 1.

Background: Wasting and inflammation are common symptoms in chronic kidney disease (CKD) patients on hemodialysis (HD). Muscle loss and malnutrition are stimulated by inflammation. Nuclear factor-kappa B (NF-xB) is a central integration site for pro-inflammatory signals that are overexpressed in HD patients and could be associated with nutritional status assessed by Subjective Global Assessment (SGA). The aim of this study was to evaluate a possible association between NF-xB expression and SGA in hemodialysis.

Methods: Eighty-three HD patients (75 men, 52 ± 14.4 yr, 60 (36-108) months on dialysis, 15.7% diabetes, BMI 24.8±3.9 Kg/m²) were enrolled. Fasting blood samples were collected and peripheral mononuclear cells were isolated. Real time PCR was performed to evaluate NF-xB mRNA expression.

Results: The 7-point SGA was performed and patients were allocated into two groups (gr1 well-nourished and gr2 malnourished). According to SGA, 32.5% presented malnutrition and a higher NF-xB expression (1.75 [0.77-2.34] when compared to well-nourished patients [1.0 [0.64 – 1.33], p=0.03).

Conclusions: In conclusion, SGA may indicate an altered NF-xB expression and an inflammatory upregulation in chronic HD patients.

FR-PO387
Lack of Polyfunctional Cytomegalovirus-Specific T Cells in Hemodialysis Patients

Fang-Yun Lui, Tzu-Ying Chou, Kai-Hsiang Shiu, Yi-Fang Chuang, Jean-San Chia, Yen-Ling Chiu, Nephrology, Far Eastern Memorial Hospital; Medicine, National Taiwan Univ Hospital; Epidemiology, National Yang Ming Univ; Graduate School of Immunology, National Taiwan Univ.

Background: Polyfunctional T cells are critical for maintaining protection against pathogens. Patients with end-stage renal disease (ESRD) are at increased risks for infectious complications and chronic inflammation. The current study intends to investigate T cell immunity and systemic inflammation by analyzing T cell differentiation and polyfunctionality response against cytomegalovirus (CMV) in patients with and without renal disease.

Methods: 17 healthy individuals, 13 patients with stage V chronic kidney disease (CKD) and 37 hemodialysis (HD) patients were enrolled in this study. All the donors were seropositive. Peripheral blood mononuclear cells were isolated by density gradient centrifugation. A panel of T cell differentiation markers were used to identify the following T cell subsets: naive (TN), central memory (TCM), effector memory (TEM) and effector memory with RA expression (TEMRA). CMV peptide pools (IE1 and pp65) were used to stimulate PBMCs and four effector functions were measured by multicolor flow cytometry (IL-2, TNFα, IFNγ and CD107α) to identify polyfunctional T cells. Statistical comparisons were performed using Kruskal-Wallis rank test.

Results: The age of the three groups were similar (mean, 60 years old). Patients with renal disease, especially the HD patients, showed decrease in CD4+ and CD8+ TN cells and increase in CD4+ and CD8+ TEM and TEMRA cells. In addition, polyfunctional cells were dramatically reduced in HD patients. HD patient also showed higher level of systemic inflammation and CMV viral load. Among healthy individuals, CKD and HD patients, CD4+ CMV/IE1-retrieval polyfunctional cell frequencies were 2.0%, 2.2%, and 0%, respectively (p=0.002) and the CD8+ CMV/pp65-reactive polyfunctional cell frequencies were 12.4%, 8.8% and 0.8%, respectively (p<0.001).

Conclusions: The lack of polyfunctional T cells in hemodialysis patients might explain the increased infectious complications in this population. Such phenomenon may contribute to subclinical cytomegalovirus activation and chronic inflammation in HD patients.

Funding: Government Support - Non-U.S.
**FR-PO388**

**Branched-Chain Amino Acids Promote Oxidative Stress, Inflammation and Migration of Human Peripheral Blood Mononuclear Cells via mTORC1 Activation**

Olha Zhenyuk,1 Esther Civantos,1 Enrique Bosch,1 Marta Ruiz-Ortega,2 Sebastian Mas,1 Jesus Egido.1 1Fundación Jimenez Diaz, Madrid, Spain; 2Univ Autonoma de Madrid, Spain.

**Background:** Leucine, isoleucine and valine are essential amino acids termed branch-chain amino acids (BCAA) due to its aliphatic side-chain. In several pathological and physiological conditions increased BCAA plasma concentrations have been described. Elevated BCAA levels predict insulin resistance development. Moreover, BCAA levels higher than 2 mmol/L are neurotoxic by inducing microglial activation in maple syrup urine disease. However, there are no studies about the direct effects of BCAA in circulating cells and the mechanisms involved.

**Methods:** We have explored whether BCAA (range 0.1 to 12 mmol/l) could promote oxidative stress and pro-inflammatory status in peripheral blood mononuclear cells (PBMCs), obtained from healthy donors.

**Results:** In cultured PBMCs, 10 mmol/L BCAA increased the production of reactive oxygen species (ROS), via both by NADPH oxidase and the mitochondria. BCAA activated mTOR and Akt signaling, as demonstrated by increased phosphorylation of mTORC1 and Akt, respectively. The redox-sensitive transcription factor NF-KB regulates many immune and inflammatory responses. BCAA caused p-p65 NF-KB phosphorylation, its nuclear translocation and increased p65-dependent DNA binding activity. BCAA also up-regulated several pro-inflammatory molecules under NF-KB control, such as interleukin-6, TNF-α, ICAM-1 and CD40L. Finally, we have found that BCAA induced PBMCs cell migration.

**Conclusions:** Elevated BCAA blood levels can promote the activation of circulating PBMCs, by a mechanism that involves ROS production and NF-KB pathway activation. These data suggest that high concentrations of BCAA could exert deleterious effects on immune cells and therefore could contribute to the pro-inflammatory and oxidative status observed in several pathophysiological conditions.

**Funding:** Government Support - Non-US.

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**FR-PO389**

**The Application of Magnetic Resonance Apparent Diffusion Coefficient in the Diagnosis of Acute Pyelonephritis**

Geng-Xi Sun,1 Hui-Qun Li,2 Wenbo Zhao.1 1The Affiliated Hexian Memorial Hospital of Southern Medical Univ, Guangzhou, Guangdong, China; 2The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.

**Background:** Acute pyelonephritis (APN) is a non-specific suppurative inflammatory process secondary to ascending or haematogenous bacterial diffusion. It is widely accepted that functional Magnetic resonance imaging (MRI) provides additional information: diffusion-weighted imaging (DWI) with the apparent diffusion coefficient (ADC) represents an additional parameter which can indicate focal lesions or changes in renal function. DWI has recently been proposed as an alternative to CT for both the diagnosis and follow-up of APN. The aim of the study was to assess reliability of ADC value for differentiating normal renal parenchyma, APN and abscesses.

**Methods:** 56 patients (mean age 39 years) with clinical suspicion of APN were retrospectively reviewed. The contrast-enhanced MRI and DWI were applied in these patients. MRI found that 34 patients had renal abscess, and 22 had no abscess. Then ADC values which were calculated at the area of healthy parenchyma, APN and abscess were compared in these cases.

**Results:** On DWI sequences inflammatory foci appeared as areas of reduced diffusivity of water molecules with high signal on DWI and low ADC values compared to healthy parenchyma (mean ADC: healthy parenchyma (2.32±0.18)×10–3 mm2/s; APN (1.52±0.24)×10–3 mm2/s; abscess (1.16±0.34)×10–3 mm2/s, b factor=600s/mm 2). The results showed the difference between ADC values of the APN and healthy parenchyma groups (P<0.05), similarly the difference between ADC values of the abscess and APN groups was significant (P<0.05). The conclusions of ADC values showed reliable in the diagnosis and follow-up of acute pyelonephritis, and it could provide a reasonable alternative to contrast-enhanced MRI. This is especially useful when administration of contrast agent is contraindicated.

**Funding:** NIHD Support

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**FR-PO391**

**The Adiponectin/Leptin Ratio as a Predictor of Mortality in a Prospective Hemodialysis Cohort**

Jerry Yu,1 Amy Seung You,1 Hamid Morardi,1 Elanir Stejra,2 Tracy Nakata,1 Kavannah Kaji,1 Nancy Lopez,1 Dani V. Nguyen,2 Csaba P. Kovcsy,2 Kamryar Kalantar-Zadeh,1 Connie Rhee,1 Frank Zaldivar.1 1UC Irvine; 2Univ of Tennessee Health Science Center.

**Background:** Adiponectin and leptin are major adipocytokines believed to play key roles in the regulation of cardiovascular and metabolic status. While animal studies show that adiponectin and leptin have inverse effects on the cardiovascular system (adiponectin reduces atherosclerosis, while leptin accelerates vascular injury), it has been suggested that the adiponectin-to-leptin (A/L) ratio may be an important predictor of cardiovascular disease and death. Despite their exceedingly high cardiovascular risk, no studies have examined the association of A/L ratio with mortality in hemodialysis (HD) patients.

**Methods:** Among 448 HD patients from the prospective Malnutrition, Diet, and Racial Disparities in Kidney Disease study who underwent adiponectin and leptin measurement over 2014-15, we examined the association of A/L ratio with mortality using Cox regression with 3 adjustment levels: unadjusted, case-mix (age, sex, race, ethnicity, diabetes, vintage, vascular access), and case-mix+laboratory (albumin, creatinine, nPCR, IL-6) adjusted models.

**Results:** The median (IQR) of adiponectin and leptin were 15.2 (9.1, 24.2) and 16.5 (5.7, 54.6) mcg/ml, respectively. When examined as tertiles, the highest A/L ratio tertile was associated with higher death risk vs. the lowest tertile across all models: HR (95%CI) 5.63 (2.18-14.50) in case-mix+laboratory analyses. When examined as a continuous variable, higher levels were associated with higher mortality risk across all models: HR (95%CI) 1.20 (1.05-1.37) for ±1-standard deviation increments of the A/L ratio.

**Conclusions:** In a prospective cohort of HD patients, a higher A/L ratio was associated with higher mortality risk. Further studies are needed to confirm findings and to determine underlying mechanistic pathways.

**Funding:** NIDDK Support

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**FR-PO390**

**Differential Effects of Angiotensin II Receptor Blocker (ARB) versus ACE Inhibitor (ACEI) on HDL Functionality in Patients on Maintenance Hemodialysis (MHD)**

Ryoei Kaseda,1 Yohei Tsuchida,1 Jianyong Zhong,2 Ichiei Narita,1 Talat Alp Ikizler,2 Valentina Kon.1 1Niigata Univ, Niigata, Japan; 2Pediatric Nephrology, Vanderbilt Univ, Nashville, TN; 3Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.

**Background:** ACEI/ARB reduce cardiovascular disease (CVD) in the general population. Although MHD are at greatly increased CVD risk, few studies have directly addressed their efficacy and recent evidence suggests differences in this population. Previously we showed HDL of MHD loses their protective function, therefore, we compared the effects of ARB or ACEI treatment on HDL functionality in MHD.

**Methods:** Following 3 weeks washout period, we randomly assigned 40 MHD to placebo, ramipril or valsartan. HDL was isolated at the starting point (B) and 3-6 months later (A). Cholesterol efflux was measured by cholesterol content in THP-1 cells after HDL exposure; anti-oxidative response and matrixylgine were measured by HPLC; inflammatory markers were evaluated by RT-PCR and serum amyloid A (SAA) by ELISA.

**Results:** Compared to placebo, ARB and ACEI maintained cholesterol efflux (%):B: 23.96 vs Placebo-A: 15.23 (P<0.01); vs ARB-A:23.92. ns; vs ACEI-A: 22.16 (P<0.01). Cellular ROS production was reduced in response to HDL isolated from MDP on either ARB or ACEI compared to HDL of placebo-treated MHD (U/ml):B: 21.03 vs Placebo-A:20.64; ns; ARB-A: 16.52 P<0.01; vs ACEI-A: 17.95 P<0.01). Neither ARB nor ACEI improved HDL anti-inflammatory effects, and ACEI rather potentiated TNF-α, IL-β response compared to placebo or ARB. Both ARB and ACEI decreased plasma asymmetric dimethylarginine (ADMA) (µM):B: 0.68 vs Placebo-A:0.58, ns; ARB-A:0.46 P<0.01; ACEI-A:0.48 P<0.01, but did not affect HDL content of ADMA. There was no difference in SAA levels in plasma or HDL among the groups.

**Conclusions:** ARB/ACEI treatment in MHD stabilized cholesterol acceptor capacity of HDL and promote its anti-oxidative effects. By contrast, neither ARB nor ACEI improve HDL's anti-inflammatory effects and ACEI may even amplify this response. ARB/ACEI did not affect postulated modulators of HDL functionality, including ADMA and SAA but reduced circulating ADMA. These results suggest a mechanism for potential superiority of ARB vs ACEI in MHD.

**Funding:** Other NIH Support - NIHPO1HL116263
FR-PO392
Pro-Inflammatory RAGE Ligand (EN-RAGE, S100A12), Circulating Soluble Receptor for AGE (sRAGE) and Mortality in Patients with Chronic Kidney Disease Stages 3-5 Marcelo M. Nascimento,1 Shirley Yumi Hayashi,2,3 Miguel C. Riella,4 Bengt Lindholm,5 *Univ Federal do Parana, Curitiba, Parana, Brazil; 1Renal Medicine & Baxter Novum, Karolinska Inst, Stockholm, Sweden; 2KTH School of Technology and Health Research, Stockholm, Sweden; 3Pro-Renal Foundation, Curitiba, Parana, Brazil.

Background: Activation of the receptor for AGE (RAGE) is implicated in development and progression of vascular complications. Here we investigated associations of circulating concentrations of RAGE ligand S100A12, also known as EN-RAGE (extracellular newly identified receptor for advanced glycation end products binding protein) and soluble receptor for AGE (sRAGE) with all-cause and cardiovascular disease mortality in patients with chronic kidney disease (CKD) stages 3-5.

Methods: In 145 CKD patients (median age 61 years, 61% males) comprising 36 hemodialysis (HD), 55 peritoneal dialysis (PD) and 54 CKD stages 3-5 patients clinical characteristics were documented, and markers of mineral metabolism (including fibroblast growth factor-23; FGF-23), inflammation (s-albumin, high-sensitivity C-reactive protein; hsCRP, and interleukin-6; IL-6) as well as plasma concentrations of S100A12 and sRAGE were measured at baseline. All survivors completed 6 months of follow-up.

Results: S100A12 and sRAGE were positively associated with 6-month mortality (p = 0.04; p = 0.05; and p = 0.04; p = 0.001) and interleukin-6 (p = 0.25; p < 0.01, and p = 0.25; p < 0.001), respectively. After up to 6-months follow-up, the survival rate by Kaplan–Meier analysis was significantly different according to S100A12 plasma levels (p = 0.001) but not to sRAGE (p = 0.19; p = 0.13). Finally, in Cox analysis, only S100A12 (HR = 2.08 (95% CI: 1.23–3.60) and RAGE (HR = 1.81 (95% CI: 1.06–3.06) were independently associated with increased risk of death.

Conclusions: Increased concentrations S100A12 associated with inflammation - possibly reflecting activation of RAGE in the context of accelerated vascular disease - and increased all-cause mortality in CKD patients.


FR-PO393
A Malnutrition-Inflammation Score Predicts Patients Survival and Gives Strategies to Improve the Mortality of Maintenance Dialysis Patients Minoru Ito, Ikuto Masakane. Nephrology and Dialysis Center, Yaibuki Hospital, Yamagata, Japan.

Background: Malnutrition-Inflammation Score (MIS) was reported as an assessment tool of malnutrition inflammation complex syndrome of dialysis patients. It consists of 10 components (weight change, dietary intake, gastrointestinal symptom, functional capacity, vitamin and morbidity, subcutaneous fat, muscle wasting, BMI, albumin, TIBC). In this study, we validated the utility of the MIS and analyzed which component had the most effect on their mortality.

Methods: 319 hemodialysis patients (209 men, 110 women; age, 65.5 ± 12.9 years) were enrolled in this study. The MIS was assessed on all 319 patients by trained nutritionists at December 2009. They were followed up for 3 years. All patients were classified into three subgroups corresponding to each MIS points, normal nutritional group (MIS 0-3), mildly impaired group (MIS 4-7), severely impaired group (MIS 8 or above) respectively. The survival rates were compared among the three groups using the Kaplan–Meier analysis. The Cox’s proportional hazard model was used in multivariate analyzes of survival data adjusted for age and diabetes.

Results: 3-year survival rates of the 3 groups were 97.9% (normal), 94.9% (mildly impaired), and 80.3% (severely impaired) respectively. We found a significant difference in the mortality between the severely impaired group and the other two groups with a Log-Rank test. Among 10 MIS components, any component didn’t affect their mortality independently. However, the total score of 10 MIS components was significant prognostic factor (HR 1.26; 95% CI, 1.14-1.38; p=0.0001).

Conclusions: MIS is a comprehensive nutritional assessment tool and consists of 10 components. According to the scores of each component, we can determine treatments for each patient with malnutrition individually. Interestingly, each component was not independent prognostic factor by itself. However, the total point of MIS was a significant predictive index for their prognosis. It shows that the nutritional status can’t be assessed by one parameter. In conclusion, a comprehensive and multidisciplinary assessment procedure is required to manage the malnutrition of dialysis patients.

FR-PO394
Plasma Protein Thiolation Predicts Mortality in Maintenance Hemodialysis Patients Shweta Bansal,1 Khadeel Khazrim,1 Daniela Giustarini,4 Sue Cunningham,3 Ranieri Rossi,3 Paolo Fanti.1 *Medicine/Renal, Univ of Texas HSC at San Antonio, TX; 2Renal Section, South Texas Veterans Healthcare System, SA, TX; 3Faculty of Medicine in Galilee Medical Centers, Bar-Ilan Univ, Safed, Israel; 4Life Sciences, Univ of Siena, Siena, Italy; 1UTHSC at Houston.

Background: Oxidative stress present in CKD is implicated in the progression and complications of this disease state; however, direct measurement of oxidants such as reactive oxygen species (ROS) is difficult. Byproducts of oxidative degradation such as oxidized lipids and nucleotide etc. predict outcomes in CKD but represent the late steps in the oxidative process and therefore, may not be modifiable. We have previously shown that plasma protein thiolation index (PTI), an expression of thiol redox balance - a critical first line of defense against ROS, is altered in dialysis patients. Now, we aim to evaluate whether PTI can predict CKD outcomes.

Methods: We selected 72 clinically stable hemodialysis patients, analyzed their baseline PTI and followed them for mortality over 2.9±0.3 years. PTI is the molar ratio of protein mixed disulfides and free protein thiols in plasma and is measured by spectrophotometry. Since it is a ratio the value is not influenced by content of plasma proteins.

Results: In univariate Cox regression, death was predicted by PTI (HR 6.44:95% CI 1.07-36.7; p=0.042), serum creatinine (HR 0.75: CI 0.62-0.91; p=0.003), and Charlson comorbidity index (CCI) (HR 1.24; CI 1.01-1.53; p=0.042). In multivariate Cox proportional hazard regression (model 1: Chi-square 14.3; p=0.002), PTI predicted mortality (HR 24.6; CI 3.03-199.9; p=0.003) when adjusted for creatinine and CCI. Moreover, the model 2 including adjustments for 10 additional co-variates showed high overall predictive power (chi-square 24; p=0.008) and independent contribution of PTI (p=0.009). Furthermore, ROC curve analysis established 0.80 as cutoff value for binary PTI. High and low PTI subgroups included 33 and 38 subjects and experienced 42.5% vs. 16.2% mortality (HR 3.06; CI 1.17-7.97; p=0.02).

Conclusions: Our data supports presence of a link between oxidative stress and clinical outcome in ESRD and identifies PTI as a suitable candidate biomarker to identify dialysis patients at higher risk of mortality.

Funding: Other NIH Support - NCCAM-AT004490, VA Support

FR-PO395
Is the Association between the Malnutrition-Inflammation Score and Mortality Modified by Age, Gender and Diabetic Status? Marcelo Barreto Lopes,1 Raissa B. Peixoto,1 Gildete Barreto Lopes,1 Priscila S. Carvalho,1 Jessica S. Fernandes,1 Marcia T. Martins,1 Luciana Ferreira Silva,1 Antonio Alberto Lopes.1 *Univ Federal da Bahia; 2Univ do Estado da Bahia, Salvador, Brazil.

Background: The malnutrition-inflammation score (MIS) has been positively associated with mortality in maintenance hemodialysis (MHD) patients but it is important to show if the association is similar for patients of different subgroups. The objective was to investigate if associations of MIS with mortality vary by age, gender and diabetic status subgroups.

Methods: Prospective study of 627 patients (mean age = 48.5±14 yr) enrolled in the PROHEMO cohort, Salvador, Brazil. MIS (range 0-30) was categorized as <6 (<n=364) and ≥6 (<n=263). Cox regression was used to estimate adjusted hazard ratios and test for interaction.

Results: The adjusted hazard of death (Table) was 52% higher for MIS ≥6. The associations followed the same direction across subgroups, without significant interaction (P values >0.2) by age, gender, and diabetic status.

* Not adjusted for age, gender, education, living with family, race, Kt/V, vintage, vascular access, hemoglobin, creatinine, erythropoietin use, diabetes, heart failure, cerebrovascular disease and peripheral vascular disease.

FR-PO396
Death Rates and Hazard Ratios of Associations between MIS and Mortality in the Total Sample and by Gender, Age and Diabetic Status

Death Rates per 100 person-years Hazard Ratio (95% Confidence Intervals) P value for Interaction

<table>
<thead>
<tr>
<th>MIS</th>
<th>Total Cohort</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>MIS=0</td>
<td>MIS=0</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>627</td>
<td></td>
<td>587</td>
<td>39</td>
<td>1.82 (1.38, 2.39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>20</td>
<td>2.03 (1.43, 2.88)</td>
</tr>
<tr>
<td>256</td>
<td></td>
<td>228</td>
<td>28</td>
<td>1.69 (1.07, 2.69)</td>
</tr>
<tr>
<td>371</td>
<td></td>
<td>303</td>
<td>68</td>
<td>1.71 (1.19, 2.45)</td>
</tr>
<tr>
<td>485</td>
<td></td>
<td>431</td>
<td>54</td>
<td>1.40 (0.90, 2.17)</td>
</tr>
<tr>
<td>142</td>
<td></td>
<td>127</td>
<td>15</td>
<td>1.66 (1.15, 2.38)</td>
</tr>
<tr>
<td>24.3</td>
<td></td>
<td>24.3</td>
<td>17.3</td>
<td>1.53 (0.94, 2.49)</td>
</tr>
</tbody>
</table>

Conclusions: The results of this Brazilian cohort provide support to the utility of MIS as a tool for predicting outcomes in MHD patients of different subgroups of age, gender and diabetic status.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**FR-PO396**

Circulating Tamm-Horsfall Protein (Uromodulin) Correlates with Sepsis Severity

Yoshitsugu Fujii, 1 Chadi A. Hage, 1 Ranjani N. Moorthi, 1 Simit Doshi, 1 Radmila Micanovic, 1 Sharon M. Moe, 1 Tarek M. El-Achkar. 1 Medicine-Nephrology, Indiana Univ and Indianapolis VA Medical Center; 2 Medicine-Palm Critical Care, Indiana Univ, Indianapolis, IN.

**Background:** Tamm-Horsfall protein (THP, also known as Uromodulin), is a glycoprotein uniquely expressed by the kidney and secreted in the urine. A small amount of THP also circulates in the plasma (pTHP), the significance of which remains unclear. In sepsis, invading pathogens overwhelm the host immune system, frequently leading to a maladaptive response of injurious inflammation. Mortality in THP-/ mice is significantly increased compared to THP+/+ after cecal ligation and puncture, suggesting that THP is protective in the setting of sepsis. Since THP may have immunomodulatory functions, we hypothesized that the level of pTHP will correlate with the severity of sepsis and be a useful biomarker.

**Methods:** This is a prospective pilot study to measure pTHP in 26 patients with severe sepsis, at the time of admission (T0), and after 48 hours (T48). Sepsis severity was assessed using the sequential organ failure assessment (SOFA) score. SOFA score incorporates 6 distinct organ associated variables, including serum creatinine.

**Results:** The average age was 57 ±15 years. Diabetes and hypertension were present in 42.3% and 73.1% of the study population, respectively. 30.7% of patients had CKD. Between T0 and T48, 15 patients (57.6%) had improvement in their SOFA score. The median pTHP trended lower between T0 and T48: 46.5 (32.7; 59.4) vs. 33.6 (25.5; 60.9) ng/ml, respectively (p=0.2). Although pTHP 0 and 48 did not correlate individually with SOFA 0 and 48, changes in pTHP between T0 and T48 positively correlated with SOFA (r=0.35, p<0.02). The increase in pTHP may be reactive and part of an acute response to limit the disease. Larger studies are needed to validate the role and use of pTHP as a biomarker of clinical utility in sepsis.

**Funding:** VA Support

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**FR-PO397**

Neutrophil-to-Lympohocyte and Platelet-to-Lympohocyte Ratios and Mortality in Incident Hemodialysis Patients

Christina J. Catabay, Yoshitsugu Obi, Elani Streja, Melissa Soohoo, Kamary Kalantar-Zadeh. UC Irvine.

**Background:** Both neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), calculated from complete blood count, were suggested as oncologic prognostic markers. Recent preliminary studies indicate that NLR and PLR may be associated with inflammatory status and mortality in hemodialysis (HD) patients.

**Methods:** We examined the association of NLR and PLR with all-cause mortality in a cohort of 107,737 HD patients from a large dialysis organization from 2007-2011 using baseline Cox proportional hazards regression with hierarchical adjustments for case-mix.

**Results:** The average age was 57 ±15 years. Diabetes and hypertension were present in 42.3% and 73.1% of the study population, respectively. 30.7% of patients had CKD. Between T0 and T48, 15 patients (57.6%) had improvement in their SOFA score. The median pTHP trended lower between T0 and T48: 46.5 (32.7; 59.4) vs. 33.6 (25.5; 60.9) ng/ml, respectively (p=0.2). Although pTHP 0 and 48 did not correlate individually with SOFA 0 and 48, changes in pTHP between T0 and T48 positively correlated with SOFA (r=0.35, p<0.02). The increase in pTHP may be reactive and part of an acute response to limit the disease. Larger studies are needed to validate the role and use of pTHP as a biomarker of clinical utility in sepsis.

**Funding:** VA Support

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**FR-PO398**

Claudia-12 Is Expressed in the Proximal Tubule and Forms a Calcium Permeable Pore


**Background:** The majority of filtered calcium, approximately 2/3rds, is reabsorbed from the proximal tubule by a passive paracellular mechanism. This process depends on active sodium and water reabsorption, and a calcium permeable pore between proximal tubule cells. Claudin-12 is expressed along the intestine and forms a calcium permeable pore in Caco-2 cells. Renal localization and function is not known.

**Methods:** We expressed Claudin-12 in OK cells and in MDCK cells using a tet-off promoter. In over-expression of Claudin-12 also decreased calcium-1-6 mRNA expression relative to cells expressing empty vector. Expression of claudin-12 under a tet-off promoter in MDCK cells did not alter endogenous claudin expression but decreased TEER and increased calcium flux, but did not alter the pNa/pCl. Over-expression of claudin-12 also decreased claudin-1 and -6 mRNA expression relative to cells expressing empty vector. Expression of claudin-12 under a tet-off promoter in MDCK cells did not alter endogenous claudin expression but decreased TEER and increased pNa/pCl.

**Results:** Claudin-12 mRNA was detected in microdissected proximal tubules. Expression of claudin-12 in OK cells decreased TEER and increased calcium flux, but did not alter the pNa/pCl. Over-expression of claudin-12 also decreased claudin-1 and -6 mRNA expression relative to cells expressing empty vector.

**Conclusions:** Claudin-12 is expressed in the proximal tubule where it forms a cation and calcium permeable pore, however, its genetic deletion does not alter urinary calcium excretion at steady state.

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

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**FR-PO399**

Acute Effects of Exercise on Serum A-Klotho, Phosphate and Glucose in Healthy Volunteers: A Pilot Study

Sven-Jean Tan, 1,2 Melissa Minhui Chu, 1 Michael Ming Xin Cai, 1,3 Timothy D. Hewittson, 1,3 Stephen G. Holt, 1,2 Nigel David Toussaint. 1,2 Nephrology, The Royal Melbourne Hospital, Parkville, Victoria, Australia; 3 Medicine (RMH), The Univ of Melbourne, Parkville, Victoria, Australia; 4 The Royal Melbourne Hospital.

**Background:** To investigate the effect of exercise on soluble a-klotho (sKl) in healthy adults. **Background:** Membrane-bound a-klotho, predominantly expressed in the kidney, functions as a co-receptor for fibroblast growth factor-23 (FGF23) to regulate phosphate excretion. Circulating sKl, derived from membrane klotho cleavage, has extra-renal actions. sKl can affect ion channels and insulin signaling pathways and is inversely associated with mortality. Effects of physical exercise on sKl are unknown.

**Methods:** Ten fasting healthy volunteers underwent a standard Bruce protocol exercise test on a treadmill. sKl, serum phosphate (sPi) and blood glucose levels were measured in samples collected 1-week prior, immediately pre (Tpre), 0 (Tpost), 30 (T30), 240 (T240), 60 minutes and 1-week post exercise. Changes were assessed using repeat measures ANOVA or Friedman’s test with Dunn’s multiple comparison.

**Results:** Median (IQR) age of participants was 47.5 (44-51) years; five (50%) were male. All study participants achieved at least 90% predicted maximum heart rate. Compared with Tpre, an acute increase in sKl was seen at Tpost (median 483pg/mL vs 602pg/mL, p<0.01) followed by non-significant decline in sKl at T30 (mean 0.94mmol/L vs 0.83mmol/L). Exercise led to a reduction in blood glucose by T240, following an initial non-significant rise, with median glucose levels at Tpre, Tpost, T30 and T240 of 6.0, 6.5, 6.3 and 5.5mmol/L respectively.

**Conclusions:** High intensity exercise is associated with a transient increase in sKl, decrease in sPi levels and delayed blood glucose reduction in healthy adults. Evaluation of long-term effects of cardiovascular fitness programs on sKl and sPi in healthy individuals and disease cohorts are required to identify potential lifestyle modifications to improve chronic disease management and long-term outcomes.

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

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**FR-PO400**

Role of Claudin-16 in Basal and PTH-Stimulated Ion Transport in the Thick Ascending Limb of Henle’s Loop

Marie-Lucile Figueres, 1,2 Claire Bardet, 1,2 Dominik Müller, 1 Catherine Chaussain, 1,2 Pascal Houillier, 1,2 ‘Centre de Recherche des Cordeliers, Renal Physiology, INSERM U1138, ERL8228, Paris, France; 2,3 Paris Descartes Univ, France; 4EA2496, Montrouge, France; 5Charité Univ, Berlin, Germany.

**Background:** Claudin-16 is specifically expressed at the tight junction of thick ascending limb segments of Henle’s loop (TALH) cells. Inactivating mutations of the gene encoding claudin-16 causes Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis

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

**Underline** represents presenting author.
(FHINC), a rare genetic disorder responsible for a renal loss in magnesium and calcium, nephrocalcinosis and early renal insufficiency. However, the role of claudin-16 in basal and parathyroid hormone (PTH)-stimulated ion transport in the TALH remains unclear.

Methods: We used in vitro microperfusion of TALH dissected from \textit{Cldn16}−/− and \textit{Cldn16}+/+ mice to measure paracellular ion permeabilities and to assess the effect of basolateral PTH (100 M) on transepithelial calcium absorption.

Results: Paracellular permeabilities to calcium (PCa) and magnesium (PMg) were significantly decreased in \textit{Cldn16}−/− mice (PCa = 0.22x10−4 versus 0.60x10−4 cm/s in \textit{Cldn16}+/+ mice (p = 0.02); PMg = 0.14x10−4 versus 0.50x10−4 cm/s in \textit{Cldn16}+/+ mice (p = 0.01)). Calcium and magnesium absorption was decreased by ~50% in TALH from \textit{Cldn16}−/− mice, relative to \textit{Cldn16}+/+ mice.

Permeabilities to sodium, chloride and potassium were unaffected in \textit{Cldn16}−/− mice. PTH significantly increased calcium reabsorption in TALH from both \textit{Cldn16}−/− and \textit{Cldn16}+/+ mice.

Conclusions: Claudin-16 is required for normal paracellular permeability to calcium and magnesium in the TALH, under basal condition. However, the lack of claudin-16 does not prevent the PTH-elicited increase in calcium absorption.

FR-PO401
Serum Calcification Propensity Is Improved by Increased Dialysate Bicarbonate and Dialysate Magnesium: \textbf{The BiMag Pilot Study Method:} We conducted a 7-week prospective open label pilot study in n=12 prevalent ambulatory dialysis patients with a baseline T50 ≥200 min. (10 male, vintage 31 [14-92] months). T50 was determined after a washout phase of 1 week. T50 was determined after a washout phase of 1 week.

Results: Serum Calcification Propensity is measured by a novel blood test, Serum Calcification Propensity can be measured by a novel blood test, and is a target for prevention. Serum Calcification Propensity is improved by increased dialysate bicarbonate and magnesium. Further studies with longer observation periods and individualized treatments are needed.

Conclusions: Serum calcification propensity is improved by increasing dialysate bicarbonate and magnesium. Further studies with longer observation periods and individualized treatments are needed.

FR-PO402
Does Reducing Serum Phosphate in Dialysis Patients Result in Improved Clinical Outcomes - Is a Large Scale Trial Feasible? Ramya Bharagava,^1 Philip A. Kalra,^2 Paul E. Brenchley,^1 Alastair J. Hutchison,^3 Manchester Royal Infirmary,^3 Salford Royal Hospital.

Background: High phosphate is associated with increased mortality in dialysis patients. However no RCTs have demonstrated that reducing serum phosphate improves quality or length of life. The required size and scope of such a trial is unknown; therefore we conducted a feasibility study in 104 HD patients randomized to lower or higher range phosphate (HRG 2.5 to 4.3mg/dL) or higher range group (HRG 3.5 to 7.4mg/dL). Non-calcium containing binders, questionnaires & an adherence self-help programme were used to achieve target phosphate. End points included - number trial required to achieved and maintained in the range over the maintenance period, consent rates, pill burden, drop-out rates & cardiovascular events.

Results: 65% patients completed the 12 month study. For phosphate the mean difference between the groups throughout maintenance period was -1.00 mg/dL, p <0.05 at weeks 10, 13 and 21. 2 patients died in HRG vs only 2 in LRG. Consent withdrawal 8 LRG vs 4 HRG. Pill burden was higher in LRG. Dialysis access problems in 9 HRG vs 3 in LRG.

Conclusions: 65% retention rate is similar to other interventional RCTs in dialysis patients. 10% mortality is as expected for this cohort, but was higher in HRG. With a 13% randomization rate and 65% annual retention rate, 3 - 4,000 patients would need to be recruited for 1000 to complete 2 years follow-up. This suggests a target dialysis population of about 25,000, necessitating a multi-national approach.

Funding: Other NHF Support - NIHR RRPB - National Institute of Health Research, Research for Patient Benefit, UK

FR-PO403
Examining Risk Factors for Caleiphylaxis Rakhee Kilani,^1 Mia Wang,^1 Douglas E. Schaubel,^1 Francesca Tentori,^2 William H. Herman,^1 Rajiv Saran,^1 Vahnak B. Shahinian,^1 Nephrology, Univ of Michigan, Ann Arbor, MI;^2Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: Caleiphylaxis or calcific uremic arteriolopathy (CUA) is a rare but serious disorder, occurring in dialysis patients and characterized by systemic medial calcification of the arteries that leads to ischemia and subcutaneous necrosis. Despite its first description over 50 years ago, clinical predictors remain to be clearly identified given that much of the work done to date has consisted of smaller and single-center studies. We therefore utilized national data on dialysis patients from the United States Renal Data System (USRDS) to examine risk factors for CUA.

Methods: Patients on chronic dialysis with Medicare as primary insurance were identified from 2007 through 2014 using USRDS data. Potential risk factors were identified from the Medical Evidence Form 2728 (age, sex, race, diabetes, vintage), dialysis claims (hematocrit, BMI, IV iron) and Medicare Part D claims (warfarin, calciumimetics, calcium-based phosphate binders) in the 6 months after cohort entry. The primary outcome was the new development of CUA based on a validated claims-based algorithm. Cox regression was used to model the rate (cause-specific hazard) of CUA, treating death and transplantation as competing risks.

Results: A total of 1413 cases of CUA were identified with results comparing characteristics of cases and non-cases presented in Table 1. In the multivariable model, younger age, female sex, longer dialysis vintage, higher BMI, diabetes mellitus, calcimimetic use and warfarin use were significant predictors of CUA.

Table1: Pre-randomization values. 65% patients completed the 12 month study. For phosphate the mean difference between the groups throughout maintenance period was -1.00 mg/dL, p <0.05 at weeks 10, 13 and 21. 2 patients died in HRG vs only 2 in LRG. Consent withdrawal 8 LRG vs 4 HRG. Pill burden was higher in LRG. Dialysis access problems in 9 HRG vs 3 in LRG.

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FR-PO403
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Conclusions: 65% retention rate is similar to other interventional RCTs in dialysis patients. 10% mortality is as expected for this cohort, but was higher in HRG. With a 13% randomization rate and 65% annual retention rate, 3 - 4,000 patients would need to be recruited for 1000 to complete 2 years follow-up. This suggests a target dialysis population of about 25,000, necessitating a multi-national approach.

Funding: Other NHF Support - NIHR RRPB - National Institute of Health Research, Research for Patient Benefit, UK
commences at values of E/P that are typical of early CKD (unpublished data). Since [PTH] and [FGF23] are direct linear functions of E/P, (Clin Nephrol 2016;85:251), we hypothesized that TRP/Ccr is a parabolic function of [PTH] and [FGF23].

Methods: We obtained morning fasting specimens of plasma, serum, and urine (u) from 30 subjects with CKD eGFR 14-49 ml/min/1.73m2 and 28 controls with eGFR > 60. [PTH] and [FGF23] were measured with ELISAAs (Scantibodies and ImmunoTools, respectively). E/P was calculated as [P]i/[crr]i/cre and TRP/Ccr as [P]i – E/P, (Clin Nephrol 2015; 83:167). Linear regressions of TRP/Ccr on 100/[PTH] and 100/[FGF23] were sought; after significance was demonstrated, we used the regression equations to compute idealized TRP/Ccr for each concentration of [P]i, [PTH] and [FGF23] and 100/[PTH] and [FGF23]. We then plotted idealized TRP/Ccr against [PTH] and [FGF23].

Results: TRP/Ccr was a linear function of 100/[PTH] and 100/[FGF23] and thus a parabolic function of [PTH] and [FGF23]. Linear and parabolic equations, R2, and P-values are summarized in the Table. TRP/Ccr fell abruptly to a nadir at about the vertical limbs of parabolas as [PTH] and [FGF23] rose in controls. Horizontal limbs commenced at the nadir, and TRP/Ccr fell minimally as [PTH] and [FGF23] rose further in CKD.

Conclusions: TRP/Ccr is a parabolic function of [PTH] and [FGF23]. Although both concentrations rise as GFR falls, the hormones inhibit P reabsorption maximally in early CKD.

FR-PO406
Low Serum Magnesium Is Associated with an Increased Risk of Prediabetes
Brenda C.T. Kieboom,1 Symen Ligthart,2 Albert Hofman,2 Robert Zietse,3 Bruno H. Stricker,1,2 Ewout J. Hoon,1 Internal Medicine, Erasmus MC, Rotterdam, Netherlands;1 Epidemiology, Erasmus MC, Rotterdam, Netherlands.

Background: Previous studies identified an association between serum magnesium and incident diabetes mellitus. However, this association may be explained by reverse causality, as hyperglycemia can lower serum magnesium through urinary magnesium loss. Prediabetes is less likely to cause urinary magnesium loss, because hyperglycemia is less severe. Therefore, we studied, for the first time, the association between serum magnesium and prediabetes.

Methods: The association was analyzed in the population-based Rotterdam Study using Cox proportional hazard models adjusted for age, sex, lifestyle factors, comorbidities, kidney function, other electrolytes and diuretic use. In addition, a mediation analysis was performed to study if the risk is mediated through insulin resistance (HOMA-IR levels) or influenced by common genetic variation in eight magnesium transporter genes.

Results: 8555 participants (mean age 64.7 years) with normal glucose levels at baseline were included; the median follow-up was 7.0 years. A 0.1 mmol/L decrease in serum magnesium levels at baseline (indirect effect: OR:1.03, 95%CI 1.01-1.05).

Conclusions: The observation that lower serum magnesium levels are not associated with diabetes but also with prediabetes makes reverse causation less likely. The effect of serum magnesium on prediabetes is partially mediated through insulin resistance.

FR-PO407
Ghrelin Stimulates the Epithelial Magnesium Channel TRPM6 via Gas Signaling
Mathias Wolf,1 Mingzhu Nie,1 Carolina Rivera,1 Denise K. Marciano,2 Manjot S. Bal.1 Pediatrics, UT Southwestern Medical Center, Dallas, TX;1 Internal Medicine, UT Southwestern Medical Center, Dallas, TX.

Background: Osteoporosis after bariatric surgery is an increasing health concern as the rate of bariatric surgery has risen significantly. In animal studies mimicking bariatric procedures, bone disease, together with decreased serum levels of Ca2+, Mg2+ and the gastric hormone Ghrelin were described. Ghrelin is a 28 amino acid peptide and regulates metabolism by binding to the growth hormone secretagogue-receptor 1a (GHSR1a). GHSR1a is also expressed in the kidney. We tested the hypothesis that Ghrelin deficiency after bariatric surgery contributes to osteoporosis via reduced upregulation of the renal calcium channel TRPV3 or the magnesium channel TRPM6.

Methods: We expressed GHSR1a with TRPV3 or TRPM6 channel in HEK293 cells and treated them with purified Ghrelin. Whole-cell current density was analyzed by patch-clamp recording.

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

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Results: After Giher exposure whole-cell current density did not change for TRPV5 but increased for TRPM6 (9 ± 5 vs 27 ± 17 PA/F for control vs Giher; p<0.001). This effect was dose-dependant. We confirmed the stimulatory role of Giher towards TRPM6 by applying the Giher mimetic-D-Trp, Ala2, D-Phe4)-OMe=SMI (6-11 amide, which increased TRPM6 current density, and Giher mimetic with GHSRI1a blocker (D-Lys4)-GHRP6, which decreased TRPM6 current density (84 ± 15 vs 219 ± 13 PA/F for control vs Giher=0.001). As GHSRI1a initiates downstream signaling via protein kinase A (PKA), we tested the effect of the PKA inhibitor H89 which abrogated TRPM6 stimulation by Giher (204 ± 22 vs 32 ± 5 PA/F for Giher vs Giher+H89; p=0.001). The role of PKA signaling in TRPM6 regulation was verified by the fact that only transfected Gna, but not the Gi alpha mutant Q227L, nor Gna, Gi4, or Gi3,3,5 upregulated TRPM6 current density. 

Conclusions: Giher stimulates TRPM6 channel via Go/PKA signaling. Rising Giher mimetic with the effect of GHRP6, GHSRI1a, and hypocalcemic and hyperphosphatemic rats without or with without alopecia. Despite more than 50 VDR mutations reported, the study of the VRD mutant on RXR-binding domains remains very rare. This study was to identify the VDR gene mutation in a family with HVDRR and alopecia, and determine the mechanisms of this VRD mutant causing the phenotype.

Methods: The genotype and phenotype with follow-up in a Chinese family with HVDRR were performed. In vitro studies included situ-directed mutagenesis for expression of mutant VDR constructs, fluorescence microscopy for the nuclear localization of different enhanced green fluorescent protein-tagged VDR proteins, and luciferase reporter driven by human CYP24A1 gene promoter for measuring transcriptional activity of VDR.

Results: A novel homoyzogous R343H mutation in the exon 11 of VDR were identified in the proband and his affected sister and not found in 200 healthy subjects. Supraphysiological dose of active vitamin D, and calcium supplement therapy improved their biochemical and radiographic abnormalities but not alopecia. This R343H mutant did not eliminate normal nuclear localization of VDR, but actually impair the CYP24A1 promoter activity in the presence of 1,25(OH)2 vitamin D.

Conclusions: Although novelVR R343H mutation in HVDRR do not affect the expression, conformation, and nuclear location of VDR. It impairs the transactivation activity of VDR on downstream transcriptional events and may account for typical clinical features with alopecia.

Salivary Pi Handling May Be under the Control of Gastrointestinal Pi Sensing Kayo Ikuta, Hiroko Segawa, Shihoko Yuki, Ichiro Kaneko, Ai Hanazaki, Toru Fujii, Aoi Kushi, Sawaiho Tsuzuki, Ken-Ichi Miyamoto, Dept of Molecular Nutrition, Tokushima University, Tokushima, Japan. 

Background: A hyperphosphaturic salivary content, which correlates linearly with serum inorganic phosphate (Pi), has been reported in hemodialysis (HD) patients and therefore the addition salivary Pi binding to traditional phosphate binders has been suggested to be a useful approach for improving the treatment of hyperphosphatemia in HD patients. In addition, gastrointestinal and salivary gland Pi sensing may be involved in improving hyperphosphatemia. In the present study, we investigated factors, which affect salivary Pi level.

Methods: Mice were used for hyperphosphatemic adenine-induced nephritis (adenine), acute kidney injury (AKI) mice, and administration of Pi solution via oral or intravenous routes. Adenine-induced nephritis, Piuria, slow salivation, and Pi levels, were given an intravenous injection of pinocapsule.

Results: Hyperphosphatemic adenine mice showed high levels of salivary Pi. In contrast, AKI mice showed hyperphosphatemia, but not hyperphosphatemic saliva. Adenine mice showed abnormal kidney parameter, e.g. low flow rates and high osmolality. In adenine mice, dietary P restriction significantly decreased the plasma and salivary Pi levels with the abnormal salivary parameter. It suggests that salivary Pi level is regulated by dietary Pi levels. Low Pi diet decreased plasma Pi, urinary Pi excretion and salivary Pi levels. In contrast, high Pi diet showed increased plasma Pi, urinary Pi excretion, and addition salivary Pi levels. Furthermore, only oral administration of Pi solution, but not intravenous injection, altered the salivary Pi level with the abnormal salivary parameter. Next, we examined the effect of different administration route on salivary Pi levels. An intravenous injection of Pi solution significantly increased plasma Pi and urinary Pi excretion, but not salivary Pi levels. In contrast, oral administration of Pi solution, orally ingested plasma Pi, urinary Pi excretion, and addition salivary Pi levels.

Conclusions: Gastrointestinal Pi level may be a determinant for salivary Pi level. This study suggests that gastrointestinal Pi sensing improves salivary Pi and renal Pi excretion levels.

Funding: Government Support - Non-U.S.

FR-PO401
Calcification Propensity (Serum T50) Predicts Longitudinal Progression of Coronary Artery Calcification in CKD: The CASCADE Study Angela Yee Moon Wang,1 Sharon Yui Ling Cheung,1 Matthias Bachtlcr,2 Ck Wong,1 Miu Ting Chu,1 YaY. Yau,1 Andreas Pasch,3 Medicine, Univ of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong; 2Clinical Chemistry, Univ Hospital Bern, Bern, Switzerland; 3Chemical Pathology, Chinese Univ of Hong Kong, Hong Kong, Hong Kong; 4Diagnostic Radiology, Central Biomedical Imaging Center, Hong Kong, Hong Kong.

Background: Calcification propensity (T50) is a measure of extra-skeletal mineral stress and predicts mortality in CKD. This study aims to determine if serum T50 predicts longitudinal progression of vascular calcification over a prospective follow-up of 24 months in CKD and may thus explain its association with mortality.

Methods: 300 non-diagnosis CKD 3-5 patients (age: 66±10yrs, 56±16men) underwent plain multi-slice computed tomography (MSCT) to estimate coronary artery calcium scores (CACS) and blood collection. MSCT was repeated after 24 months to determine changes in CACS over 24 months. Those with changes in CACS in the upper tertile (n=88) were defined as progressors while those in the middle and lower tertiles were defined as non-progressors.

Results: The mean T50 of all CKD subjects was 281±59 mins. The progressors were older (P=0.001), had higher systolic blood pressure [P<0.001], serum phosphate [P<0.001] and intact parathyroid hormone [P=0.001], but lower serum albumin [p=0.014], T50 [268 ± 63 vs 289 ± 56mins; P=0.006], magnesium [P=0.047] and eGFR [64±20 vs 71±18; P=0.001]. In the stepwise multiple logistic regression adjusting for age, gender, background diabetes, atherosclerotic vascular disease, Framingham risk factors, baseline CACS, eGFR, high sensitivity C-reactive protein and intact parathyroid hormone, T50 significantly predicted CACS progression over 24 months [adjusted odds ratio (OR), 0.99, 95% confidence intervals (CI), 0.987 – 1.000, P=0.044]. Adjusting for the same covariates, phosphate, an important determinant of T50, marginally lost significance in predicting CACS progression [P=0.069].

Conclusions: These data for the first time show that calcification propensity is related to progression of CACS in CKD 3-5, adding evidence to support its usefulness in reflecting mineral stress in CKD.

Funding: Pharmaceutical Company Support - Sanofi; the study was also supported by the Hong Kong Society of Nephrology Research Grant, Government Support - Non-U.S.

FR-PO411
Hepatocyte Nuclear Factor 1 Homeobox B as Novel Transcriptional Regulator of the Kir4.1/Kir5.1 Potassium Channel Joost Hespenheide,1 Andreas Kompatscher,1 Jeroen H.F. De Baaij,1 Karam S. Aboudehen,2 Peter Igarashi,3 René J. Bindels.1 Physiology, Radboud Inst for Molecular Life Sciences, Nijmegen, Gelderland, Netherlands; 2Medicine, Univ of Minnesota Medical School, Minneapolis, MN.

Background: Patients with mutations in transcription factor hepatocyte nuclear factor 1 beta (HNF1B) present with autosomal dominant tubulointerstitial kidney disease (ADTIDK-HNF1B), which is characterized by renal cysts and electrolyte loss. Strikingly, it was found that ~50% of mutation carriers were affected with hypomagnesemia. The origin of hypomagnesemia in patients with HNF1B mutations can be traced to the distal convoluted tubule (DCT) of the kidney, where the final urinary Mg2+ excretion is determined. The aim of this research is to explain hypomagnesemia in HNF1B patients by identifying target genes of HNF1B in the DCT.

Methods: To find targets of Hnf1b that are relevant to Mg2+ reabsorption in the kidney, a chromatin immunoprecipitation and subsequent sequencing (chip-seq) was performed in an immortalized mouse DCT cell line. Luciferase assays, siRNA-mediated knockdown of Hnf1b in DCT cells and RT-qPCR on HNF1B mutant mouse kidneys were performed to assess the transcriptional regulation of Hnf1b on candidate genes in vitro and in vivo.

Results: By performing a chip-seq on Hnf1b, >7000 Hnf1b binding sites were detected genome-wide, which could be mapped to >3000 unique genes. A conserved Hnf1b binding site was found in the promoter of the Kir16 gene, encoding Kir1.5. Luciferase assays demonstrated that Hnf1b increases the activity of the Kir16 promoter. siRNA knockdown of Hnf1b resulted in decreased Kir16 transcript levels. Furthermore a decrease in expression of the Kir16 gene, encoding Kir1.5, was observed. Decreased expression of Kir16 and Kir5 was also found in the kidneys of Hnf1b mutant mice. 

Conclusions: These results implicate HNF1B as an enhancing transcriptional regulator of Kir1.5. Active transport of Mg2+ in the DCT requires the constant extrusion of K+ channel Kir1.5 for Kir1.5, therefore, impaired regulation of Kir1.5 in HNF1B mice may explain the hypomagnesemia found in HNF1B patients.

Funding: Government Support - Non-U.S.
Regional Expression of NaPi-IIb, PiT1 and NHE3 mRNA in the Proximal Small Intestine of Rats and Humans
Evans O להב, 1, Laura אלהב, 1, Lars פיידריקס, 2, Anna כסלברט, 3 Robert J. עוז, 1, Joanne מקס, 1 1Dept of Neuroscience Physiology and Pharmacology, Univ College London, Rowland Hill Street, London, United Kingdom; 2Dept of Gastrointestinal Research and Education, Inst of Clinical Sciences, Univ of Gothenburg, Sahlgrenska Academy, Sweden.

Background: Previous findings have shown that the proximal small intestine is responsible for the absorption of dietary phosphate in rats and humans. Several studies investigating NaPi-IIb inhibitors, which target the transporter considered responsible for intestinal phosphate absorption, have been carried out in rats, but the effectiveness of these agents in the treatment of hyperphosphatemia in humans is still uncertain. We aimed to understand the difference in the efficacy of these therapeutic agents by comparing the mRNA levels of phosphate transporters in the different regions of rat and human proximal small intestine.

Methods: Total RNA was isolated from gut mucosa scraped obtained from paired rat duodenum (2cm distal to pylorus) and jejunum (5cm distal to ligament of Treitz). Paired duodenal (20cm distal to pylorus) and jejunal (5cm distal to ligament of Treitz) biopsies were collected from healthy volunteers. NaPi-IIb, PiT1 and NHE3 transcript levels were established using qPCR.

Results: Our results show that the regional profile for NaPi-IIb in humans is different from that in rats. The mRNA expression levels of NaPi-IIb were significantly higher in the human duodenum compared with the jejenum (D=0.096±0.028 vs. J=0.017±0.006; p<0.05; n=5), which is in contrast to the finding of higher NaPi-IIb expression levels in the rat jejenum (D=0.002±0.001 vs. J=0.028±0.004, p=0.0001, n=6). A trend for increased PiT1 expression in the human duodenum was observed, in contrast to higher PiT1 expression in the rat jejenum. The expression of NHE3, which is also a proposed regulator of phosphate transport, has a similar regional profile in both species.

Conclusions: Our results suggest that the seeming lack of therapeutic efficacy of NaPi-IIb inhibition in treating hyperphosphatemia in humans may result from differences in the regional profile of the phosphate transporters compared with rats in which NaPi-IIb inhibitors have been shown to be effective.

Funding: Private Foundation Support

Improvised Mortality Predictability of Total Serum Calcium by Novel Correction Equation in Hemodialysis Patients
Yoshitsugu 오, 1 Elani 스트리ja, 1 Matthew B. Rivara, 2 Wei Ling Lau, 2 Connie 류, 1 Csaba P. Kovácsy, 3 Rajinie Sheevasugum, 1 Kamyar Kalantar-Zadeh, 1 UC Irvine; 2Univ of Wash., 3Univ of Tenn.

Background: Hidden hypercalcemia, characterized as high ionized calcium with normal albumin-corrected total calcium, has been reported to be associated with high mortality in hemodialysis (HD) patients. We hypothesized that the development of a new correction equation offers better mortality predictability.

Methods: In a national cohort of HD patients in the US, a novel equation comprising total calcium, albumin, and phosphorus was derived and validated among 808 hemodialysis patients with measured ionized calcium data. We then categorized 87,779 HD patients according to calcium status (i.e., low [<8.6 mg/dL], low-normal [8.6-9.4 mg/dL], high-normal [9.4-10.2 mg/dL], and high [>10.2 mg/dL]) based on the novel vs. conventional correction equation. The association with all-cause death was evaluated using multivariable normal and high (<9.4–10.2 mg/dL), and high (>10.2 mg/dL) based on the novel vs. conventional correction equation. The association with all-cause death was evaluated using multivariable normal and high albumin-corrected total calcium, has been reported to be associated with high mortality in hemodialysis patients. We then categorized 87,779 HD patients according to calcium status (i.e., low [<8.6 mg/dL], low-normal [8.6–9.4 mg/dL], high-normal [9.4–10.2 mg/dL], and high [>10.2 mg/dL]) based on the novel vs. conventional correction equation. The association with all-cause death was evaluated using multivariable normal and high albumin-corrected total calcium, has been reported to be associated with high mortality in hemodialysis patients.

Results: Our results suggest that the seeming lack of therapeutic efficacy of NaPi-IIb inhibition in treating hyperphosphatemia in humans may result from differences in the regional profile of the phosphate transporters compared with rats in which NaPi-IIb inhibitors have been shown to be effective.

Funding: Private Foundation Support

Effect of Dialysate Calcium Conversion on Mineral Metabolism in Maintenance Hemodialysis Patients
Han Ro, 1 Ae Jin Kim, 1 Ji Young Jung, 1 Jae Hyun Chang, 1 Hyun Hee Lee, 1Wooyong Chung, 1Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea.

Background: The recommended dialysate calcium (DCa) concentration has been changed several times and the appropriate DCa concentration remains controversial. Our hemodialysis center reduced the default DCa concentration from 1.75 to 1.5 mmol/L in February 2013. This study compared the effect of DCa on serum markers of mineral bone disorders and drug requirements between conversion and no conversion (1.75 mmol/L) groups.

Methods: We retrospectively reviewed the patients undergoing maintenance hemodialysis using a consistent DCa concentration for the period between February 2012 and January 2014. We compared the serum markers of mineral metabolism and drug utilization before and after 1 year of DCa conversion between the two groups. Data were collected at 3-month intervals for 2 years. Our hemodialysis center reduced the default DCa concentration from 1.75 to 1.5 mmol/L in February 2013.

Results: Thirty-two patients were maintained at a DCa of 1.75 mmol/L and 26 patients underwent conversion of DCa from 1.75 to 1.5 mmol/L. DCa conversion to low calcium increased total equivalent dose of phosphate binder (p=0.012), especially calcium based phosphate binder (p=0.040).

Conclusions: In conclusion, our results demonstrate that comparing with maintaining 1.75 mmol/L, DCa, lowering DCa from 1.75 to 1.5 mmol/L lead to a significant change in mineral metabolism and drug requirements of phosphate binder in maintenance hemodialysis patients. Therefore, DCa conversion to low calcium increased total equivalent dose of phosphate binder (p=0.012), especially calcium based phosphate binder (p=0.040).
Tannoxin Causes Hypophosphatemia and Phosphaturia through the Downregulation of NaPi-IIa Expression in the Rat Kidney Proximal Tubule Hassane Amal, Sihame Amal, Sulaiman Sheriff. Internal Medicine, Univ of Cincinnati, Cincinnati, OH.

Background: Estrogen regulates renal inorganic phosphate (Pi) handling in women as well as in experimental animals. We recently showed that estrogen directly targets proximal tubule cells and downregulates NaPi-IIa in rats and both NaPi-IIa and NaPi-IIc in mice. The objective of this study was to test whether Specific Estrogen Receptor Modulators (SERMs) can also target Pi transport in the kidney proximal tubule.

Methods: Ovariectomized rats were placed in metabolic cages with free access to rodent chow and water. After acclimation period, rats were divided into 3 groups and treated with 500mg/kg/day of tamoxifen (tamox) or Raloxifene (RAL) or vehicle (Control). Daily food intake, water intake and urine volume were monitored. After 3 days, rats were sacrificed for blood and kidney collection. Cortex tissues were isolated and used for molecular studies.

Results: Only rats treated with TAM exhibited a significant hypophosphatemia vs. Control. The effect of TAM on Pi transport is dose-dependent. Pi creatinine excretion decreased by 75% in TAM over control group. The mRNA expression and protein abundance of NaPi-IIa were sharply downregulated in TAM vs. Control animal. In RAL group, Pi creatinine excretion was decreased and correlated with food intake and NaPi-IIa protein was not significantly altered vs. Control group.

Conclusions: Tannoxin causes phosphaturia and hypophosphatemia in female rats. The effect results from the downregulation of NaPi-IIa at both mRNA and protein levels. For the same dose, phosphaturia and hypophosphatemia are more pronounced in TAM than in RAL-treated rats. Hence, TAM is the most potent estrogen agonist with respect to its effect on Pi transport in the kidney, and could be used to correct hyperphosphatemia in chronic kidney disease with significant residual renal function or other conditions associated with impaired Pi balance.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO417

Contributors to Mortality in Calcific Uremic Arteriopathy: Role of Site and Severity of Skin Lesions Chamberlain I, Obiako,1 Alexander Quarshie.2 1Dept of Medicine, Morehouse School of Medicine, Atlanta, GA; 2Clinical Research Center, Morehouse School of Medicine, Atlanta, GA.

Background: Calcific Uremic Arteriopathy [CUA] is often fatal with mortality that ranges from 50 -80%. Adverse prognostic factors include: advanced age, female gender, large body mass index [BMI], and severity of skin lesions. Survival outcome has been improved with the use of calcimimetics, acid-base and BUN are normal in all groups. Food intake decreased sharply in TAM- and only slightly in RAL-treated vs. Control group. Despite the reduction in food/Pi intake, Pi creatinine excretion slightly increased in TAM over control group. The mRNA expression and protein abundance of NaPi-IIa were sharply downregulated in TAM vs. Control animal. In RAL group, Pi creatinine excretion was decreased and correlated with food intake and NaPi-IIa protein was not significantly altered vs. Control group.

Conclusions: Tannoxin causes phosphaturia and hypophosphatemia in female rats. The effect results from the downregulation of NaPi-IIa at both mRNA and protein levels. For the same dose, phosphaturia and hypophosphatemia are more pronounced in TAM than in RAL-treated rats. Hence, TAM is the most potent estrogen agonist with respect to its effect on Pi transport in the kidney, and could be used to correct hyperphosphatemia in chronic kidney disease with significant residual renal function or other conditions associated with impaired Pi balance.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO418


Background: High dietary phosphorus (P) intake increases phosphorus retention or load, serum FGF23 and PTH levels, and finally causes hyperphosphatemia and poor prognosis of CKD. Therefore, decrease in dietary P intake should be required for CKD patients. Here, we propose “Phosphatemic Index: PI” to evaluate the effect of P-containing foods on serum P homeostasis.

Methods: Twenty healthy young subjects (10 men and 10 women, 20-30 y.o.) were recruited. In this study, 10 different foods (pork, ham, soy bean, tofu, milk, processed cheese, egg, buckwheat noodle, red sea beard, broccoli) containing 200 mg of P were randomly ingested with an interval of 7 days or more as lunch. Blood were collected at 0, 0.25, 0.5, 1, 2, 4, and 6 h after the food ingestion, and measured serum P and PTH level. Then, each amount (mg of sodium phosphate) (AUC) of time-P concentration curve was calculated. PI of the tested food was calculated by following equation: PI = (AUC of tested food) x 100 / (AUC of 200 mg of sodium phosphate). This study was performed by open-label crossover study and approved by ethical committee of Tokushima University Hospital.

Results: As PI of sodium phosphate was 100, PI of milk was 108, processed cheese was 99, ham was 75, pork 54, soy bean was 33, tofu was 20. We found that PIs of vegetable foods including soy and tofu was lower than that of those animal foods. In addition, PI of pork showed lower than that of ham. This result might be due to food additives containing P. Furthermore, in milk and cheese, because they showed significant low secretion of PTH and low urinary excretion of P, we discussed that high calcium in milk would suppress the secretion of PTH and urinary P excretion and resulted to show high PI.

Conclusions: PI can appropriately reflect the effect of P-containing foods on serum P levels. It is a useful tool to evaluate and select foods by CKD patients who need P restriction.

Funding: Pharmaceutical Company Support - Ostuka Pharmaceutical Co., Ltd.

Government Support - Non-U.S.

FR-PO419

Green Tea Increases Urinary Excretion of Phosphorus, Magnesium, and Calcium in Rats Claudia Helou, Igor Oliveira Da Silva, Talita R. Sanchez, Maiira Santinlho, Lucia Andrade. Laboratório Pesquisa Básica LIM12, Faculdade de Medicina da USP, São Paulo, São Paulo, Brazil.

Background: The consumption of green tea (GT) is increasing worldwide, and there is a lack of data in the literature regarding its effect on renal tubular function.

Methods: Male Wistar rats were housed in individual cages and randomly assigned to have spontaneous access to GT (Feel Good®) or tap water (Control). On day 8, all rats were moved to metabolic cages and collected 24-h urine samples under oil, in order to evaluate renal function. The rats were then anesthetized, and a catheter was placed in the abdominal aorta to measure blood pressure (BP) and collect blood samples. We quantitated creatinine and electrolytes in urine and plasma samples. We removed the kidneys to quantify protein expression (PE) of ion transporters in the cortex and outer medulla (OM), by Western blot. We used unpaired t-test for statistical analyses.

Results: GT increased diuresis, as well as increasing urinary excretion of UV (phosphorus, Mg, magnesium), calcium (Ca) and potassium (K).

Conclusions: Green tea increases urinary excretion of P, Mg, and Ca, with possible effects of anti-oxidant and anti-hypertensive.

Funding: a) KAKENHI Grant 16K19879 b) CEM/CPqD/2015/0019 c) JSPS KAKENHI Grant 16K09587.

FR-PO420

Serum Phosphorus and Pill Number Per Day in Hyperphosphatemic Hemodialysis Patients (N=306) Prescribed Sucroferric Oxyhydroxide for 12 Months Linda H. Fiocchi, Vidhya Parameswaran, Carly R. Van Zandt, Norma J. Olfshin, Claudia Mullen, Franklin W. Maddux, Robert J. Kossmann. Fresenius Medical Care North America (FMCNA), Waltham, MA.

Background: DOPPS data show that even though phosphate binders (PB) are widely used, 35% of hemodialysis (HD) patients have hyperphosphatemia (serum phosphorus (P) levels >5.5 mg/dL). This analysis assessed whether the addition of sucroferric oxyhydroxide (SO), a chewable iron-based PB, to lower sP to ≤5.5 mg/dl over a one-year period.

Methods: De-identified data was extracted from electronic records for all adult, HD patients with first SO prescription between 3/1/2014- 3/1/2015 and SO prescription for 12 months (F1-F12). Patients on combination PB therapy were excluded. Baseline was defined as the 6 months before SO (BL1-BL6). Descriptive analyses of month to month changes are described and corrected with linear mixed-effects regression for continuous data and Cochran’s Q and McNemar’s chi-square test for categorical data. The real-world effectiveness of sucroferric oxyhydroxide (SO), a chewable iron-based PB, to lower sP to ≤5.5 mg/dl over a one-year period.

Results: At BL6, mean sP was 7.1 mg/dL and only 17.5% of patients had sP ≤5.5 mg/dL. During the months of SO follow-up (F1-F12), 31%-42% of patients had a sP ≤5.5 mg/dL, a 77%-141% increase (all comparisons p<0.001) from BL6. Mean PB pills/day decreased (p<0.001) from 8.3 pills at BL6 to 4.1-4.3 pills during F1-F12. Percent of patients with sP from 5.6-8.5 mg/dl decreased (p<0.001) from 64.7% at BL6 to 50.6% at F12.

Conclusions: Taken together, our findings indicate that GT inhibits ion transporters in the thick ascending limb of Henle’s loop, which increases diuresis and ion losses.

Funding: Fresenius Medical Care North America (FMCNA), Waltham, MA.
Results: When starting FC, 21 patients (23%) were binder naïve, 36 (39%) were on sevelamer only (average of 11 tablets/day), 20 (22%) were on calcium-based binder only (average of 9 tablets/day) and 15 (16%) on combination (average of 16 tablets/day) or other binder. The mean starting dose of FC was 6 tablets/day increasing to 7 tablets/day at 6 mo of treatment. Before the start of FC, 22% of patients had a serum phosphorus within target range of <5.5 mg/dL increasing to 65% at 6 mo of FC treatment. Phos, TSAT, ferritin and Hgb values are shown in Table 1 (data presented as mean±SEM). 6 patients discontinued FC within 6 mo of treatment.

Conclusions: In a retrospective analysis, switching to FC lowered serum phos and raised TSAT, ferritin and Hgb. Results of serum phos and anemia markers observed in this small retrospective cohort were similar to those in previous FC studies.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

FR-PO423
Serum Calcification Propensity Is Largely Genetically Determined in the General Population

Edward Picin,1 Matthias Bachtler,1 Olivier Devuy,2,3 Uyen Huyhn-Do,1,4 Murielle Boichud,5,4 Andreas Pasch,1,5,6 *Clinical Research, Univ Bern, Bern, Switzerland; *Nephrology, Univ Hosp. Lausanne, Lausanne, Switzerland; *Physiology, Univ Zurich, Zurich, Switzerland; *Nephrology, Univ Hosp, Bern, Bern, Switzerland; *Social and Preventive Medicine, Univ Hosp. Lausanne, Lausanne, Switzerland.

Background: A novel blood test (T50-Test) quantifies serum calcification propensity by determining the transformation time point T50 from amorphous to crystalline calcium phosphate in the presence of human serum. T50 is associated with all-cause and cardiovascular mortality in patients with chronic kidney diseases (CKD). Here we investigated T50 in the general population.

Methods: T50 and fetuin-A were determined in 1033 sera from the Swiss Kidney Project on Genes in Hypertension (SKIPOGH) cohort, the heritability of T50 was calculated and a genome wide association study (GWAS) and multivariate analysis performed.

Results: T50 was normally distributed in the population (mean±SD, 298±58 min.), and the heritability of T50 was estimated to be 50.8% (p=0.01). GWAS identified a strong SNP association between T50 and SNPs in the ANG/Tf/Db gene locus on Chromosome 3 (e.g. rs2593813 p=7.7e-28). Individuals homozygous for the minor allele had a significantly lower T50 than those homozygous for the wildtype allele (254±54 vs. 315±54 min., p=0.01). Serum fetuin-A concentrations were lower in those homozygous for the minor allele (0.33±0.06 vs. 0.43±0.08 g/L, p<0.01). Multivariate analyses identified age, eGFR, and phosphate as determinants associated with worse (i.e. accelerated) and fetuin-A, magnesium and bicarbonate as determinants associated with improved (i.e. delayed) serum calcification propensity.

Conclusions: Serum calcification propensity (T50) is highly heritable in the general population and largely depends on the same determinants as in renal patients. Calcification propensity may reflect a general physiological system of crystalization control inherent in blood.

Funding: Government Support - Non-U.S.

FR-PO424
Phosphorus Control and Pill Burden among In-Center Hemodialysis (ICHD) and Peritoneal Dialysis (PD) Patients Converting to Sucroferric Oxycitrate (SO) Phosphate Binder (Auryxia)

Kathryn S. Gray,1 Linda H. Ficociello,1,2 Claudy M. Mullon,1 Steven M. Brunelli,1,2 *DaviVac Clinical Research, Minneapolis, MN; Fresenius Medical Care, Waltham, MA.

Background: SO is a new iron-containing phosphate binder (PB). In developmental studies, SO showed equivalent phosphorus reduction to sevelamer. However, the effects of SO in real-world populations have not been extensively studied. We retrospectively examined SO use among patients who converted from another PB to SO.

Methods: From among ICHD and PD patients at a large dialysis organization (LDO) receiving benefits through the LDO’s pharmacy program, we identified those converting to SO from another PB: defined from prescription fill data as having had supply of another PB and receiving benefits through the LDO’s pharmacy program, we identified those converting to SO from another PB: defined from prescription fill data as having had supply of another PB and received benefits through the LDO’s pharmacy program, we identified those converting to SO from another PB: defined from prescription fill data as having had supply of another PB and received benefits through the LDO’s pharmacy program, we identified those converting to SO from another PB: defined from prescription fill data as having had supply of another PB and received benefits through the LDO’s pharmacy program, we identified those converting to SO from another PB: defined from prescription fill data as having had supply of another PB. After a first fill of SO, and subsequently not refilling the initial PB such that supply exhausted for at least 30 days. Longitudinal indices of phosphorus control and PB burden were compared.

Results: There were 656 ICHD SO converters: mean age, 50 years; 47% female; 45% black; median vintage, 43 months. Prior to SO initiation, mean serum phosphorus was 7.1 mg/dL, during follow-up it fell to 6.6 mg/dL, percentage of patients with phosphorus ≤5.5 mg/dL rose from 17% to 32%. Daily SO pill burden was 3.0-3.9; total daily PB pill burden fell from 7.5 prior to SO initiation to 5.5 during follow-up. There were 105 PD SO converters: mean age, 47 years; 52% female; 29% black; median vintage, 33 months. Prior to SO initiation, mean serum phosphorus was 7.0 mg/dL, during follow-up it fell to 6.2 mg/dL, percentage of patients with phosphorus ≤5.5 mg/dL rose from 18% to 26%. Daily SO pill burden was 3.2-4.0; total daily PB pill burden fell from 8.7 prior to SO initiation to 5.4 during follow-up.

Conclusions: In a small retrospective cohort similar to those in previous SO studies, SO showed equivalent phosphorus reduction to sevelamer. However, the effects of SO in real-world populations have not been extensively studied. We retrospectively examined SO use among patients who converted from another PB to SO.

Funding: Government Support - Non-U.S.
The Dietary Adenine Rat Model of Chronic Kidney Disease Produces Hyperphosphatemia in the Absence of High Phosphate Diet

**Background:** Chronic kidney disease (CKD) induces hyperphosphatemia, which associates with cardiovascular events and vascular calcification. Animal models of CKD demonstrate similar pathologies and outcomes to CKD patients. However, a rat adenine model examining the effects of dietary phosphate (PO4) levels after slow induction of CKD is unknown. This study is a refinement of the dietary adenine model of CKD.

**Methods:** Male Sprague Dawley rats (15-16 weeks) were fed a 0.25% adenine, 0.5% PO4 diet to establish stable CKD (creatinine >250 uM), 5 weeks. At 5.5 weeks, rats were divided into 0.5% (N=8), 1% (N=8), and 1.5% (N=6) PO4 groups. Control rats were fed 0.5% PO4 diet (N=8). Serum creatinine, PO4, FGF-23, and PTH were measured. At sacrifice, tissue levels of calcium and PO4 were determined.

**Results:** Rats in 0.5, 1, and 1.5% PO4 groups had similar creatinine levels throughout the experiment. From 0-5.5 weeks, all CKD rats were similar in serum PO4 and significantly higher than control throughout. At 5 weeks, CKD rats had 3.2±0.6 mM PO4 versus 2.5±0.3 mM PO4 control. When removed from adenine diet, the 0.5% group returned to control PO4 levels by 6.5 weeks with no calcification or further increase by 7 weeks in FGF-23 (3.1±2.7 vs 0.47±0.15 ng/ml Control) and PTH (0.41±0.18 vs 0.17±0.08 Control ng/ml). The 1.0 and 1.5% groups had significant large increases by 7 weeks in PO4 (5.0±1.0, 5.8±1.4 mM), PTH (2.4±1.3, 3.1±0.6 mg/ml), and FGF-23 (47±18, 35±17 ng/ml), aortic calcification in 80% of rats.

**Conclusions:** These results demonstrate that a high phosphate diet greater than 0.5% is required for mineral bone disorder and calcification in the rat adenine model of CKD. The dietary adenine model of CKD produced a significant increase in serum PO4 on low PO4 diet, that returned to normal levels within 1.5 weeks of removal of adenine. Researchers should use caution in comparing serum PO4 levels in animals on or off adenine-containing diets.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care

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**FR-PO425**

Increased Phosphate Burden from Medications Prescribed to In-Center Hemodialysis Patients

**Background:** Maintaining phosphorus balance in in-center hemodialysis (IHD) patients is problematic despite dietary restriction (800 – 1000 mg/day if serum P levels ≥5.5 mg/dL), dialysis, and phosphate (P) binder use. High-flux IHD can remove ~30 mmol (900 mg) P/session; P intake should not exceed ~750 mg/day for a 60 kg patient. Rarely is the P channel blockers (22%), proton pump inhibitors (PPIs; 18%), acetaminophen-opioid (AO; 13%), angiotensin-converting enzyme inhibitors (ACEs; 10%) and α2-agonists (9%). The top five medication orders were amiodarone, lisinopril, clonidine, acetaminophen, and

**Conclusions:** Both normal and very high Phos levels were associated with higher early post-ESRD hospitalization rates. The finding of normal Phos levels being associated with increased risk was unexpected and suggests further analysis as this could impact existing recommendations of targeting an achieved Phos level to the normal range. Further studies are also needed to determine if using dietary and medication interventions to attain this Phos range confers better early dialysis outcomes in this population.

**Funding:** NIDDK Support

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**FR-PO426**

Both Normal and Very High Serum Phosphorous Levels prior to Transition to Dialysis Are Associated with Early Dialysis Hospitalization in U.S. Veterans: A Transition of Care in CKD Study

**Background:** Recent studies suggest that serum phosphorous (Phos) levels are predictors of hospitalization in patients with chronic kidney disease. However, the impact of Phos levels prior to end-stage renal disease (ESRD) on post-ESRD hospitalization is unknown.

**Methods:** In 85,505 US veterans who transitioned to dialysis between 10/2007 and 3/2014, we identified 19,610 patients with available Phos measurements within the last 6-month period (prior to ESRD). We examined the association of Phos (averaged over 6 months) as a categorical predictor of hospitalization within the first 6 months post transition, using Poisson models adjusted for demographics, comorbidities and laboratory covariates.

**Results:** The cohort was (mean±SD) 66±11 years old, among whom 34% were African-American, and 50% had diabetes listed as their primary cause of ESRD. The mean±SD Phos of the cohort was 5.1±1.3 mg/dl prior to ESRD. We observed a reverse-J shaped association between pre-ESRD Phos and 6-month post-ESRD hospitalization rate. Patients with Phos levels ≤5.5 mg/dL and ≥6.5 mg/dL demonstrated incrementally higher hospitalization rates compared to the referent group (Phos 5.5-<6 mg/dL).

**Conclusions:** Both normal and very high Phos levels were associated with higher early post-ESRD hospitalization rates. The finding of normal Phos levels being associated with increased risk was unexpected and suggests further analysis as this could impact existing recommendations of targeting an achieved Phos level to the normal range. Further studies are also needed to determine if using dietary and medication interventions to attain this Phos range confers better early dialysis outcomes in this population.

**Funding:** NIDDK Support
FR-PO428
Pill Burden and Serum Phosphorus in Hemodialysis Patients Switched from Sevelamer to Sucroferric Oxophosphate 
Vidyah Parameswaran, Linda H. Ficociello, Carly R. Van Zandt, Norma J. Ohshun, Claudiy Mullon, Franklin W. Maddux, Robert J. Kossmann. Fresenius Medical Care North America, Waltham, MA.

Background: Recent DOPPS data show a trend towards greater phosphate binder (PB) non-adherence and higher number of prescribed PB pills per day. Also, non-adherence was associated with serum phosphorus (sP) >5.5 mg/dl (Fissell et al. 2016). The current retrospective analysis examined PB pills/day and achievement of sP ≤5.5 mg/dl in patients switched from sevelamer (Sev) to sucroferric oxophosphate (SO) as part of routine care.

Methods: Adult, hemodialysis patients with first SO prescription between 3/1/2014-3/1/2015, recorded SO prescription for 10-12 months and Sev prescription at baseline (previous 6 months) were included (n=277). Patients on combination PB therapy were excluded. Descriptive analyses of quarterly changes were described and linear mixed-effects regression and Cochran’s Q/McNemar were used to test for statistical significance.

Results: Mean quarterly PB pills/day and percent sP ≤5.5 mg/dl are presented in the table. The Sev2 quarter as the reference (8.9 pills/day), a >50% decrease in number of PB pills/day was observed for each quarter after the switch to SO (4.0, 4.4, 4.3, 4.4 pills/day SO1-SO4, respectively). Percent of patients achieving sP ≤5.5 mg/dl increased by 45%, 93%, 131% and 119%, comparing Sev2 to SO1-SO4, respectively.

**p-value <0.0001, *p-value <0.05. Observation periods include 6 month Sev and 12 month SO. Each quarter is represented as Sev and SO.**

Conclusions: In a cohort of patients switched from Sev to SO, a >50% reduction in PB pills/day was observed along with improvements in the percent of patients achieving sP ≤5.5 mg/dl during SO follow-up.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO429
Evidence for Increased Absorption of Phosphate in Experimental Adenine-Induced Chronic Kidney Disease 
Paul S. Jeromine, Cynthia M. Pruss, Bruce Svaeger, Mandy E. Turner, Kimberly J. Laverty, Emilie C. Ward, Melissa A. Hinkle, Yvonne M. Holden, Michael A. Adams. Biomedical and Molecular Sciences, Queen’s Univ, Kingston, ON, Canada; Medicine, Queen’s Univ, Kingston, ON, Canada.

Background: Hyperphosphatemia is a common manifestation of chronic kidney disease (CKD) and is a risk factor for cardiovascular morbidity and mortality (e.g. vascular calcification). It is widely acknowledged that the kidney is a primary site of phosphate (P) metabolism. However, it is poorly understood how other organs, including the gut, contribute to this control. Despite homeostatic mechanisms regulating serum phosphate within a narrow range the gut normally absorbs 70% of dietary phosphate through paracellular and sodium-dependent phosphate cotransporter (NPT2b) mechanisms. The objective of this study was to determine how disposition of phosphate is altered by impaired renal function to this control. Despite homeostatic mechanisms regulating serum phosphate within a narrow range the gut normally absorbs 70% of dietary phosphate through paracellular and sodium-dependent phosphate cotransporter (NPT2b) mechanisms. The objective of this study was to determine how disposition of phosphate is altered by impaired renal function.

Methods: Male Sprague Dawley rats (n=42) were fed an adenine containing diet (0.25% adenine with 0.5% phosphate) for 5-6 weeks to establish moderate to severe CKD. Samples were obtained from 36 rats. Serum creatinine, FGF-23 and PTH were measured using established methods 15.4 ± 2.9 mg/dl for adenine, 75.5-148.8 mg/dl for sevelamer, 2.9-7.2 mg/dl for clonidine, 0 mg for AO, and 204.8-234 mg for sevelamer per day.

Conclusions: Increased P content in medications prescribed to IHD patients may contribute to the overall daily P load, requiring more P binders, increasing the daily pill burden and affecting compliance.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America; Fresenius Medical Care Renal Therapies Group

FR-PO430
Warfarin Induced Aorta Calcification and LV Dysfunction in a Remnant Kidney Mouse Model 
Ying-Ying Chen,1 Szu-Yuan Li,2 Der-Cheng Tang,1 1Div of Nephrology, Dept of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; 2Faculty of Medicine, National Yang-Ming Univ, Taipei, Taiwan.

Background: Some studies have suggested that warfarin is beneficial for stroke prevention in dialysis patients with atrial fibrillation. However, consistent with the clinical uncertainty regarding the benefits of stroke prevention with warfarin, the most recent KDIGO guidelines neither supported nor rejected the use of warfarin therapy in dialysis patients. Moreover, warfarin, a vitamin K antagonist, can inhibit γ-carboxylation of glutamic acid residues in matrix Gla protein (MGP) in arterial smooth muscle cells, and is thus involved in the process of arterial calcification.

Methods: Therefore, this study was designed to explore the promoting effects of warfarin in aortic calcification in vivo experiments. After 5/6 nephrectomy, B6 mice were divided into four groups: 5/6 NX, warfarin (3 mg/kg/day), Vitamin D3 (100 mg/kg/day), and Vitamin D3 plus warfarin groups (n=10~12 each group) for 4 months.

Results: In the fourth group only, the Vit-D plus warfarin group had micro-CT detectable vascular calcifications and 3-D reconstruction of the micro-CT images illustrated a pipe-like diffused calcified aorta. Histological staining confirmed the severe vascular calcification in the Vit-D plus warfarin group, but no remarkable aorta calcification in the other groups. 5/6 nephrectomy mice had a moderate left ventricular (LV) dysfunction as compared to sham operation group, however, Vit-D plus warfarin is able to induce significant LV dysfunction in remnant kidney mice (figure1).

Conclusions: Warfarin potentially promotes vascular calcification and exaggerates LV dysfunction in CKD mice.

FR-PO431
Analysis of Acidity and Phosphorus Levels in Commonly Consumed Sodas 
Uma D. Alapanna,1 Raj Alapanna.2 1Science, Brookstone School, Columbus, GA; 2Nephrology, Renal Associates LLC, Columbus, GA.

Background: Increased phosphorus intake in CKD patients causes significant morbidity and mortality. The purpose of this study is to determine the prevalence of contents in commonly consumed sodas, specifically their pH, titratable acidity, phosphorus (P), phosphoric acid (H3PO4) and phosphate levels (PO4). As this information is not readily available.

Methods: The Metrohm 799 GPT Titrino and the Optima 880 Series of ICP-EOS Spectrometers were used to estimate the pH, titratable acidity, and phosphorus content of various sodas respectively. The PO4, P, and H3PO4 contents were calculated using proportions and the pHophorus content of the Phosphorus. A survey, inquiring soda preference, weekly intake, possible soda health effects, and consumer demographics, was administered to several high school students and faculty members, as well as to random participants in Columbus, GA.

Results: 124 participants were surveyed (n=124); Male:42 (33.9%), Female:82 (66.1%). The mean age was 31.46 years. 103 (83.1%) consumed sodas and 21 (16.9%) did not. The most frequently consumed sodas were Coca-Cola products, 62 (60.2%), Sprite products, 12 (11.7%), and Dr. Pepper products, 10 (9.7%). The weekly soda can and phosphorus consumption in those ≤18 years, 19-49, and 50+ was 5.6, 5.4, and 4.1 cans; and 713.0 mg/L, 748.1 mg/L, and 514.3 mg/L, respectively.

**p-value <0.0001, *p-value <0.05. Observation periods include 6 month Sev and 12 month SO. Each quarter is represented as Sev and SO.**

Conclusions: Warfarin potentially promotes vascular calcification and exaggerates LV dysfunction in CKD mice.

FR-PO432
Adherence to Bone-Mineral Metabolism Guidelines among Kidney Transplant Candidates 
Meteb M. AlBugami,2 Fahad Eid Alotaiba,1 Khalid Bel’eed-Akkani.1 1Multi-Organ Transplant Center; King Fahad Specialist Hospital, Damman, Saudi Arabia; 2Dept of Internal Medicine, College of Medicine, Univ of Dammam, Dammam, Saudi Arabia.

Background: Chronic kidney disease-mineral and bone disorders (CKD-MBD) is linked to cardiovascular disease (CVD). Since CVD is the most common cause of death after kidney transplantation (KT), it would be prudent to optimize CVD-MBD treatment in KT candidates. This study aimed to measure the extent to which KT candidates complied with the National Saudi Bone Biochemistry Guidelines.

Methods: All potential KT recipients evaluated at the Kidney and Pancreas Transplant Department, King Fahad Specialist Hospital-Dammam, between January 2009 and December 2013 were reviewed. Data were collected from electronic database. Blood samples were obtained during patients’ initial visit to the pre-transplant evaluation clinic. For patients on hemodialysis, pre-dialysis samples were obtained.

Conclusions: The default regular sodas had the most acidity and phosphorus content, while the light diet sodas had the least. Coca-Cola, the commonest consumed soda, had one of the highest phosphorus contents of all sodas, suggesting high phosphorus intake. Diet Coca-Cola had the least amount of phosphorus of all dark sodas suggesting low phosphorus intake. Fanta, a light soda, had phosphorus due to a sodium hexametaphosphate preservative. Diet 7-Up had no phosphorus and was the least acid soda. As the survey results showed, soda intake generally decreases as one gets older.
Results: A total of 1014 candidates were evaluated, with a mean age of 43±13.7 years, and 589 (58%) of the subjects were males. Data were missing in 132 (13%) of the cases. Mean phosphate level was 1.70±0.35 mmol/L, and 44% achieved the guideline target. Mean calcium level was 2.27±0.24 mmol/L, and 42% achieved the guideline target. Median PTH 439.2 pg/ml (IQR 243.4 – 506.7), and 19% only achieved the guideline targets. 395 subjects (45%) had a PTH level >500 pg/ml, while 126 subjects (14%) had PTH less than 150 pg/ml. Only 2.3% of patients met all the 3 standards for corrected calcium, phosphorus and PTH.

Conclusions: Substantial proportion of KT candidates referred for pre-transplant evaluation failed to meet the Saudi national guideline targets of CKD-MBD. This should prompt us to place greater and more rigorous emphasis on adherence measures to the guidelines in order to improve the cardiovascular risk of transplant recipients.

FR-PO433

Acid-Base and Phosphorus Homeostasis in Chronic Kidney Disease: Results from the Chronic Renal Insufficiency Cohort (CRIC) Study

Pascale Khairallah,1 Tamara Isakova,2 John R. Asplin,3 L. Lee Hamm,4 Mirela A. Dobre,5 Mahboob Rahman,6 Kumar Sharma,7 Mary B. Leonard,8 Edgar R. Miller,9 Bernard G. Jaar,9 Carolyn S. Brecklin,6 Wei Yang,10 Harold I. Feldman,11 Myles S. Wolf,12 Julia J. Scialla.13 Duke Univ; Northwestern Univ;1 Litholink Corporation; Tulane Univ; Case Western Reserve Univ;1 Univ of California San Diego; 2 Stanford Univ; 3 Johns Hopkins Univ; 4 Univ of Illinois; 5 Univ of Pennsylvania.

Background: Kidneys excrete acid either as ammonium or as titratable acids (TA). Phosphate binders are used as a buffer. In CKD, impaired ammoniagenesis promotes metabolic acidosis. In vitro, acids stimulate phosphaturic hormones, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23), possibly to increase buffer for TA. These in vitro findings have not been confirmed in humans.

Methods: In 980 CRIC participants with CKD (eGFR 44±14 ml/min/1.73m²), we measured net acid excretion (NAE) in 24h urine, potential renal acid load (PRAL) by food questionnaire, and serum bicarbonate. Using adjusted linear and log-linear regression, we modeled associations between acid parameters and 24h urine phosphorus, serum phosphorus, FGF23, and PTH.

Results: 24h urine phosphorus was higher at higher NAE, higher PRAL, and lower bicarbonate (all p-trends<0.05). Serum phosphorus was higher with higher NAE and lower bicarbonate (both p-trends<0.001). Higher NAE or PRAL were not associated with FGF23 or PTH, but not FGF23 (p=0.62), 26% higher (P<0.001) when serum bicarbonate was < vs. ≥22 meq/L. Results were similar if stratified by eGFR categories, or if adjusted for iohalamate GFR, energy intake, urine urea nitrogen, or dietary phosphorus, where available.

Conclusions: Acid loading may augment phosphaturia in CKD to maintain NAE. Mechanisms may include higher serum phosphorus and not primary increase in FGF23 or PTH. Effect of acid load on phosphorus homeostasis must be tested in trials.

Funding: NIDDK Support

FR-PO434

Novel Non-Absorbed, Calcium-Free, Highly Effective Phosphate Binders Derived from Gum Arabic: 1 Ruth Wu-Wong, Yang-Wu Chen, Jerry Weissale, Vidasyn, Chicago, IL.

Background: Inadequate control of serum phosphate in chronic kidney disease can lead to pathologies of clinical importance. Effectiveness of on-market phosphate binders is limited by safety concerns and low compliance (high pill size/burden and gastrointestinal (GI) discomfort).

Methods: We have developed a series of novel, highly effective phosphate binders from metal ions and gum Arabic (GA), ingredients commonly used in food.

Results: In vitro studies show that VS-505 (Fe-GA), VS-605 (Mg-GA) and VS-705 (Zn-GA) have high densities (e.g. 1.95 g/cm³ for VS-505 vs. 2.7 g/cm³ for sevelamer) and low swell volumes when exposed to phosphate buffer or simulated gastric fluid (e.g. 0.4 cm³/0.1 g for VS-505 vs. 4 cm³/0.1 g for sevelamer). VS-505, VS-605 and VS-705 bind phosphate within a wide physiologically relevant range of pH, enabling them to bind phosphate along much of the GI tract. In normal SD rats, increasing the dietary phosphate led to an increase in serum phosphate, which was prevented in rats treated with VS-505, VS-605, or VS-705 (0.2 - 5% in food). Urinary phosphate increased by >10-fold in the vehicle-treated group; VS-505, VS-605 or VS-705 reduced urinary phosphate, and increased fecal phosphate in dose-dependent manners. No significant changes were observed for serum calcium, while urinary calcium increased from 1.4 ± 0.2 mg/24 hr before dosing to 9.2 ± 1.0 mg/24 hr in the 5% sevelamer group, and to 3.6 ± 0.5, 3.0 ± 0.7, and 5.2 ± 1.6 mg/24 hr in the 5% VS-505, VS-605, and VS-705 groups, respectively. In SD rats made uremic by 5/6 nephrectomy (5/6 NX rats) on a high phosphate diet, urinary and serum phosphate levels were significantly elevated in untreated rats, which were reduced by VS-505 and sevelamer: VS-505 increased fecal phosphate levels in a dose-dependent manner. More aortic calcification was observed in 5/6 NX rats treated with 5% sevelamer, but not in rats treated with VS-505.

Conclusions: These results demonstrate that these novel metal ion-GA phosphate binders effectively control phosphate imbalance in rats by removing phosphate from the GI tract via the feces. VS-505 is currently being evaluated in a clinical trial in Australia involving hemodialysis patients (ClinicalTrials.gov #: NCT02496497).

Funding: Other NIH Support - NIAMS, Pharmaceutical Company Support - Vidasyn

FR-PO435

Lower Serum Magnesium Levels Are Associated with an Increased Risk of Hip Fracture in Hemodialysis Patients - A Nationwide Cohort Study


Background: Hip fracture is common in dialysis patients, which leads to an increased mortality and substantial economic burden. Although magnesium is an essential mineral for normal bone metabolism, little is known about the relationship between magnesium and a risk of fractures. Here we analyzed the association of serum magnesium levels (sMg) with an incidence of hip fracture in hemodialysis patients.

Methods: We utilized a database of the Japanese Society for Dialysis Therapy-Renal Data Registry that covers nearly all dialysis patients in Japan. We included hemodialysis patients without a prior history of hip fracture. Patients living in a nursing home or aged more than 90 years old were excluded. sMg were divided into quartiles (Q1 to Q4).

Results: Among a total of 113,086 hemodialysis patients enrolled in the analysis, a new hip fracture occurred in 2,267 patients (2.0%). The incidence rate of hip fracture decreased as sMg quartiles increased (2.61%, 2.06%, 1.74%, and 1.47% in Q1 to Q4, respectively; p <0.001 for trend) (range of sMg (mg/dL): Q1, -2.3; Q2, 2.4-2.6; Q3, 2.7-2.8, Q4, 2.9-). After an extensive adjustment for demographic and clinically relevant factors including parathyroid hormone levels, patients in Q4 had a 26% higher odds for hip fracture than those in Q1 (p <0.001). A population attributable fraction analysis indicated that 15.4% (95%CI: 5.6-24.2; p = 0.003) of all hip fractures in this population could have been prevented by increasing sMg to the range of Q4.

Conclusions: Low sMg may be an unignorable risk factor for hip fracture among hemodialysis patients.

FR-PO436

Hypophosphatemia following Hepatectomy and Pancreatectomy: Role of the Phosphaturic Factor NAMPT


Background: Clinically significant postoperative hypophosphatemia is common and is associated with a lower risk of liver failure after hepatectomy but a higher rate of complications after pancreatectomy. The mechanisms involved are unclear but presence of
phosphaturia suggests a role for phosphaturic factors such as parathyroid hormone (PTH) or non-PTH mediated phosphaturic mediators. The current study evaluates the role of PTH and NAMPT have on development of postoperative hyperphosphatemia.

Methods: Patients who underwent open liver (n=48) and pancreas (n=30) resections were enrolled, and those deemed unsuitable were used as controls (n=21). Serum and urinary phosphate and creatinine were measured preoperatively and on postoperative day (POD)1-7. Serum PTH (immunoassay) and NAMPT (ELISA) were analyzed preoperatively and on POD2.

Results: Phosphate levels significantly decreased from POD1 to POD2 in all 3 groups preceded by an increase in phosphaturia. NAMPT levels were significantly increased from preoperative to POD2 in resected patients but not in controls. Phosphate levels did not change in any of the groups.

[Table of phosphate levels and urinary phosphate excretion.]

**FR-PO437**

The Serum Calcification Propensity of Hemodialysis Patients Is Strongly Modified by Serum Phosphate, Magnesium and Bicarbonate

**Florian O. Beara, Susan L. Furtado, Constantinos D. Mehta, Nora M. Perez Perez, Francois Francois, and Nora M. Perez Perez.**

**Background:** Several easily measurable and modifiable parameters correlate with the T50 precipitation time in vitro. These parameters include phosphate, magnesium, calcium, albumin, and bicarbonate. The current study evaluates the role of phosphorus, magnesium, and bicarbonate to inhibit calcification propensity. Although the present data may be influenced when altering these parameters from the minimum to the maximum measured in the study population, it remains unknown. Recently, we reported that heparin-induced hyperphosphatemia is due to abnormal PAM metabolism. Partial heparin (PH) rats exhibited markedly decreased levels of intestinal NaPi-IIa and NaPi-IIc-dependent Pi transport activity. In the current study, we evaluated the role of phosphorus, phosphosubstitutes (NAMPT; catalyzes the first rate-limiting step in converting NAM to NAD) on Pi handling in the small intestine.

**Methods:** We used a PH rat model and NAMPT<sup>−/−</sup> mice to investigate the molecular basis of Pi handling in the small intestine through NAMPT activity.

**Results:** PH rats showed hyperphosphatemia and hyperphosphaturia. PH rats also exhibited elevation of plasma NAM concentration and reduction of intestinal NaPi transport and NaPi-IIb protein. In addition, cellular NAMpt and NAD levels were significantly increased in the small intestine. In vitro analyses using NaPi-IIb-expressing human intestinal epithelial cells (Caco2-BBE), treatment with NAMPT and NAD led to a marked decrease in the NaPi-IIb protein levels compared with treatment with NAM alone. In contrast, FK866 (a specific inhibitor to NAMPT)-treated mice (C57BL/6) showed no effect on NaPi-IIb expression. PH mice with FK866, urinary Pi excretion was significantly decreased. In addition, NAMPT<sup>−/−</sup> mice showed elevation of intestinal NaPi-IIb and upregulation of intestinal Pi transport activity. These observations suggest that cellular NAMpt activation is an important factor for the downregulation of intestinal NaPi-IIb levels.

**Conclusions:** In PH animals, the downregulation of intestinal Pi transport may be due to increased Pi reabsorption and secretion. We now report on the potential value of NAM (NAMPT) in treating hyperphosphatemia in CKD patients.

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

**FR-PO439**

Effect of Antibiotic Treatment on Oxalobacter Formigenes (OF) Colonization and Urinary Oxalate Excretion

**Lama Nazzal, Norrotong K. Jongtrakul, and Hiroko Segawa.**

**Background:** OF, a member of the human colonic microflora, plays a major role in net urinary oxalate absorption and secretion. We now report on the potential value of NAM (NAMPT) in treating hyperphosphatemia in CKD patients.

**Methods:** We followed 65 healthy subjects tested for Helicobacter pylori (HP) gastric colonization. Those who were HP<sup>+</sup> treated with antibiotics (amoxicillin and clarithromycin) for 2 weeks (w) for HP eradication. Using species-specific PCR, we tested for OF colonization. Urine samples 3h after a standard meal were analyzed for Uox, factored for creatinine (Cr). Both assessments were done at baseline and at follow-up.

**Results:** Of the 65 subjects (MF 23:42), mean age 25.2 ± 5.7 years, 37 (56%) were positive at baseline. Of 7 OF<sup>+</sup> subjects at baseline who received antibiotics for HP elimination 6 became OF<sup>−</sup> at 12 w. Of these, 2 reverted to OF<sup>+</sup> at week 24, and 4 remained OF<sup>−</sup> at follow up (Mean 22.5 ± 4.2w). For 42 untreated subjects, 18 of whom were OF<sup>−</sup> at baseline, 16 (89%) remained OF<sup>−</sup> at follow-up (Mean 23.0 ± 4.2w). OF<sup>−</sup> subjects, only 3 (12%) were OF<sup>+</sup> at follow-up (Mean 20.2 ± 6.8w; p=0.001 compared to initial OF<sup>+</sup>). We assessed Uox/Cr in 137 samples from 46 subjects with no antibiotic exposure. OF-positivity was associated with 14% lower Uox/Cr compared with OF-negativity (17.0 ± 0.0 vs 19.4 ± 0.1mg/g, p=0.04). From 5 antibiotic treated OF<sup>+</sup> subjects, we assessed Uox/Cr at baseline and 24 weeks following antibiotic exposure and found no significant increase in urine oxalate (16.6 ± 16.7 vs 18.5 ± 12.6mg/g, p=0.5).

**Conclusions:** We conclude that detectable OF-positivity remains stable over several months, but that antibiotic exposure suppresses or eliminates colonization in most subjects.

**Funding:** Private Foundation Support

**FR-PO440**

Prevalence of LMWP and CLCN5 Mutations in Proteinuric Cohorts

**Ladis Berra Lasic, Andrea G. Cogal, Xiangling Wang, Felicity T. Enders, Susan L. Furtado, Mehta, Zeynep E. Tuzcu, Howard Trachtman, Steven J. Scheinman, David S. Milliner, Peter C. Harris, and John C. Lieske.**

**Background:** Dent disease type 1 (DDD) is a rare X-linked disorder caused by CLCN5 mutations. Some patients present only with nephrotic range proteinuria leading to erroneous diagnosis and immunosuppressive treatment of focal segmental glomerulosclerosis (FSGS).

**Methods:** CLCN5 mutations were screened using samples from the following cohorts: Chronic Kidney Disease in Children (CKiD); n=112; Multicenter FSGS-Clinical
Trial (FSGS-CT) and Novel therapies for resistant FSGS Trial (FONT) (n=126). The CKD cohort included patients with FSGS, chronic GN, familial nephritis, congenital nephrotic syndrome, reflux nephropathy, and medullary cystic disease. Urinary a, microglobulin (a,M), albumin (A) and total protein (TP) were assessed in urine from CKD subjects (n=104); DD1 patients (n=14) and DD1 carriers (DC, n=8).

For the CNL5 knockdown experiments, Drosophila kidney tissue was dissected from CaOx crystal-positive flies. TP/CR was similar in CKD and DD1 but lower in DC (P<0.001). A/CR was significantly less elevated in DC while a,M/CR was higher in DD1 (P<0.001) compared to CKD cohort. a,M/TP was similar in DD1 and DC and higher than CKD (P<0.001), while the A/TP was lower in DD1 compared to CKD (P<0.01).

Conclusions: CLCN5 mutations are rare. Even though TP excretion did not differ, the protein pattern of DD1 could be distinguished from CKD subjects due to a significantly higher a,M/CR and significantly lower A/TP. Although the TP excretion of DC was low, DC has proportionally lower A,M/CR, mimicking DD1. Assessment of urinary LMWP such as a,M is a good screen for DD1 among male patients with proteinuria. A/TP could also be considered as a simple screening test for Dent since it is readily available and provides good differentiation from other pediatric proteinuric renal diseases.

<table>
<thead>
<tr>
<th>TP/CR (mg/g)</th>
<th>A/CR (mg/g)</th>
<th>a,M/CR (mg/g)</th>
<th>A/TP</th>
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</thead>
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<tr>
<td>CKD</td>
<td>2275 (3917)</td>
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<td>247 (120)</td>
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<td>18 (8%)</td>
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<tr>
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<td>80 (112)</td>
<td>15 (19)</td>
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Funding: NIDDK Support, Other NIH Support - NCATS

FR-P0441

Drosophila Model Indicates Role of OSR1/SPAK Signaling in Calcium Oxalate Kidney Stone Formation via Regulation of Slc26a4 Mediated Cl–/Oxalate(2–) Exchange. Jacob B. Anderson,1,2 Taku Hirata,1,2 Adam Joseph Rossano,3,4 Greg M. Landry,3,4 Michael F. Romero,1,2 1Physiology & Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN; 2Biological Engineering Research Center, Mayo Clinic, Rochester, MN; 3Nephrology & Hypertension, Mayo Clinic College of Medicine, Rochester, MN. Background: Kidney stones (12% male; 6% female) are costly, painful and lead to renal injury. Calcium oxalate (CaOx) are >70% of stones. Oxalate is a metabolic end-product eliminated via the kidneys and intestine. Oxalate-secretion is mediated by Slc26a4 (Drexin in flies), a Cl–/Oxalate(2–) exchanger. Voltage clamping of oocytes expressing Drehcin/Slc26a4 (OSR1/SPAK) indicate that these kinases trigger Cl–/Oxalate exchange activity. Therefore, we hypothesized that the incisation of CaOx crystals (kidney stones) could be reduced if oxalate excretion were reduced from the Malpighian tubule (MT) and shifted to the gut by reducing oxalate transport via inhibition of OSR1 in MTs.

Methods: Using a Drosophila model of kidney stones (Hirata, PMID 22993075), we made tissue specific knockdowns (MT or gut) of Drosophila OSR1 (CG7693, frayed). Flies were used to investigate the signaling regulation of oxalate secretion, CaOx crystallization, in MTs.

Results: Ex vivo CaOx crystallization experiments show a 34% reduction in average crystal count when OSR1 knockdown (via RNAi: 51% knockdown) flies are compared to feeding experiments with MT-specific OSR1 knockdown also reduces the crystal count recapitulating ex vivo experiments. Preliminary in vivo data for gut-specific OSR1 knockdown indicates increasing average crystal counts.

Conclusions: From this data, we conclude that regulation of oxalate transport via OSR1 signaling is sufficient to reduce average CaOx crystal count. This data also suggests that manipulation of OSR1/SPAK signaling may be a new and important target for the development of therapies for kidney stones.

Funding: NIDDK Support, Other NIH Support - R52-GM075148

FR-P0442

Development of Biomimetic Randall’s Plaque Using Decellularized Porcine Kidneys. Saeed B. Khan,1 Archana Lovett,1 Laurie Gower,2 1Pathology, Univ of Florida, Gainesville, FL; 2Materials Science and Engineering, Univ of Florida, Gainesville, FL.

Background: Idiopathic calcium oxalate stones are commonly found attached to Randall’s plaques (RP), calcium phosphate (CaP) deposits in the renal papillae. Plaques originate as concentrically laminated apatic spherules, and grow by mineralization of interstitial collagen fibrils and vesicles. We hypothesize that such distinct CaP morphologies form by non-classical crystallization mechanisms. The polymer-induced liquid–liquid phase separation (PILP) process, in which highly acidic macromolecules sequester ion clusters to induce liquid–liquid phase separation of hydrated, ion-enriched nano-droplets. PILP droplets have fluidic character and thus coalesce into mineral coatings, or infiltrate into the interior of collagen fibrils, producing mineral products which differ from the classical crystallization mechanism.

Methods: Decellularized porcine kidneys were mineralized using a 4.5 mM calcium and 2.1 mM phosphate solution (pH 7.4). The PILP process was induced by addition of 50 µg/ml of poly-Llysine or osteopontin. At specific intervals, specimens were removed, and characterized using SEM and TEM.

Results: Analysis of the tissues shows features that resemble native Randall’s plaques, such as concentrically laminated spherules and collagen fibrils with interstitial fibrillar, and with differing morphologies in the basement membrane versus interstitium. In contrast, the classical crystallization produced large apatic spherulites, which is a very different morphology, but one which is also found in some stones.

Conclusions: CaP deposition on decellularized kidney substrate appears to produce biomimetic plaque similar to the native RP with respect to calcification of collagen and production of apatic spherules. Both classical and non-classical mechanisms might be at play. We are planning to study overgrowth of biomimetic plaques with CaOx in a rat model of hyperoxaluria.

Funding: NIDDK Support

FR-P0443


Background: Randall’s plaques (RP) are an important precursor of urinary stone formation. However, RP cannot be noninvasively detected. This study investigated urinary EVs as biomarkers of RP.

Methods: RP were assessed by videoate and quantitative image processing in 47 consecutive idiopathic calculus oxalate stone formers undergoing stone removal. Cell-free urinary EVs from different nephron segments carrying protein biomarkers of renal fibrosis and injury were quantified in biobanked urine by digital flow cytometry and thiorochrome conjugated antibodies.

Results: Urine from 40 low RP (<5% papillary surface RP) and 7 high RP (≥5% surface RPC patients demonstrated that EVs from multiple nephron segments expressing MCP-1 and NGAL were significantly greater in the low RP group. Osteopontin-positive EVs did not differ.

Conclusions: Urinary EV biomarkers consistent with renal injury (NGAL) and inflammation (MCP-1) were increased in CaOx stone patients with low amounts of RP. These findings may reflect pathologic cellular events that drive stone formation in low RP patients, or perhaps protective responses that limit RP development in this group. Urinary EVs are a promising source of biomarkers for pathogenic events in USD.

Funding: NIDDK Support

FR-P0444

Contribution of Tubular Segments to a Calcium Corticopapillary Gradient. Suresh Krishna Ramakrishnan,1 Muriel Auberson,1 Candice Stoudmann,1 Olivier Bonny,2 1Dept of Pharmacology, Univ of Lausanne, Switzerland; 2Service of Nephrology, Lausanne Univ Hospital, Switzerland.

Background: Renal papillary calcification and Randall’s plaque formation are largely dependent on urinary calcium excretion. Mathematical models of renal transport predict a cortico-papillary calcium gradient in physiological conditions, but this has not been observed in vivo. We aimed at deciphering this gradient and at identifying which part of the nephron may contribute to its formation.

Methods: Small pieces representative of cortex, medulla and papilla were isolated from mouse kidneys, and calcium, phosphate and sodium content were measured, as well as regulatory parameters. In experiment 1, C57Bl/6J mouse kidneys were harvested. In experiment 2, mice were previously injected with 1 dose of furosemide (20mg/kgBW), or hydrochlorothiazide (25mg/kgBW) or vehicle. In experiment 3, mice were injected daily for 7 days with furosemide (20mg/kgBW). In experiment 4, kidneys of mice with disrupted distal calcium reabsorption (Pck-LC1-Cre NCX1°° mice) and WT controls were harvested. And in experiment 5, mice were fed daily dihydroxycholesterol (1.5mg/kg food) for 7 days.

Results: Results showed higher calcium and sodium content in the papilla of mouse kidneys compared to cortex or medulla, but lower phosphate. Acute furosemide treatment disrupted the sodium cortico-papillary gradient, but not the calcium one. Hydrochlorothiazide and removal of calcium NCX1°° had no effect on any gradient. Chronic dihydroxycholesterol treatment led to hypercalcemia and hypercalciuria, and blunted the calcium cortico-papillary gradient; sodium gradient was unchanged.

Conclusions: We conclude that the renal calcium cortico-papillary gradient exists in the mouse kidney, with higher calcium concentration in the papilla, while phosphate had a mirror gradient. Distal transepithelial calcium transport does not contribute to the calcium gradient, while thick ascending limb calcium transport may modulate it. Further studies exploring TAL and proximal tubule contribution are warranted.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Urine Proteomic Analysis Confirms a Higher Degree of Bone Disease in Medullary Sponge Kidney against Nephrolithiasis

Alessandra Dalla Gassa,1 Antonio Fabris,1 Giovanni Candiano,2 Maurizio Bruschi,2 Gianluigi Zaza,3 SimonaGranata,2 Giovanni Gambaro,2 Antonio Lupo,1 1Renal Unit, University of Verona, Italy; 2Laboratory on Pathophysiology of Uremia, Istituto G. Gaslini, Genoa, Italy; 3Div of Nephrology and Dialysis, Catholic Univ Hospital, Rome, Italy.

Background: Medullary sponge kidney (MSK) is a genetic malformative disease characterized by cystic formations of the distal ducts, hypercalciuria, nephrolithiasis and kidney stones. Metabolic bone disease is very frequent in MSK and idiopathic calcium nephrolithiasis (NL). We hypothesized that pathways involved in bone remodeling are characterized by cystic formations of the distal ducts, hypercalciuria, nephrocalcinosis and increased osteoclastogenesis.

Methods: In 11 MSK vs. 12 NL pts were studied; urine proteins (UP), 24-h urine biochemistry and bone mineral content (BMC). All pts had normal PTH and eGFR=60 ml/min/1.73m2. UP were analyzed with STRING version 10.0. UP were selected if ≥2-fold difference in spectral counts and ≥0.05 p-value.

Results: Prevalence of F was 64.5% and 67.3% in MSK and NL, respectively. Mean age±sd was 53±19 yr in MSK and 54±15 yr in NL. 24-h urine(UP) and BMC in MSK and NL, pts, mean and (SD) are shown: U.Ca(mg/d)317(107)222(107)p=0.045, U.Nat(meq/d)204.36(49)139(47)p=0.004, Z-score.(S -1.40.5)7.6(0.8)p=0.038, T-score.(S -1.650.45)1.040.67)p=0.018. MSK differed from NL pts in 328 PP. 100 UP were overexpressed in MSK, 228 downexpressed. Some UP are involved in annotated pathways:PP2C2,LA,MB2,H5P90A21.3P3AK-Akt pathway,CDH15,PTPRM in cell adhesion molecules. PI3K-Akt pathway induces osteoclastogenesis by activating PKCδ and Rac in osteoclast precursors, and osteoblast differentiation, PI3Kγ was responsible for decreased BMC in a murine model. Down regulated UP,CDH1,CDH3,CDH6,CDH11,CDH13 are involved in Ca-dependent trans-dimerization of cadherin, cadherin/catenin complex; IGF1,AP1,RA,C4,R3,GNG12 in regulation of actin. Cadherins are linked to the actin cytoskeleton via binding to catenins in adherens junctions. PI3K/AKT complex is essential for osteoblast differentiation and osteogenesis by controlling Wnt and PI3K/Akt signaling.

Conclusions: All these findings show that osteogenetic pathways are more active in MSK than in NL, confirming their role in nephrocalcinosis and in the more severe BMC observed in MSK.

FR-PO445

Cystine Capacity (CysCap) and Risk of Kidney Stone Events in Cystinuria

Frank Moderstizik,1 Lisa M. Harvey,2 Dean G. Assimos,1 David S. Goldfarb,1,3 1Medicine, NYU Langone Medical Center, New York, NY; 2Urology, Univ of Arizona, Birmingham, AL; 3Nephrology, New York Harbor FAMC, New York, NY.

Background: Cystinuria, a rare genetic disease characterized by renal stone formation, is a disorder of amino acid excretion. Stone-free, diseased kidneys, and increased urinary excretion of cystine. We examined the association of CysCap values, consistent with underusurated urine, with fewer stone events.

Methods: Patients were divided into CysCap+ and CysCap- groups based on baseline 24 hr urine. Underusurated urine takes up cystine from preformed cystine crystals, giving a positive (CysCap+) value; supersaturated urine gives up cystine to added cystine crystals, giving a negative (CysCap-) value. 49 patients from 2 Rare Kidney Stone Consortium sites were enrolled and followed prospectively. Stone activity was defined as radiologic new stone or stone growth, urolodic stone removal or spontaneous stone passage.

Results: Participants without 24 hr urine and information about stone activity were excluded. 26 participants remained; 13 male, 13 female. Mean age was 45y. A total of 17 (10F/7M) participants had a positive CysCap (mean 120 mg/L) and 9 (3F/6M) participants had a negative CysCap (mean -167 mg/L) at baseline. Table shows urine results: CysCap+ had more urine, higher pH, less cystine. Follow-up for the total group was 20 months. We identified 34 stone events that affected a total of 17 participants: fewer events were counted among those with CysCap+ values. Specific data (%) included development of a new stone: CysCap+ 29 vs. CysCap- 44; stone growth: CysCap+ 41 vs. CysCap- 22; urolodic stone removal: CysCap+ 25 vs. CysCap- 44; stone passage without intervention: CysCap+ 18 vs. CysCap- 33, 9 participants (CysCap+ 41 vs. CysCap- 22), had no events during observation period. Comparing CysCap groups for all stone events, CysCap+ was significantly better (p=0.03, McNemar test).

FR-PO446

Selective Protein Enrichment in Calcium Oxalate Stone Matrix

Jeffrey Wesson,1 Dwayne B. Romero,1 1Urology, Univ of Arizona, Birmingham, AL.

Background: Urine proteins are thought to control calcium oxalate (CaOx) stone formation, but over 1,000 proteins have been reported in stone matrix yielding little insight into their relative importance. We hypothesize that proteins critical to stone formation will be more highly expressed, thus increased abundance in stone matrix compared to their urinary abundance, so quantitative proteomic data were acquired and compared for both stone former urine and CaOx stone matrix proteins.

Methods: Urinary proteins were isolated by ultrafiltration (>10kDa membrane) from random urine samples from 25 CaOx stone forming patients. CaOx stone matrix proteins were isolated from 8 CaOx stone samples (>90% CaOx content) by dissolution in EDTA/SDS solution followed by ultrafiltration. Proteomic analyses were performed on each
sample independently at the Medical College of Wisconsin Innovation Center using label-free spectral counting mass spectrometry methods. Only proteins with 2 or more peptide matches at >85% confidence were included. Keratin and redundant proteins were removed.

**Results:** Only 5 proteins were prominently enriched in matrix, accounting for >34% of matrix protein mass, but only 3.4% of urine protein mass. Many highly abundant urinary proteins like albumin and uromodulin were present in stone matrix, but at reduced relative abundance compared to urine. Furthermore, isolectric point distribution analysis showed that the stone matrix proteome was highly enriched in both highly anionic (pI<5, like osteopontin) and highly cationic (pI>10, like histone) proteins; most of which are normally found in intracellular or nuclear compartments.

**Conclusions:** Relatively few proteins were enriched and appeared to be critically important to CaOx stone formation, while most highly abundant urine proteins found in matrix were likely included non-selectively. The presence of both highly anionic and highly cationic proteins which aggregate at low concentrations suggests that protein aggregation may trigger CaOx stone formation, while a cell injury process is implicated by the presence of many intracellular proteins. These observations present a new paradigm for CaOx stone research.

**Funding:** NIDDK Support, VA Support, Private Foundation Support

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**FR-PO451**

**Risk of Urolithiasis in Anorexia Nervosa: A Population-Based Cohort Study Using the Health Improvement Network**

Michelle Denburg,1 Mary B. Leonard,1 Thomas Jemicka,1 Neville H. Golden,2 Gregory Edward Tassign,3 Lawrence A. Copelovitch,1,2 Children’s Hospital of Philadelphia; 1Univ of Pennsylvania; 2Stanford Univ.

**Background:** Case reports and uncontrolled studies suggest urolithiasis is a complication of anorexia nervosa (AN). The objective of this large cohort study was to determine if AN is associated with a higher risk of urolithiasis.

**Methods:** We performed a population-based retrospective cohort study using The Health Improvement Network. The median calendar year for the start of the observation period was 2005. We identified 9302 females <60 years of age with AN and 92,959 randomly selected age- and practice-matched females. Multivariate Cox regression was used to estimate the hazard ratio (HR) for incident urolithiasis.

**Results:** Median age at start of observation was 29.8 years. 23 participants with AN (0.25%) developed incident urolithiasis compared to 154 unexposed participants (0.17%). Median age at start of observation was 29.8 years. 23 participants with AN (0.25%) developed incident urolithiasis compared to 154 unexposed participants (0.17%). Median age at start of observation was 29.8 years. 23 participants with AN (0.25%) developed incident urolithiasis compared to 154 unexposed participants (0.17%).

**Kaplan-Meier observed survival curves and Cox predicted curves in females <40 years of age**

For participants with AN, the median time from diagnosis of AN to incident urolithiasis was 12.4 years. The distribution of diagnosis codes for urolithiasis differed significantly between the groups (p=0.04), with a higher proportion of codes for uric acid urolithiasis in the AN (16.2%) versus unexposed group (5.0%).

**Conclusions:** Although urolithiasis is relatively uncommon in women under 40 years of age, we demonstrated a more than two-fold greater risk in those with AN. There were more uric acid based calculi than expected among patients with AN compared to females without eating disorders. We speculate that these were likely ammonium urate stones and related to laxative abuse.

**Funding:** NIDDK Support, Other NIH Support - UL1 RR24134

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**FR-PO452**

Proton Pump Inhibitors, Histamine Receptor-2 Blockers and the Risk of Incident Kidney Stones

Pietro Manuel Ferraro,1 Gary C. Curhan,2 Giovanni Gambaro,3 Eric N. Taylor,1,2 Fondazione Policlinico Univ A. Gemelli - Catholic Univ of the Sacred Heart, Rome, Italy; 1Harvard Medical School, Boston; 2Maine Medical Center, Portland.

**Background:** Proton pump inhibitors (PPI) and histamine receptor-2 (H2) blockers are commonly used drugs for the treatment of heartburn, gastroesophageal reflux and peptic ulcer. Although PPI and H2 blockers potentially affect urinary excretions of lithogenic factors such as calcium and oxalate, the association between use of these medications and kidney stone formation has never been explored.

**Methods:** 187,330 participants of the Health Professionals Follow-up Study (HPFS), Nurses’ Health Study (NHS) I and II provided data about chronic PPI use. During a cumulative follow-up of 1,903,725 person-years, there were 3,245 incident symptomatic kidney stone events. Cox proportional hazards regression models were adjusted for age, race, BMI, physical activity, smoking status, comorbidities, use of medications and intake of nutrients. Multivariable linear regression models were used to analyze cross-sectional associations between PPI and H2 blocker use and 24-h urinary excretions in a subgroup of 6,520 participants.

**Results:** After multivariable adjustment, use of PPI was associated with higher risk of incident kidney stones (HR 1.13, 95% CI 1.02, 1.24, p-value = 0.02). HRs were similar independent of duration of use and after restricting the analysis to incident PPI users and attenuated somewhat employing a 2-year time-lag analysis. Similar results were found for use of H2 blockers (HR 1.13, 95% CI 1.02, 1.24, p-value = 0.02). Use of PPI was associated with lower urinary excretion of calcium (-18 mg/24h, p-value <0.001, e.g., citrate (-48 mg/24h, p-value <0.001), and magnesium (-10 mg/24h, p-value <0.001), whereas urine pH was not significantly different.

**Conclusions:** Use of PPI and H2 blockers is associated with a small increase in risk of incident kidney stones.

**Funding:** NIDDK Support, Other NIH Support - DK094910, DK91417, CA186107, CA176726 and CA167552

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**FR-PO453**

Intake of Zinc and Other Trace Elements and the Risk of Incident Kidney Stones

Pietro Manuel Ferraro,1 Gary C. Curhan,2 Giovanni Gambaro,1 Eric N. Taylor,3 Fondazione Policlinico Univ A. Gemelli - Catholic Univ of the Sacred Heart, Rome, Italy; 1Harvard Medical School, Boston; 2Maine Medical Center, Portland.

**Background:** Recent pre-clinical [Tang J, et al. Am J Nephrol 2012] as well as pre-clinical [Chi T, et al. PLoS One 2015] studies suggest that zinc may play a role in the development of kidney stones. Other studies also hinted at the role of other trace elements such as copper and manganese [Słojewski M, et al. Adv Clin Exp Med 2012]. Longitudinal prospective studies on the risk associated with intake of zinc and other trace metals, however, have not been published.

**Methods:** We performed a prospective analysis of 193,551 participants of the Health Professionals Follow-up Study (HPFS), Nurses’ Health Study (NHS) I and II. Participants were divided into categories of total (<100, 100-199, 200-399, 400-599, 600-999, ≥1,000 IU/day) and supplemental (none, <400, 400-599, 600-999, ≥1,000 IU/day) vitamin D intake with updating over time. During a follow-up of 3,316,846 person-years, there were 6,576 incident kidney stone events. Cox proportional hazards regression models were adjusted for age, BMI, comorbidities, use of medications and intake of other nutrients.

**Results:** After multivariable adjustment, there was no statistically significant association between total intake of vitamin D and risk of incident stones in HPFS (HR for ≥1,000 vs <100 IU/day 1.08, 95% CI 0.80, 1.47, p-value for trend = 0.92) and NHS I (HR 0.99, 95% CI 0.73, 1.35, p-value for trend = 0.70), whereas there was a suggestion of higher risk in NHS II (HR 1.18, 95% CI 1.94, 1.48, p-value for trend = 0.02). Similar results were found for supplemental vitamin D intake. No interaction was found for total calcium intake.

**Conclusions:** Total vitamin D intake in typical amounts was not statistically associated with risk of kidney stone formation, though higher risk with substantially higher doses than those studied here cannot be excluded.

**Funding:** NIDDK Support, Other NIH Support - DK094910, DK91417, CA186107, CA176726 and CA167552
Results: After multivariate adjustment, there was no statistically significant association between risk of stones and intake of zinc (HR for highest compared with lowest quintile 0.94, 95% CI 0.77, 1.14, p-value for trend = 0.54), iron (HR 1.04, 95% CI 0.90, 1.20, p-value for trend = 0.48), and copper (HR 1.07, 95% CI 0.97, 1.18, p-value for trend = 0.26). Dietary manganese was associated with lower risk (HR 0.80, 95% CI 0.72, 0.90, p-value for trend < 0.001). For total manganese intake (supplemental plus dietary) the HR was 0.90 (95% CI 0.80, 1.02, p-value for trend = 0.06).

Conclusions: Intake of zinc, iron and copper is not associated with risk of kidney stone formation, whereas higher intakes of manganese may be associated with lower risk.

Funding: NIDDK Support, Other NIH Support - DK049910, DK91417, CA181607, CA167026 and CA167552

FR-PO454

Urinary Stones Associate with Arterial Stiffness and Peripheral Artery Disease: A Population-Based Study of 10,000 Chinese Participants

Xiaohong Fan,1 Sagar U. Nagwekar,2 Wenling Ye,1 Sophia Zhao,2 Jie Ma,2 Sahir Kallim,3 Jie Cui,2 Wei Zhang,1 Ravi I. Thadhani,4 Xuemeli Li.1

1Nephrology, Peking Union Medical College Hospital, Beijing, China; 2Nephrology, Massachusetts General Hospital, Boston, MA.

Background: Previous studies investigating cardiovascular health in the context of urinary stone disease (USD) have focused on coronary artery disease and stroke. The risk associated between USD and arterial stiffness and peripheral arterial disease (PAD) has not been examined in detail.

Methods: We performed a cross-sectional study of 10,547 participants in rural China. All underwent renal ultrasound examination to detect USD, brachial-ankle pulse wave velocity (baPWV) measurement to estimate arterial stiffness, and ankle-brachial index examination to detect PAD (defined as ankle-brachial index ≤ 0.9 for at least one side of body). Univariate and multivariate regression analyses were performed to investigate associations between USD and PAD.

Results: Mean age was 55.0±10.4 years and 47.2% were males. Among participants, 5.6% had USD, mean baPWV was 1551±317 cm/s, and 4.0% had PAD. Compared to subjects without USD, subjects with USD had higher baPWV (1548±316 vs 1610±326 cm/s, p<0.01) and higher prevalence of PAD (3.9 vs. 6.0%, p<0.01). The prevalence of USD was increased with higher quartiles of baPWV (Q4 vs Q1: 7.0% vs. 4.3%, p<0.001). In univariate and multivariable analyses, USD was associated with increased risk of PAD.

Association between kidney stone and peripheral artery disease

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Conclusions: USD associates with increased risk of arterial stiffness and PAD in a rural Chinese population.

Funding: Government Support - Non-U.S.

FR-PO455

Trends in the Incidence of Symptomatic Kidney Stones among the Residents of Olmsted County, MN from 1984 to 2012

Wonnwarn Kittanamontrukolai,1 Lisa E. Vaughan,2 Felicity T. Enders,3 John C. Lieske,1 Andrew D. Rule.2

1Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN.

Background: Studies have reported increased kidney stone incidence but lack of validation and granular detail regarding stone types.

Methods: Adult incident symptomatic stone formers in Olmsted County, MN from 1984 to 2012 were identified and validated by manual chart review. Available data included stone composition, body mass index (BMI), and medications associated with kidney stones (calcium, vitamin C, vitamin D and Topamax). The incidence rates of kidney stones per 100,000 person-years(100K py) were estimated based on the Olmsted County population census. Poisson regression models were used to calculate incidence rate ratios.

Results: There were 3,338 validated incident symptomatic stone formers (age 45±15 years, 60% male and 89% white). The overall incidence from 1984 to 2012 increased dramatically in women (9.45±18.100K py; p<0.001) and modestly in men (12.86±14.100K py; p<0.001). The increase in incidence was significant in women across all age groups (18-39, 40-59, 60+), with the highest increase observed in those 40-59 y. In men, the increase was significant only in the 18-39 age group. For each stone composition, the relative change in the incidence rate per 5-years was 1.00 (95% CI 0.99-1.01, p<0.001) for calcium oxalate dihydrate, 1.10 (95% CI 1.07-1.13, p<0.001) for hydroxypatite, 0.90 (95% CI 0.86-0.95, p<0.001) for uric acid and 1.15 (95% CI: 1.14-1.16; p<0.001) for stones of unknown composition. Calcium use, vitamin D use, Topamax use and BMI among incident stone formers increased over the time period, with Vitamin D use rising at a higher rate in women than in men (p<0.01 for interaction).

Conclusions: The incidence of symptomatic kidney stones increased dramatically in women, and more modestly in men over the last 3 decades. The increase was most evident in younger age groups. Obesity and medications associated with kidney stones may be contributing to the increased incidence of kidney stone disease in the general population.

Funding: NIDDK Support

FR-PO456

Risk of Adverse Birth Outcomes Associated with Maternal Hospitalization for Nephrolithiasis during Pregnancy

Rachel M. Engen,1 Kelsey L. Richardson,1 Julie Rivers,1 Eric Chow,2 Alysson J. Littman.1

1Seattle Children’s Hospital; 2Univ of Washington.

Background: Nephrolithiasis is the most common non-obstetric cause of hospitalization among pregnant women, but current information on birth outcomes after hospitalization for nephrolithiasis during pregnancy is conflicting. We sought to determine if maternal nephrolithiasis hospitalization is associated with an increased risk of premature delivery, induction of labor, Cesarean delivery, low birth weight (< 2500 grams), or delivery of a small for gestational age (SGA) infant.

Methods: We conducted a population-based retrospective cohort study in Washington State using a statewide hospitalization discharge database linked to singleton birth certificate data for 2004-2013. Women hospitalized for nephrolithiasis during pregnancy were identified by ICD-9 codes {n=2083} and compared with a cohort of women without documented hospitalization for nephrolithiasis (n=8600) frequency matched 1:4 on birth year. Birth outcomes were assessed using birth certificate data and birth hospitalization ICD-9 codes. Data were analyzed using stratified analysis with Mantel-Haenszel adjustment.

Results: Nephrolithiasis hospitalization during pregnancy was associated with an increased risk for premature delivery (RR = 1.6, 95% CI 1.3-1.8) and induction of labor (RR = 1.5, 95% CI 1.3-1.6), but a decreased risk of SGA delivery (RR = 0.82, 95% CI:0.70-0.96) compared to women without hospitalization for nephrolithiasis during pregnancy. Nephrolithiasis hospitalization was not associated with low birth weight, nor was it associated with Cesarean delivery after adjusting for prior Cesarean delivery. Trimester of nephrolithiasis hospitalization and procedural intervention did not significantly alter these associations.

Conclusions: This study adds to existing evidence that maternal hospitalization for nephrolithiasis during pregnancy is associated with an increased risk of subsequent preterm delivery and induction of labor. Women hospitalized for nephrolithiasis during pregnancy should be counseled about these risks.

Funding: NIDDK Support

Poster/Friday

Low Bone Density and Bisphosphonates and the Association with Kidney Stones and 24-Hour Urine Calcium Excretion

Megan Prochaska,1 Eric N. Taylor,2 Gary C. Curhan.1

1Renal Div, Brigham and Women’s Hospital, Boston, MA; 2Div of Nephrology and Transplantation, Maine Medical Center, Portland, ME.

Background: Previous studies have demonstrated lower bone density in patients with kidney stones (KS). No studies have evaluated KS risk in participants with low bone density. Small studies with short follow-up reported lower 24-hour urine calcium excretion in bisphosphonate users. We examined history of low bone density and bisphosphonate use and the association with incident KS and the association with 24-hour calcium excretion.

Methods: To evaluate the association between history of low bone density and bisphosphonate use and risk of incident KS, we conducted a prospective analysis of 98,078 women participants in the Nurses’ Health Study II. We used Cox proportional hazards models to adjust for age, BMI, thiazide use, bisphosphonate use, fluid intake, and dietary factors. We also conducted a cross-sectional analysis of 2567 participants using multivariate linear regression to compare 24-hour urinary calcium excretion between participants with and without a history of low bone density and with and without bisphosphonate use.

Results: The multivariate adjusted relative risk (MVR) of an incident KS for participants with history of low bone density compared with participants without was 1.35 (95% CI 1.13-1.61; p<0.001) The MVR for an incident KS for bisphosphonate use was 0.90 (95% CI 0.88-0.92, p=0.047). In the cross-sectional analysis of 24-hour urine calcium excretion, the multivariate adjusted mean difference in 24-hour calcium was 13 mg/day (95% CI 4 to 22, p=0.003) higher for participants with history of low bone density. The multivariate adjusted mean difference in 24-hour calcium was 9 mg/day (95% CI -9 to 27, p=0.47) higher for participants on bisphosphonates. Results of the urine calcium analysis were similar in an analysis limited to participants with history of low bone density.

Conclusions: History of low bone density is an independent risk factor for incident KS and higher 24-hr urine calcium excretion. Bisphosphonates use was not independently associated with KS or 24-hr urine calcium excretion.

Funding: NIDDK Support
FR-PO458

Hyponatraemia Is Associated with Increased Kidney Stones in a Large U.S. Health System Population  Nao Tohmiyama,1 Stephen Fernandez,2 Mihiye Mete,2 Nawar M. Shara,3 Joseph G. Verbalis.1 1Div of Endocrinology and Metabolism, Georgetown Univ Medical Center; 2Dept of Biostatistics and Bioinformatics, MedStar Health Research Inst.

Background: Kidney stones (KS) impose a large and growing public health burden. Up to 80% of KS is predominately composed of calcium oxalate (CaOx), and urinary oxalate is a major risk factor for CaOx KS formation. Numerous studies have shown that hyponatraemia (HN) is associated with increased risk for osteoporosis and bone fractures, which are also known to be associated with KS. It is therefore reasonable to hypothesize that HN may be related to the occurrence of KS.

Methods: To assess the potential relationship between HN and KS, we designed a matched case-control study using the electronic health records of the MedStar Health system with more than 3.2 million unique patient records accumulated as of March 2016. Data were extracted via the Experity tool on clinical factors including labs, medications, and ICD-9 and/or ICD-10 diagnoses for patients with KS (case) and those without KS (control).

Results: Cases (n=21,232) and controls (n=21,232) were matched with a 1:1 ratio on age, sex, race and the duration of encounter window (mean age 44.3 years, 48.4% female, 61.1% Caucasian and mean follow-up days 1345 days). Case and control exposures for each of the HN variables were defined by serum Na+ laboratory measurements reported within the encounter windows, and divided into 4 categories: prior HN, chronic HN, recent HN, and chronic and recent HN. Bivariate analyses using conditional logistic regression models confirmed increased risk of KS among patients with risk factors such as hypertension (OR 1.87, 95% CI 1.68-2.13), diabetes (OR 1.56, 95% CI 1.38-1.77). In addition, the risk of KS increased in all of HN categories: prior HN OR, 1.10 [95% CI, 1.03-1.18]; chronic HN OR, 1.43 [95% CI, 1.17-1.75]; recent HN OR, 2.30 [95% CI, 2.02-2.62]; chronic and recent HN OR, 5.18 [95% CI, 3.08-8.70]. Preliminary results of multivariate analyses adjusted for potential confounders confirm increased associations of both HN and chronic HN and KS.

Conclusions: These results therefore support the hypothesis that HN is a significant and clinically important risk factor for KS in both inpatients and outpatients in the U.S.

FR-PO459


Background: Over the past 2 decades, the prevalence of kidney stones in black non-Hispanics has increased by 150%, yet there is a paucity of literature regarding African American (AA) stone-formers. Small studies suggest certain urinary parameters do not significantly differ between racial groups. We asked whether AA stone formers have metabolic differences compared to Caucasians.

Methods: AA patients with known stone composition undergoing metabolic stone evaluation (at least 3, 24 hr urine specimens per patient and paired serum studies) were retrospectively identified by self-reported race from 1995-2016 and sex and age-matched 1:2 to Caucasian patients with known stone composition from the same year. Metabolic data were compared between groups by stone type and race using ANOVA. Majority stone type was defined as >50%.

Results: Fifty-five AA (calcium (Ca) oxalate (CaOx) = 29; Ca phosphate (CaP)=9; Urinary calcium (Ca) = 7; Urinary uric acid (UA) = 4; Phosphorus (P) = 8) and fifty-five Caucasian (CaOx=27; CaP=19; UA=33; P=16) had complete pre-treatment metabolic data. Despite similar supersaturation (SS) for their stone type, AA had significantly lower SS for their stone type; AA had significantly lower SS for their stone type; AA patients had significantly lower SS for UA, P and citrate than CA patients (min-max, 135 vs. 225 mg, p<0.0001). Urine oxalate levels, were significantly lower than those for CA (135 vs. 225 mg, p<0.0001). Urine oxalate and citrate did not differ by race. Serum phosphate also differed by race, and was significantly lower in AA males than in CA males (3.1 vs. 3.45, p<0.001); women did not differ.

Conclusions: While physical chemistry dictates that SS drives risk for stone formation, we demonstrate racial differences in determinants of SS. Previously unknown and significant metabolic differences exist between AA and Caucasian stone formers.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO460

Variation in Reported Oxalate Content: Implications for Research and Patient Counseling  Roy A. Jhaagor1, Kristina L. Penniston.1 1Medicine - Nephrology, UW Madison, Madison, WI.

Background: Oxaluria is a major risk factor for calcium oxalate stone disease. For designing research studies that limit or attempt to standardize the oxalate intake of subjects, and also for the appropriate counseling of patients in the clinical setting, accurate food oxalate values are needed, and agreement on the use of standard food oxalate values is needed.

Methods: Analyze patients' reported oxalate content from 4-day weighed diet records, using standard nutrient analysis software, and compare values with the "gold standard" database for food oxalate. Assess the congruence of food oxalate data of two records, using standard nutrient analysis software, and compare values with the "gold standard" database for food oxalate. Analyze the congruence of food oxalate data of two records, using standard nutrient analysis software, and compare values with the "gold standard" database for food oxalate. Assess the congruence of food oxalate values with the "gold standard" database for food oxalate. Assess the congruence of food oxalate data of two records, using standard nutrient analysis software, and compare values with the "gold standard" database for food oxalate.

Results: Up to 80% of KS is predominately composed of calcium oxalate (CaOx), and urinary oxalate is a major risk factor for CaOx KS formation. Numerous studies have shown that hyponatraemia (HN) is associated with increased risk for osteoporosis and bone fractures, which are also known to be associated with KS. It is therefore reasonable to hypothesize that HN may be related to the occurrence of KS.

Methods: To assess the potential relationship between HN and KS, we designed a matched case-control study using the electronic health records of the MedStar Health system with more than 3.2 million unique patient records accumulated as of March 2016. Data were extracted via the Experity tool on clinical factors including labs, medications, and ICD-9 and/or ICD-10 diagnoses for patients with KS (case) and those without KS (control).

Results: Cases (n=21,232) and controls (n=21,232) were matched with a 1:1 ratio on age, sex, race and the duration of encounter window (mean age 44.3 years, 48.4% female, 61.1% Caucasian and mean follow-up days 1345 days). Case and control exposures for each of the HN variables were defined by serum Na+ laboratory measurements reported within the encounter windows, and divided into 4 categories: prior HN, chronic HN, recent HN, and chronic and recent HN. Bivariate analyses using conditional logistic regression models confirmed increased risk of KS among patients with risk factors such as hypertension (OR 1.87, 95% CI 1.68-2.13), diabetes (OR 1.56, 95% CI 1.38-1.77). In addition, the risk of KS increased in all of HN categories: prior HN OR, 1.10 [95% CI, 1.03-1.18]; chronic HN OR, 1.43 [95% CI, 1.17-1.75]; recent HN OR, 2.30 [95% CI, 2.02-2.62]; chronic and recent HN OR, 5.18 [95% CI, 3.08-8.70]. Preliminary results of multivariate analyses adjusted for potential confounders confirm increased associations of both HN and chronic HN and KS.

Conclusions: These results therefore support the hypothesis that HN is a significant and clinically important risk factor for KS in both inpatients and outpatients in the U.S.
Medication

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Swiss Kidney Stone Formers

Changes of Urinary Risk Profile after Short Dietary Intervention in T2D patients and correlated with increased albuminuria and glomerular damage. miR-146a and miR-146a upregulated in the diseased glomeruli, suggesting induction of TGFb signaling. Treatment and dairy products does not seem to increase the risk for CaOx stone formation. However, rKSF. The recommendation of a low salt diet in a population with too little dietary milk occurred on the low calcium diet (0.39±0.26 vs 0.39±0.19 mmol/d, p=0.277). Calculated calcium. Urine volume remained unchanged. Notably, no increase in oxalate excretion reduction in 24-h urinary sodium and calcium excretions: from 201±89 at baseline to 128±88 low calcium diet.

Background: Calcium-containing kidney stones are frequent with high recurrence rates. Several studies have described a significant relation between nephrolithiasis and adverse renal outcomes, including ESRD. While hypercalciuria is a well-known risk factor, restricted intake of animal protein and salt, combined with normal calcium, has been shown to be more effective in stone prevention compared with a low-calcium diet. Notably, the average salt intake in Switzerland is twice as high as the WHO recommends, while surprisingly the intake of milk and dairy products is low. Thus, we wanted to test the effect of a low salt and low calcium diet on the urinary risk profile of recurrent calcium oxalate (CaOx) kidney stone formers (rKSF).

Method: Standardized metabolic evaluation was performed, including a first 24-hour urine collection (normal diet), followed by a second collection after a 7-day low salt and low calcium diet. Results: Out of 215 patients, 169 patients had calcium oxalate-containing stones. Of these 169 patients, 49 were hypercalciuric at baseline. Diet produced a highly significant reduction in 24-h urinary sodium and calcium excretions: from 201±89 at baseline to 128±88 mmol/d for sodium (p=0.0001), and from 5.67±3.01 to 4.06±2.46 mmol/d (p=0.0001) for calcium. Urine volume remained unchanged. Notably, no increase in oxalate excretion occurred on the low calcium diet (0.39±0.26 vs 0.39±0.19 mmol/d, p=0.277). Calculated Psl values were only predictive for calcium phosphate stones. Conclusion: In conclusion, diet low in calcium, as in the wider Swiss population, and here tested as a short intervention did not result in an increase in oxalate excretion in rKSF. The marked decrease in low salt diet in a population with too little dietary milk, and dairy products does not seem to increase the risk for CaOx stone formation. However, assessment and correction of low calcium intake in hypercalciuric KSF remains important.

Changes of Urinary Risk Profile after Short Dietary Intervention in Swiss Kidney Stone Formers

Harald Seeger,1 Pietro Manuel Ferraro,2 Robert J. Unwin,1 Carsten A. Wagner,3 Nilufar Mohrieebi,1 Div of Nephrology, Univ Hospital Zurich, Zurich, Switzerland; Fondazione Policlinico Univ A. Gemelli, Catholic Univ of the Sacred Heart, Rome, Italy; Centre for Nephrology, Univ College London, London, United Kingdom; Inst of Physiology, Univ of Zurich, Zurich, Switzerland.

Background: Calcium-containing kidney stones are frequent with high recurrence rates. Several studies have described a significant relation between nephrolithiasis and adverse renal outcomes, including ESRD. While hypercalciuria is a well-known risk factor, restricted intake of animal protein and salt, combined with normal calcium, has been shown to be more effective in stone prevention compared with a low-calcium diet. Notably, the average salt intake in Switzerland is twice as high as the WHO recommends, while surprisingly the intake of milk and dairy products is low. Thus, we wanted to test the effect of a low salt and low calcium diet on the urinary risk profile of recurrent calcium oxalate (CaOx) kidney stone formers (rKSF).

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Absence of mir-146A Increases Risk of Diabetic Glomerulopathy via Upregulation of ErbB4 and Notch-1 in Podocytes

Shehray J Khalidahina,1 Samia Khan,1 Ha Won Lee,1 Mehmet M. Altintas,1 Florian Gramhmer,2 Terese D. Geraghty,1 Kwi Hye Koh,1 Nicholas J. Tardi,1 David J. Cimbaluk,2 Katalin Susztak,2 Pierre-Louis Tharaux,3 Tobias B. Huber,1 Matthias Kretzler,2 Markus Bitzer,3 Jochen Reiser,1 Vincet Gupta,1 Rush Univ,1 Univ of Pennsylvania,2 Univ Medical Center Freiburg,3 INSERM,4 SGBRM.

Background: MicroRNAs play a significant role in maintaining podocyte health and in diabetic glomerular disease pathogenesis. miR-146A is a negative regulator of myeloid cells. It’s also expressed in podocytes, but its role is unclear. We examined the role of podocyte mir-146A in diabetic glomerulopathy (DGP). Method: We used qRT-PCR to determine mir-146A expression in isolated glomeruli from a cohort of patients with type 2 diabetes (T2D) and correlated it with kidney function in these patients. We also studied mir-146A target expression levels in T2D patients, BTBR+/+ mice and mir-146A deficient (mir-146-) mice. To investigate the role of mir-146A in glomerular function in vivo, we induced hyperglycemia in WT and mir-146A-/- animals using streptozotocin (STZ) and tested whether ErbB4 inhibition with Erbomith provides efficacy. Results: We show that podocyte mir-146A expression decrease in the glomeruli of T2D patients and correlated with increased albuminuria and glomerular damage: mir-146A levels were significantly reduced in the glomeruli of BTBR+/+ mice that spontaneously develop T2D. mir-146+-/- mice displayed accelerated development of glomerulosclerosis upon STZ-induced hyperglycemia. mir-146A targets, Notch-1 and ErbB4, were significantly upregulated in the diseased glomeruli, suggesting induction of TGFβ signaling. Treatment with Erbolimab significantly suppressed diabetic glomerular injury and albuminuria in WT and mir-146A-/- mice. TGFβ treatment to podocytes in vitro resulted in increased levels of Notch-1 and ErbB4, and increased phosphorylation of ErbB4 and its partner EGFR. Increased phosphorylation of ErbB4/EGFR also increased levels of Notch-1 and MCP-1 induced protein, a suppressor of miR-146A, suggesting an autocrine loop. Conclusion: We suggest a novel role for podocyte mir-146A in protecting against DGP. Also, ErbB4 is a novel therapeutic target for DGP intervention, especially since several ErbB4 inhibitors are clinically available.

Developing T2D. miR-146a

Markus Katalin

Karl Leon Skorecki.

Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: Transient Receptor Potential channel C6 (TRPC6) is a calcium-conducting ion channel expressed at the slit-diaphragm of podocytes. TRPC6 gain-of-function mutations and glomerular TRPC6 overexpression are associated with proteinuria. The underlying mechanisms that link TRPC6 to podocyte injury remain elusive. Activation of the calcium-dependent protease calpain-1 was suggested to mediate renal injury through cleavage of the podocyte cytoskeletal protein talin-1. We hypothesized that the calcium-dependent protease calpain-1 is involved in TRPC6-mediated podocyte injury. Method: Podocytes, transfected with scrambled, TRPC6 or calpain-1 siRNA, were injured using adriamycin and treated with the TRP channel activator 1-oleoyl-acetyl-sn-glycerol (OAG), calpain inhibitor calpeptin or TRPC channel blocker 2-APB. TRPC6-dependent calcium influx was measured by FURA-2. Calpain activity and talin-1 expression were determined by calpain activity assay and in situ zymography or Western blot. In vivo, calpain inhibition was tested in adriamycin induced nephropathy (AN), the model for human FSGS. Urine and kidney biopsies of human FSGS patients were tested for calpain activity and protein expression as well as talin-1, TRPC6 and nephrin expression. Results: Adriamycin and OAG increased calpain activity in podocytes, which was prevented in rTRPC6 Kd or calpain 1 KD cells, and by 2-APB or calpeptin. TRPC6 KD in podocytes showed that adriamycin-induced calcium influx was TRPC6-dependent. The TRPC6-dependent calpain activation led to talin-1 cleavage. Calpain activity in urine and glomeruli was increased in rat AN and associated with increased proteinuria, which could be prevented by calpain inhibition. Urine and glomeruli from FSGS patients also showed increased calpain activity, along with increased glomerular TRPC6 and reduced talin-1 and nephrin expression. Conclusion: We have elucidated a novel mechanism that directly links TRPC6-dependent calcium influx to calpain-1 activation, talin-1 cleavage, subsequent podocyte injury, and proteinuria in vitro, in vivo, and in humans. Therefore, calpain-1 and/or TRPC6 inhibition could be a novel therapeutic option to treat FSGS.
Annexin2A-S100A10 Complex Is the Binding Partner of PLA2R in Podocytes

Maryline Fresquet, Thomas A. Jowitt, Edward A. Mckenzie, Rachel Lennon, Paul E. Brenchley.
Wellcome Trust Centre for Cell-Matrix Research, Univ of Manchester, United Kingdom.

Background: PLA2R is the major podocyte antigen targeted by autoantibodies in membranous nephropathy (MN). We have shown that anti-PLA2R in absence of complement activation induces change in podocyte shape, monolayer permeability, free radical production and apoptosis. How anti-PLA2R induces these changes and disrupts PLA2R function is unknown. PLA2R cannot mediate intracellular signalling implying other receptors are involved. We seek to identify binding partners of PLA2R in podocytes.

Methods: The PLA2R binding partners were isolated from human podocytes by immunoprecipitation and analyzed by mass spectrometry. The interactions with the identified candidates were confirmed by surface plasmon resonance (SPR), quartz crystal microbalance with dissipation (QCM-D) and immunofluorescence.

Results: Pull down experiments identified an interaction between PLA2R and Annexin2A (Annex2). Annex2 can exist as a heterotetrameric complex (A2x) coupled with S100A10, this complex being the predominant form present at the plasma membrane. We tested the binding by SPR between PLA2R and A2x complex and found a high affinity interaction with cooperativity. We analyzed these partners individually and showed that PLA2R interacts with A2x via S100A10 with strong affinity (Kd=8x10^{-10} M). This is the first evidence that PLA2R is another receptor interacting with the A2x complex. Moreover we showed using QCM-D that A2x/PLA2R complex binds to lipids in calcium-dependent manner providing a potential mechanism for PLA2R trafficking to the cell membrane.

Conclusions: This study describes a novel PLA2R/A2x complex on the podocyte plasma membrane and identifies S100A10 as a potential mediator of PLA2R translocation to the cell surface. Blocking PLA2R expression on the cell membrane may protect the podocyte from the consequences of autoantibody attack in MN.

Funding: Private Foundation Support.

The Transcription Factor Dach1 Is Essential for Podocyte Differentiation and Function

Nicole Endlich, Felix Kliewe, Katharina Schmidt, Frantisek Kindt, Nadine Arct, Maja Lindeinmeyer, Clemens D. Cohen, Franziska Döring, Regina Maciejewski, Andreas W. Kühl, Kerstin U. Amann, Nazanin Kabgani, Marcus J. Moeller, Antje Blumenthal, Karlhans Endlich.1

1Anatomy and Cell Biology, Univ Medicine Greifswald, Germany; 2Medical Clinic and Polyclinic IV, LMU, Munich, Germany; 3Human Genetics, Univ Medicine Greifswald, Germany; 4Nephropathology, Univ Hospital Erlangen, Erlangen, Germany; 5Internal Medicine II, RWTH Aachen Univ Hospital, Aachen, Germany.

Background: Dedifferentiation and loss of podocytes are the major causes of chronic kidney disease. The locus of Dach1, a transcription factor, which is essential for cell fate, was found in genome wide association studies to be associated with glomerular filtration rate.

Methods: To investigate the role of Dach1 in transdifferentiation of parietal epithelial cells to podocytes in vitro, we transfected murine parietal epithelial cells (PECs) with a plasmid encoding for Dach1, and analyzed the cells by immunocytochemistry, qRT-PCR and Western blot. For studying the function of Dach1 in vivo, we used the zebrafish model - larval zebrafish (4 days post fertilization) that were injected with a plasmid encoding GFP-LC3. APOL1 knockdown was performed by siRNA. To study autophagy in vivo we used a transgenic GFP-LC3 zebrafish strain (Tg(CMV:EGFP::map(LC3b)). Live imaging of the expression of GFP-LC3 in the zebrafish pronephros was performed by 2-photon microscopy. APOL1 knockdown was generated by morpholino (MO) injection in zebrafish (standard and tmRNA). Knockdown efficiencies of sRNA and MO were confirmed by RT-PCR and Western blot. Human kidney sections from FSGS patients were stained with LC3 and APOL1 antibodies.

Results: APOL1 knockdown in cultured human podocytes and in zebrafish larvae increased an increase of LC3 in podocytes. Moreover, Apol1 knockdown in zebrafish larvae resulted in pericardial edema, a hallmark of kidney disease. Live imaging of zebrafish larvae (4 days post fertilization) that were injected with Vivo-MO against Apol1 showed an induction of autophagy independent of a developmental defect. Additionally, in kidney biopsies from patients suffering from FSGS, APOL1 expression was significantly decreased combined with an increase of LC3 spots in podocytes.

Conclusions: APOL1 is important for proper kidney function. Loss of APOL1 induces autophagy in podocytes as determined by an increased LC3 expression in vitro and in vivo.

Funding: Government Support - Non-U.S.

Role of Podocyte Receptor Podo-GPCR2 in Diabetic Nephropathy

Sonia Zambrano Sevilla, Patricia Rodriguez, Jaakko Patrakka. Laboratory Medicine, Karolinska Inst, Stockholm, Sverige, Sweden.

Background: Podocyte injury is associated with progressive kidney disease and correlate with diabetic kidney disease (DKD). However, molecular mechanism leading to podocyte injury in DKD is still poorly understood. By using large-scale expression profiling we have identified a novel highly podocyte-specific G-protein receptor, podo-GPCR2. Previously, this orphan GPCR has been related with the regulation of Wnt3/1,

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

Underline represents presenting author.

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fcatenin pathway in the neocortex. This pathway has been linked previously to podocyte damage in DKD. The aim of this work is to study the function of podo-GPCR2 in podocytes and its role in DKD.

Methods: In vitro, we generated a stable cell line of human podocytes over expressing podo-GPCR2. In these cells we carried out studies of gene expression of different component of the Wnt3/βcatenin pathway as well as luciferase experiments using luciferase reporter for activated fcatenin. We used zebrafish and mouse as in vivo models. In zebrafish, podo-GPCR2 was inactivated using morpholinos. In mouse podo-GPCR2 was inactivated using gene targeting. KO and control mice were challenged with LPS that is known to cause podocyte injury and proteinuria.

Results: In cultured cells, we saw that fcatenin was significantly upregulated in human podocytes overexpressing podo-GPCR2. Moreover, the gene expression of Axin3 and DKK2 (two components downstream of Wnt3 pathway) was elevated in over expressing podo-GPCR2. In addition, a luciferase reporter we could validate that fcatenin was activated in podocytes overexpressing podo-GPCR2. In zebrafish, the inactivation of podo-GPCR2 resulted in podocyte foot process effacement, glomerular basement membrane abnormalities and proteinuria – all features of human DKD. In mice, the absence of podo-GPCR2 did not affect normal development and function of the glomerulus. However, KO animals were more prone to LPS-induced podocyte damage as they developed higher albuminuria after LPS injection than control animals.

Conclusions: Podo-GPCR2 is a novel highly podocyte-specific GPCR that seems to be involved in the pathogenesis of podocyte injury through Wnt signaling pathway. Podo-GPCR2 may be a new target molecule to treat glomerular diseases.

FR-PO472

Molecular Regulation of the Antifibrotic Protein Follistatin by Caveolin-1 in Mesangial Cells: A Potential Therapeutic Target

Qi Dong, Zhendong Li, Tony Nuo Wang, Agata Gava, Pavithra Parthasarathy, Bo Gao, Jian C. Krepsinsky. Nephrology, McMaster Univ, Hamilton, ON, Canada.

Background: Glomerular fibrosis is a key pathologic feature of chronic kidney disease (CKD), with mesangial cells (MC) being a major contributor to the excess extracellular matrix production. We previously showed that caveolin-1 (cav-1) is required for MC synthesis of matrix proteins both basally and in response to several profibrotic stimuli. Here we sought to identify the molecular basis of this protection.

Methods: MC isolated from cav-1 wild-type (WT) and knock-out (KO) mice were used and studies conducted using standard molecular biology techniques.

Results: Using microarray, we identified significant upregulation of the anti-fibrotic secreted glycoprotein follistatin (FST) in cav-1 KO compared with WT MC. We confirmed that KO MC had significantly elevated FST transcript and protein levels. Cav-1 re-expression reduced FST expression and increased basal matrix production, which was similarly increased by FST downregulation with siRNA. The ability of KO MC to respond to Activin A, a TGFβ family member most potently inhibited by FST, was blunted. Activity of a FST mouse promoter (-1.4kb) reporter was higher in KO MC, indicative of higher transcription rates. To identify the promoter region regulated by cav-1, we created and tested a series of deletion constructs. Surprisingly, deletion -1236bp did not eliminate the higher promoter activity in KO cells. This region contains 2 potential binding sites for the transcription factor Sp1, shown to regulate FST promoter activity in intestinal epithelial cells. ChIP studies showed greater Sp1 binding to this region in KO MC, and higher Sp1 transcription activity in KO cells was confirmed using a luciferase reporter assay. Downregulation of Sp1 with siRNA attenuated FST promoter activity, and deletion of both Sp1 sites from this promoter in KO cells was confirmed using a luciferase reporter assay. Downregulation of Sp1 with siRNA attenuated FST promoter activity, and deletion of both Sp1 sites from this promoter in KO cells was confirmed using a luciferase experiment using reporters for activated fcatenin. We used zebrafish, mouse and mouse as in vivo models. In zebrafish, podo-GPCR2 was inactivated using morpholinos. In mouse podo-GPCR2 was inactivated using gene targeting. KO and control mice were challenged with LPS that is known to cause podocyte injury and proteinuria.

Results: In cultured cells, we saw that fcatenin was significantly upregulated in human podocytes overexpressing podo-GPCR2. Moreover, the gene expression of Axin3 and DKK2 (two components downstream of Wnt3 pathway) was elevated in over expressing podo-GPCR2. In addition, a luciferase reporter we could validate that fcatenin was activated in podocytes overexpressing podo-GPCR2. In zebrafish, the inactivation of podo-GPCR2 resulted in podocyte foot process effacement, glomerular basement membrane abnormalities and proteinuria – all features of human DKD. In mice, the absence of podo-GPCR2 did not affect normal development and function of the glomerulus. However, KO animals were more prone to LPS-induced podocyte damage as they developed higher albuminuria after LPS injection than control animals.

Conclusions: Podo-GPCR2 is a novel highly podocyte-specific GPCR that seems to be involved in the pathogenesis of podocyte injury through Wnt signaling pathway. Podo-GPCR2 may be a new target molecule to treat glomerular diseases.

FR-PO474

APOL1 Confers Cytotoxicity through Alteration of Vesicle pH, Leading to Altered Membrane Homeostasis

Jurgen Heymann,1 Patrick D. Dummer,1 Michael Kruhla,2 Alison B. Hickman,3 Cheryl Ann Winkler,2 Jeffrey B. Kopp,4 1NIH-NIDDK, 2NIH-NCI.

Background: APOL1 protein L (APOL1) C-terminal mutations are risk alleles for glomerular disease in African descent populations. We studied three potential cytotoxicity mechanisms.

Methods: Experiments used HEK293 kidney cells, stably expressing APOL1 common allele G0 and risk alleles G1 and G2.

Results: APOL1 variants displayed different levels of cytotoxicity (G0>G2>G1). We examined whether APOL1 acts as a BH3-only pro-death protein based on the presence of a predicted BH3 domain. We found that the APOL1-BH3 domain is translocated into the endoplasmic reticulum (ER) lumen and, as Bcl2 is cytosolic, there was no APOL1-Bcl2 interaction. We examined APOL1 interactions with vesicle-associated membrane protein (VAMP) family members as candidate for the final orthology of the trypanosomal protein SRA, which binds the APOL1 C terminus and inhibits APOL1 lytic properties. Although APOL1 trafficked to VAMP6(+) late endo-lysosomes, the predicted interaction between the two proteins is unlikely, as we show that the APOL1 C terminus has a luminal orientation, whereas the relevant, N-terminal VAMP6 domain faces the cytoplasm. Cytosplasmically-expressed APOL1 also showed co-localization with VAMP6(+) late endo-lysosomes. Deletion of the APOL1 membrane-addressing domain abolished trafficking to GFP-VAMP6(+) membranes. Together, these findings suggest that APOL1 trafficking relies on lipid interactions rather than on protein interactions. In lipid binding experiments, APOL1 preferentially bound to acidic phospholipids. APOL1 resisted extraction from microsomal membranes by alkaline sodium carbonate, which indicates strong protein-lipid interactions. However, we found that APOL1 does not span the ER membrane, and is unlikely to form pores/channels there. Dextran uptake experiments showed that APOL1 expression increased mean vesicle pH (G0>G2>G1), which would compromise vesicle trafficking. These data suggest that APOL1 toxicity is only acquired later in biogenesis, through membrane insertion.

Conclusions: These data suggest that APOL1 targets cell membranes by lipid binding and that risk alleles compromise vesicle acidification, leading to a general defect in vesicle trafficking.

FR-PO475

Silibinin Improves Mitochondrial Function of Podocytes in Diabetic Mice through Regulation of Sirtuin 3 Expression

Zhengyun Ye, Meijun Si, Wenbo Zhao, Ming Li, Cheng Wang, Tan-Qiu Lou. Dept of Nephrology, The Third Affiliated Hospital Sun Yat-sen Univ, Guangzhou, China.

Background: Mitochondrial dysfunction of podocytes plays essential role in diabetic nephropathy. Our previous study showed that expression of Sirtuin 3 (Sirt3) was decreased in diabetic db/db mice, which lead to reducing mitochondrial complex I activity in podocytes. This study is to investigate the potential protective effect of silibinin and its underlying mechanisms in improving mitochondrial function of podocytes in diabetic mice.

Methods: Diabetic (db/db) and non-diabetic (db/+m) mice were administrated with silibinin for 16 weeks after 8-week old. Moreover, diabetes was induced in Sirt3-knockout mice by Streptozotocin (STZ) injection, and silibinin was administrated to these mice for 16 weeks after the induction of diabetes. To assess the expression of Sirt3 and mitochondrial complex I activity, mitochondria were isolated from podocytes of diabetic and non-diabetic mice. The expression of Sirt3 was measured by western blotting. Mitochondrial complex I activity was detected by microplate assay kit purchased from Abcam.

Results: We found that silibinin can increase the expression of Sirt3 in podocytes of db/db mice and STZ induced diabetic mice. Administration of silibinin can also ameliorate the mitochondrial function of podocytes in diabetic mice, but had no effect in Sirt3−/− mice. In vitro studies, we also find that silibinin can ameliorate high glucose-induced dysfunction of mitochondria in podocytes by increasing Sirt3 expression, including the increased activity of mitochondrial complex I and the level of mitochondrial DNA.

Conclusions: Collectively, these data suggest that silibinin improves mitochondrial function of podocytes in diabetic mice through regulation of Sirt3 expression. Thus, enhancing Sirt3 by silibinin to improve mitochondrial function in podocytes has potential as a strategy for improving outcomes of renal injury in diabetes.

Funding: Government Support - Non-U.S.
Expression of Thrombomodulin Type I Domain-Containing 7A (THSD7A) in Developing Glomeruli

Young-Soo Song, Hong Ma, Sudhir Kumar, Weinig Lu, David J. Salant, Laurence H. Beck. Renal Div, Dept of Medicine, Boston Univ Med Center, Boston, MA.

Background: Membranous nephropathy (MN) is a common cause of adult nephrotic syndrome. Autoantibodies to the podocyte proteins PLAR2 and THSD7A are found in primary MN in approximately 75% and 5% of cases, respectively. Unlike PLAR2 which is not expressed by the mouse, THSD7A is expressed on the basal surface of both human and mouse podocytes. The role of THSD7A is unclear, but the protein has been found in focal adhesions in human umbilical vein endothelial cells. We sought to investigate the temporal expression of THSD7A in developing mouse glomeruli to help better understand the role of THSD7A.

Methods: We localized THSD7A by confocal immunofluorescence microscopy in developing mouse kidney (E14.5, E17.5, and P1) using serum from a patient with primary MN known to be anti-THSD7A positive. Specificity of the serum for THSD7A was demonstrated using blocking fragments of recombinant human THSD7A. The different stages of glomerular development (cap mesenchyme, C-shaped body, s-shaped body and capillary loop) were identified using differential interference contrast microscopy as well as commercial antibodies to S1X2 (cap mesenchyme), laminin (C- and S-shaped body) and nephrin (capillary loop).

Results: Human anti-THSD7A autoantibody did not detect THSD7A in S1X2-positive cap mesenchyme at E14.5 or in laminin-positive C- and S-shaped bodies at E17.5. However, there was very prominent linear staining of THSD7A along the basal surface of podocytes of the developing glomeruli at E17.5 and nephrin partially colocalized. The specificity of THSD7A staining was shown by the complete inhibition of the glomerular signal after preincubation with the recombinant N-terminal fragment of THSD7A.

Conclusions: THSD7A appears to be first expressed by the podocyte at the capillary loop stage of mouse glomerular development. Further studies are needed to investigate its potential role at the basal surface of the podocyte.

Funding: NIDDK Support

Can Extracellular Vesicles Regulate Glomerular VEGF Homeostasis in Chronic Kidney Disease?

Sargis Sedrakyan1, Stefano Porta, Valentina Villani, Nikita Triiparaneni, Astig Petrosyan, Stefano Da Sacco, Hasmik Soloyan, Roger E. De Filippo, Benedetta Bussolati, Laura Perin.1 Urology, Children’s Hospital Los Angeles, Los Angeles, CA; 2Molecular Biotechnology, Univ of Turin, Turin, Italy.

Background: Tight regulation of paracrine VEGF signaling between podocytes and glomerular endothelial cells (GEC) is required for maintenance of the glomerular filtration barrier (GFB) structure and function. Disruption of VEGF homeostasis has been implicated in various types of glomerular diseases. However, clinical therapies neither specifically target the glomerulus nor the VEGF pathway but in addition present multiple side effects. Therefore, identification of new approaches aimed at restoring local VEGF remains a potential therapeutic target to treat glomerular disease. We previously showed that astin fluid stem cells (ASCs) are renoprotective in Alport Syndrome (AS), a model of CKD. They home within the diseased glomeruli and secrete extracellular vesicles (EVs). EVs play a role in stem cell differentiations, including the podocyte. Herein, we demonstrate that ASCF derived EVs regulate VEGF/VEGFRs signaling balance in AS GEC via modulation of sFlt1, the soluble isoform of VEGFR1.

Methods: We measured VEGF expression in AS glomeruli by WB. We assessed VEGF/VEGFR activity in GEC, including the sFlt1. We characterized ASC EVs cargo by FACS and by miRNA arrays and evaluated their potential to affect VEGF biology in GEC.

Results: Glomeruli from AS mice showed increased VEGF activity through increased phosphorylation of VEGFR-2 early on during progression accompanied by modulation of sFlt1. These observations were associated with GEC damage that showed altered VEGFR signaling. Importantly, EVs presented with VEGFRs and angiomodulatory microRNA. These EVs successfully integrated within GEC and modulated VEGF activity. EVs' lacking both the full and soluble VEGF-1 failed to rescue GEC from VEGF inflicted damage.

Conclusions: In conclusion, we demonstrated for the first time the aberration of VEGF signaling within AS glomeruli. We further showed that ASCF derived EVs play important role in maintaining glomerular homeostasis of VEGF signaling, presenting a potential for a new targeted therapies in CKD.

Funding: Private Foundation Support

Urotensin II Contributes to Hyperproliferation and Extracellular Matrix Accumulation in High Glucose-Challenged Glomerular Mesangial Cells

Adelbove Adebiyi, Hitesh Soni. Physiology, Univ of Tennessee Health Science Center, Memphis, TN.

Background: Glomerular mesangial cell (GMC) hyperproliferation and matrix expansion are pathological hallmarks of many kidney diseases, including diabetic nephropathy (DN). Although the circulating level of urotensin II (UII) and kidney tissue expression of UII and UII receptors are elevated in DN, it remains unclear whether UII regulates mesangial cell growth and matrix accumulation.

Methods: Using a murine GMC line, we examined the role of UII-induced Ca2+ signaling in the mechanisms that regulate mesangial proliferation and matrix accumulation under normal and high glucose ambiance.

Results: UII promoted GMC growth and matrix production; effects dependent on TRPC4 channel-mediated store-operated Ca2+ entry (SOCE) and sequential activation of Ca2+-dependent mitogen-activated protein kinase II (CaMkkII) and Ca2+/calmodulin-dependent protein (CREB) transcription factor. Exposure of GMCs to high glucose (HG) concentration stimulated UII synthesis, proliferation, and type IV collagen (cV) production in the cells. HG-induced GMC hyperproliferation and cV synthesis were attenuated by pretreatment with recombinant II receptor antagonist, ML204, a TRPC4 channel blocker, BAPTA an intracellular Ca2+ chelator, KN-93, a CAMKKII inhibitor, and SGC-CBP30, an inhibitor of the transcriptional co-activators CREB binding protein with p300.

Conclusions: UII-induced SOCE via TRPC4 channels stimulates CaMkkII/CREB-dependent GMC proliferation and matrix accumulation. Our data also suggest that increased UII synthesis contributes to HG-induced GMC hyperproliferation and matrix production. Conceivably, UII-induced Ca2+ signaling is involved in the pathophysiological mechanisms of mesangial matrix expansion in DN.

Funding: NIDDK Support

Intermediate Filament Protein Nestin to Wilm’s Tumor Suppressor WT1 mRNA Ratio in Urinary Viable Podocyte Correlated with Proteinuria

Moon Young Choi,1 Mirae Lee,2 Taejeon Kim,3 Seung Kyu Kim,4 Soo Hyun Choi,5 Young Cheon Park.1 1Dept of Internal Medicine, Gangnam Severance Hospital, Yonsei Univ College of Medicine, Seoul, Korea; 2Dept of Pathology, Yonsei Univ College of Medicine, Seoul, Korea; 3Dept of Internal Medicine, Yong-In Severance Hospital, Gyeong-do, Korea.

Background: Measurement of mRNA of podocyte proteins in urine sediment has been suggested as a useful tool monitoring glomerular disease activity. Nestin, an intermediate filament protein has been reported to play an important role in maintaining normal podocyte function in the human kidney. Furthermore, nestin is expressed at different stages of kidney development and regulated by the Wilm’s tumor suppressor WT1. We performed this study to investigate whether the nestin-to-WT1 mRNA ratio in the urine-excreted viable podocytes could mirror disease activity and be a useful biomarker in proteinuric glomerular disease.

Methods: We used fresh urine from patients with nephrotic range proteinuria was collected and urine sediments were cultured for viable podocytes. Viable cells derived from urine cultures were stained for podocyte-specific markers such as podocalyxin and WT-1. The number of cells and the duration at the time of subculture were measured. The total urine protein and albumin mRNA ratio was purified and real-time PCR was performed.

Results: Viable and proliferating podocytes were derived from fresh voided urine. More than 70-80% of viable cells positively stained for podocalyxin and WT-1. The number of podocytes recovered at the first subculture was not associated with degree of proteinuria. The urine podocyte WT-1 mRNA expression showed significant negative correlation with proteinuria (r=−0.622, p=0.018), while nestin mRNA expression was not significantly correlated. Moreover, nestin-to-WT-1 mRNA ratio expression showed a significant correlation with proteinuria (r=0.676, p=0.011).

Conclusions: Our results demonstrate correlation of mRNA ratio of the viable podocytes derived from fresh voided urine could be a useful biomarker to predict degree of proteinuria in glomerular disease.

Reduced ABCA1 and SOAT1 Are Required to Cause Podocyte Injury in Diabetic Kidney Disease

Gloria Michelle Ducasta,1 Christopher E. Pedro,1 Mayrin Correa,2 Tahreem Hashmi,1 Ali Mitrofanova,1 Alexis J. Sloan,1 Armando Mendez,3 Robert G. Nelson,4 George William Burke,4 Sandra M. Merscher,2 Alessia Fornoni,1 Katz Family Center/Div of Nephrology, Univ of Miami, Miami, FL; 1NIDDK, Phoenix, AZ; 2Diabetes Research Inst, Univ of Miami, Miami, FL; 3Surgery, Univ of Miami, Miami, FL.

Background: Decreased podocyte number and glomerular cholesterol accumulation are associated with albuminuria in diabetic kidney disease (DKD). The contribution of cholesterol to podocyte injury remains unknown. We hypothesize that both decreased ATP Binding Cassette A1 (ABCA1) expression and sterol acyltransferase 1 (SOAT1) activity are required to cause free cholesterol mediated podocyte apoptosis.

Methods: Patients enrolled in the Pima Indian cohort were enrolled into Majors and non-progressors (dGFR=97±9.8±2.8±15 and +40±2.6±8.6±16, respectively) based on change in the glomerular filtration rate (dGFR) between enrollment and last examination (10±1.7 years). Human podocytes were treated with patient sera. ABCA1 expression, cholesterol efflux and SOAT1 activity were measured. SiRNA ABCA1 podocytes (siABCA1) and SOAT1 podocytes (siSOAT1) were analyzed for cholesterol content, efflux and caspase 3 activity in the presence or absence of a SOAT inhibitor (SI) and/or cyclohexolin (CD), a cholesterol sequestering agent. Podocyte specific ABCA1 knockout mice were developed.

Results: Progressor-sera treated podocytes showed reduced ABCA1 expression (p<0.05) and ABCA1 mediated cholesterol efflux was reduced (p<0.001) and SOAT1 activity (p=0.05). SiABCA1 treated podocytes showed increased cholesterol efflux and caspase 3 activity in the presence or absence of SOAT inhibitor (SI) and/or cyclohexolin (CD), a cholesterol sequestering agent. Podocyte specific ABCA1 knockout mice were developed.

Conclusions: Our data indicate that reduced ABCA1 expression and SOAT1 activity are required to cause podocyte injury. Podocytes with reduced ABCA1 expression and SOAT1
activity experience free-cholesterol mediated podocyte apoptosis, which is prevented by CD suggesting that strategies to restore ABCA1 and SOAT1 function may be beneficial to inhibit podocyte loss in DKD.

Funding: NIDDK Support, Private Foundation Support

**FR-PO481**

**Glucocorticoids and Mifepristone Provide Beneficial Effects against Nephrotic Syndrome via Similar and Different Glomerular Expression**

Shira Agra J, 1 Melinda A. Chanley, 1 Tetsuya Kitao, 1 James Fitch, 2 Peter White, 3 William E. Smoyer. 1, 12

**CTC, The Research Inst at Nationwide Children’s Hospital, Columbus, OH; 2CMP, The Research Inst at Nationwide Children’s Hospital, Columbus, OH; 3Pediatrics, The Ohio State Univ, Columbus, OH.**

**Background:** Glucocorticoids (GCs) are the primary therapy for nephrotic syndrome (NS), although GCs have serious side effects and are ineffective in 20-50% of patients. We previously reported the role of the GC receptor (GR) antagonist/partial agonists mifepristone (Mif) in modulating the GR pathway in podocytes. We hypothesized that Mif could also provide reduction in proteinuria seen with GCs during NS via similar and/or different pathways.

**Methods:** Proteinuria was induced in Wistar rats by single PAN injections (50 mg/kg). Treatment groups received PAN+Mif (2.5-15 mg/kg) and PAN+high-dose GCs (15 mg/kg). Analyses included proteinuria and glomerular gene expression by RNA-Seq. 11 days after PAN injection. Alignment was performed to the rat reference assembly from NCBI and differentially expressed features calculated using DESeq2.

**Results:** PAN induced severe proteinuria, which was significantly reduced by high-dose GCs as well as low-dose Mif. PCA plots segregated the PAN-injured glomeruli from control group along the 1st principal component. The global expression pattern shifted robustly towards the control in PAN/GC group, but only slightly in PAN/Mif group. Moreover, while 673 genes were significantly differently expressed (fold change > 2) in PAN-injured glomeruli compared to control, and 476 in PAN+GCs compared to PAN. Furthermore, 627 genes were differentially expressed between GC and Mif treatment groups. Specifically, genes that were highly differently expressed upon PAN injury, and either restored by both GCs and Mif or by GCs alone, have also been identified.

**Conclusions:** GR antagonists/partial agonists such as Mif may provide the same beneficial effects against NS as GCs, although via similar and/or different pathways. This may be helpful as new treatment option if they can circumvent the side effects associated with the use of GCs.

Funding: NIDDK Support, Private Foundation Support

**FR-PO482**

**The Role of Growth Hormone Action in the Glomerulus: Studies of the Podocyte-Specific Growth Hormone Receptor Gene-Disrupted Mouse**

Peter Köhler, 1 Daniel B. White, 2 Markus R. Blüthner, 1 Martin Brittain, 3 Felix J. Brittain, 1 L. Chanley, 1 Ram Menon, 2 John Kopchick. 1

1Dept of Biology, Ohio Univ, Athens, OH; 2Dept of Pediatric Endocrinology, Univ of Michigan, Ann Arbor, MI.

**Background:** Growth hormone (GH) has been implicated in the development of kidney disease in animal and human models of both type 1 diabetes (T1DM) and acromegaly. Even if increased glomerular size and sclerosis in these conditions suggest that excess GH action exacerbates glomerular damage. The podocyte is a crucial cell in the glomerular filtration barrier and is dysfunctional in many models of nephropathy. This cell is also a target of direct GH action. To explore the mechanisms by which GH impacts the glomerulus, we have developed a transgenic mouse model, the podocyte-specific GH receptor gene-disrupted mouse (podGHR-/-).

**Methods:** PodGHR-/- mice were generated on a C57BL/6 background using Cre-Lox transgenic methods. At various time points, urine and blood were collected from these mice and age-matched controls, and numerous measurements were taken, including body composition and tail-cuff blood pressure. Animals were sacrificed at 16, 18 and 30 weeks for histological studies. Supplementary cell culture studies were performed using the MPC-5 immortalized podocyte line exposed to exogenous GH.

**Results:** PodGHR-/- mice display significant variation in markers of fluid balance, including changes in urinary electrolyte concentration, tail-cuff blood pressure and total body fluid composition. These mice also show differences in the urinary albumin-to-creatinine ratio. Some of these differences are sex-specific and age-dependent. In vitro studies show that GH action directly increases collagen production from the podocyte.

**Conclusions:** Our results suggest a novel mechanism for GH action in the podocyte as a determinant of total body fluid balance, possibly through alteration of matrix proteins in the glomerular basement membrane.

Funding: NIDDK Support, Private Foundation Support

**FR-PO483**

**Quantitative Deep Mapping of Podocytes Identifies Proteostatic Shifts during Differentiation**

Markus M. Rinschen, Christina Barbara Schroeter, Sybille Köhler, Martin Kain, Thomas Benzing, Paul T. Brinkkötter. Internal Medicine, Univ Hospital Cologne, Cologne, Germany.

**Background:** The renal filtration barrier is maintained by the renal podocyte, an epithelial postmitotic cell. Immortalized mouse podocyte cell lines – both in the differentiated and undifferentiated (37 °C vs. 15 °C) state – are widely utilized tools to evaluate podocyte injury and cytoskeletal rearrangement processes in vitro.

**Methods:** We performed deep proteomic mapping of podocyte proteins from 50 µg of primary. The method consists of protein solubilization, tryptic digestion, strong-cation exchange fractionation and analysis of peptides by nLC-MS/MS on a quadrupole-orbitrap mass spectrometer.

**Results:** We mapped the cultured podocyte proteome at a depth of more than 8800 proteins, quantifying 73% of the proteome. We identified many proteins of hereditary nephrotic syndrome or focal segmental glomerulosclerosis (FSGS) were assessed. We found that cultured podocytes express abundant copy numbers of endogenous receptors such as tyrosine kinase membrane receptors, the ANP receptor, and several poorly characterized GPCRs. The dataset was correlated with deep mutational mRNA sequencing (“mRNAseq”) data from the native mouse podocyte, the native mouse podocyte proteome and staining intensities from the human protein atlas. The generated dataset was similar to these previously published datasets, but several native and high-abundance podocyte-specific proteins were not identified in the dataset. Notably, these data detected perturbations in proteostatic mechanisms as a dominant alteration during podocyte differentiation, with high proteasome activity in the undifferentiated state and markedly increased expression of lysosomal proteins in the differentiated state. Phosphoproteomic analysis at a resolution of more than 3000 sites suggested a preference of phosphorylation of actin-filament associated proteins in the differentiated state.

**Conclusions:** The dataset obtained here provides a resource and provides the means for deep mapping of the native podocyte proteome and phosphoproteome in a similar fashion. This comprehensive resource of podocytes affects cell cycle, proteostatic mechanism and phosphorylation of the cytoskeleton.

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

**FR-PO484**

**Human Mesangial Enriched Transcription in Health and Glomerular Disease**

Wenjun Ju, 1 Julie Williams, 2 Lisbeth N. Fink, 2 Anna Reznichenko, 2 Tao Wei, 2 James P. Conway, 2 Felix H. Eichinger, 2 Maria Chiara Magnone, 2 Kevin L. Duffin, 2 Daniel B. Timmernann, 2 Matthew D. Brever, 2 Carol Patricia Moreno Quin, 2 Tomo Mk, 2 Matisa Kretzler, 2 1Univ of Michigan; 2Novo Nordisk; 3Eli Lilly and Co; 4AstraZeneca; 5MedImmune.

**Background:** Mesangial cells are critical players in the initiation and progression of glomerular disease and are an attractive therapeutic target. However, we lack knowledge of specific mesangial cell function. To address this challenge we aimed to identify mesangial cell lineage-enriched transcripts using in silico nano dissection (ND), a genome-scale machine learning-based approach. ND leverages high-throughput transcriptomics data from human microdissected kidney biopsy homogenates, for definition of cell type specific mRNA profiles.

**Methods:** Lists of mesangial- and non-mesangial-specific genes were curated by 5 experts through literature mining and used as positive- and negative-standard-gene inputs for the prediction. Novel human mesangial cell-enriched transcripts were predicted using ND. The prediction efficiency was evaluated by AUC and density plot. Genes with a probability score above 0.8 were validated using independent public resources including HPA, GUDMAP, and PUBMED. Mesangial cell-enriched transcript levels were tested for differential regulation in glomerular disease and association with GFR.

**Results:** 84 genes were predicted with high probability to be novel human mesangial cell-enriched transcripts. GAS2, FLH2, AEBP1, POSTN, THBS2, GUCY1A36, and AGTR1 were genes with confirmed mesangial-enriched expression by at least one independent resource. The expression of the 84 mesangial gene signature showed significant upregulation in mesangial-proliferative glomerular diseases and in aggregate showed a strong correlation with eGFR.

**Conclusions:** We identified human mesangial cell-enriched transcripts and reported the association of their expression with impaired kidney function in CKD. Our work can provide starting points to capture the function of this cell lineage in glomerular disease and support the development of new treatment options.

Funding: Pharmaceutical Company Support - AstraZeneca PLC, Eli Lilly and Company, MedImmune LLC, Novo Nordisk

**FR-PO485**

**M1 Macrophage-Induced Loss of KLF15 Promotes Chronic Podocyte Injury**

Seung Sook Han, 1, 2 Yong Chul Kim, 1, 2 Sunhwa Lee, 1, 2 Haejong Lee, 1, 2 Ran-Hui Cha, 1 Jung Pyo Lee, 1, 2 Dong Ki Kim, 1, 2 Yon Su Kim, 1, 2 Seung Hee Yang, 1 1Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; 2Kidney Research Inst, Seoul, Korea.

**Background:** Krüppel-like factor 15 (KLF15), kidney-enriched transcription factor, is known to participate in the differentiation of podocyte. However, the clinical implication of KLF15 in chronic podocyte injury remains uncorroborated particularly in the relationship with the phenotypic influence of macrophage.

**Methods:** 5/6 nephrectomized and C57-LK mouse receptor type 5 (CCR5) -/- mouse models were used to determine chronic podocyte injury and explore exclusive role of M1 macrophage in terms of KLF15 expression, respectively. Concurrently, primary podocytes were flow-cytometrically isolated and cultured to emulate the injury process in the in vitro system. Biopsied kidney tissues were obtained from the patients with diabetic nephropathy (n=21) to elucidate the relationship between glomerular KLF15 expression and subsequent outcomes (i.e., doubling creatinine and detected perturbations).

**Results:** When 5/6 nephrectomy was predisposed to progressive kidney damage, the fibrosis markers (e.g., fibronectin and collagen type I) increased, but the KLF15 expressions decreased in the site of podocytes. Shrinking KLF15 was strengthened by the forced switch of the contribution to M1 subset. Moreover, the KLF15 loss for CCR5 and subsequent Th1 milieu, which resulted in more intense fibrosis [Figure 1]. We also observed corresponding trend.

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

Underline represents presenting author.
in human primary podocytes, such as increase in fibrosis markers and decrease in KL15 protein (RKT. We demonstrate that Plg treatment of POD upregulates NADPH oxidase isoforms (Atg7). Autophagic activity and localization of autophagosome in MPCs were examined by western blot and immunofluorescence. To assess cell motility, we performed scrape (Atg7). Autophagic activity and localization of autophagosome in MPCs were examined by western blot and immunofluorescence. To assess cell motility, we performed scrape

FR-PO486

Both HIV and Interferon (IFN)-gamma Induce APOL1 Expression in Parietal Epithelial Cells through Down Regulation of miR193a Xi'an Lan, Nirupama Chandel, Vinod Sharma, Manoj K. Tembre, Abheepsa Mishra, Vinita Vishnoi, Ashwani Malhotra, Catherine Meyer-Schwesinger, Karl Leon Skorecki, Pravin C. Singhali. 1Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; 2Medicine, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany; 3Medicine, Rambam Health Care Campus, Haifa, Israel.

Results: IFN-γ down regulated miR-193a and PAX2 but up regulated WT1 in PECs. AB-071 inhibited the expression of miR-193a in a dose dependent manner. AB-071 also down regulated miR-193a and PAX2. AB-071 up regulated WT1 in PECs.

Conclusions: The small molecule AB-071 could be beneficial to treat nephrotic syndromes.

Prevention of the decline in autophagy flux observed in podocytes pharmacologically might together, our data suggest that autophagy may regulate turnover of β1 integrin in MPCs. Filamentous actin (F-actin) in MPCs was observed by phalloidin staining. By flow cytometry and immunofluorescence. To examine signal transduction for motility, we performed scrape (Atg7). Autophagic activity and localization of autophagosome in MPCs were examined by western blot and immunofluorescence. To assess cell motility, we performed scrape

FR-PO487

A Role of Autophagy in Regulation of Podocyte Motility Ryusuke Yotsuda, Kumiko Torisu, Kazuhiko Tsuura, Takamani Kitazono. 1Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka City, Fukuoka, Japan; 2Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka City, Fukuoka, Japan.

Background: Podocyte-specific deletion of autophagy-related gene results in podocyte injury. The role of autophagy in podocyte motility is still unclear. We hypothesized that autophagy regulates podocyte motility.

Methods: We utilized human podocytes in culture and

Conclusions: Autophagy-inhibited MPCs were hypermotile in our assay. In autophagy-inhibited MPCs, β1 integrin was expressed less on cell surface, whereas accumulated in cytoplasm. Cytoplasm accumulation of β1 integrin and autophagosomes. Taken together, our data suggest that autophagy may regulate turnover of β1 integrin in MPCs. Prevention of the decline in autophagy flux observed in podocytes pharmacologically might be beneficial to treat nephrotic syndromes.

FR-PO488

Exogenous Laminin as a Treatment for Pierson Syndrome Mei-Hua Lin, Jeffrey H. Miner. Div of Nephrology, Dept of Internal Medicine, Washington Univ School of Medicine, St. Louis, MO.

Background: Pierson syndrome is a congenital nephrotic disorder that targets the glomerular basement membrane (GBM), an important part of the glomerular filtration barrier. We tested the efficacy of exogenous human laminin α5β2 in preclinical nephrotic range proteinuria in a Pierson syndrome mouse model with a null mutation in laminin j2 (Lamb2).

Methods: Lamβ2−/− mice were infused i.v. with hLAM-521 daily from P12 to P16 by retro-orbital injection. Mice were monitored for proteinuria by urinary albumin to creatinine ratio (mg/mg). hLAM-521 was infused at 100 μg/mouse/day. Proteinuria and immune response by immunofluorescence and histology.

Results: Injected hLAM-521 deposited into all GBM segments of Lamβ2−/− mice and remained there for at least 2 weeks. hLAM-521 treatment inhibited progression of proteinuria through P18 in mutants with low proteinuria prior to treatment. In contrast, all untreated mutant mice showed moderate or high proteinuria at P18. The inhibitory effect of hLAM-521 treatment on proteinuria was accompanied by reduced injury to podocytes as judged by lack of desmin, a podocyte injury marker. The ectopic deposition of laminin αl observed in the GBM of Lamβ2−/− mice was also reduced compared to untreated mutants. While hLAM-521 treatment was able to remedy the proteinuria of Lamβ2−/− mice until P18, it did not inhibit progression to nephrotic range proteinuria at P25. Injection of hLAM-521 induced production of circulating antibodies against hLAM-521 and accumulation of immunoglobulins in the GBM, which likely counteracted the efficacy of hLAM-521 treatment after P18. The inability of hLAM-521 to maintain glomerular permselectivity was not associated with immune cell infiltration in glomeruli.

Conclusions: hLAM-521 treatment inhibited progression of proteinuria in Lamβ2−/− mice with low proteinuria until the immune response caused damage to glomeruli. Future studies will include co-injection of an immunosuppressant and the use of immunodeficient Lamβ2−/− mice. Despite the immune response, this study demonstrates the feasibility of repairing GBM defects using exogenous delivery of macromolecules.

Funding: NIDDK Support

FR-PO489

Podocyte Injury: Role of Proteinuria, Urinary Plasminogen and Oxidative Stress as “Second Hit” in Glomerular Injury Leonoldo Raji, Runxia Tian, Jenny Wong, John C. He, Kirk N. Campbell. Nephrology, FAMC, Univ of Miami & SFVA, Miami, FL; Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Podocytes (POD) are a key target of injury in proteinuric glomerulonephritis (GN) that result from increased podocyte loss, FSGS and renal failure. In animal and human nephrotic urinary aberant Glom filtration of Plasminogen (Pig) is activated to biologically active Plasin by urokinase type plasminogen activator (uPA). In vivo, Amlidore a specific inhibitor of uPA mitigates FSGS in several proteinuric models including 5/6 nephrectomy.

Methods: We utilized human podocytes in culture and Tg26 HIV and Cd2ag mice models of proteinuria, POD injury and FSGS.

Results: Here we show 2-3 fold urinal Pig increase in Tg26 HIV and Cd2ag mice respectively shows that human uPA and cd2ag mice have increased POD. hLAM-521 is a potent anti-plasminogen activator and is able to prevent POD in mice with glomerular diseases. The inhibitor of Plg/Plasmin activation EACA significantly prevented all Pig induced actions. Importantly all molecules that reduce oxidative stress and Glom disease progression. The inhibitor of Plg/Plasmin activation EACA significantly prevented all Pig induced actions. Importantly all molecules that reduce oxidative stress (ROS) Apocynin, inhibitor of NADPH oxidase; AICAR, activator of AMPK and Mito Tempo, inhibitor of mitochondrial ROS as well as Amlidore, significantly prevented (p<0.05) Pig induction of POD CD36 and Endothelin-1.

Conclusions: We demonstrate novel pathophysiological mechanisms suggesting that following disruption of the Glom filtration barrier at the onset of proteinuric disease, POD are exposed to Pig/ Plasmin resulting in further injury mediated by oxidative stress. We propose that chronic exposure to Pig serves as a “second hit” in glomerular diseases and that Pig is potentially an attractive target for therapeutic intervention.

Funding: Other NIH Support - R01DK10 302201, Private Foundation Support

FR-PO490

p66Shc Regulates Endothelin-1 Induced Calcium Response in Glomerular Mesangial Cells Kevin Levin, Night Bradley S. Miller, André Sorokin. 1Dept of Medicine, Div of Nephrology, Cardiovascular Center, Medical College of Wisconsin, Milwaukee, WI.

Background: In the kidney, glomerular mesangial cells (GMC) function to regulate glomerular filtration area and secrete extracellular matrix. Endothelin-1 (ET-1) is a critical signaling molecule which triggers an influx of calcium (Ca2+) and subsequent contraction of GMC. Our goal was to assess the contribution of the adaptor protein p66Shc, a known ET-1 receptor, to the mesangial ET-1 signal effector, in the regulation of Ca2+ handling and contraction in the GMC. Our goal was to assess the contribution of the adaptor protein p66Shc, a known ET-1 receptor, to the mesangial ET-1 signal effector, in the regulation of Ca2+ handling and contraction in the GMC.

Methods: Primary GMC isolated from either wild type (WT) Dahl Salt-Sensitive (SS) rats, or from p66Shc mutant rats (on the SS genetic background). In these GMC

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

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which either lacked p66Shc (M4) or have the regulatory Ser36 mutated (S36A), we measured viability of the cells in contrast when embedded in a collagen matrix upon ET-1 stimulation. Additionally, we measured ET-1-mediated changes in intracellular calcium levels (Ca"²). We also assayed GMC cells for changes in Ca"² dependent signaling upon ET-1 stimulation. Lastly, in vivo assessment of glomerular filtration rate (GFR) was conducted on WT and mutant rats prior to onset of hypertension, on both high salt (1%) and low salt (0.4%) conditions.

Results: We show WT and mutant cells contract collagen disks to the same extent over 15 minutes after treatment with ET-1. There are, however, differences in collagen disks and injury. Interestingly, MDM2 mediates podocyte MC not via classic p53 pathway but activation. Consistently genetic silencing of Notch1 prevented HG-mediated podocyte MC. Podocytes exposed to HG. Knocking down MDM2 attenuated Numb reduction and Notch1 cell death. Our results suggest p66Shc may also function similarly in vivo.

Funding: NIDDK Support

FR-PO491

MDM2 Is Implicated in High Glucose Induced Podocyte Mitotic Catastrophe via Numb/Notch1 Signaling 1Hui Tang, 2Hua Su, 1Chun Zhang. 1Nephrology, Union Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.

Background: Podocyte injury and death are essential events involved in the pathogenesis of diabetic nephropathy (DN). As a terminally differentiated cell, podocyte is restricted in 'post-mitosis' state and unable to regenerate. Reentering cell cycle will cause podocyte disastrous death which is defined as mitotic catastrophe (MC). Murine diabetic nephropathy (DN) is induced by a high glucose (HG) diet, with the progressive accumulation of mesangial matrix, glomerulosclerosis and mesangial cell (MC) proliferation.

Methods: Patients diagnosed with DN were enrolled in this study, and DN model was constructed on C5BL/6 mice by a single intra-peritoneal injection of STZ. In vitro study human podocyte cell line was employed, and exposed to different treatments after differentiation. Nutlin-3a was used as an inhibitor for MDM2-p53 interaction. The expression of MDM2 and Notch1 was suppressed by genetic deletion.

Results: Knockdown of MDM2 with multi-nucleation were observed in DN patients as well as DN mice. Simultaneously the expression of MDM2 in podocytes of DN patients and mice was elevated comparing to control group. In vitro, HG exposure upregulated MDM2's abundance and forced podocytes to enter into S phase or transit G2/M phase with enhanced expression of Ki67 and mitotic markers (Aura B, p-H5) which were partly reversed by MDM2 genetic deletion. Moreover HG-induced podocyte injury was alleviated by MDM2 knocking down but not by nutlin-3a treatment. Interestingly, we found Numb, an antagonist of Notch1, was decreased in glomeruli from DN mice and podocytes exposed to HG. Knocking down MDM2 attenuated Numb reduction and Notch1 activation. Consistently genetic silencing of Notch1 prevented HG-mediated podocyte MC.


Funding: Government Support - Non-U.S.

FR-PO492

Deiodinase 3 Dysfunction in Thyroid Hormone-Induced Kidney Disease 1Nicholas J. Tardi, 2Chuan Chen, 2Joao Pedro Tardi de Castro, 3Jochen Reiser. 1Int. Med., Rush Univ, Chicago, IL; 2Endocrinology, Rush Univ, Chicago, IL.

Background: Thyroid hormone (TH) is a circulating, lipid soluble molecule that plays an important role in physiology and development in nearly all cell types. Accordingly, precise control of TH activity is crucial to maintain homeostasis in several tissues, including the kidney. Disruption of TH can lead to tubular dysfunction and tissue growth retardation. However, cases of reversible proteinuria and biopsy-proven glomerular disease associated with hyper/hypothyroidism have been reported in children and adults. TH homeostasis is maintained by deiodinases, which turn on/off tri-iodothyronine (T3), the metabolically active TH hormone. While TH regulation via deiodinases has been studied in endocrine tissues, the role of deiodinases in proteinuric kidney disease has not been addressed. Of particular interest is deiodinase 3 (D3); a catabolic enzyme that inactivates thyroxine and triiodothyronine (T3). Aberrant deiodinase 3 expression was associated with hyper/hypothyroidism and accelerated tubular injury in patients with AL-amyloidosis or light chain deposition disease (LCDD).

Methods: To complement the changes in D3 expression was greatly diminished at the cell membrane, yet remained concentrated in the golgi and perinuclear region where metabolically active T3 resides. Additionally, D3 is downregulated in glomerular mesangial cells collected from patients with focal segmental glomerulosclerosis and minimal change disease compared to healthy donors.

Conclusions: Our data suggests D3 downregulation is the source of hyperthyroidism in podocytes, and D3 dysfunction may be a mechanism of TH induced kidney disease in humans.

Funding: NIDDK Support

FR-PO493

Mesenchymal Stem Cells Acquire Morphological and Functional Features of Mesangial Cells as They Repair the Damaged Mesangium 1Errin Teng, 1Chun Zeng, 2Elba Turbat-Herrera, 3Guillermo A. Herrera. 1Pathology and Translational Pathobiology, Louisiana State Univ Health Sciences Center in Shreveport, Shreveport, LA; 2Medicine / Feist-Weiller Cancer Center, Louisiana State Univ Health Sciences Center in Shreveport, Shreveport, LA; 3Cellular Biology and Anatomy, Louisiana State Univ Health Sciences Center in Shreveport, Shreveport, LA.

Background: Some studies dealing with mesenchymal stem cells (MSCs) have indicated that they only produce paracrine effects when engaged in the process of tissue repair. In order to assess the specific role of MSCs in mesangial repair, a model of mesangial injury by glomerulopathic light chains was used.

Methods: A 6-D live cell imaging system was used as the in-vitro system and to address the issue. Mesangial cells (MCs) were incubated with light chains obtained from the urine of patients of AL-amyloidosis (AL-Am) and light chain deposition disease (LCDD). The light chains were also perfused through the renal artery in the ex-vivo platform. The respective lesions were reproduced in both platforms. Then, tagged MSCs were introduced. Immuno-fluorescence, immunohistochemistry and electron microscopy were used to evaluate samples obtained at different time frames. States for smoothelin, CD68 and CD29 were used to monitor phenotypic transformation of MSCs in the process of repair. Electrical field stimulation to assess the ability of cells to contract was utilized to assess functionality.

Results: MSCs transformed from an undifferentiated to a macrophage phenotype. The light chains transformed MSCs phagocytosing cellular debris resulting from apoptotic MCs, damaged matrix, amyloid, After the cleaning. MSCs acquired morphologic, functional, and immunophenotypic characteristics of MCs as they proceeded to lay down new mesangial matrix.

Conclusions: MSCs manifest great plasticity as they proceed to repair the damaged mesangium. The fact that they transform allows them to perform different crucial functions. The restored mesangium is possible as new MCs derived from MSCs are able to reproduce the normal mesangium and function as normal MCs.

Funding: Private Foundation Support

FR-PO494

Distinct and Overlapping Requirements for Nck1/2 Adaptors in Podocyte Cytoarchitecture 1Claire E. Martin, 1Mira Kendrel, 1Nina Jones. 1Molecular and Cellular Biology, Univ of Guelph, Guelph, ON, Canada; 2Cell and Developmental Biology, SUNY Upstate Medical Univ, Syracuse, NY.

Background: Podocytes contribute to blood filtration selectivity through a network of actin-based extensions termed podocytic foot processes. The ability of these extensions to sustain normal glomerular hemodynamic and strain maintenance filtration barrier integrity is proposed to be tied to their unique and flexible cytoarchitecture. However, the molecular mechanisms that regulate such mechanotransduction are not well understood. We have previously established that the Nck1/2 family of actin adaptors is essential in podocytes for both induction and maintenance of foot process homeostasis. The ability of Nck to simultaneously associate with proteins both cytoskeletal and signaling, coordinate mechanical signals within the podocyte.

Methods: Importantly, Nck1/2 family of actin adaptors is essential in podocytes for both induction and maintenance of foot process homeostasis. The ability of Nck to simultaneously associate with proteins both cytoskeletal and signaling, coordinate mechanical signals within the podocyte.

Results: Strikings disruptions in actin organization are present in Nck1/2 deficient podocytes, characterized by loss of lamellar sheets and radial stress fibres, with remaining stress fibres appearing haphazard, shortened and highly bundled. Consistent with this, Nck1/2 MCs display defects in cell spreading, migration and response to calcium switch injury. Molecular analysis has revealed overexpression of the actin bundling protein alpha-actinin 4 in Nck1/2 MCs, in cells and animals, and mislocalization of this protein within focal adhesions. Intriguingly, intermediate and distinct phenotypes are present in Nck1/2 MCs, with Nck1", Nck2" MCs, Nck1" MCs, Nck2" animals showing increased susceptibility to foot process effacement and proteinuria in multiple acute injury models.

Conclusions: We conclude that Nck proteins regulate podocyte actin bundling and focal adhesion dynamics, and that a threshold level of both Nck1 and Nck2 is required to maintain homeostasis. The ability of Nck to simultaneously associate with proteins both within the slit diaphragm and along the basal compartment positions Nck as a hub to coordinate mechanical signals within the podocyte.

Funding: NIDDK Support, Government Support - Non-U.S.
The Kynurenine Pathway in Podocytes and Parietal Epithelial Cells as a Potential Contributor to Kidney Disease

**Patricia Bolanos-Palmieri, Hermann G. Haller, Patricia Ann Schroeder, and Mario Schiffer**

**Background:** The kynurenine pathway (KP) is responsible for the catabolism of tryptophan resulting in the generation of NAD+ and a series of metabolically active intermediate products that participate in a number of cellular processes. In the kidneys, this pathway remains largely unexplored however an increasing amount of evidence suggests that changes in the activity and expression pattern of KP enzymes, as well as the accumulation of intermediate products are associated with disease. This study aims to provide an initial insight to the role played by the KP in the health and function of glomerular cells and its relationship to kidney disease.

**Methods:** Knock down (KD) of the enzymes in the KP was performed by morpholino injection in transgenic zebrafish Tg-fhag:DpH(EGFP). The phenotype of the morphant was determined according to the severity of the yolk sac edema and pericardial effusion. The maximum fluorescence in the retinal vessel plexus was taken as a measure of integrity of the glomerular filtration barrier. To assess the cellular repercussions of KP inhibition we will use URPF480 to block the pathway and analyze variations in oxygen consumption, extracellular acidification rate, as well as changes in actin cytoskeleton and response to stimuli in Podocytes and PEC.

**Results:** Our initial KD results show a 2-10 fold reduction in mRNA levels of the KP enzymes and by reducing their expression we are able to induce the formation of edema and detect signs of proteinuria in the MO injected fish. The proportion of fish with severe edema is higher, and the fluorescence is lower when the enzymes AFMID, KMO or KYNU are knocked down, indicating problems in the filtration barrier shown by the excretion of the fluorescent protein in the urine.

**Conclusions:** Taken together these results suggest that the KP is important in the maintenance and proper function of the filtration barrier, however the cellular and molecular mechanisms by which tryptophan metabolites affect cell function are yet to be elucidated.

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

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**FR-PO496**

**Elucidation of the Roles of Tissue Transglutaminase in Mesangial Proliferative Glomerulonephritis**

**Akihiro Kato,1 Tomohiro Mizuno,2 Kazuo Takahashi,1 Hideki Tatsukawa,1 Masashi Mizuno,1 Kyotaka Hirumi,1 Yuuki Togashi,1 and Kenzo Fujita2**

**Background:** Tissue transglutaminase (Tg2) is a calcium ion-dependent protein-cross-linking enzyme that plays an important role in fibrosis and inflammation. Tg2 is ubiquitously expressed enzyme and mainly distributed intracellularly as a catalytically inactive state due to low calcium concentration in the cells. We have established a method using a Tg2-specific FITC-labeled highly reactive substrate peptide for the detection of TG2 activity in renal biopsy tissue. We applied this method to detect active form of Tg2 in human renal biopsy tissues (n=241), and found that Tg2 activities were high in mesangial areas in patients with IgA nephropathy and lupus nephritis (J Am Soc Nephrol, 2015;26:723A). Thus, we hypothesized that the activation of TG2 in mesangial areas may result from its shifting from the intracellular to the extracellular space by complement mediated cell damages. As a complement-mediated stimulus, human glomerular mesangial cells (HGMCs) were stimulated with human serum (HS). The levels of TG2 in the culture supernatants as well as those in the intracellular compartment were measured by using ELISA. In addition, human recombinant Tg2 and Platelet-Derived Growth Factor (PDGF) were added to HGMCs and cell growth was examined by performing a colony assay.

**Results:** Complement-mediated stimulation of HGMCs was accompanied by a significant increase in Tg2 levels in the culture supernatant and a decrease in the intracellular Tg2 levels. The reaction was not observed in inactivated normal human serum, and was inhibited in the presence of C1 esterase inhibitor. When human recombinant Tg2 and PDGF were added to HGMCs, cell growth was significantly promoted. We hypothesized that the activation of TG2 in mesangial areas may result from its shifting from the intracellular to the extracellular space by complement mediated cell damages. As a complement-mediated stimulus, human glomerular mesangial cells (HGMCs) were stimulated with human serum (HS). The levels of TG2 in the culture supernatants as well as those in the intracellular compartment were measured by using ELISA. In addition, human recombinant Tg2 and Platelet-Derived Growth Factor (PDGF) were added to HGMCs and cell growth was examined by performing a colony assay.

**Conclusions:** The extracellular shift and activation of Tg2 may be due to complement activation in mesangial cells and could be involved in the progression of mesangial proliferative glomerulonephritides such as IgA nephropathy and lupus nephritis.

**Funding:** National Institutes of Health, National Heart, Lung, and Blood Institute.

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**FR-PO497**

**Puromycin Aminonucleoside Induces Endoplasmic Reticulum Stress and Apoptosis in Podocyte**

**Tae-Sun Ha, Pediatrics, Chungbuk National Univ, Cheongju, Chungbuk, Republic of Korea.**

**Background:** Puromycin aminonucleoside (PAN) is known to be a podocytotoxin, therefore, PAN-induced nephropathy is a widely studied animal model of human idiopathic nephropathic systemic sclerosis. Endoplasmic reticulum (ER) stress is the common finding in various pathogenic microenvironments, contributing to the progression of various podocyte diseases. Abnormal protein accumulation associated with ER stress in the ER of podocytes produces structural and functional damage in the cells, which in turn leads to podocyte dysfunction and dedifferentiation. In the present study, we investigated the effect of PAN on ER stress and apoptosis in in vitro podocytes.

**Methods:** We cultured rat and mouse podocytes and treated with various concentrations of PAN and evaluated ER stress markers by western blotting and apoptosis FACS and TUNEL assays.

**Results:** PAN-treatment increased GFP78 protein, an ER chaperone, as early as at 2 hrs, which was not ameliorated by anti-oxidants. PAN also increased ER stress markers, such as, ATF6α and caspase 12 at 12 and 24 hrs, which were improved by ATF6 siRNA and chemical chaperones such as, sodium 4-phenylbutyric acid (PBA) and TUDCA, however, not by Necd siRNA. PAN treatment increased oxidative stress level of podocytes significantly with the induction of Nox4. In addition, PAN induced podocyte apoptosis significantly in concentration- and time-dependent manners in FACS and TUNEL assays, which were improved by Nod4 siRNA, ATF6 siRNA, and chemical chaperones. Therefore, PAN induced ER stress, thereafter, increased oxidative stress, subsequently induced podocyte apoptosis.

**Conclusions:** Our studies suggest that PAN could induce podocyte ER stress of main ATF6α and caspase 12 pathways, which would contribute to the development of podocyte apoptosis via oxidative stress.

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

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**FR-PO498**

**RNA Binding Protein Staufen 2 is Required for Normal Podocyte Adhesion**

**Jessica J. Harris,1 George J. Cope,1 Valerie A. Schumacher,1 and Gary J. Schroder,2**

1.1 Department of Urology, Boston Children’s Hospital, Boston, MA; 2Cardiff Univ, Cardiff, United Kingdom.

**Background:** Podocytes are critical for the maintenance of the glomerular filtration barrier and need to be able to adapt to changes such as variations in pressure or cellular injury, to do so they may need to alter cell-matrix interactions. Failure in the ability to respond to such changes can lead to the irreversible loss of podocytes from the GBF. Our preliminary data supports the novel concept that podocytes store mRNAs in cytoplasmic RNA granules in the cells until protein is needed and the mRNAs locally translated to regulate cell adhesion. The localization of mRNAs within a cell can be regulated RNA binding proteins such as Staufen2. Our main focus is to determine how Staufen2 regulates the formation and maintenance of cell-matrix adhesions within the podocyte up on injury and up on adhesion of cells.

**Methods:** Adriamycin (ADR) treatment was used as a model of injury. siRNA was used to knockdown Staufen2 in vitro. Detachment of cells was monitored using a crystal violet assay. Phase contrast microscopy and ImageJ analysis were used to investigate cell spreading and western blotting used to study cell signaling.

**Results:** Using an in vivo model we show that ADR induced injury results in an increase of the phosphorylation of S6 protein indicating an increase in protein. This correlates with an increase of ribosomes within podocyte foot processes. Staufen2 is expressed in podocytes and localizes to focal adhesions in vitro. Podocytes lacking Staufen2 detach over time and have smaller paxillin positive focal adhesions compared to control cells. ADR induced cellular injury enhances this decrease in adhesive area. We investigated the role of Staufen2 up on podocyte adhesion to laminin and find that Staufen2 deficient podocytes show a defect in spreading. We also show that glycosylation of integrin b1 is altered in podocytes lacking Staufen2 and that there is a reduction in phosphorylation of key adhesion related molecules.

**Conclusions:** Staufen2 is localized to adhesion complexes in podocytes and is required for podocyte adhesion and maintenance of adhesion. Knockdown of Staufen2 leads to defects in glycosylation and signaling.

**Funding:** NIDDK Support, Private Foundation Support

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**FR-PO499**

**Diet1 Is A Novel Gene Associated with Albuminuria**

**Jessica Ong,1,3 Laurent Vergnes,1 Ira Kurtz,2 Karen Reue,1,2,3 Human Genetics, Univ of California, Los Angeles; 2David Geffen School of Medicine, Univ of California, Los Angeles; 3Molecular Biology Inst, Univ of California, Los Angeles, CA.**

**Background:** Diet1 is a gene previously identified from a naturally occurring null mutation in an inbred mouse strain. Studies in this mouse strain showed that Diet1 plays an important role in bile acid signaling by modulating FGF15/19 secretion. In situ hybridization demonstrated Diet1 expression exclusively in the small intestine and in the proximal tubule. At present, nothing is known about the role of Diet1 in the kidney, but a GWAS study for urinary albumin excretion has revealed a significant association with a polymorphism in DIET1.

**Methods:** To investigate the role of Diet1 in the kidney, we created a congenic mouse strain carrying the Diet1 null mutation on a C57BL/6J background. Male and female Diet1+/+ and Diet1–/– mice were studied on standard mouse chow and an atherogenic diet. Twenty-four hour urine samples were collected and assessed for albumin and creatinine excretion rates. In addition, on the atherogenic diet, blood chemistries and kidney tissue were obtained for histology, electron microscopy, and gene expression studies.

**Results:** On standard mouse chow, there was no difference in albumin excretion rates of Diet1–/– compared to Diet1+/+ mice. However, on the atherogenic diet, Diet1–/– mice exhibited a significantly greater urinary albumin excretion compared to Diet1+/+ (77.3% in males and 81.1% in females) without any difference in creatinine excretion. In situ hybridization and ultrastructural studies of the glomeruli and proximal tubules did not reveal significant differences between Diet1+/+ and Diet1–/– mice, suggesting that Diet1 may have a regulatory role in albumin absorption by the kidney.
FR-PO502

Transcriptional Reprogramming by WT1 in Murine Podocytes Affected by Hereditary FSGS

Mahdieh Rahmatolahi, Martin Kann, Maximilian O. Lenz, Bernhard Schermer, Thomas Benzing.

Dept II of Medicine, Nephrology, Rheumatology and Diabetology and Center for Molecular Medicine Cologne, Univ of Cologne, Cologne, Germany.

Background: Mutations in several podocyte transcription factors (TF) including WT1 are known to cause hereditary FSGS. However, the gene regulatory networks governed by these TFs in healthy and diseased podocytes are as yet poorly characterized. Here, we investigate WT1 dependent gene regulatory reprogramming at an early stage of podocyte damage in a mouse model of hereditary FSGS.

Methods: Heterozygous deletion of WT1 (WT1het) was chosen as a murine model of hereditary FSGS. WT1 gene regulatory function was assayed in WT1het mice and control littermates by ChIPseq for WT1 at age 4 weeks, an early proteinuric yet not sclerotic stage of glomerular damage. Results were computationally analyzed using standard ChIPseq algorithms.

Results: WT1het mice showed a consistent phenotype of proteinuria present at age 4 weeks and glomerulosclerosis at age 15 weeks. WT1 ChIPseq at age 4 weeks identified several thousand conserved WT1 binding sites (peaks) in both, WT1het and control animals. WT1 peaks were reproducible, conserved, predominantly located in putative enhancers, and harbored the established WT1 DNA binding motif in either condition. In principal component analysis, ChIPseq data clustered according to genotype. Differential binding analysis between WT1het mice and controls identified changes in binding strengths corresponding to gene regulatory reprogramming events at one third of all WT1 peaks. Reduction of WT1 binding strengths was predominant upon glomerular damage with a small cluster of novel WT1 peaks occurring. The majority of reprogramming events took place at putative enhancers, highlighting their importance to gene regulatory networks. Gene ontology analysis revealed key reprogramming events to be enriched at genes associated with podocyte damage signaling pathways such as Tgf-beta and Wnt, involving WT1 in transcriptional regulation of such pathways at an early disease stage in this FSGS model.

Conclusions: In a murine model of hereditary FSGS, WT1 is involved in gene regulatory reprogramming of signaling pathways relevant to podocyte damage at an early stage of disease.

Funding: Government Support - Non-U.S.

FR-PO503

BRAF Signalling Pathway Inhibition Causing Glomerular Injury

Lucia Perico,1 Mario Mandala,1 Arigo Schieppati,1 Carrullo Carrara,1 Paola Rizzo,1 Sara Conti,1 Lorenza Longaretti,1 Ariela Benigni,1,2 IRCSS - Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; 3ASST Papa Giovanni XXIII, Bergamo, Italy.

Background: The glomerulus is uniquely susceptible to chemotherapeutic injury, though molecular targets have not been fully identified. Dabrafenib and trametinib, BRAF and MEK inhibitors, are effective targeted therapies for malignant metastatic melanoma but less is known about their nephrotoxicity. While initial trials with BRAF inhibitors suggested no renal side effects, recent case reports uncovered significant nephrotic events. Whereas most of the published data revealed tubulointerstitial injury as the main renal consequence of these drugs, none depicted nephrotic syndrome (NS) and glomerular damage.

Methods: Starting from the case of a patient with metastatic melanoma who developed NS starting from the case of a patient with metastatic melanoma who developed NS following the combination of dabrafenib and trametinib, we evaluated glomerular ultrastructural changes by electron microscopy analysis and the molecular mechanisms underlying the targeted therapy-induced NS by combining in vitro experiment in podocytes and ex vivo analysis in the patient biopsies.

Results: Electron microscopy analysis showed diffuse loss of podocyte cytoarchitecture, extensive foot process effacement and glomerular capillary injury in the patient’s biopsy during drug treatment. Renal function and glomerular damage recovered after drug withdrawal. In vitro experiments documented that BRAF inhibition was the primary culprit in the podocyte slit diaphragm impairment via reduction of Ptc1 and nephrin expression, leading to increased albumin permeability. BRAF and MEK inhibitors jointly altered the overall glomerular functional properties by inhibiting the podocyte VEGF system. The above mechanisms were corroborated ex vivo in the patient biopsies.

Conclusions: We demonstrate that MAPK pathway inhibition alters slit diaphragm architecture and we provide direct experimental evidence that this inhibition is a possible novel pathogenic mechanism leading to NS. Besides its implications for NS pathophysiology, we suggest that patients should be monitored closely for potential glomerular damage during treatment since the dabrafenib and trametinib combination is a standard treatment for melanoma patients.

FR-PO504

The Neonatal Fc Receptor (FcRn) Is Required for IgG but Not Albumin Trafficking in Podocytes

Mozhgan Beni,1,2,3,4 Vincenzo Donato,1,2,3,4 Victoria Galli,1,2,3,4 Sara Beni,1,2,3,4 Ali Khan,1,2,3,4 Annamaria Arrigo,1,2,3,4 Sara Beni,1,2,3,4

1Medicine, Univ of Colorado Denver, Aurora, CO; 2ORS, NIH, Bethesda, MD; 3NIDDK, NIH, Bethesda, MD.

Background: The Neonatal Fc Receptor (FcRn) is a transmembrane protein that acts as an anion exchanger and is essential for the uptake and recycling of IgG from the neonatal circulation into the maternal circulation and vice versa. The FcRn is also expressed in a variety of other epithelial cells and has been implicated in the regulation of albumin homeostasis. However, the role of the FcRn in albumin trafficking has not been fully elucidated.

Methods: We used immunoblotting and cell proliferation assays to evaluate the effects of targeted deletion of FcRn in podocytes. We also analyzed the expression of FcRn in podocytes isolated from FcRn−/− mice.

Results: Our results showed that FcRn−/− podocytes had reduced expression of FcRn and reduced mRNA expression of the FcRn gene. In addition, we observed a decrease in albumin uptake and recycling in FcRn−/− podocytes.

Conclusions: These findings suggest a role for FcRn in albumin trafficking in podocytes and highlight the importance of this receptor in maintaining proper albumin homeostasis.

Funding: NIDDK Support

FR-PO501

Characterizing the Differential Regulation of Podocyte ANLN Expression by AKT1 and AKT2

Deborah J. McCarthy, Kevin J. McCarthy.

Dept of Pathology and Translational Pathobiology, LSU Health Sciences Center, Shreveport, LA.

Background: We previously demonstrated that mutations in the F-actin bundling and cell cycle regulatory protein ANLN cause FSGS. Additionally, we have shown that ANLN is expressed in podocytes and that ANLN is required for the proper folding and assembly of the slit diaphragm. These findings suggest that the upregulation of ANLN may play role in the pathobiology of podocyte damage in FSGS.

Methods: We used tetracycline-inducible AKT1-shRNA and AKT2-shRNA podocyte lines.

Results: We observed a significant reduction in ANLN expression in AKT1-depleted podocytes compared to control podocytes. This reduction in ANLN expression correlated with a decrease in podocyte ANLN transcript levels.

Conclusions: These data suggest that AKT1 and AKT2 negatively regulate ANLN expression in podocytes. This finding may have implications for the development of targeted therapies for FSGS.

Funding: NIDDK Support

FR-PO500

The Effects of Diabetes Mellitus on Cell Surface Heparan Sulfate Proteoglycans: The Uncoupling of Syndecan-4 in Podocytes due to Early Loss of N-Sulfated Heparan Sulfate

Megan Spurney,1,2,3,4 Deborah J. McCarthy, Kevin J. McCarthy.

Dept of Pathology and Translational Pathobiology, LSU Health Sciences Center, Shreveport, LA.

Background: Previous work from our laboratory showed that the loss of heparan sulfate (HS) or the depletion of N-sulfated groups (NS) on HS attached to cell surface proteoglycans (PG) led to the development of podocyte (PTD) foot process effacement in vivo and compromised cell-matrix adhesion in vitro, mediated by the “uncoupling” of syndecan-4 (Sdc4) from matrix protein ligands. This study extends this concept to explore the loss of NS in the glomerular basement membrane (GBM) of diabetic animals.

Methods: Control and db/db mice 16 weeks of age were sacrificed, the kidneys removed and processed for paraffin, frozen, and transmission electron microscopy (TEM). Frozen sections were double label immunostained for total HS and N-sulfated HS, Sdc4 and either nephrin, synaptopodin, or a-actinin 4. Paraffin sections were stained with PAS/Alcian Blue to demonstrate glomerular hypertrophy and mesangial expansion. Tissue sections were imaged using an Olympus IX-70 microscope equipped for epifluorescent illumination or for TEM, a Hitachi TEM.

Results: PAS/Alcian Blue staining of glomerular of db/db mice showed glomeruli ranging from normal to glomerular having glomerular hypertrophy and early mesangial expansion. Immunostaining for NS and HS in glomeruli from control animals revealed expansion. Immunostaining for NS and HS in glomeruli from diabetic glomeruli showed a breakdown in the linear co-distribution of Sdc4 and the PGs contained normal HS species. GBM staining of diabetic glomeruli showed the glomerular capillaries whose GBMs stained positive for both NS and HS, indicating that expansion. Immunostaining for NS and HS in glomeruli from control animals revealed expansion. Immunostaining for NS and HS in glomeruli from diabetic glomeruli showed the presence of PGS lacking NS but whose total HS content remained unchanged. Capillaries in the diabetic glomeruli showed a breakdown in the linear co-distribution of Sdc4 and a-actinin 4 along the length of the GBM.

Conclusions: Our data show that in the early stages of diabetic nephropathy there is a loss of NS on HS associated with Sdc4, one of the cell surface proteoglycans that are now known to be critical in Pod-matrix interactions. This change is associated with uncoupling of Sdc4 ectodomain from its GBM ligands which, in turn, leads to disruption of the a-actinin 4-cytoskeleton linkage in PODs and foot process effacement.

Funding: NIDDK Support

FR-PO505

Proteinuria is strongly associated with kidney disease progression.

Braja Prakash,1 Linda Lewis,2 Patricia M. Zerfas,2 Avi Rosenberg,2 Jeffrey B. Kopp,2 Judith Blaine,1 Medicine, Univ of Colorado Denver, Aurora, CO; 2ORS, NIH, Bethesda, MD; 3NIDDK, NIH, Bethesda, MD.

Background: We have documented for the first time a role for Diet1 in renal albumin handling in mice. Given the localized expression of Diet1 in the proximal tubule, our results suggest a new modulatory pathway whereby Diet1 plays a role in proximal tubule albumin absorption depending on the dietary lipid content.

Funding: Other NIH Support - T32 GM080042, P01 HL28481

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

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remain to be fully determined. Previously, we have shown that transcytosis is the major pathway for microalbuminuria (MA) and AMPK activation increases podocyte permeability to albumin and podocyte dysfunction, as evidenced by zona occludens-1 translocation to the membrane. Since omentin reduced protein levels of NADPH oxidase Nox4 in podocytes, we speculated that these protective effects of omentin were caused by the reduction of oxidative stress.

Conclusions: In conclusion, increased serum omentin levels predict the progression from microalbuminuria to macroalbuminuria and macroalbuminuria to ESRD in diabetic patients. In our in vitro findings suggest that omentin is a key regulator of albuminuria, likely acting through the AMPK pathway to modulate oxidative stress in podocytes.

FR-PO507

Microtubule and Actin Crosstalk in Podocytes Kamalika Mukherjee, Changkyu Gu, Sanja Sever. Dept of Medicine/Div of Nephrology, Massachusetts General Hospital/Harvard Medical School, Charlestown, MA.

Background: Podocyte injury, dysfunction and loss have been implicated in a number of diverse kidney diseases such as focal segmental glomerulosclerosis, diabetic nephropathy and HIV-associated nephropathy. It is known that structural and functional alteration of the podocyte actin cytoskeleton culminates in foot process effacement and proteinuria. The coordinated organization of the cytoskeleton is crucial for maintaining the physiological function of podocytes. The two predominant cytoskeletal proteins present in major processes and foot processes of podocytes are microtubules and actin respectively. We therefore sought to investigate the crosstalk between microtubules and actin in podocytes and identify regulatory proteins that may modulate such interactions.

Methods: Tubulin, actin and parxillin were immunostained to observe the effect of microtubule- and actin- regulating small molecules on podocytes. Dynamin oligomerization was assessed by monitoring dynamin’s ability to hydrolyze GTP over time. Microtubule polymerization and depolymerization in the presence of dynamin or small molecules were monitored using a DAPI based fluorescence assay.


Conclusions: Altering microtubule cytoskeleton in podocytes results in reorganization of podocyte architecture and vice versa. This finding demonstrates the existence of a crosstalk between the two cytoskeletal proteins in podocytes. There is evidence that dynamin oligomerization promote actin polymerization. Here, we report that dynamin self-assembly around microtubules and promotes depolymerization of microtubules and inhibits tubulin polymerization into microtubules. Taken together, dynamin oligomerization regulates polymerization activity of both microtubules and actin. Our findings therefore strongly suggest that dynamin may be one of the regulatory proteins that facilitate actin microtubule crosstalk in podocytes.

Funding: NIDDK Support

FR-PO508

Par3A and Par3B Exhibit Compensatory Roles to Maintain aPKC Mediated Polarity Signaling at the Slit Diaphragm Sybille Köhler,1 Wilhelm Bloch,2 Bernhard Schermer,1,2 Thomas Benzing,1,2 Paul T. Brinkkötter.1 1Dept of Internal Medicine and Center for Molecular Medicine, Univ of Cologne, Cologne, Germany; 2Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Univ of Cologne, Cologne, Germany; 3Dept of Dermatology and Center for Molecular Medicine Cologne, Univ of Cologne, Cologne, Germany; 4Systems Biology of Aging Cologne (Sybaloc), Univ of Cologne, Cologne, Germany; 5Dept of Molecular and Cellular Sport Medicine, German Sport Univ Cologne, Cologne, Germany; 6Clinical Inst of Pathology, Medical Univ of Vienna, Vienna, Austria.

Background: Polarity signaling through the aPKC-Par polarity complex is essential for the development and maintenance of the podocyte architecture and the function of the glomerular filtration barrier of the kidney. Despite its well-established role in aPKC-mediated signaling, Par3A appears to be dispensable for the function of the glomerular filtration barrier.

Results: An mRNA-seq data from primary podocytes revealed high levels of Par3B in podocytes, which were much higher in comparison to Par3A levels. Interestingly, Par3B localized to the slit diaphragm as demonstrated by immunofluorescence staining and immunogold-labellings suggesting a role of Par3B at the slit diaphragm. To study the function at the slit, we generated a novel podocyte-specific Par3B knockout mouse model. Loss of Par3B did not cause glomerulosclerosis or albuminuria. To study potential compensatory mechanisms between Par3A and Par3B, we generated podocyte-specific Par3A/B double knockout mice. Par3A/B double knockout mice were born following fertilization but did not develop severe proteinuria in comparison to control mice. To further study the interplay between the different Par3 proteins we utilized Drosophila nephrocytes and silenced expression of the Par3A/B homolog bazooka which also resulted in disturbed nephrocyte morphology and a severe functional defect.

Conclusions: Taken together, these findings support the hypothesis of potential compensatory mechanisms between Par3A and Par3B to maintain aPKC mediated polarity signaling at the slit diaphragm.
Regulation of Canonical Wnt Signaling by the Transcription Factor HNF-1β

Background: Hepatocyte nuclear factor-1β (HNF-1β) is a tissue-specific transcription factor that is required for kidney development and tubular function. Mutations of HNF-1β produce autosomal dominant tubulointerstitial kidney disease (ADTKD) characterized by tubular cysts, renal fibrosis, and progressive loss of kidney function. To understand the functions of HNF-1β, we generated HNF-1β-deficient mIMCD3 renal epithelial cells.

Methods: Gene editing with CRISPR/Cas9 was used to delete exon 1 of HNF-1β by non-homologous end joining (NHEJ). HNF-1β-deficient cells were characterized by RNA-seq, western blotting (WB), and assays of proliferation and cell migration.

Results: Three independent HNF-1β-deficient mIMCD3 cell lines and three paired control cell lines were established. qRT-PCR and WB confirmed the complete absence of HNF-1β expression. RNA-seq analysis of HNF-1β-deficient cells showed upregulation of 1,135 genes and repression of 759 genes compared to control cells. ChIP-seq analysis identified HNF-1β binding sites in the Lef1 locus by ChIP and luciferase reporter assays. HNF-1β-deficient cells were hypersensitive to Wnt3a as evidenced by upregulation of canonical Wnt target Axin2, Sp5 and Lef1. Deletion of the -β-catenin-binding domain in Lef1 partially rescued the hypersensitivity to Wnt3a. Increased expression of Axin2 and Lef1 was confirmed in vivo by qRT-PCR analysis of kidneys from HNF-1β mutant mice.

Conclusions: Increased expression of Lef1 contributes importantly to the activation of canonical Wnt signaling in HNF-1β mutant cells through a feed-forward mechanism. Characterization of genes activated by Wnt in HNF-1β mutant renal epithelial cells may identify new therapeutic targets for the treatment of cystic kidney disease.

Funding: NIDDK Support

FR-PO510
Inactivation of Transcription Factor HNF-1β with CRISPR/Cas9 Induces Epithelial-Mesenchymal Transition

Background: Hepatocyte nuclear factor-1β (HNF-1β) is a tissue-specific transcription factor that is essential for the development of the kidney. Mutations of HNF-1β produce autosomal dominant tubulointerstitial kidney disease (ADTKD) characterized by tubular cysts, renal fibrosis, and progressive loss of kidney function. To understand the functions of HNF-1β, we generated HNF-1β-deficient mIMCD3 renal epithelial cells.

Methods: Gene editing with CRISPR/Cas9 was used to delete exon 1 of HNF-1β by non-homologous end joining (NHEJ). HNF-1β-deficient cells were characterized by RNA-seq, western blotting (WB), and assays of proliferation and cell migration.

Results: Three independent HNF-1β-deficient mIMCD3 cell lines and three paired control cell lines were established. qRT-PCR and WB confirmed the complete absence of HNF-1β expression. RNA-seq analysis of HNF-1β-deficient cells showed upregulation of 1,135 genes and repression of 759 genes compared to control cells. ChIP-seq analysis showed that 75% of the differentially expressed genes were direct targets of HNF-1β. qRT-PCR and ChIP-assays confirmed the repression of 1135 genes and activation of 759 genes.

Conclusions: Loss of HNF-1β in renal epithelial cells is sufficient to induce EMT. HNF-1β-deficient mIMCD3 cells created by gene editing will be a useful reagent for unravelling the HNF-1β mutant phenotype.

Funding: NIDDK Support
situation hybridization and aberrant increases in sonic hedgehog (Shh) ligand immunostaining in sub-populations of non-dilated P7 mutant PTs that were unlikely to represent the stromal GIIS. As ectopic tubular Shh is seen after acute kidney injury (AKI), we examined other AKI markers and found that increases in kidney injury molecule-1 (Kim1) and chemokine Ccl2 (macrophage chemotactic protein-1), also in non-dilated mutant PT cells in vivo. In cysts, we observed many lining cells that had lost expression of PT differentiation markers (e.g. LTL), re-expression of de-differentiation markers such as Pax2 and Ncam (often seen in regeneration after AKI), and inappropriate increases in phospho-Crebl staining, a readout of cAMP-protein kinase A activity (a pathway known to drive cyst growth in PKD and that is also active after AKI).

Conclusions: Together, these observations suggest that aberrant early AKI and post AKI regenerative pathways may drive renal pathogenesis in PKD.

Funding: NIDDK Support

FR-POS14

Smyd2 Regulates Renal Fibrosis via TGF-β-Smad2/3 Signaling in ADPKD

Xiaoyan Li, Ewoud Agborbesong, Xia Zhou, James P. Calvet, Xiaogang Li. Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.

Background: In polycystic kidney disease (PKD), expansion of cysts and loss of renal function are associated with progressive fibrosis, which has been identified as the most significant manifestation associated with an increased rate of progression to ESRD. Anti-fibrotic therapy should be an effective adjunct to treatment of ADPKD. Smyd2, as a SET-domain-containing histone (lysine) methyltransferase, methylates both histone and non-histone proteins, including PKD-associated p53, Rb and HSP90, to regulate gene expression and protein function, respectively. We found that Smyd2 promotes renal cyst growth in ADPKD via STAT3 and NF-kB signaling. However, the mechanisms by which Smyd2 regulates renal fibrosis remain unknown.

Methods: To understand the role of Smyd2 in renal fibrosis in vivo, we investigated renal fibrosis in Pkd1 and Smyd2 double conditional knockout mice (Pkd1<sup>flox/flox</sup>; Smyd2<sup>flck/flox</sup>) and in Pkd1<sup>homo</sup> mice and Pkd1<sup>homo</sup> Pkd1<sup>homo</sup> CAG-driven transmembrane-Cre mice treated with a Smyd2-specific inhibitor, AZ505. To explore the pathways underlying Smyd2-mediated renal fibrosis, we also tested renal fibroblasts with AZ505.

Results: We found that knockout of Smyd2 and inhibition of Smyd2 with AZ505 not only delayed cyst growth but also decreased renal fibrosis in kidneys of Pkd1 conditional knockout mice as examined by Trichrome Masson and Picrosirius red staining. Pkd1 and Smyd2 double knockout mice lived longer, to a mean age of 25 days, while Pkd1 knockout mice died at a mean age of 17 days (p < 0.001). Treatment with AZ505 blocked TGF-β induced upregulation of fibroblastic markers, including Col1A1, Col3A1, a-SMA and fibronectin, and decreased the phosphorylation of Smad3/4 in rat kidney interstitial fibroblasts (NRK-49F) as analyzed by qRT-PCR and Western blot. We also found that TGF-β can induce the expression of Smad3 in a time-dependent manner in these cells. Inhibition of Smyd2 with AZ505 decreased NRK-49F cell proliferation.

Conclusions: Smyd2 promotes renal fibrogenesis in ADPKD through the canonical TGF-β-Smad2/3 signaling pathway. Targeting Smyd2 with its inhibitor should not only delay cyst growth but also prevent interstitial fibrosis in ADPKD.

Funding: NIDDK Support

FR-POS15

SAHA Reduced cAMP Levels and Inhibited Renal Cyst Growth through HDAC6

Xin Li, Weimei Shi, Ming Wu, Changlin Mei. Dept of Nephrology, Kidney Inst, Shanghai Changzheng Hospital, Shanghai, China.

Background: Inhibition of cyclic adenosine monophosphate (cAMP) by using Tolvaptan can delay disease progression in patients with autosomal dominant polycystic kidney diseases (ADPKD). However, it has not been approved by USA FDA because of its side effects. Recent study shows that inhibition of Histone deacetylases 6 (HDAC6) reduced cAMP levels and inhibited kidney growth in ADPKD animal models. We therefore hypothesized that treatment with suberylandine hydroxamic acid (SAHA), a FDA approved HDAC inhibitor, could retard PKD progression and lower cAMP levels in cystic kidneys.

Methods: Male rats were treated with 50mg/kg/day SAHA or vehicle at 4 weeks of age by gavage for 5 weeks. ADPKD cells were treated with various concentrations of SAHA.

Results: Five weeks SAHA treatment reduced BUN and creatinine level by 37.7% (11.50±1.78mmol/L vs 18.15±2.98 mmol/L) and 40.3% (57.62±30.89mmol/L vs 97.26±15.60 mmol/L) respectively in cystic Cy/+ and Pan64 rats treated with cys6 Cy/+ Harbored rats with cystic Cy/+ Harbored rats treated with vehicle. Administration of SAHA decreased the two kidney weight/total body weight ratio and cystic volume density in Cy/+ rats by 25.2% (0.0205±0.1768 vs 0.0248±0.0642泊液) and 39.7% (0.3373±0.0205 vs 0.5355±0.0221 respectively) respectively. The cell proliferation was inhibited by SAHA in cystic kidneys as shown by Ki-67 staining. SAHA reduced cAMP levels in Cy/+ kidneys, which was correlated with the down-regulation of HDAC6 expression and reduced phosphorylation of CREB. The inhibitory effect of SAHA on HDAC6 expression and cAMP levels was confirmed in ADPKD cells. In addition SAHA reduced protein levels of β-catenin and C-myc in cystic kidneys.

Conclusions: SAHA reduced cAMP levels and inhibited kidney growth in PKD, which may be mediated through HDAC6.

Funding: Government Support - Non-U.S.

FR-POS16

Structural nephropathy: 3D analysis of fibrocytosis/polyductin bound to DNA


1Center for Translational Science, Children’s National Health System, Washington, DC; 2Virginia Tech Carilion Research Inst, Roanoke, VA.

Background: ARPKD results from mutations in PKHD1, a transcriptionally complex gene that encodes a set of secreted and membrane-bound isoforms collectively referred to as FPC. The longest mRNA encodes a membrane-bound FPC that undergoes Notch-like proteolytic cleavage to generate a carboxy terminal domain (CTD-FPC) that translocates to the nucleus. We hypothesize that within the nucleus CTD-FPC assembles into gene regulatory complexes.

Methods: Mouse CTD-FPC was cloned into the modified pXFLAG-CMV-71 vector, sequenced-verified, and transfected into mMCD-3 cells. Cells lysates were prepared and separated into cytoplasmic and nuclear fractions, with the purified nuclear fraction subjected to the “Affinity capture” technique (Sci Rep, 2015) to identify the nuclear assemblies that interact with the CTD-FPC. Captured complexes were examined using single particle Electron Microscopy (EM) and Chromatographic (Chrom) methods.

Results: We found that Affinity-capture, natively-formed CTD-FPC nuclear assemblies were abundantly integrated into DNA networks (Fig 1). In parallel, we examined purified CTD-FPC assemblies using single particle EM. Classification-based computational routines revealed that these assemblies had some degree of heterogeneity, but that most complexes were ~15 nm in diameter. Representative 3D reconstruction of these complexes exhibited a ring-shaped architecture consistent with known DNA-binding motifs.
Conclusions: EDN1 is increased in serum of ADPKD patients and EDN1 polymorphisms are associated with ADPKD severity. Our data suggest misregulation of EDN1-MAPK signaling as an early initiation of renal cystic disease that merits further exploration.

**Funding:** NIDDK Support

### FR-PO518

**Expression of Activated BRAF(V600E) in Collecting Ducts Accelerates Cyst Growth and Fibrosis in Renal Cystic Disease**

**Archara Raman, Stephen C. Parnell, Aditi Khanna, Yuqiao Dai, Grant Aaron Johnson, Gael Reif, Timothy A. Fields, Darren P. Wallace.** Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.

**Background:** In polycystic kidney disease (PKD), aberrant cell proliferation is responsible for the growth of fluid-filled cysts leading to enlarged kidneys and progressive decline in function. Agonists of the PKD genes are thought to cause dysregulation of intracellular Ca²⁺, leading to reduced basal intracellular Ca²⁺ levels in cystic cells compared to normal kidney cells and cAMP-dependent activation of the BRAF/MEK/ERK pathway. This pathway is thought to be important for driving aberrant cell proliferation in PKD.

**Methods:** To determine the role of BRAF on renal cyst formation, we generated mice that conditionally express BRAFV600E, a novel activating mutation in BRAF found in cancer. We used Pkd1-Cre to selectively overexpress BRAFV600E in collecting ducts (CD) of wildtype (WT) mice. BRAFV600E was also expressed in cystic epithelial cells by cross-breeding these mice with pcy/pcy (pcy), a slowly progressive model of PKD that develops predominantly CD-derived cysts.

**Results:** CD-specific expression of BRAFV600E in WT mice caused hyperproliferation and cystic dilation of CD, formation of small cysts, and prominent interstitial fibrosis. CD-specific expression of BRAFV600E in pcy mice caused a striking increase in kidney weight to body weight, cyst number and size, and total cystic area compared to littermate pcy mice. There was also a significant increase in phosphorylated ERK and Ki-67 positive cells, consistent with elevated MEK/ERK-dependent cell proliferation. There was extensive infiltration of immune cells and a four-fold increase in interstitial fibrosis that extended through the cortex of the cystic kidneys.

**Conclusions:** Our results demonstrate that activation of the BRAF/MEK/ERK pathway in renal epithelial cells is sufficient to induce cyst formation and accelerate the progression of cystic disease.

**Funding:** NIDDK Support

### FR-PO519

**Genetic Interaction between XBPI and Pkd1 Modulates Cyst Progression in ADPKD**

**Sarit V. Edgel, Yasunobu Ishikawa, Rachel Gallagher, Stefan Sonnlo. Internal Medicine/Nephrology, Yale School of Medicine, New Haven, CT.

**Background:** Pkd1 is one of the two genes responsible for autosomal dominant polycystic kidney disease (ADPKD). XBPI encodes a small, secreted protein of the ER unfolded protein response. Sec63 is one of the genes mutated in isolated familial polycystic liver disease (PCLD). Sec63 and XBPI interact genetically to modulate Pkd1 function in PCLD. In the current work we investigated whether XBPI can exhibit a direct genetic interaction with Pkd1 independently of Sec63.

**Methods:** Pkd1‡‡‡-Pkd1-Cre (SKO) and Pkd1‡‡‡-XBPI‡‡‡-Pkd1-Cre(DKO) mouse models with conditional inactivation of Pkd1 and XBPI alone or together in the collecting duct were evaluated at P24 by morphological and biochemical parameters: kidney to body weight, cyst number and size, and total cystic area compared to littermate WT mice. XBPI expression was not different between the WT and SKO animals expressing XBPI, indicating that baseline levels of XBPIs to SKO animals alone (4.7% vs. 0.1%, ***p<0.001) with no changes in proliferation. The decrease in KW/BW, 0.5+/-0.1 vs. 1.4+/-0.2 respectively, ***p<0.001). These changes were further explored

**Results:** Our data demonstrate that N12 signaling is critical for renal cystogenesis in ADPKD induced by Pkd1 mutation.

**Funding:** Private Foundation Support

### FR-PO521

**The Lonidamine Derivative H2-Gamzadole Inhibits Cyst Growth in Pkd1-Deficient Kidneys by Targeting Numerous Cellular Pathways**

**Xia Zhou,1 Brenda S. Magenheimer,1 Gunda I. Georg,2 Joseph S. Tash,1 Xiaogang Li,1 James P. Calvet.1 1Univ of Kansas Medical Center, Kansas City, KS; 2Univ of Minnesota, Minneapolis, MN.

**Background:** Cyst growth and polycystic kidney disease (PKD) progression involve abnormal cellular processes including increases in cell proliferation, fluid secretion, inflammation, and fibrosis. H2-gamzadole (H2-GMZ) is a small molecule indazole carboxylic acid that is well-tolerated in animal studies and is currently under investigation for PKD therapy. H2-GMZ appears to function as an Hsp90 inhibitor, but also targets CTRF chloride channel activity, and the actin cytoskeleton. To better understand the extent to which H2-GMZ is able to improve kidney function we investigated global gene expression changes in kidney tissue treated with H2-GMZ. This pathway is thought to be important for driving aberrant cell proliferation in PKD.

**Methods:** H2-GMZ treatment was carried out on Pkd1 floxed, Pkd1-Cre mice using daily i.p. injections of 20 mg/kg H2-GMZ from postnatal (PN) day 8 to 18. Total RNA was isolated from PN 19-day wild-type and cystic kidneys that were H2-GMZ treated or vehicle treated. Kidney tissue from three mice (2 males, 1 female) from each group was separately analyzed. RNA was synthesized and analyzed by CLC Genomics Workbench and Ingenuity Pathway Analysis (IPA).

**Results:** Mice treated with H2-GMZ had significantly reduced cystic index, kidney weight to body weight (KW/BW), and improved blood urea nitrogen (BUN). Continued treatment with H2-GMZ increased expression of genes involved in cystogenesis. RNAseq analysis showed that genes up- or down-regulated in

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

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cystic kidneys were normalized by H2-GMZ. Among the most significant changes in cystic kidneys were upregulation of immune pathways and their effectors and downregulation of calcium signaling, among others.

Conclusions: The significant improvement in kidney function and mortality suggests that H2-GMZ may be effective in treating PKD. This was supported by RNA expression analysis which indicated that there were minimal effects on wild-type kidneys and that gene expression pathways were normalized by H2-GMZ. Of particular interest was the observation of a decrease in calcium signaling and a robust acute phase response in cystic kidneys, both of which were normalized by H2-GMZ.

Funding: NIDDK Support, Private Foundation Support

FR-PO523

PRKAR1A Controls Renal Cystogenesis Hong Ye,1 Xiaofang Wang,1 Megan M. Constands, Caroline R. Sussman,1 Maria V. Irazabal,1 William F. Young,1 Peter C. Harris,2 Lawrence S. Kirschen,2 Vicente E. Torres,1 Mayo Clinic, Rochester, MN; 2Ohio State U, Columbus, OH.

Background: Although cAMP signaling is thought to be upregulated in PKD, a role for PKA has not been directly demonstrated in vivo. PKA exists as an inactive holoenzyme with two catalytic (C) and two regulatory (R) subunits (R inhibiting C). Binding of cAMP to C or R subunits are released and activated. The knockout of the R1s encoding gene (Prkar1a) is embryonic lethal. PRKAR1A mutations cause autosomal dominant Carney complex (a multiorgan tumoral syndrome) which shares features with ADPKD (loss of heterozygosity and haploinsufficiency mechanisms, proliferative response to cAMP).

Methods: To investigate the role of R1a in PKD we created a kidney specific knockout by crossing Prkar1aLOX/LOX and Pkd1 Cre mice. This was also bred into a Pkd1LOX/LOX background. To ascertain whether cystic disease is associated with PRKAR1A mutations in humans we reviewed abdominal MR or contrast enhanced CT scans of 9 patients (2 M, 7 F; 39:18 yo, range 12-63) with Carney complex (six with proven PRKAR1A mutations).

Results: Kidney specific Prkar1a knockout by itself resulted in increased P-CREB and P-ERK levels, epithelial cell proliferation, numerous bilateral cysts (positive for THP, EMA and AQP2), interstitial inflammation and fibrosis, and elevated plasma urea (Figure 1A-B). Prkar1a, which contains cAMP response elements in its promoter region, was overexpressed in Pkd1LOX/LOX mice. Prkar1a renal homologous or heterozygous knockout in Pkd1LOX/LOX mice markedly increased renal cAMP (likely due to PKA induced phosphorylation and inhibition of PDE1) and cortical density (Figure 1A-C). Four of the 7 of the 9 patients had renal (3.3 per patient, range 1-9) and hepatic (3.9, range 1-8) cysts, respectively.

Conclusions: These observations confirm the importance of PKA in the pathogenesis of PKD and that the expression of Prkar1a controls this cystogenic pathway.

Funding: NIDDK Support

FR-PO524

Developing a Mouse Model Better Reflecting ARPKD Renal Disease Severity Rory Olson,1 Katharina Hopp,2 Vladimir Gainullin,3 Peter C. Harris,1 1Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Div of Renal Diseases and Hypertension, Univ of Colorado, Denver, CO.

Background: Autosomal recessive polycystic kidney disease (ARPKD) is the most common infantile form of PKD, associated with perinatal lethality and childhood ESRD. The disease is caused by mutations to PKHD1, however, the function of the PKHD1 gene product, fibrocystin/polyductin (FPC), remains unknown. Of note, mice Pkd1 null models have relatively mild renal disease and hence are unsuitable for detailed pathomechanistic analyses.

Methods: Breeding Pkd1 null (Pkd1lox/lox) animals to the Pkd1 hypomorphic model (p.R3277C, RC) (Pkd1RC/RC), we generated Pkd1/−/− Pkd1RC/RC mice, and homozygous/ heterozygous combinations. The phenotype was assayed by percent kidney weight to body weight (%K/W BW), cyst index, IF of tubule markers and expression differences analyzed, including by RNA-Seq.

Results: The digenic, homozygous mice (Pkd1−/−:Pkd1RC/RC) died exclusively postnatally (median survival time=17, p=0.0001) with enlarged kidneys due to rapid expansion of collecting duct-derived cysts, a phenotype similar to human ARPKD, whereas Pkd1−/− or Pkd1RC/RC animals presented no or mild disease (%K/W BW at P0: 2.63±0.49 vs. 1.09±0.29, 1.43±0.16, respectively, p<0.0001 [A/B, A/A]). Interestingly, at the %K/W BW and cyst index of Pkd1−/−:Pkd1−/− and Pkd1−/−:Pkd1RC/RC animals were not significantly different from single homozygote controls (%K/W BW: 1.57±0.12 and 2.01±0.15). These results suggested a threshold effect where 3 mutant alleles did not significantly modulate the disease phenotype, but 4 mutant alleles (no FPC and ~40% PCL) resulted in severe PKD. Targeted analysis of altered pathways in the digenic homozygous animals showed upregulation of c-MYC. To further understand the pathways altered, RNA-Seq analysis was completed, revealing signaling signatures for severe and mild cyst progression.

Conclusions: This mouse model, which reflects the human severity of ARPKD, can be effectively used to reveal the molecular defects associated with the loss of Pkd1. These results indicate shared signaling events between ARPKD and ADPKD, suggesting that therapeutic intervention for ADPKD may also be beneficial to ARPKD patients.

Funding: NIDDK Support

FR-PO525

Fibroconnectin Signaling Modulates Cyst Progression in Models of Autosomal Dominant Polycystic Kidney Disease Ming Ma,1 Rachel B. Simon,2 Yasunobu Ishikawa,3 Xin Tian,1 Ke Dong,4 Yiqiang Cai,1 Chao Zhang,1 Takao Sakai,2 Stefano Somo,1,4 1Dept of Internal Medicine, Yale School of Medicine, New Haven, CT; 2Louisiana State University, College, University, New York, NY; 3Dept of Molecular and Clinical Pharmacology, Inst of Translational Medicine, The Univ of Liverpool, Liverpool, United Kingdom; 4Dept of Genetics, Yale School of Medicine, New Haven, CT.

Background: Loss of cilia suppresses cyst growth in genetic models of autosomal dominant polycystic kidney disease (ADPKD) suggesting that cilia harbor a signal that stimulates cyst progression when polycystin function is impaired. Integrin receptors for extracellular matrix (ECM) proteins have been shown to be expressed on the cilia membrane and integrin β1 (IgB1) receptor knockout has been shown to be protective in an early onset mouse model of ADPKD. Moreover, ECM remodeling has been observed in multiple models of cystic kidney disease, including ADPKD models. We investigated whether integrin signaling is one of the drivers of cyst formation in ADPKD.

Methods: We examined expression of integrin signaling pathway components in cilia and inactivated components of integrin signaling in early onset and adult inducible Pkd1 and Pkd2 mouse models of ADPKD.

Results: We confirmed that IgB1, IgA3 and IgA5 are expressed in the cilia of LLC- PK1 cells and that loss of IgB1 in collecting duct cells suppresses cyst growth in an early developmental model. Surprisingly, we found that inactivation of IgB1 does not protect, and may actually promote, cyst growth in the adult inducible mouse models of ADPKD. In contrast, inactivation of the integrin ligand fibroconnectin in the kidney tubules suppresses cyst growth and preserves renal function in both the early and adult onset ADPKD models.

Conclusions: IgB1 exhibits discordant roles for cyst progression in developmental and adult models of ADPKD, excluding a role for ciliary IgB1 as the cilia dependent signal for cyst formation in ADPKD. Fibroconnectin produced by kidney tubule cells promotes cyst growth in Pkd1 and Pkd2 models suggesting that targeting fibroconnectin or other ECM molecules may offer therapeutic benefits for the treatment of ADPKD.

Funding: NIDDK Support, Private Foundation Support

FR-PO526

The AAA ATPase Ruvbl1 Is Essential for the Maintenance of Tubular Architecture and Renal Function In Vivo Claudia Dafinger,1,2 Markus M. Rinschen,3,5 Martin Höhne,1,3,4 Rachel H. Giles,4 Dorien J.M. Peters,3 Thomas Benzing,1,3,4 Bernhard Schermer,1,3,4 Max Liebau,1,3,4 1Dept II of Internal Medicine and Center for Molecular Medicine, Univ Hospital of Cologne, Cologne, Germany; 2Dept of Pediatrics, Univ Hospital of Tübingen, Cologne, Germany; 3Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Univ of Cologne, Cologne, Germany; 4Systems Biology of Ageing Cologne (Sybac), Univ of Cologne, Cologne, Germany; 5Depts of Human Genetics, Leiden Univ Medical Center, Leiden, Netherlands; 6Dept of Nephrology and Hypertension, Univ Medical Center Utrecht, Utrecht, Netherlands.

Background: Cystic kidney diseases are among the most common causes of end stage renal disease in childhood and adolescence. Despite the recent progress in the understanding of the underlying molecular mechanisms, the pathogenesis of cystic kidney diseases remains incompletely understood. We recently identified the highly conserved AAA ATPase Ruvbl1 as a cilia-associated protein and could show that targeted deletion of Ruvbl1 in the distal tubule leads to a severe renal phenotype in mice.

Methods: To understand the role of Ruvbl1 for maintenance of tubular function and tubular architecture beyond renal development we generated an inducible tubule-specific Ruvbl1 knockout mouse. To identify components of the Ruvbl1 protein complex we also performed interaction and interactome data suggest both non-ciliary and cilia-associated functions of Ruvbl1.

Results: Induced deletion of Ruvbl1 is associated with progressive weight loss and deterioration of kidney function as well as minor cyporic tubular changes. Histological and interactome data suggest both non-ciliary and cilia-associated functions of Ruvbl1.

Conclusions: Ruvbl1 is a novel cilia-associated protein required for maintenance of tubular architecture and renal function in mice.

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

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

483A
Microcrystals Promote Cystogenesis and Exacerbate Polycystic Kidney Disease
Jacob A. Torres,1 Mina Rezaei,1 Louis Lin,1 Caroline M. Broderick,1 Saeed R. Khan,1 Vicente E. Torres,1 Benjamin D. Cowley,1 Thomas Weimbs,1
1Molecular Cellular Developmental Biology, Univ California Santa Barbara, Santa Barbara, CA; 2Dept of Pathology, Univ of Florida, Gainesville, FL; 3Dept of Pathology, Univ of Michigan, Ann Arbor, Michigan, ROCHE, 3; 4Dep of Medicine, Oklahoma Univ, Oklahoma City, OK.

Background: ADPKD is a slowly progressive disease characterized by the accumulation of fluid-filled cysts that slowly replace normal functioning kidney tissue resulting in renal failure. The rate of disease progression is highly variable amongst individuals suggesting that it is affected by unknown environmental factors. Individuals with ADPKD suffer from a number of renal pathologies including nephrolithiasis. Its therapeutic and prophylactic options are limited to secondary to ADPKD and are merely aimed at the prevention of improper kidney function. Microcrystals formed in the urinary tract, are usually cleared through luminal passage but may lodge in tubules leading to obstruction.

Methods: Han/SPRD rats were challenged with ethylene glycol leading to CaOx crystal deposition in renal tubules. To investigate whether PKD progression is specific only to CaOx crystals, PKC rats were fed a high phosphate diet leading to tubular calcium phosphate crystal deposition in renal tubules.

Results: We found that calcium oxalate or phosphate crystal deposition in renal tubules of the Han/SPRD and PKC rats respectively, lead to rapid increases in tubule diameters and activation of mTOR, Scc and STAT3 signaling pathways.

Conclusions: Tubule dilation and mTOR, Scc and STAT3 signaling pathways are aberrantly activated in ADPKD. We hypothesized that crystal deposition may act as a trigger for pathology in ADPKD. Han/SPRD rats challenged with ethylene glycol led to an increase in cyst size and cyst numbers as did CaP crystals. Together, these results suggest that PKD progression and activation of mTOR, Src and STAT3 signaling pathways.

Background: Mitochondrial Dysfunction Contributes to Cyst Proliferation of Autosomal Dominant Polycystic Kidney Disease
Yu Ishimoto,1 Masami Nagakura,1 Masanori Kuigi,1 Shizuko Nagao,1 Akira Shimizu,2 Jing Zhou,1 Reiko Inagi,1 1Nephrology and Endocrinology, Tokyo Univ, Tokyo, Japan; 2Education and Research Center of Animal Models for Human Diseases, Fujita Health Univ, Aichi, Japan.

Background: Pathological derangements characteristics of autosomal dominant polycystic kidney disease (ADPKD), such as continuous proliferation of cyst epithelial cells, show marked similarities to those of solid tumors. Mitochondria of tumor cells have been reported to differ functionally from those of normal cells and contribute to tumor progression. Therefore, we focused on mitochondrial function in ADPKD.

Methods: Compared mitochondrial DNA (mtDNA) copy number, PGC-1α (a master regulator of mitochondrial biogenesis) expression, and mitochondrial morphology by electron microscopy utilizing ADPKD model rat (Han/SPRD Cy rat) and cultured human primary and immortalized kidney epithelial cell lines. We investigated mitochondrial reactive oxygen species (mROS), ERK1/2 activity, intracellular calcium flux, and calcineurin activity were assessed in vitro. Further, the effect of mitochondria targeted therapy with MitQ on cyst cell proliferation was evaluated.

Results: Renal mtDNA copy number was decreased with disease progression from early stage of ADPKD and PGC-1α expression was reduced in the cyst lining cells compared with normal tubules (p<0.05). These changes were associated with swelling and fragmentation of mitochondria in cyst epithelial cells. Similar results were observed in vitro. Of note, we found that decreased intracellular calcium level reduced PGC-1α expression through inactivation of calcineurin, and thereby deranged mitochondrial biogenesis, which induced cyst cell proliferation via increased mROS and activation of ERK1/2. Moreover, the reduction of mROS with MitQ significantly suppressed the cyst cell proliferation.

Conclusions: Mitochondrial dysfunction contributes to cyst epithelial cell proliferation in ADPKD. Mitochondria may be a new therapeutic target for ADPKD.

Beta-1 Integrins and Extra-Mitochondrial Electron Transport Contribute to Aerobic Glycolysis in Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Wassim El-Jouni,1 Brian D. Adair,2 Wondong Kim,3 Rachid Alki,3 Eugene P. Rhee,1 Georges El Fakhri,1 M. Amin Arnaout,1 1Dept of Medicine/Nephrology, Massachusetts General Hospital, Boston, MA; 2Dept of Radiology, Massachusetts General Hospital, Boston, MA.

Background: Increased cell proliferation in ADPKD imposes a critical requirement for nutrients, a demand achieved by increasing glucose uptake and diverting cell metabolism away from mitochondrial oxidative phosphorylation towards aerobic glycolysis. This metabolic switch converts glycolytic pyruvate into lactate in the cytoplasm despite the presence of oxygen and a functional mitochondrial TCA cycle. Little is known about the cellular pathways leading to this metabolic switch in ADPKD.

Methods: We analyzed cultured DBA mouse embryonic kidney cells isolated from Pkd1 E15.5 embryos and wild type littermates using 18F) Fluoro-2-deoxy-D-glucose (18F) FDG single cell positron emission tomography (SPECT) imaging, metabolomics, and real time measurements of cellular respiration (oxygen consumption rate, OCR, extracellular acidification rate, ECAR).

Results: We made the following observations. 1) 18F)FDG SPECT revealed increased glucose uptake at the single cell level. 2) LC-MS-based metabolomics profiling of Pkd1+ vs. WT cells showed increased glycolytic intermediates, associated with significant increases in pentose phosphate pathway metabolites and decreases in several TCA cycle intermediates in the Pkd1 null cells. 3) An extra-mitochondrial sedox pathway, located in the plasma membrane and blocked by a specific inhibitory, plays a major contribution to glucose-

Quantitative Proteomic and Phosphoproteomic Analyses of Vasopressin V2R Dependent Signaling in Cultured Collecting Duct Cells with and without Primary Cilia
Caroline Palmheyer,1 Thomas Benzing, Malte P. Bartram, Bernhard Schermer, Markus M. Rinsch.1 1Dept of Internal Medicine, Univ Hospital Cologne, Cologne, Germany.

Background: The role of primary cilia in the pathogenesis of autosomal-dominant polycystic kidney disease (ADPKD) is well established. ADPKD progression is promoted by activation of the vasopressin V2-receptor and dysregulated downstream kinase pathways. At this point the impact of cilia or ciliary signaling is ambiguous. We analyzed whether ablation of cilia per se could interfere with vasopressin signaling in collecting duct cells.

Methods: We generated collecting duct cell lines expressing a dominant negative Kif3A to ablate ciliogenesis. We performed quantitative proteomic and phosphoproteomic perturbations of the V2-receptor signaling in both cell lines at different timepoints.

Results: Comparison of the proteome of uncluated Kif3A HL cells with control cells confirmed that membrane proteins and proteins belonging to the ciliary core, the axoneme, were significantly down regulated. In the control cell line, kinases under V2R phosphorylation and phosphopeptide dependent changes in signaling were largely similar to previous studies. In addition, we found that ciliary ablation per se had only minor effects on the long-term response of vasopressin dependent signaling. However, analysis of short-term responses to vasopressin revealed that ciliary ablation modulated ERK-MAPK kinases whereas proteins in the ciliary ablated condition were also interactors of Map-kinases-kinases. VPR dependent ERK inhibition, however, was present in both cell lines.

Conclusions: In summary, our data reveal only subtle changes of long-term and short term response of V2R-induced signaling caused by ciliary ablation. Thus, the switch in global vasopressin signaling network which occurs in ADPKD cells might not primarily be modulated by cilia or ciliary signaling.

Funding: Private Foundation Support, Government Support - Non-U.S.
driven cellular oxygen consumption and proliferation of Pod/ γ cells. 4) Stable silencing of integrin β1 inhibited OCR in Pod/ γ cells, suggesting a critical role for β1 integrin signaling in aerobic glycolysis in these cells.

Conclusions: These studies elucidate important mechanisms underlying abnormal cell metabolism in murine ADPKD, and identify potential targets for therapeutic intervention.

Funding: NIDDK Support

FR-PO532

Suppressing Both Renin and Angiotensin Synthesis Increases Slowly Averaged Cystogenesis Induced by Unilateral Nephrectomy in Pkd1 Mice Takamitsu Saijusa,1 Yujiing Dang,1 Catalin F. Baicu,2 Michael Zile,1 Adam E. Milllick,3 Wayne R. Fitzgibbon,3 and Darwin Bell.3 1Div of Nephrology, Medical Univ of South Carolina (MUSC), Charleston, SC; 2Div of Medicine, MUSC, Charleston, SC; 3Div of Nephrology, Univ of Alabama at Birmingham, Birmingham, AL; 1Tonis Pharmaceutical, Carlsbad, CA.

Background: Intrarenal renin angiotensin system (RAS) is activated in polycystic kidney disease. We have recently shown in Pkd1 mice, that Gene 2 antisense oligonucleotide (ASO) which suppresses angiotensinogen (AGT) synthesis, is efficacious in slowing kidney cyst formation compared to losartan. The suppression of AGT was notable for a compensatory increase in kidney renin content. Therefore, inhibiting both AGT and renin might further suppress intrarenal RAS and slow cyst kidney disease. Here we compared aliskiren+AGT ASO (Ali/Agt) to AGT ASO or control in an accelerated cystic model induced by nephrectomy.

Methods: Adult Pkd1 conditionalfoxed male mice expressing cre were administered tamoxifen resulting in global knockout of Pkd1. Two weeks after tamoxifen injection, mice underwent left unilateral nephrectomy. Mice were then treated with AgtASO (66mg/kg/wk), aliskiren (20mg/kg/d) or Agt or control (no drug) for 8 wks.

Results: Both Agt ASO and Ali/Agt treatment significantly reduced plasma and urinary sodium levels present in tubules with intact cilia, but there were no differences in mRNA for PC1 and ENaC subunits.

Conclusions: These results indicate that suppressing Agt alone is insufficient to slow an accelerated form of PKD induced by nephrectomy in Pkd1 mice. However, concomitant use of aliskiren and AGT ASO, was efficacious in slowing cyst expansion compared to Ali/Agt alone or control.

Funding: NIDDK Support

FR-PO533

Loss of Primary Cilia Increases Polycystin-2 and TRPV4 Resulting in the Appearance of a Non-Selective Cation Channel at the Apical Membrane of Mouse Cortical Collecting Duct Principal Cells Takamitsu Saijusa,1 Marlene Amjad Bunni,2 Qian Yue,2 Tiffany L. Thai,1 P. Darwin Bell,2 and Douglas C. Eaton.1 1Div of Nephrology, Medical Univ of South Carolina; 2Div of Nephrology, Univ of Alabama at Birmingham; 3Dept of Physiology, Emory Univ.

Background: Polycystic kidney disease (PKD) is a ciliopathy disorder, which results in numerous kidney cyst mostly arising from the collecting duct. The mechanism by which the loss of the primary cilium promotes cyst formation is unknown. There are several TRP channels with long mean open time (72±17 ms), P<0.05), and this beneficial effect was not affected by the overload of high salt in HWS (1.31 ± 0.10, HWI vs HWS: NS).

Conclusions: Although high blood pressure was induced by high NaCl intake, the effect of HWI was not adversely affected by salt in renal cyst expansion in PCK rats. This work was supported by Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research.

Funding: Government Support - Non-U.S.

FR-PO535

Increased Salt Intake Does Not Deteriorate Renal Cyst Disease Progression in High Water Loaded PCK Rats Masanori Kuwata,1 Tamio Yamaguchi,2 Yoichi Nagamura,2 Harold M. Aukema,3 Shizuko Nagao.1 1Education and Research Center of Animal Models for Human Diseases, Fujita Health Univ, I-9-8 Dengakugakubo Kutsukake Toyoake, Aichi, Japan; 2Dept of Clinical Nutrition, Saga Univ of Medical Science, Saga, Mie, Japan; 3Dept of Human Nutritional Sciences, Univ of Minnesota, Minneapolis, MN, Canada.

Background: We reported that high water intake (HWI) reduced the kidney/body weight ratio (KBW%), improved renal function and limited serum AVP levels in PCK rats (Nagao et al: JASN 2006). However, HWI in ADPKD patients resulted in higher total kidney volume, urine sodium and urine volume, which could be a consequence of high salt intake (Fugashihara et al: NDT 2014). In the current study, we loaded high salt in PCK rats with HWI.

Methods: PCK rats, an orthologous model of human autosomal recessive polycystic kidney disease, were randomly assigned to the control group (CONT: distilled water), high water intake group (HWI: 5% glucose) or high water intake with high salt group (HWS: 5% glucose+0.45% NaCl) and treated from 4 to 20 wk of age.

Results: Total water intake during the experimental period was 1.86 and 2.37 times higher in HWI (P<0.001) and HWS (P<0.01), respectively, compared with CONT, whereas total food intake was not different between all groups. Sodium intake in HWI was 5.71 or 5.94 times higher than CONT (P<0.001) or HWI (P<0.001), respectively. Systolic blood pressure (SBP) started to increase in HWS compared with HWI (P<0.05) at one week after high salt loading. SBP became significantly higher in HWS (164 ± 2 mmHg) compared with CONT (146 ± 1 mmHg, P<0.05), or HWI (146 ± 1 mmHg, P<0.05) at 20 wk of age.

Conclusion: Early high blood pressure was induced by high NaCl intake, the effect of HWI was not adversely affected by salt in renal cyst expansion in PCK rats. This work was supported by Japan Society for Promotion of Science Grants-in-Aid for Scientific Research.

Funding: Government Support - Non-U.S.

FR-PO535

Effects of Sodium-Deficient and High Salt Diets on Cysts Formation in ARPKD Daria Itatovskaya, Vladimir Levchenko, Jessica L. Barnett, Tengis S. Pavlov, Alexander Staruschenko. Physiology, Medical College of Wisconsin, Milwaukee, WI.

Background: Polycystic kidney diseases (PKD) are a group of nephropathies marked with the formation of fluid-filled cysts along the nephron. Generally, patients with PKD restrict their dietary sodium intake to 100 mmol/day or less, as it is expected to reduce blood pressure and albuminuria. We have shown that inhibition of epithelial Na Channel (ENaC) with benamizole aggravates cyst formation in PCK rat, a model of ARPKD. Here we hypothesize that general manipulation with sodium content in the diet can alter cyst formation.

Methods: Immunohistochemistry, Western blotting, GFR measurements in conscious animals, and routine molecular biology approaches were utilized to assess renal function in PCK rats fed a normal, high salt, and sodium-deficient (0.4% (NS), 4% (HS), and 0.01% (SD) NaCl, respectively) diets for 8 weeks (starting at 6 weeks of age).

Results: Compared to NS, both HS and SD diets resulted in a dramatic increase in the cyst formation: SD and HS diet groups exhibited 43.6% and 39.5% of cystic area compared to 28.5% in NS group). However, the development of cysts was different between HS and SD diets. HS diet provoked cyst enlargement in a manner seen in NS group. In contrast, SD diet caused extensive growth of small cysts in the cortex, and hypertrophy of the renal tissue (2K/BW ratio was 15.9 ± 0.7 when fed SD diet vs 11.5 ± 0.9 in NS and 13.7 ± 0.8 in HS groups). Urinary output was significantly higher in the HS animals compared to both SD and NS groups; interestingly, food intake did not differ. GFR levels were 3.9 ± 0.5, 6.5 ± 0.3, and 9.8 ± 1.1 µL/min/BW in SD, NS and HS fed rats, respectively. Plasma electrolytes (K+, Na+, Cl-, and Ca2+) were significantly lower in PCK rats fed HD and NT diet and not different between NS and HS groups. Consolidated with other data, BUN was almost 130 mg/dL in the SD group compared to < 20 mg/dL in NS and HS animals.

Conclusions: Both HS and SD diets significantly increase cystic area in PCK rats, although cyst formation and its effects on kidney function are different between these two groups.

Funding: NIDDK Support, Other NIH Support - NHLBI, Private Foundation Support
FR-PO536

The Recessive PKD Proteins, Fibrocystin/Polyductin and Cystin, Act Independently to Regulate Myc Expression in Human Renal Cystic Epithelia

Background: Myc overexpression in renal epithelia has been reported in several PKD mouse models, as well as human ADPKD. Transgenic mice overexpressing Myc develop renal cystic disease. Therefore, Myc has been proposed as an inducer of cystogenesis, but little is known about Myc expression in recessive PKD. In previous studies, we have shown 1) cystin, encoded by Cys1, the gene disrupted in the cpk mouse, undergoes regulated nuclear trafficking; 2) cystin downregulates Myc expression; and 3) the PKD1 gene product FPC undergoes proteolytic cleavage with nuclear translocation of the carboxy-terminus (CTD-FPC).

In the current study, we evaluated Myc expression in recessive PKD kidneys and cell lines, assessed whether CTD-FPC regulated Myc expression, and determined the effects of cystin on Myc expression.

Methods: Lysates and sections prepared from the Crys1, Bicc1m, Phkd1m mouse kidneys and lysates from wild-type and Crys1 mutant collecting duct cells were examined by immunoblotting and immunofluorescence using standard protocols. Luciferase reporter assays were conducted per our published protocol (PLOS ONE, 2013).

Results: When compared to controls, Myc is overexpressed in Crys1 and Bicc1m cystic kidneys, as well as the Crys1 cell line. In addition, we observed variable levels of MYC upregulation in ARPKD kidneys. In contrast, Myc expression was not upregulated in kidneys from the spontaneously occurring Phkd1m mutant, which does not express a renal cystic phenotype. In CTD-FPC overexpressing cell lines, Myc was upregulated and the luciferase reporter assay demonstrated that the CTD-FPC significantly enhanced the activity of Myc P1 promoter, a functional effect that was cystin-independent.

Conclusions: Our data demonstrate that Myc overexpression is a common signature of renal cystic epithelia in recessive PKD. Further, we show that in vitro assays, the CTD-FPC and cystin act independently to regulate Myc expression. The absence of Myc overexpression in Phkd1m kidneys may explain the absence of a renal cystic phenotype.

FR-PO537

Differential Expressions of miR-378a-3p/ADAMTS1 in cpk Mice, a Model of ARPKD

Background: Fibrocystin/Polyductin and cystin act independently to regulate Myc expression. The absence of Myc overexpression in Phkd1m kidneys may explain the absence of a renal cystic phenotype.

Methods: To assess roles of miR-378a-3p, previously identified by our miRNA microarray, as well as ADAMTS1, a target molecule of miR-378a-3p, we investigated the expression levels of those molecules using real-time PCR, western blotting and immunohistochemistry in kidney and urine of cpk mice.

Results: Real-time PCR confirmed that miR-378a-3p expression was significantly down-regulated in cpk kidney (day 14, n=14, 20%, p<0.01) and that ADAMTS1 mRNA was significantly up-regulated in cpk kidney (day 14, n=20, 1.4-fold, p=0.01; day 21, n=12, 3.5-fold, p=0.01) compared to control. Western blotting revealed that ADAMTS1 expression was increased in cpk kidney (day 14, n=4, 2.7-fold, p=0.02; day 21, n=4, 2.4-fold, p=0.02). Immunohistochemistry for ADAMTS1 supported these findings. Urinary miR-378a-3p expression by real-time PCR was significantly down-regulated in cpk (day 14, n=8, 15%, p<0.01).

Conclusions: Recently, dysregulation of miR-378a-3p axis is a topic in various carcinomas. Elevated ADAMTS1 promotes pro-tumorigenic changes such as increased tumor cell proliferation and altered extracellular matrix environment. Our results suggest that miR-378a-3p and ADAMTS1 axis is involved in cpk, and give us a rationale for future intervention studies for disease-specific treatments. Moreover, urinary miR-378a-3p might be a potential biomarker for PKD.

Funding: Government Support - Non-U.S.

FR-PO538

Deregulation of Long Non-Coding RNAs in Autosomal Dominant Polycystic Kidney Disease

Background: Autosomal dominant polycystic kidney disease (ADPKD) represents the most common monogenic cause of kidney failure in humans. ADPKD is characterized by progressive cyst formation in renal tubules and is caused by mutations in PKD1 or PKD2. Long non-coding RNAs (lncRNA), defined by a length >200 nucleotides and absence of a long open reading frame, have been implicated in a range of diseases. However, the role of lncRNA in PKD has not been fully understood.

Methods: We performed deep RNA sequencing to identify alterations in the expression of lncRNAs in cystic kidneys from conditional Phkd1 and Phkd2 mutant mice. We also performed de novo transcriptome assembly to discover novel lncRNAs.

Results: We identified 66 known lncRNAs and 80 non-annotated transcripts that were commonly deregulated in both mouse models. The majority of the 66 annotated lncRNAs were located in intergenic regions or were antisense transcripts. Five lncRNAs were sense transcripts, and four localized to gene introns. Characterization of 44 highly deregulated lncRNAs revealed that 82% displayed developmental changes in expression between embryonic, neonatal, and adult mouse kidney. Comparison of the expression in the kidney to other organs in the mouse revealed that 17 lncRNAs were widely expressed and four lncRNAs were kidney-specific. RNA fractionation experiments showed that 89% of the lncRNAs were predominantly located in the nucleus, suggesting that ADPKD-associated lncRNAs may be involved in transcriptional regulation. Consistent with this role, a subset of lncRNAs showed alterations in the expression of neighboring protein-coding genes in both mouse models.

Conclusions: Collectively, these studies identify a subset of developmentally regulated and tissue-specific lncRNA that may be involved in the pathogenesis or progression of ADPKD.

Funding: Other NIH Support - R37DK042921

FR-PO539

The Intron 40 Transcript from the HmPKD1 Gene Induces Major Changes in Protein Expression of NIH 3T3 Cells

Background: Informatic analysis of the HmPKD1 gene identifies 46 transcripts produced from this gene. One small transcript expressed from intron 40 of HmPKD1 is the subject of this communications. The intron 40 transcript, begins at intron 40, runs into exon 41 and then splices the 3’ end of intron 41 to the 5’ end of exon 43. Thereafter the sequence uses the standard splices site from full-length polycystin-1 (PC-1).

Methods: The sequence from the intron 40 cDNA was performed to confirm the identity of the clone relative to its identification in the UC Santa Cruz genome browser. To confirm the reading frame we cloned the construct into pRSET and used the proprietary XPRESS antibody to determine in frame expression. Based on sequence analysis we found significant homology between sequences in the intron 40 transcript and 200 bases of amino acids from the c-terminal of PC-1. Antibodies raised against c-terminal sequences of human PC-1 confirmed expression of the intron 40 transcript in NIH 3T3 cells. MS MS mass-spectroscopy was performed on cell lysates obtained from mock transfected NIH 3T3 cells and intron 40 cDNA transfected NIH 3T3 cells.

Results: Inmunoblot analysis revealed a 40 kDa protein whose molecular weight is in agreement with the predicted open reading frame. Mas spectroscopy and 2D DIGE studies revealed over 200 proteins whose expression was changed by expression of the intron 40 transcript. Major pathways down regulated include glutathione biosynthesis, colanic acid biosynthesis, GMP-mannose biosynthesis, phagosome maturation and NRF2-mediated oxidative stress response. Upregulated pathways include cysteine degradation, glutathione biosynthesis and fatty acid oxidation.

Conclusions: Intron 40 of HmPKD1 expresses a 1200 bp message that produces a 40 kDa protein. Transfection of the intron 40 produced cDNA into NIH 3T3 cells results in significant changes in expression levels of 200 proteins.

Funding: Private Foundation Support

FR-PO540

The Roles and Mechanisms of ADP Ribosylation Factor-Like GTPase 13B in Mouse Kidney

Background: ADP ribosylation factor-like GTPase 13B (Arl13b) encodes a small GTPase that regulates the Rab protein network. ARL13B mutations in patients do not cause kidney cysts.

Methods: Intron 40 of HmPKD1 expresses a 1200 bp message that produces a 40 kDa protein. Transfection of the intron 40 produced cDNA into NIH 3T3 cells results in significant changes in expression levels of 200 proteins.

Funding: Private Foundation Support
**FR-PO541**

**Centrosome Amplification Disrupts Kidney Development and Causes Cystic Kidney Disease**

**Moe Mahjoub**, 1,2 Kyuhwan Shim, 1,3 Lai Kuan Dionne, 1 Masato Hoshi, 1,4 Veronique Marthiens, 1 Amanda Knott, 1 Renata Basto, 1 Sanjay Jain. 1

1 Div of Nephrology, Dept of Medicine, Washington Univ in St Louis, MO; 2Dept of Cell Biology and Physiology, Washington Univ in St Louis, MO; 3Inst Curie, Paris, France.

**Background:** Cystic kidney diseases are characterized by hyperproliferation of normally quiescent renal epithelial cells, which proliferate after the organ architecture and impaired renal function. It is well established that defects in two essential microtubule-based organelles, the centrosome and cilia, contribute to the cyst transformation of renal epithelial cells. The centrosome-cilium complex acts as a cellular signaling center to organize and regulate the activity of various developmental signaling pathways. Recent studies have noted the presence of ectopic centrosomal structures (meaning too many centrosomes per cell) in renal epithelial cells isolated from patients and animal models of polycystic kidney disease. Surprisingly, this phenotype has been mostly ignored, and considered a potential secondary effect of cystic cell transformation and proliferation. However, we hypothesize that abnormal centrosome biogenesis may play an important causal role in the pathogenesis of the disease.

**Methods:** In this study, we make use of novel genetic mouse models with which we can alter centrosome biogenesis in vivo. We induce the formation of ectopic centrosomes in progenitor cells of the metanephric mesenchyme and the ureteric bud epithelium. Kidneys are analyzed at various stages of embryonic and postnatal development.

**Results:** We demonstrate, for the first time, that the formation of ectopic centrosomes disrupts embryonic kidney development and results in rapid cystogenesis. We also find that ectopic centrosomes sensitizes kidneys in adult mice, causing cystogenesis following renal injury.

**Conclusions:** These results indicate that ectopic centrosome biogenesis alone is sufficient to trigger cyst formation and growth, even in the absence of mutations in cystic genes. These studies further our understanding of the fundamental cellular events that trigger cystogenesis, and characterize a potentially new therapeutic target for treatment of cystic kidney disease.

**Funding:** NIDDK Support

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**FR-PO542**

**Depletion of Ciliary Gate Protein FBF1 Promotes Cystogenesis in Pkd1RC/RC Mice**

**Tao Xu,** 1,2,3,4 Nephrology and Rheumatology, Shanghai Jiao Tong Univ Affiliated Sixth People’s Hospital, Shanghai, China; 2Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 3Mayo Translational PKD Center, Mayo Clinic, Rochester, MN.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorder resulting from mutations in either PKD1 or PKD2 and characterized by massive bilateral renal cyst formation. Dysfunction of sensory organelle cilia has been tightly correlated with the pathogenesis of cystogenesis. Renal cyst is a common manifestation in various ciliopathies, but intriguingly, removal of cilia also suppresses cyst growth in ADPKD rodent model, suggesting cystogenesis mechanism between ciliopathies and ADPKD may be distinctly different. We previously discovered that FBF1 is a key component of the poorly understood transition fibres (TFs), which regulates cilogenesis imitation and selective gating of various ciliary proteins.

**Methods:** By combining genetics, cell biology, and model organisms, we study the conserved role of TFs in regulating polycystin pathway across cilia species. **Results:** Surprisingly, we found that Fbf1+/−/− knockout mice show negligible cystogenesis in the kidney or liver. Notably, combining Fbf1+/−/− with Pkd1−/− results in aggravated cyst growth in Pkd1−/− mice in both kidney and liver. By using genetic model C. elegans, cultured mammalian kidney cells, and isolated MEFs from knockout mice, we demonstrated that FBF1 and its homologue play a highly conserved role in regulating the proper homeostasis of ciliary polycystins across ciliated species.

**Conclusions:** The defective ciliary trafficking of polycystins upon depletion of FBF1 explains the severe renal and liver manifestations of Fbf1+/−/−, Pkd1−/− double mutants, and also reveal an important role for TF-mediated cilia gating in the pathogenesis of cystogenesis.

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

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**FR-PO543**

**Suppressed Autophagy Leads to Increased Apoptosis in Pkd1 Knockout Models**


**Background:** Increased proliferation and apoptosis play a role in cyst growth. The link between autophagy and apoptosis in PKD is not known. When autophagy is suppressed, there is accumulation of p62 that results in activation of caspase-8 and subsequent activation of caspase-3, the major mediator of apoptosis.

**Methods:** 90 (early PKD) and 150 d old mice with a kidney specific tamoxifen-inducible Pkd1 knockout or Human Pkd1−/− (WT 9-12) RTEC cells with a homozygous mutated Pkd1, were treated with the lysosomal inhibitors, bafilomycin (Baf) or chloroquine (CQ), to measure autophagic flux. LC3-II (autophagic flux), cleaved caspase-3 (CC-3), cleaved caspase-8 (CC-8), p62 (apoptagy/apoptosis crosstalk) was measured by immunoblot. Annexin-V staining (apoptosis) was measured by flow cytometry.

**Results:** Baf resulted in an increase in LC3-II in +/- and a decrease in LC3-II in Pkd1−/− kidneys (decreased autophagic flux) associated with increased p62, CC-3 and CC-8. CQ resulted in an increase in LC3-II in control RTEC (+/-) but not in Pkd1−/− cells suggesting decreased autophagic flux. Decreased autophagic flux and increased p62 in Pkd1−/− cells was associated with increased apoptosis (annexin V staining), increased CC-3 and increased CC-8.

**Conclusions:** The lack of effect of the lysosomal inhibitors to increase LC3-II in Pkd1−/− mice and Pkd1−/− cells suggests a defect in autophagy resulting from a block of autophagosome-lysosome fusion and degradation. Suppressed autophagy is associated with increased apoptosis and apoptosis/apoptophagy crosstalk. Autophagy inhibition with Baf or Chloroquine leads to increased apoptosis in Pkd1−/− models.

**Funding:** Pharmaceutical Company Support - ICMeditec

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**FR-PO544**

**Identification of a Novel Ciliary Targeting Sequence in Polycystin**

**Liu Lian, Xiaoyu Su, Maoqiong Wu, 1,2 David Verkaik, 1 Junhui Guan, 1,3 Jing Zhou. 1Harvard Center for Polycystic Kidney Disease Research and Renal Div, Dept of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 2Kidney Disease Center, The First Affiliated Hospital, School of Medicine, Zhejiang Univ, Hangzhou, Zhejiang Province, China.

**Background:** Mutations of PKD1 cause 85% autosomal dominant polycystic kidney disease (ADPKD) cases. Previous studies by us and others have shown that many pathogenic mutations result in defective ciliary localization of polycystin-1 (PC1), suggesting that the ciliary trafficking of PC1 might be a functional assay for ADPKD. However, how PC1 traffics to primary cilia remains poorly understood. A ciliary targeting sequence (CTS) is thought to be involved in this process. The VAP motif present in the C-terminal tail of PC1 was reported to function as a CTS through an Arf4/ASAP1 dependent manner similar to rhodopsin trafficking to the primary cilia. However, this motif is dispensable for full-length PC1 targeting to cilia. The ciliary targeting motif(s) in PC1 is to be identified.

**Methods:** A set of chimeric constructs with different motifs in PC1 including mutations that correspond to human ADPKD patients were made. These constructs were transiently transfected into JMDC3 cells, and the ciliary trafficking ability of these constructs was evaluated by immunofluorescent staining.

**Results:** Here we show that an ~40 amino acid sequence is sufficient to drive chimeric proteins to the primary cilia. This region consists of several highly conserved motifs. Multiple deletion and point mutation analyses further led to the discovery of an eight amino acid sequence that functions at an efficiency similar to the 40 amino acid sequence of the full-length PC1 targeting to cilia. The ciliary targeting motif(s) in PC1 is to be identified.

**Conclusions:** Through a systematic analysis, we have identified a novel ciliary targeting motif in PC1 responsible for targeting chimeric proteins into the primary cilia. Ongoing studies include testing its function and its regulation in full-length PC1.

**Funding:** NIDDK Support

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FR-PO545
Primary Cilia Regulate Kupffer Cell/Resident Macrophage Activation, Monocyte Recruitment, and Hepatic Fibrosis in a Mouse Model of PKD
Cell Developmental and Integrative Biology, UAB, Birmingham, AL.

Background: Patients with hepatorenal fibrocystic diseases (HRFD) including PKD develop extra-renal complications including biliary cysts and periporal fibrosis. While many HRFD genes are known, the underlying processes that drive liver cyst formation and progression are not well understood.

Methods: To better define mechanisms involved in HRFD liver disease, we used an Ift88<hi> mouse model with an insertional mutation in the IFT88 gene leading to reduced IFT88 protein, short dysfunctional cilia, and severe cysts in the kidney and liver by 4 weeks. In this study, we investigated 4 week old Ift88<hi> mice expressing the pro-fibrotic genes Col1a1 and Col3a1 and have increased collagen protein in periporal regions as indicated by picrosirius red stain. In addition, live from these mice show an accumulation of F4/80 positive macrophages in periporal regions containing smooth muscle actin (SMA) positive activated myofibroblasts and cell sorting (FACS) data indicate that a majority of the macrophages present in 4 week old Ift88<hi> mice are the pro-fibrogenic Ly6c<bb> monocytes. Whole liver transcript analysis shows a substantial increase in multiple muscle actin positive cells. Fluorescent activated cell sorting (FACS) data indicate that a

Results: In conclusion, we demonstrate that primary cilia defects alter hepatic immune responses including resident macrophage/kupffer cell activation. We show that activated kupffer cells overexpress MCP1, a known chemoattractant, that triggers the influx of Ly6c<bb> pro-fibrogenic monocytes leading to development of periporal fibrosis.

Funding: NIDDK Support, Other NIH Support - NIAIA

FR-PO546
Unilateral Nephrectomy in Adult Pkd1 Knockout Mice Accelerates Kidney Cystogenesis
Wynne R. Fitzgibbon, Yujing Dang, Marlene Amjad Bunnii, P. Darwin Bell, Takamitsu Saigausa. Div of Nephrology, Medical Univ of South Carolina, Charleston, SC; Div of Nephrology, Univ of Alabama at Birmingham, Birmingham, AL.

Background: One explanation for the variability in disease progression in patients with polycystic kidney disease (PKD) can be attributed to “third hit” signaling. We reported that unilateral nephrectomy induces hypertrophic signaling and accelerates kidney cyst formation in adult Ift88 mice, a model of recessive PKD (PMID: 21493775). Whether this applies to other PKD mouse models and the mechanism of how unilateral nephrectomy accelerates cystogenesis are both unknown. Therefore, we tested the effects of unilateral nephrectomy on cystogenesis in autosomal dominant PKD mice.

Methods: Adult Pkd1<hi> conditional floxed allele mice (C57B6 background) without cre (Pkd1<hi>) and with cre (Pkd1<hi>) were administered tamoxifen. Some mice underwent left unilateral nephrectomy (1K) and others retained both kidneys (2K). Kidneys from all 4 groups (1K&2K Pkd1<hi> and 1K&2K Pkd1<hi>) were examined for cystic development. High-throughput RNA sequencing (RNAseq) (SE50) were performed on kidney RNA extracted using Illumina HiSeq2500.

Results: Four weeks after nephrectomy, 1K Pkd1<hi> mice increased kidney/body weight and became significantly larger compared to 2K Pkd1<hi> mice. Both 1K and 2K Pkd1<hi> mice had no cyst in kidney and liver. Analysis of the RNAseq data from the 1K vs 2K Pkd1<hi> mice revealed no differences in gene regulation. However, Pkd1<hi> mice revealed, 1,335 significantly different transcripts (p<0.04) when 1K was compared to 2K kidney. Gene ontology analysis demonstrated significant enrichment of terms including cell migration and regulation of cell motility (Bonferroni adjusted p<0.003). Pathway analysis, revealed significant enrichment of genes involved in the extracellular matrix pathway (78:264 genes, Bonferroni adjusted p<0.560).

Conclusions: In summary, unilateral nephrectomy in adult Pkd1 conditional knockout mice results in accelerated kidney cyst formation compared to 2K Pkd1<hi> mice. Analysis of kidney RNAseq data demonstrated that, unilateral nephrectomy in Pkd1<hi> mice, significantly enriched and upregulated transcripts and genes compared to 2K Pkd1<hi> mice.

Funding: NIDDK Support

FR-PO547
Acute Kidney Injury and Polycystic Kidney Disease Share Common Signaling Mechanism
Marie Trokel, Almira Kurbergovic. Molecular Genetics and Development, Inst de Recherches Cliniques de Montreal, Montreal, QC, Canada.

Background: Acute kidney injury (AKI) and polycystic kidney disease (ADPKD) are both characterized by mouse models that were nucleofected into mIMCD-3 cells. Cells were synchronized at G0/G1 using simvastatin treatment.

Results: Immunoblotting confirmed that the Arl3 protein level was substantially decreased in the Arl3<hi> cells and c-Myc was overexpressed in these cells compared to control cell lines. The elevated c-Myc expression was rescued by over-expression of cysteine<hi> or cysteine<hi> (a myristoylation-deficient variant that has decreased ciliary membrane association but preserved nuclear localization and function.

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

Underlines represents presenting author.
Conclusions: We propose that the renal cystic phenotype observed in the Ar13 mice results from functional sequestration of cystin by UNC119B due to the absence of Ar13. Our data implicate cystin-UNC119B-Ar13 in a functional complex that is required to maintain normal ciliary signaling and renal epithelial homeostasis. In this functional model, loss of either Ar13 or cystin results in renal cystic disease.

FR-P0550

Cystin, the Protein Disrupted in the cpk Mouse, Is Implicated in Pkd1 Transcriptional Regulation  Jacob A. Watts, Candice Wolf, Chaozhe Yang, Maqing Wu, Naoe Harafugi, Lisa M. Guay-Woodford. Center for Translational Science, Children’s National Health Systems, Washington, DC.

Background: ARPKD results from mutations in PKHD1. However, gene-targeted Pkd1-/- mouse models and the spontaneous Pkd1+/+ mutant express limited or no kidney disease. In contrast, the cpk mouse with defects in Cystin phenotypes human ARPKD. This cross-species phenotypic similarity suggests that cystin (Cyst) and FPC (Pkd1) may function in common pathway(s) that are differentially regulated in mouse and human renal epithelia. In the current study, we sought to identify cystin-binding partners, elucidate the nuclear function of cystin, and define a potential functional interaction between cystin and FPC in mouse renal epithelia.

Methods: Cystin, α from a myristoylation deficient variant that preferentially targets to the nucleus was cloned into a TAP vector. The cystin-TAP construct, double-tagged with Strep and FLAG at the N-terminus, was stably transfected into mIMCD-3 cells. Following the TAP procedure, mass spectrometry (MS), informatics analysis (STRING v10), and targeted co-IP studies were performed. Mitigene assays and RT-PCR were conducted as described (J Mol Med, 2014).

Results: MS identified several putative cystin interacting partners, including the nuclear-extract regulatory proteins, importin α1, α2, and β2, as well as several splicing-related proteins. Our previous studies demonstrated that Pkd1 is transcriptionally complex and implicated the splicing regulator Srsf5 as a major factor in Pkd1 alternative splicing. We now show that 10 of the 12 Srsf genes, including Srsf5, are expressed in mIMCD-3 cells. Co-IP studies indicate that cystin and Srsf5 interact. In mitigene assays, a construct containing Pkd1 exons 6-7-51 (the latter with an Srsf5 binding motif) is differentially expressed in wild-type versus Cyst-/- collecting duct cells.

Conclusions: Our data: 1) indicate that cystin localizes to the nucleus via importin-regulated pathways and 2) implicate a role for cystin in the transcriptional regulation of Pkd1. These data provide the first experimental evidence functionally linking cystin and FPC in mouse renal epithelia.

FR-P0551

Four-Jointed Knock-Out Causes a Delay in Kidney Failure in an Autosomal Dominant Polycystic Kidney Disease Model with Renal Injury  Chiara Formica,1 Hester Happé,2 Kimberley Verraar,2 Sandra Kunnen,3 Marion Schärfenecker,3 Dorien J.M. Peters.1 ‘Human Genetics, Leiden Univ Medical Center, Netherlands; ‘Pathology, Leiden Univ Medical Center, Netherlands.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is characterized by the development of fluid-filled cysts, which leads to renal failure. In the majority of cases the disease is caused by a mutation in the PKD1 gene. In a previous study, we demonstrated that injury-induced tubular epithelial cell proliferation accelerates cyst formation in kidneys of inducible Pkd1-deletion (iKspPkd1+/-) mice (Happé et al., Hum. Mol. Genet, 2009). In particular, our results suggested a role for the Planar Cell Polarity (PCP) regulator Four-jointed (Fjx1), in the injury-repair mechanism. Therefore, we studied the role of Fjx1 in cyst formation and PKD progression.

Methods: We generated several mouse models, i.e. Fjx1-/- mice, iKspPkd1+/- mice as well as Fjx1-/-iKspPkd1+/- mice (double knock-out mice). After Pkd1 gene inactivation, we induced nephrotoxic injury using 1,2-dichlorovinyl-cysteine (DCVC) or PBS as control, and characterized tissue-repair and cyst formation in the different models.

Results: We confirmed that nephrotoxic injury can allow activation of cyst formation in iKspPkd1+/- mice, while this was not observed in the Fjx1-/-iKspPkd1+/- mice, which showed longer survival (median survival: 14 weeks vs 20 weeks; p=0.005). PCP, assessed by measuring Golgi position, was comparably aberrant in both iKspPkd1+/- and Fjx1-/-iKspPkd1+/- mice, early already after DCVC. This suggests a more complex regulation of PCP, and excludes a causal role for this pathway in prolonged survival. Also proliferation, Hippo signaling and cystic indices were comparable. However, fibrosis was significantly less in the double knock-out mice, consistent with the delayed kidney failure observed in this genotype.

Conclusions: Our data suggest that in PKD, Fjx1 disruption is protective against renal failure by delaying fibrosis. Further analyses to unveil the mechanism are ongoing.

FR-P0552

Ouabain Induced Differences in [Ca2+]i Response in NHK and ADPKD Cells Depend on L-type Calcium Channels  Jessica D. Venugopal,1,3 Gail Reif,2 Darren P. Wallace,2 Gustavo Blanco.1,3 ‘Molecular and Integrative Physiology, Kansas Univ Medical Center; ‘Internal Medicine, Kansas Univ Medical Center; ‘The Kidney Inst, Kansas Univ Medical Center, Kansas City, KS.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the progressive growth of renal cysts that alter the structure and function of the kidney. We have shown that the hormone ouabain enhances cell proliferation in cystic kidney epithelial cells from patients with ADPKD (ADPKD cells); but does not affect normal human kidney epithelial cells (NHK). The mechanisms involved in this dissimilar response are unclear. Due to the essential role of intracellular calcium concentration ([Ca2+]i) in ADPKD, we explored the effect and mechanisms of ouabain action on [Ca2+]i levels in NHK and ADPKD cells.

Methods: We used the calcium dye Fura-2AM as a reporter to follow [Ca2+]i changes in primary cultures of NHK and ADPKD cells, after treatment with 3 nM ouabain.

Results: Ouabain increased [Ca2+]i elevation in NHK cells was blocked by Ca2+ removal from the medium, suggesting that plasma membrane ion channels are involved in the response. Ouabain induced Ca2+ increase in NHK cells was abrogated by the L-type calcium channel (LTCC) inhibitor verapamil. Moreover, LTCC agonists restored the ouabain-dependent [Ca2+]i increase, in ADPKD cells to levels similar to those of NHK cells. LTCC agonists also blocked ouabain induced proliferation of ADPKD cells. Protein expression levels of full-length LTCC were lower in ADPKD cells than NHK cells. Concomitantly, ADPKD cells expressed higher amounts of LTCC cleavage products and greater activity of calpain, a protease involved in LTCC cleavage.

Conclusions: Our data shows that ouabain stimulates [Ca2+]i increase in NHK cells by facilitating its uptake from the extracellular space via LTCC. Instead, ouabain cannot elevate [Ca2+]i in ADPKD cells, due to low LTCC levels, which may be secondary to enhanced LTCC cleavage by calpain. The lack of [Ca2+]i response to ouabain in ADPKD cells helps enhance ADPKD proliferation, an event that exacerbates the ADPKD phenotype.

FR-P0553

Characterization of a 2R2X7 Knockout in PCK Rats, a Model of ARPKD  Tengis S. Pavlov,1,2 Daria Italovskaya,1 Vladislav Levchenko,1 Aron M. Geurts,1 Melinda R. Dwinnell,1 Alexander Staruschenko.1 ‘Physiology, Medical College of Wisconsin, Milwaukee, WI; ‘Hypertension and Vascular Research, Henry Ford Health System, Detroit, MI.

Background: Over the last decade, accumulating evidence suggests that the autocrine and paracrine effects of ATP (through F2 receptors) could be detrimental for the progression of PKD. High ATP release and concentrations were reported in cystic fluid. P2X family receptors are non-selective ion channels, permeable for Ca2+ ions; these channels are characterized by high affinity to intracellular extracellular ATP, which makes them critical for controlling cortical depended intracellular ATPases. P2X, (P2RX7) gene is expressed in the collecting ducts (CD), as well as in cysts formed from CD in ARPKD. We hypothesize that interfering with P2X, signaling precludes cystogenesis. To study this hypothesis we generated the knockout of the P2RX7 gene in PCK rat strain, an established model of ARPKD characterized by a mutation in the PKD1 gene.

Methods: P2RX7 knockout was performed within a CRISPR/Cas9 approach targeting exon 2 that resulted in a single base insertion of a ‘T’ which induced a frameshift. F2 and further litters were used to establish the colony and run pilot experiments. For characterization of the new strain, 8-weeks old animals were anesthetized and the kidneys were flushed with phosphate buffer and collected with other organs. Western blotting analysis of total kidney lysate was performed to evaluate P2X expression. To assess severity of ARPKD, H&E histological staining of central kidney slices were analyzed to calculate cyst area as percentage of total slice area.

Results: Western blotting revealed lower P2X2 expression in heterozygous compared to wild type rats (44.7%), and lack of the protein in homoygous animals. Homoyyogous animals were viable and born at Mendelian ratios from intercrosses between heterozygotes. Initial characterization of the first litters showed reduction in cyst area in the homoyogous compared to wild type or heterozygous male animals.

Conclusions: P2X2 signaling might be involved in cystogenesis in the ARPKD rodent model.

Funding: NIDDK Support, Other NIH Support - K99/R00 HL116603, R01 HL108880, K99/R00 DK105160, R24 HL114474, AHA 16161A16270006

FR-P0554

Comprehensive Metabolomics Analysis Shows Evidence of TCA Cycle Dysregulation in a Rat Model of Polycystic Kidney Disease  Ivan Vuckovic, Song Zhang, Petras Dreja, Slobodan Macura, Peter C. Harris, Vicente E. Torres, Maria V. Izrakbal. Mayo Clinic.

Background: Autosomal Dominant Polycystic Kidney Disease is a leading cause of end-stage renal disease. Many of the metabolic dysregulations contributing to cystogenesis remain to be elucidated. Using a comprehensive metabolomics approach (proton nuclear magnetic resonance, H-NMR and gas chromatography-mass spectrometry, GC-MS) we investigated the metabolic pathways associated with cystogenesis in the kidney of PCK compared to Sprague-Dawley (SD) wild-type rats.

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

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489A
Methods: We included male and female, PCK and SD rats, treated with dDAVP (PCK, D, n=16 or SD, D, n=12) to aggravate the cystic phenotype or saline solution (PCK, S, n=16 or SD, S, n=12) as controls. Kidney metabolites were identified from tissues collected at euthanasia (P37) and correlated with kidney volume byabdominal MRI (P35).

Results: Partial least squares-discriminant analysis (PLS-DA) score plots showed a significant separation between the groups (Fig 1A). Sixty five metabolites were identified by GC-MS and 42 by 1H-NMR of which 30 were significantly different between PCK_S and SD_S, and 10 of the 30 remained significant (p<0.05) between PCK_S and PCK_D. The resulting metabolic profiles demonstrated significantly increased tissue and urine levels of most TCA cycle metabolites, including citrate, isocitrate, o-ketoglutarate, succinate, fumarate and malate in PKD (Fig 1B). Moreover, tissue TCA cycle metabolites levels correlated directly with kidney volumes (Fig 1C).

Conclusions: Comprehensive metabolomics analysis showed significant increases in TCA cycle metabolites in PKC rats. Furthermore, these levels were even higher in PCK dDAVP treated rats. Studies with state of the art stable isotope (13C, 13C) labeling techniques are ongoing to investigate metabolite fluxes and carbon sources, and will aid in determining dysregulations in metabolic pathways for therapeutic interventions.

FR-PO555

Characterization of Two Pkd1 Rat Models Megan M. Constand, Diana L. Escober, Jessica M. Smith, Aron M. Geurts, Vicente E. Torres, Peter C. Harris. 1Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Genome Editing Rat Resource Center, Medical College of Wisconsin, Milwaukee, WI.

Results: Rats are well established as an experimental model of renal physiology but to date no ADPKD rat model exists. In mice, Pkd1 nulls are embryonic lethal with clear PKD at ~E14.5, while heterozygotes develop few cysts, but the V2 receptor agonist dDAVP aggravates cystic disease. The CRISPR/Cas9 system allows mutants to be generated in alternative model organisms, including rats, such that novel gene knockout models can be generated which may be more experimentally tractable. Here we describe the generation and characterization of two Pkd1 rat models.

Methods: A plasmid expressing Cas9 and short RNAs targeting exon 29 of the Pkd1 gene were injected into Lewis strain embryos and founder animals with putative Pkd1 mutations were identified. Breeding to wildtype determined germline transmission, and two mutant lines were aged to 6 months. MRI and histology characterized the heterozygous phenotype and these animals were also treated with dDAVP daily from P7 to P35.

Results: Pkd1 models were generated with either an inframe, c.9790_9801del12; p.S3273_T3276del (del12), or a frameshifting, c.9793_9800del8, p.R3274fs (del8), deletion. Analysis for homozygotes showed no live born pups for either model from 3 litters, with embryonic analysis at E14.5 not identifying any live embryos. Heterozygotes showed no significant renal enlargement at 6 months, but MRI and histological analysis showed multiple renal cysts in the cortex and medulla (median 7, range 4 to 15) are evident at P21 from a cohort of heterozygous animals. dDAVP aggravated the development of cyst number and size by ~2-fold.

Conclusions: Analysis of these new models shows heterozygous Pkd1 rats having more kidney cysts than the corresponding mice, which are aggravated by dDAVP as in the PCK rat model of ARPKD. Embryonic analysis suggests earlier lethality in the rat compared to mouse models. These new models will enhance the understanding of slowly progressive ADPKD in a rodent model.

Funding: NIDDK Support

FR-PO556

Microvascular Endothelial Dysfunction in a Rat Model of Autosomal Recessive Polycystic Kidney Disease David M. Pollock,1 Anthony K. Cook,1 Chunhua Jin,2 Robert A. Kesterson,3 Bradley K. Yoder,4 Michal Mrug,4 Edward W. Inscho,4 1Div of Nephrology, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL; 2Dept of Cell, Developmental & Integrative Biology, Univ of Alabama at Birmingham, Birmingham, AL; 3Dept of Genetics, Univ of Alabama at Birmingham, Birmingham, AL.

Background: Hypertension is a common early complication of polycystic kidney diseases (PKDs) including the autosomal recessive PKD (ARPKD). Hypertension is often associated with endothelial dysfunction, that is a lack of endothelial-dependent relaxation and an inability to buffer vasoconstriction. Thus, we hypothesized that the ARPKD rat should display impaired endothelial function.

Methods: Male, 2-month old ARPKD (PCK/Crl-Crl-Pkd1<sup>+/−</sup>) and control (Crl/Crl(SDL)) rats from Charles River were maintained on normal salt (NS 0.49% NaCl) diet prior to study. Rats were anesthetized and afferent arterioles (AA) visualized using the blood-perfused juxtamedullary nephron technique. AA diameters were measured in response to different concentrations of the endothelial dependent vasodilator, acetylcholine (ACH; 10<sup>−8</sup>-10<sup>−10</sup> M), or the endothelial independent vasodilator, sodium nitroprusside (SNP; 10<sup>−4</sup>-10<sup>−6</sup> M). An additional series of experiments were conducted in anesthetized rats surgically prepared to determine renal blood flow (RBF) responses to intravenous angiotensin II (ultrasonic flow probe).

Results: As expected, both ACH and SNP (1.0 mM) significantly increased AA diameters in kidneys from control rats (134±2% and 133±2%, respectively, n=4, p<0.05). The vasodilator response to ACH was significantly attenuated in ARPKD vessels (118±2% compared to controls while the relaxation in response to SNP was similar between strains (123±2%). Decreases in RBF following intravenous bolus of angiotensin II in ARPKD rats were significantly greater in ARPKD rats compared to controls (ARBF -47±5±4.6% vs -27±3.8%, p<0.05).

Conclusions: These results support the hypothesis that renal microvascular dysfunction in ARPKD results from endothelial dysfunction and may contribute to vascular complications in PKDs.

Funding: Private Foundation Support

FR-PO557


Background: The renin-angiotensin-aldosterone system (RAAS) plays a critical role in renal physiology and pathology. Inhibitors of RAAS, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are commonly used in the management of polycystic kidney disease (PKD). However, despite initial success in reducing aldosterone, concentrations return to pretreatment levels in 30-40% of patients. This “aldosterone escape” significantly limits the therapeutic effectiveness of current RAAS
inhibitors. An attractive novel alternative approach to target RAAS is to inhibit aldosterone synthase (AS), the enzyme encoded by the CYP11B2 gene, which is directly responsible for aldosterone production. We identified a promising new series of inhibitors of AS. Lead compound ANG3586 has potent AS inhibitory activity, has excellent selectivity against other P450 enzymes, is orally bioavailable in rodents and appears to be generally well tolerated.

Methods: Male PCK rats (PCK/Crlj-Pkd1/JcrPattern2tf) were treated with ANG3586 (25 mg/kg, po, bid) from the age of 6 weeks to the age of 10 weeks. A comprehensive panel of renal and liver endpoints was evaluated to assess the effect of compound treatment. Results: Male PCK rats at the age of 6 weeks showed markedly enlarged kidneys and livers, with evident cyst formation in both of these organs, indicating the establishment of polycystic kidney and liver disease by this age. When these animals were treated for 4 weeks with ANG3586, the kidney weight as a percentage of body weight was reduced compared to vehicle treated animals. Progression of renal cyst formation and renal fibrosis, as well as readouts of renal function such as proteinuria were also improved. Liver fibrosis was similarly ameliorated by ANG3586 treatment.

Conclusions: In preclinical experiments, the novel aldosterone synthase inhibitor ANG3586 shows promise as a possible treatment for PKD.

Funding: NIDDK Support

FR-PO559

Does the Copy Number Variation of APOL1 Gene Associate with the Susceptibility or Clinical Manifestations of Focal Segmental Glomerulosclerosis

Guiren Li, Li Wang. Renal Div and Inst of Nephrology, Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: Focal segmental glomerulosclerosis (FSGS) is a primary glomerular disease characterized by diffuse fusion or effacement of podocyte foot processes. Lots of studies demonstrated that genetic mutations can be sufficient to cause or increase susceptibility to FSGS by combining the effects of environmental factors. APOL1 gene mutation (G1 and G2) in African individuals show strongly association with FSGS, but it was not replicated in Chinese FSGS patients. The copy number variation (CNV) is another type of important genetic variations. In this study, we examined the APOL1 gene copy number in Chinese FSGS, and analyzed the relationship between CNV of APOL1 gene and the susceptibility to FSGS as well as clinical manifestations.

Methods: The copy number assay was custom designed to amplify and detect a 142bp region in the last exon of APOL1. The assay was performed using Applied Biosystems 7900HT quantitative real time PCR system by using 3ul of genomic DNA (50ng/ul). The results were analyzed using Copycaller software version 2. We analyzed 127 FSGS patients and 123 individuals without kidney disease for the presence of APOL1 gene duplication.

Results: The Copycaller results show that in case group and control group, 14 cases and 12 controls with one copies of APOL1, 91 cases and 92 controls with two copies of APOL1, 20 cases and 17 controls with three copies of APOL1, both cases and controls is only one sample with four copies of APOL1 and one sample didn’t be detected. There was no statistical significance between the case group and control group upon the APOL1 gene copy number (p=0.34). The serum creatinine and urine proteinuria in the patients with three or four copies was obviously higher than patients with one or two copy of APOL1 gene.

Conclusions: In this study, the CNV of APOL1 gene does not associate with the susceptibility to Chinese Han FSGS patients. But the patients with high copy have higher serum creatinine and urine proteinuria.

Funding: Private Foundation Support

APOL1 Nephropathy Risk Variants Alter PON1 Activity in African Americans

Orlando M. Gutierrez, Tamara Keenan, G.m. Anantnathammaiah. UAB.

Background: APOL1 nephropathy risk variants are associated with higher risk of kidney function decline and cardiovascular disease in African Americans (AA). The reasons for these associations are unclear. We reported that greater numbers of APOL1 risk variants were associated with higher circulating concentrations of small HDL subfractions linked to increased cardiovascular disease risk in population-based studies. Whether this has an impact on HDL function by APOL1 genotype is unclear.

Methods: We recruited 11 AA with two APOL1 risk variants (G1,G1; G2,G2, or G1,G2) and matched them by age and sex with 11 AA with one risk variant (G1 or G2) and 11 AA with zero risk variants. Participants provided plasma for HDL extraction and assessment of PON1 activity, indexed by paraoxonase/arylesterase enzymatic activity, and anti-oxidative capacity indexed by production of lipid hydroperoxides (LOOH) via dichlороflourescin diacetate (DCFCA) assay. We also measured these outputs in 11 European Americans (EA).

Results: All participants were healthy and free of kidney disease.

Conclusions: No association of APOL1 risk variants in AA participants (Figure 1A). In contrast, LOOH levels did not differ by number of APOL1 risk variants in AA participants (Figure 1B).

Funding: Private Foundation Support

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

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APOL1 Risk Genotype in a Cohort of French FSGS Patients

Methods: APOL1 plasmids (EV, G0, G1, and G2) were transfected into HEK 293T cells. Cell line transfected with EV (vector only), G0, G1, and G2 were evaluated for APOL1 expression by immunoblotting (using three different commercially available antibodies) as well as FACS analysis. To determine the effect of reticulum stress or misfolded protein on APOL1 variant expression, podocytes stably expressing APOL1 and APOL1 variants were analyzed for the expression of GRP78. To determine the stability of APOL1 proteins, bioinformatics analysis (MUPRO and I-Mutant 2.0) was carried out. APOL1 mRNA transcript stability was tested after actinomycin D pulsing.

Results: APOL1 variant expression was observed to be significantly lower than that of the G0 control. Podocyte cell lines stably expressing APOL1 transgenes also showed lower levels of APOL1 expression of APOL1 variants (G1 and G2) compared to APOL1G0. The enhanced expression of GRP78 by podocytes expressing APOL1 variants suggested ongoing ER stress. Bioinformatics evaluation predicted that APOL1 variants are less stable than APOL1 G0. APOL1 G0 mRNA transcript decayed 10–15% within 0.5 to 3 hours and APOL1 G2 mRNA transcript decayed 15–20% within 0.5 to 3 hours.

Conclusions: Attenuated APOL1 protein expression of APOL1 variants are due to compromised transcription and decay of the APOL1 variant transcripts.

Funding: NIDDK Support

FR-PO562

Mother and Baby APOL1 High Risk Alleles in Births Complicated by Preeclampsia

Background: APOL1 Risk Genotype in a Cohort of French FSGS Patients with African or West Indies origin and to analyze associations with clinical outcome.


Results: We studied 152 patients in 139 families: 75 patients originated from French West Indies (49.0%) and 77 (51.0%) from Africa. The two risk allele (HR) genotype was considered any combination of G1 and G2 and was found in 43.1% of subjects. Patients in the HR group were more likely to originate from French West Indies than from Africa (45.8% vs 30.4%, p<0.001). At diagnosis, patients in the HR group were more often older than 18 years than in the low risk (LR) group (34 [51.5%] vs 22 [25.6%], p=0.001) and had a lower eGFR (78.9 vs 95.2 ml/min/1.73m2) by MDRD, (p=0.03). All patients had similar evolution to end stage renal disease (ESRD) but patients were older at ESRD in the HR group (27.9±13.3 vs 16.6±12.3 years, p=0.007). There were more familial cases in the HR group than in the LR group (28 [42.4%] vs 13 [15.1%], p=0.0002). Causative mutation in known monogenic steroid-resistant nephrotic syndrome genes was found in only one individual in the HR group (NPHS1) compound heterozygous mutation associated with G1 (G1 two risk allele) and in 7 patients in the LR group. In two families, only 3/4 and 1/2 patients, respectively, had the two risk allele genotype.

Conclusions: The two risk allele genotype is found in 43% of French FSGS patients with African ancestry, compared to 13% in other population-based studies of French patients. It is more frequent in adult FSGS patients than in children and is usually not associated with other causative mutation in known monogenic steroid-resistant nephrotic syndrome genes.

Funding: Government Support - Non-U.S.
activation and dysmetabolism (eg. oxidoreductase) in CKD. Functional changes. Both analyses highlighted pathways associated with immune system (WGCNA) to identify key transcriptional nodules that correlate with structural and pathological parameters reflecting glomerular, tubulointerstitial, and vascular compartments. Hypertensive Kidney Disease

Idiopathic membranous nephropathy (IMN), more common in elderly male in developed country, is becoming the most popular primary glomerular disease in China. The reason is not clear. Phospholipase A2 receptor, PLAR1 and HLA-DQA1 genes contribute the most to IMN. It is presumed gene and air pollution were associated with the incidence of IMN. In this study, we performed a multi-center cross-sectional study in Hebei province (north China, near Beijing), to validate the increased trend of MN and the roles of gene-environment interaction.

Methods: 5785 IMN patients over 16981 who accept renal biopsy from 28 hospitals in northern China were enrolled. 339 controls were selected from 110964 DNA samples. We classified MN patients according to age (≤20, 20-40, ≥40) and air pollution level (non-risk, mid-risk and high-risk). SNPs were genotyped by TaqMan assays. Rs466308 in PLAR1 and rs2187668 in HLA-DQA1 were to validate gene roles in IMN. Gene-environment interaction was performed by epinet-calculation.

Results: From 2009 to 2013, proportion of MN in primary glomerular disease (PGN) were 27% (298/1135), 36.9% (474/1283), 45.6% (861/1942), 54.7% (1048/1917), 62.6% (1409/2250), 71.8% (1508/2092) and 78.1% (273/350) respectively, and their trend is significantly increasing, respectively. In terms of geographic and pollution level, IMN accounted for 38.6% ± 25.3% and 23.4% of PGN in middle (high risk), northwest (mid-risk) and northeast (risk) region, with the middle south mostly increased. Genotype analysis showed that IMN was significantly associated with MN (p=4.8×10−10, χ2=401.8, df=1), but not for Mn2+ levels in non-risk area. The results were consistent in multi-center interaction showed a 38 times [OR=38.72, 95%CI (12.0-125.5) p<0.01, RERI 25.0 (3.4-53.4), AP 0.8 (0.7-0.9), S 6.92, 9-16.5] of risk for developing MN.

Conclusions: IMN is the leading cause of glomerular disease in northern China. PLAR1 gene and environment interaction might contribute to the increased MN incidence.

Comprehensive mRNA Sequencing Analysis of Human Diabetic and Hypertensive Kidney Disease

Clayman, Matthew Palmer,1 Meiyun F. Hu,1 Michael J. Pullen,1 Paolo Guarnieri,2 Gregory R. Warnes,1 Carine Boustany,1 Steven S. Pullen,1 Katalin Susztak,1 Department of Medicine, Renal Electrolyte and Hypertension Div, Univ of Pennsylvania, Philadelphia, PA; 2Pathology and Laboratory Medicine at the Hospital, Univ of Pennsylvania, Philadelphia, PA; 3Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.

Background: One in ten people in the United States suffers from chronic kidney disease (CKD). Progress in CKD research and drug development has been limited, and no drugs have been registered for the last 15 years. One key limitation has been that animal models do not recapitulate common forms of CKD (diabetic and hypertensive kidney disease). The aim of the current study was to collect and analyze a large number of human kidney tissue samples and identify transcript level changes in microdissected human glomeruli and tubules.

Methods: Human kidney tissue samples were collected in RNAlater from non-neoplastic regions of tumor nephrectomies. Detailed clinical information was collected using an “最容易 broker” system. Histologic sections were scored for 19 independent pathologic parameters reflecting glomerular, tubulointerstitial, and vascular compartments. RNA sequencing of 256 human kidney tissue samples (154 control and 102 CKD) was performed on glomeruli and tubules separately using Illumina TruSeq v3 library kits and HiSeq2000 instruments. Reads were aligned using STAR aligners and annotated using Genecode human genome (GrCh37). Data analysis was performed with R/Bioconductor using a regression model.

Results: Glomerular filtration rate was best associated with tubulointerstitial fibrosis. Using statistical modeling, a large number of genes showed correlation with fibrosis and glomerulosclerosis. In addition, we applied weighted gene co-expression analysis (WGCNA) to identify key transcriptional nodules that correlate with structural and functional changes. Both analyses highlighted pathways associated with immune system activation and dysmetabolism (eg. oxidoreductase) in CKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Boehringer Ingelheim Pharmaceuticals.
in intercalated cells including SLC4A1/AE1/Band3 transcribing two kinds of mRNAs encoding the Cl⁻/HCO₃⁻ exchanger in erythrocytes and that expressed in o-intercalated cells (KAE1).

Methods: Sixty-eight unrelated Japanese uraethiopathy patients who had previously undergone histopathology were investigated regarding their capacity for renal tubular acidification function. For genomic DNAs of patients who showed urine acidification abnormality, the SLC4A1/AE1/Band3 gene was amplified in fragments encompassing all exons except exon 1 and directly sequenced. Errythroid introns 3, 7, and 17 of participants (n=13 for incomplete dRTA and n=29 for non-dRTA) were further amplified and directly sequenced. Intron 3 of the AE1 gene of an incomplete dRTA variant and a non-dRTA control were amplified and subcloned into pGL4.17 [Luc2/Neo] reporter vector. Those tester constructs as well as pNL1.1.TK [Nluc/TK] control vector were used to transfect MDCK and HEK293 cells. The normalized strength of the firefly luciferase activity was calculated by the firefly luciferase activity of each well divided by the NanoLuc luciferase activity of the same well.

Results: With the acid-loading test, 25% of uraethiopathy patients were diagnosed with incomplete dRTA. In erythroid intron 3 containing the promoter region of KAE1, n999716 SNP showed a significantly higher minor allele frequency (A) frequency in incomplete dRTA compared with non-dRTA patients. The promoter regions of the KAE1 gene with the minor allele A at rs999716 downstream of the TATA box showed reduced promoter activities compared with that with the major allele G.

Conclusions: The minor allele A at rs999716 may express less KAE1 mRNA and protein in the intercalated cells, developing incomplete dRTA. This relatively common polymorphism can cause uraethiopathy frequently in population.

FR-PO571
Will Exome Sequencing Increase the Number of Patients Referred to Nephrology Clinics? Hila Milo Rasouly, David Fasel, Adele Mitrotti, Simone Sanna-Cherchi, David B. Goldstein, Ali G. Gharavi. Medicine, Columbia Univ, New York, NY.

Background: A growing number of individuals are undergoing whole exome sequencing (WES) for diagnosis of kidney or non-kidney disorders. We studied the prevalence of variants in genes associated with kidney diseases in healthy individuals to assess the potential for incidental findings related to these disorders.

Methods: Using OMIM and Pubmed, we identified 355 genes associated with congenital disorders. We investigated 788 individuals of European ancestry, without any known medical issues, who had undergone WES using the Roche exome capture kit at the Institute of Genomic Medicine at Columbia University, as controls for non-kidney diseases. WES results were analyzed using the in-house software, ATAD, to filter by minor allele frequency (MAF range 0.01-0.001 in ExAC and EVS databases), perform functional annotation, and select likely deleterious variants as predicted by Polyphen2 and CADD scores. We also investigated prior reports of pathogenicity in ClinVar and HGMD.

Results: 509 individuals (52.5%) carried at least 5 rare, predicted deleterious variants in the 355 kidney genes (MAF<0.01, CADD>10, Polyphen >0.9). In 199 genes causing recessive disorders, 37 individuals (4.7%) were homozygous or potentially compound heterozygous for rare predicted deleterious variants. In 126 genes causing dominant disorders, 55% of individuals carried at least 2 such variants. Furthermore, 114 individuals (14.5%) carried novel predicted deleterious variants (absent in ExAC and EVS, CADD>20) and 37 individuals (4.7%) carried variants reported in HGMD and in ClinVar as pathogenic for dominant disorders associated with kidney diseases.

Conclusions: WES interpretation based solely on MAF and in-silico prediction methods may lead to misdiagnosis or erroneous assignment of multiple renal disorders to patient with nephropathy and also generate many referrals for incidental findings for individuals with no kidney disease. These data suggest the need for robust genetic criteria and consideration of prior clinical context for interpretation of genetic variants for renal disorders.

Funding: NIDDK Support, Other NIH Support - NHERI

FR-PO572
Tissue-Specific MicroRNA Expression Patterns in Four Types of Kidney Disease Maria Angeles Baker, Seth J. Davis, Pengyuan Liu, Kevin R. Regner, Yong Liu, Kenneth A. Iezkowski, Mingyu Liang. 1Center of Systems Molecular Medicine, Dept of Physiology, Medical College of Wisconsin; 2Div of Nephrology, Dept of Medicine, Medical College of Wisconsin; 3Dept of Pathology, Medical College of Wisconsin.

Background: MicroRNAs (miRs) are small RNAs that primarily bind to target mRNAs to reduce protein abundance. Several miRs have been shown to contribute to the development of kidney disease. However, previous analyses of miR expression in human kidney diseases were limited by the tissue heterogeneity of biopsy samples or the inclusion of only one pathology type.

Methods: In the present study, laser-capture microdissection was used to obtain glomerular and podocyte mRNAs from human kidney biopsy tissues for miR expression analysis using deep sequencing.

Results: Nearly 100 patients with four different types of kidney diseases including diabetic nephropathy (DN), focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), and membranoproliferative glomerulonephritis (MPGN) and a control group of patients with minimal kidney injury were analyzed. The deep sequencing detection 205 known human miRs and 173 potentially new miRs. A miR was considered differentially expressed if the adjusted p-value was lower than 0.05 compared against the control sample. In the glomeruli, 21, 17, 18, 16, and 16 miRs were respectively dysregulated in DN, FSGS, IgAN, and MPGN, compared to control. Fewer than 5 miRs were differentially expressed between any two of the four disease conditions. Nevertheless, miR-3182 was significantly downregulated in IgAN compared to all other conditions tested and several variants in miRs 146a-5p and 30a-5p distinguished DN from all other conditions.

Conclusions: In conclusion, we have identified tissue-specific miR expression patterns associated with several types of kidney pathologies. The identified miRs could serve as biomarkers of kidney diseases and might be involved in the disease mechanisms.

Funding: Other NIH Support - NHLBI

FR-PO573
Mutations of Upper Tract Urothelial Carcinoma in Chronic Kidney Disease in Taiwan Chih-Chuan Yu, Daw-Yang Huang. Div of Nephrology, Kaohsiung Medical Univ, Kaohsiung, Taiwan.

Background: Urothelial carcinoma is the most common malignant tumor of the urinary tract. In Europe and the USA, the incidence in the bladder account for more than 85% of all urothelial carcinoma with a male to female ratio of about 2:5:1. However, the upper tract urothelial carcinoma (UTUC) accounts for 40% of all kidney cancers, and the male to female ratio was 1:1.3 in Taiwan. Furthermore, dialysis patients had more urothelial carcinoma than renal cell carcinoma in Taiwan.

Methods: Sixty-four paired cancer and normal tissues of chronic kidney disease patients who were diagnosed of upper tract urothelial carcinoma were examined. Target re-sequencing was performed by using Fluidigm 48.48. Access Array and MiSeq. The panel included 1 (one) oncogenes (TXNIP, ELF, CDKN1A, MD2M, KLFL, ERCC, KDM6A, FBXW7, ARID1A, TP53, PIK3CA, CDKN2A, FBXW7, CTNNB1, KRAS, PTEN, FGFRI, FGFIR3, NFE2L2, HRAS) and 2) potential actionable receptor tyrosine kinase (FGFR1, FGFR2, FGF2, ALK, ROS1, NTRK1, NTRK3, RET, PDGFRA, PDGFRB, FLT3). CLCbio Genomic Workbench was used to analyzed data and compared with dbsNP database and COSMIC database.

Results: A high mutation rate in TP53 (45%), RET (34%), FGFIR3 (30%), FGFIR3 (22%), ARID1A (21%), and FBXW7 (17%) were found in our cohort, which is in accordance to previous bladder cancer and UTUC studies. However, several tyrosine kinase mutations, including ROS1, ALK, NTRK1, NTRK3, and PDGFRA, were found with relative high mutation incidence in our UTUC cohort.

Conclusions: Our study showed that the UTUC mutation profiles in Taiwan were similar in many well-known oncogenes as in the bladder cancer. However, differences existed in the possible actionable tyrosine kinases between bladder cancer and UTUC. This high throughput method provided mutation detection, drug applications, and cancer follow up.

Funding: Government Support - Non-U.S.

FR-PO574
Characterization of Coding Variation in the Urtrate Transporter GLUT9, a Key Determinant of Serum Uric Acid: Absence of Gain-of-Function Phenotypes Asim Mandal, 1Hyon Choi, 2Tony Merriman, 2David B. Mount. 1Renal Div, Brigham and Women’s Hospital, Boston, MA; 2Dept of Biochemistry, Univ of Otago, Dunedin, New Zealand; 3Div of Rheumatology, Massachusetts General Hospital, Boston, MA.

Background: Genetic variation in SLC2A9 encoding the GLUT9 urate transporter is the single biggest genetic contributor to serum uric acid (SUA) and hyperuricemia; loss-of-function mutations also cause genetic “renal hypouricemia”. Transcriptional initiation at different promoters generates GLUT9 isoforms with different N-termini and membrane targeting; the GLUT9a protein traffics to the basolateral membrane of epithelia whereas GLUT9b traffics to the apical membrane. Multiple common coding single nucleotide polymorphisms (eSNPs) in SLC2A9 affect SUA, with considerable population heterogeneity.

Methods: We assessed the phenotypic transport function of 30 SLC2A9 eSNPs, generating point mutants in GLUT9a/b and measuring urate transport activity in Xenopus oocytes under both depolarized and non-depolarized conditions. We also resequenced SLCO2A1 in 800 subjects with extremes in SUA, i.e. hyper/hypouricemia.

Results: We identified 14 eSNPs that generated a loss-in-function, including variants in several transmembrane domains. However, mutants corresponding to five other eSNPs were different from wild-type. Other eSNPs reduced the urate uptake activity of GLUT9a/b to similar in many well-known oncogenes as in the bladder cancer. However, differences existed in the possible actionable tyrosine kinases between bladder cancer and UTUC. This high throughput method provided mutation detection, drug applications, and cancer follow up.

Funding: Government Support - Non-U.S.
FR-PO575

Creation of Complement Factor H Mutations in Human C5a-Receptor Knock-In Mice as a Model to Assess the Effects of C5aR Antagonism in Complement-Mediated Renal Diseases

chi Li, Linda Erlt, Pirow Beckers, Israel Charo, Thomas J. Schall. Chemocentryx, Mountain View, CA.

Background: C3 glomerulopathy (C3G), and atypical hemolytic uremic syndrome (aHUS) are complement-mediated renal diseases. Mutations of complement factor H (CFH), a negative regulator of alternative complement activation, are associated with these diseases. In mouse, CFH deficiency results in a phenotype that resembles C3G, and C-terminal truncation of CFH leads to spontaneous development of aHUS. In this study, we aimed to generate these CFH mutations in mice whose complete C5a receptor (C5aR) was replaced with its human homolog, in order to assess the effects of C5aR antagonism using an inhibitor that is specific for human C5aR.

Methods: Using CRISPR technology, guide RNAs targeting the start codon (for complete deficiency) and Cysteine 937 (for C-terminal truncation) were injected into fertilized oocytes from human C5aR knock-in mice. Mutations were identified by PCR and DNA sequencing.

Results: gRNAs targeting the start codon lead to small deletions of this region and completely ablated CFH expression. In these CFH deficient mice, the C3 concentration in the circulation was dramatically reduced due to over-consumption, and renal function was impaired as evidenced by modest increase of urine albumin/creatinine ratio (UACR), even at young age. Effects of C5aR antagonists in both spontaneous andaccelerated disease settings are currently being investigated. The gRNA targeting Cys937 generated a larger deletion and unexpectedly resulted in the deletion of exon 17 of CFH, and produced a mutant CFH protein lacking amino acid 880-949. C3 levels in CFH exon 17 deletion mice are not significantly changed, and the functional consequence of this deletion is being further investigated.

Conclusions: These mice represent a new tool for assessing the contribution of C5a/ C5aR signaling to the underlying pathophysiology for complement mediated renal diseases, and will allow assessment of the therapeutic potential of specifically blocking the C5a receptor in destructive diseases such as C3G and aHUS.

Funding: Pharmaceutical Company Support - Chemocentryx

FR-PO576

New Complement Factor H (CFH) Mutations in a Patient with Pregnancy Associated aHUS

Domenico Santoro,1 Anna Perri,2 Renzo Bonofiglio.1 1Univ of Messina, Messina, Italy; 2Hospital Cosenza, Cosenza, Italy.

Background: Pregnancy-associated thrombotic microangiopathy (P-TMA) is a rare disorder associated with a significant perinatal or maternal morbidity and mortality. P-TMA may be related to acquired or constitutional deficiency in ADAMTS13, a von Willebrand factor (vWF)-processing enzyme and gene mutations for proteins involved in regulation or activation of the alternative pathway of complement. The last one can safely and successfully treated with an anti-C5 therapy (eculizumab) to induce terminal complement blockade.

Methods: S.T. 39 years female. First pregnancy (twin pregnancy) after assisted reproduction. No therapy before pregnancy. At 32 week she referred strong pain in the epigastrium. Serum analysis showed: elevated live enzymes, acute hemolytic anemia, elevation of lactate dehydrogenase, thrombocitopenia. Twin delivery was induced (2.190Kg). Serum analysis showed: elevated live enzymes, acute hemolytic anemia, thrombocitopenia. Twin delivery was induced (2.190Kg). Serum analysis showed: elevated live enzymes, acute hemolytic anemia, thrombocitopenia. Twin delivery was induced (2.190Kg).

Genetic investigations on alternative pathway regulatory proteins have been performed. The screening of the CFH gene showed a splice-site mutation on SCR11 domain in +1/GA position of the exon 12-13, not yet described in the literature.

Conclusions: Our case show the identification of a new gene mutations coding for complement factor H (CFH). Moreover, it emphasizes the importance of an early diagnosis of aHUS for a prompt start of therapy with eculizumab in order to avoid dialysis and induce a rapid renal recovery. Future studies will help to understand how long such therapy needs to be prolonged.

FR-PO577

Apoe-1 Complementation Factor: A Novel Mediator of Renal Function

Jin Lin, Yao Wang, Alanna Strong, Kiran Musumuru. Medicine, Perelman School of Medicine at the Univ of Pennsylvania, Philadelphia, PA.

Background: A recent genome-wide association study identified rs10994886 as a genetic variant associated with higher eGFR in non-diabetic humans. This variant is located in the 5’ untranslated region of A1CF (apoe-1 complementation factor), a mRNA binding protein known to facilitate the editing of apolipoprotein B (apoB) mRNA into different isoforms in other organ systems. With little known about A1CF in the renal context, we used an unbiased approach to investigate its role in the kidney.

Methods: A1cf knockout (KO) mice were generated through the CRISPR/Cas9 system, with embryonic microinjection of (1) guide RNAs to target exons 9 of A1cf (2) RNA encoding Cas9 nuclease. Plasma was collected for KO and wildtype (WT) mice 12-20 weeks of age, and whole kidneys were processed for histopathology and tissue lysate immuno blotting. In addition, RNA from whole kidneys of mice from both groups was processed for RNA sequencing (N = 6 per group).

Results: A1cf/KO mice had over 90% decrease in A1cf mRNA expression compared to their WT littermates (FDR adjusted P < 0.01). Mean plasma Cr values for KO (N = 10) and WT (N = 14) were 0.84 mg/dl and 0.66 mg/dl, respectively (P = 0.05), although no significant differences in tissue fibrosis were observed by trichrome or Sirius red staining. Immunoblot for apoB revealed low renal apoB protein expression and no differences in apoB-48/40-ApoB isoform abundance between A1cf KO and WT mice despite elevated plasma triglycerides in the KO mice (138.4 vs. 83.4 mg/dl, P < 0.01). RNA-seq of whole kidneys revealed 229 differentially expressed (DE) genes (FDR adjusted P < 0.05) between A1cf KO and WT mice. We identified top canonical cell pathways enriched within these DE genes as retinol X receptor signaling (P = 4.8E-05), insulin growth factor-1 signaling (P = 6.4E-05), and acute phase response (P = 6.5E-05). The top scoring gene networks for the DE genes included renal tubular injury, embryonic development, and lipid metabolism.

Conclusions: A1CF may have causal roles in renal function through metabolic pathways independent of apoB. Further studies in renal injury models are warranted.

Funding: Other NIH Support - KLTR0001390

FR-PO578

Low Copy Numbers of FCGR3A and FCGR3B Associated with Chinese Patients with Lupus Nephritis and Anti-Neutrophil Cytoplasmatic Antibody-Associated Renal Vasculitis

Yuan-Yuan Qi,1 Xujie Zhou,1 Ping Hou,2 Jicheng Li,2 Hong Zhang,1,2 Renal Div, Peking Univ First Hospital; 2Peking Univ Inst of Nephrology.

Background: Low copy number (CN) of FCGR3B had been implicated in systemic lupus erythematosus (SLE). However, conflicting results were reported for anti-neutrophil cytoplasmatic antibody-associated systemic vasculitis. The genetic role of CN of FCGR3A had seldom been addressed for these two autoantibody-mediated diseases. Here, we aimed to determine whether CNs in FCGR3A and FCGR3B were associated with lupus nephritis (LN) and ANCA-associated renal vasculitis in Chinese individuals.

Methods: A total of 1118 individuals were enrolled, including 320 LN, 95 SLE without renal involvement, 139 ANCA-associated renal vasculitis and 564 healthy controls. FCGR3A and FCGR3B CNs were determined by both parallel ratio test and TaqMan quantitative PCR assay. The FCGR3A and FCGR3B CN genotypes were compared between controls and among patients stratified according to clinical characteristics.

Results: By comparison of results from >800 DNA samples with CN measurements by two different methods, we validated the reliability of method at first (FCGR3A r = 0.903, p = 0.001, FCGR3B r = 0.837, p < 0.001). And in susceptibility associations, a low FCGR3B CN was significantly associated with both LN (p = 3.68*10^-7, OR 2.02, 95% CI 1.37-2.99) and ANCA-associated renal vasculitis (p = 0.04, OR = 1.72, 95% CI 1.02-2.88). And a low FCGR3A CN was also significantly associated with both LN (p=1.29*10^-4, OR 2.36, 95%CI 1.53-6.94) and ANCA-associated renal vasculitis (p = 0.042, OR 2.64, 95%CI 1.00-6.93). No similar associations were observed in lupus patients without nephritis. Further sub-phenotype analysis showed that lower FCGR3A CN associated with presence of antineutelial antibody (p = 0.036) and lower FCGR3B CN associated with anti-dsDNA and low complement (p = 0.013, p = 0.035, respectively).

Conclusions: In a large case-control study with Chinese ancestry, we identified that low CNs of FCGR3A and FCGR3B were common risk factors for LN and ANCA-associated renal vasculitis.

Funding: Government Support - Non-U.S.
FR-PO579

Development and Confirmation of Gene Classifiers of Human Clear Cell Renal Cell Carcinoma Using Next-Generation Sequencing Oystein Solberg Ekrem,1 Andreas Scherer,2 Lea Landolt,1 Hans-Peter Marti,1 Philipp Strauss.3 1Dept of Clinical Medicine, Univ of Bergen, Bergen, Norway; 2Spharmacia, Kontiolahti, Finland.

Background: We recently reported on the feasibility of RNAseq technology for capturing disease biology of clear cell renal cell carcinoma (ccRCC) and presented initial results for CA9 and TNFAIP6 as possible biomarkers of ccRCC ("discovery set"). To confirm these results we included another, independent cohort of 12 patients ("confirmation set") with biopsies from both cancer and peritumoral normal renal tissue.

Methods: From each of 12 patients undergoing nephrectomy, two core biopsies were obtained with a 16g needle. RNA sequencing libraries were generated with Illumina TruSeq® Access library preparation protocol. Comparative analysis was done using linear modeling (voom/lmm; R Bioconductor).

Results: The FFPE discovery and confirmation data yielded 9597 and 11047 detected transcripts, respectively. Each of these two datasets shared 1193 of differentially expressed genes with each other. The average expression and the log2 fold changes of differentially expressed transcripts in both datasets correlated with $R^2=0.95$, and $R=0.94$, respectively. Among transcripts with the highest fold changes in both datasets were carbonic anhydrase 9 (CA9), neuronal pentraxin-2 (NPTX2) and uromodulin (UMOD). The diagnostic accuracy of CA9 was 100% and 93.9% when using the discovery set as training and the confirmation data as test set, and vice versa, respectively. Our data further support TNFAIP6 as a novel biomarker of ccRCC. On the average, TNFAIP6 had an accuracy of 98.5%. TNFAIP6 and CA9 expression abundances on the protein level was confirmed by immunohistochemistry.

Conclusions: We provide confirmatory data of potential use of CA9 and TNFAIP6 as biomarkers of ccRCC. This enables the investigation of well defined retrospective cohorts for transcriptomic analyses from FFPE kidney biopsies.

FR-PO580

Value of Genome Copy Number Variation in Predicting Responses to a Prescribed Chinese Herbal Medicine in the Treatment of Idiopathic Membranous Nephropathy(IMN) Lin Wang,1 Shihui Li,1 Xianwen Zhang,1 Jianhui Tian,1 Ming Yang,1 Min Li,1 Yun Peng,1 Men,1 Yan Liu,2 Qian,3,4 Jianhui Wang.1,3,4 1Dept of Pathology and Molecular Medicine, McMaster Univ, Hamilton, ON, Canada; 2Dept of Medical Genetics, McMaster Univ, Hamilton, ON, Canada; 3Dept of Pathology and Molecular Medicine, McMaster Univ, Hamilton, ON, Canada; 4Population Health Research Inst, McMaster Univ, Hamilton, ON, Canada.

Background: IMN is one of the leading causes of nephrotic syndrome. Current treatment of IMN is far from satisfactory. ShenQiGranule (SQ) is a prescribed Chinese herbal medicine used to treat IMN in China for decades with significant efficacy but different clinical responses among patients. Clinical responses to IMN treatment may be genetically co-determined. To explore this hypothesis, we assessed a correlation between genome-wide copy number variation (CNV) and the clinical responses to SQ treatment in a cohort of IMN patients.

Methods: 80 patients were divided into 4 groups: complete remission (CR) of SQ(SQR, n=36); no remission (NR) of SQ (SNR, n=11); CR of herbal medicine used to treat IMN in China for decades with significant efficacy but different clinical responses among patients. Clinical responses to IMN treatment may be genetically co-determined. To explore this hypothesis, we assessed a correlation between genome-wide copy number variation (CNV) and the clinical responses to SQ treatment in a cohort of IMN patients.

Results: CNV partition called 921 CNV regions, among which 654 are gained regions, 267 are lost regions. The lengths of the CNV regions ranged from 310 bp to 3,248,859 bp, with the median size 50,365 bp. The 3 most significant CNVs regions (p<0.05) are chromosomes 5, 6, and 8). The CNV of HLA gene family, located on chromosome 6, showed gain in chromosomes 5, 6, and 8) while SNR group showed more loss (6, 3 and 5 on chromosomes 5, 6, and 8). The CNV of HLA gene family, located on chromosome 6, showed gain in IMN patients of SCR group, but loss on patients of SNR group. There were no significant differences in CNVs between SCR and INR group.

Conclusions: The differences in genetic background of IMN patients may explain some of the different clinical responses to SQ treatment. The CNVs of HLA gene family may serve as a predictive factor of the response to SQ treatment.

FR-PO581

PER1 Coordinates Kidney-Specific Sodium Trafficking and Liver-Specific Lipid Metabolism via Timing Mechanism in Nephropathy Rats Peipei Chen, Ruiyu Zhang, Lijun Mou, Xuemi Li, Yan Qin. Renal Div, Peking Union Medical College Hospital, Beijing, China.

Background: The circadian gene Per1 regulates various genes involved in sodium transport in kidney and metabolism processes in liver. We have identified the circadian rhythm of blood pressure(BP) and urine sodium excretion synchronized with the core clock genes oscillating in normal rats kidney. The present study was to explore the potential role of Per1 in communications between the peripheral organs in nephropathy rats.

Methods: Adriamycin(ADR) rats and Sprague-Dawley (SD) rats were housed in a 12:12 hour light-dark cycle and sacrificed in six time points(ZT=2,6,10,14,18,22) for 24-hr, respectively. The circadian expression of kidney and liver genes involved with clock gene per1 evaluated by the real-time quantitative PCR and the data were analyzed by a stepwise regression.

Results: 1. Per1 gene showed 24-hr and 4.8-hr rhythm in kidney and liver of SD rats, respectively. It is more significant difference in rhythm features compared with other core clock genes(Clock, Bmal1, Cry1, Cry2 and Per2) with a robust 24-hr period in both two tissues (p<0.05):2. The oscillated expression of Per1 was completely abolished in both two tissues of ADR rats. Moreover, liver presented a high level of Per1 expression and kidney showed a low level(MESOR 5.29 vs. 0.81, p<0.05):3. Kidney-specific sodium trafficking genes(eNaC, NCC and NHE3) regulated by Per1 with 24-hr rhythm in SD rats. However, ADR rats lost all oscillations of above clock and clock-controlled genes which were coupled with the disturbed circadian rhythm of BP and urinary sodium excretion in the nephrotic syndrome model:4. Per1 knockdown in HEK293 cells, the disruption of rhythmic expression of liver-specific steroid regulatory element binding protein-1c (SREBP-1c) and ATP binding cassette transporter A1(ABCA1) were regulated by Per1 involved with lipid metabolism in nephrotic syndrome.

Conclusions: The clock gene per1 plays a coordinating role in regulating sodium trafficking via eNaC, NCC and NHE3 in kidney and lipid metabolism processes in liver via SREBP-1c and ABCA1 genes. It shed new light on the molecular mechanisms of communications between the peripheral organs via circadian timing system in renal diseases.

Funding: Government Support - Non-U.S.

FR-PO582

Mendelian Randomization Study of HDL and LDL Cholesterol as Risk Factors for Chronic Kidney Disease Matthew Lanktree,1 Sebastian Thériault,1,2 Nilka Ladd,1,2,3,4 Guillermine Paret,1,2,3,4 1Dept of Medicine, McMaster Univ, Hamilton, ON, Canada; 2Dept of Pathology and Molecular Medicine, McMaster Univ, Hamilton, ON, Canada; 3Dept of Clinical Epidemiology & Biostatistics, McMaster Univ, Hamilton, ON, Canada; 4Population Health Research Inst, McMaster Univ, Hamilton, ON, Canada.

Background: Dyslipidemia is a risk factor for vascular disease, but its role in progression of chronic kidney disease is unclear. We sought to utilize Mendelian randomization (MR) analysis of public datasets to assess a causal role for dyslipidemia in chronic kidney disease.

Methods: Using data from the Global Lipid Genetics Consortium (n = 173,000) and 1000 genomes project, the effect of independent polymorphisms (r² = 0.01) on inverse normalized high-density lipoprotein (HDL) (124 polymorphisms) and low-density lipoprotein (LDL) (97 polymorphisms) cholesterol was obtained. The effect of those same polymorphisms on inverse normalized HDL. A 17 mg/dl genetic increase in HDL corresponded to a 2% increase in eGFR and 32% reduced risk of CKD. A genetic increase in LDL was associated with a 0.81 mg/dl increase in inverse normalized HDL. A 17 mg/dl genetic increase in HDL corresponded to a 2% increase in eGFR and 32% reduced risk of CKD. A genetic increase in LDL was weakly associated with higher eGFR (β = 0.008; P = 0.0001) and decreased CKD risk (OR = 0.68; 95% CI: 0.58 - 0.81; P = 7.4 x 10⁻¹⁰) per 1 unit increase in inverse normalized HDL. A 17 mg/dl genetic increase in HDL corresponded to a 2% increase in eGFR and 32% reduced risk of CKD. A genetic increase in LDL was weakly associated with higher eGFR (β = 0.005; P = 0.01), but no effect was seen for CKD risk (OR = 1.00; 95% CI: 0.85 - 1.17; P = 0.97) per 1 unit increase in inverse normalized LDL. Observed effects were similar if diabetic patients were excluded from analyses.

Conclusions: MR analysis supports a genetic increase in HDL as causally associated with eGFR and CKD risk. Genetically increased LDL did not change risk of CKD.

FR-PO583

HLA-DQA1 Variants and Risk of Steroid Sensitive Nephrotic Syndrome in Children Rasheed A. Ghadegi,2,3 Christopher Escobar,1 Larry A. Greenbaum, Mahmoud Kallash, Cynthia J. D’Alessandri-Silva, Tracy E. Hunley, Nikla deJesus-Gonzalez, Gentzon Hall, Brandon M. Lane, Megan Chryst-Ladd, Guanghong Wu, Adevobble A. Adeyemo. Pediatrics, Div of Nephrology, Duke Univ Medical Center, Durham, NC.

Background: There is relatively little known about the genetic variants underlying the risk of developing steroid sensitive nephrotic syndrome (SSNS) in children. Recently, the first exome array association study identified the missense variants C34Y (rs1129740) and F41S (rs1071630) in the first exome array association study identified the missense variants C34Y (rs1129740) and F41S (rs1071630) in HLA-DQA1 as significantly associated with SSNS in South Asian and European ancestry children. The objective of this study is to further refine this locus and evaluate its role in other ethnicities.
Methods: We screened for the C34Y and F41S in a cohort of 68 African American children with SSNS by direct sequencing. Imputation of classical alleles and amino acids in HLA-DQ41 was done in 363 South Asian children to further refine the association.

Results: We extend our original findings to African American children (C34Y p<5.7x10^-11, OR=3.53, 95% CI 2.32, 5.5, F41S p<1.2x10^-10, OR=4.08, 95% CI 2.70, 6.28). Both variants are significant cis-eQTLs for HLA-DQ41 in lymphoblastoid cell lines. Imputation of classical HLA alleles and amino acids in SA children revealed that HLA-DQ41*0201, HLA-DQBI*0201, and HLA-DRB1*0701 (p=1.5x 10^-8) are the most significant classical HLA-alleles. The most significantly associated amino acid positions are HLA-DQ41 positions (p<8.1x 10^-8) and 69 (p=6.8x 10^-7) which are in the functional domain of the protein and are located on the dimer interface of the structural model of the protein. Conditional analysis revealed that there was no residual association after conditioning on HLA-DQ41 positions 56 and 76, indicating that these are most likely the functional amino acids accounting for the observed association.

Conclusions: We have demonstrated that HLA-DQ41 is an important locus for SSNS in children of European, Asian and African ancestries and further refined the association to the critical amino acid positions of the HLA-DQ41 molecule.

Funding: NIDDK Support, Private Foundation Support

FR-PO584

Integrative Analysis of Disease-Related and Gene-Expression-Driving Genetic Variants Highlights Genes Likely Mediating Chronic Kidney Disease Development Yv-An Ko,1 Huiyuang Yi,2 Chengxiang Qiu,2 Jihuan Park,3 Anna Korttgen,2 Katalin Susztak.4 1Univ of Freiburg, Germany.

Background: Genome-wide association studies (GWAS) identified single nucleotide polymorphisms (SNPs) significantly associated with chronic kidney disease (CKD). These variants are localized to non-coding genomic regions and how they cause CKD is not understood. Expression quantitative trait loci (eQTL) is a method to identify gene-expression changes driven by genetic variations. We hypothesized that an integrative analysis of eQTL and GWAS could identify target genes of GWAS signals.

Methods: eQTL analysis was performed in 99 CEU control human kidney samples by correlating genotype with RNAseq gene expression levels. Genetic variants passed genome-wide significance and associated with CKD were manually curated. Other disease-trait GWAS signals were obtained from the National Human Genome Research Institute GWAS Catalog. Enrichment analysis was performed using colcop, a Bayesian colocalization method. Linkage disequilibrium and p-values from both GWAS and kidney eQTL were integrated in the analysis.

Results: Integrating eQTL analysis with GWAS signals identified target genes for several non-coding GWAS loci. The overlap between the kidney eQTL dataset and CKD GWAS was greater than for other disease traits (immune, cardiovascular, metabolic and other diseases), indicating variants driving CKD development are functional in the kidney. Using colcop, we identified 4 regions corresponding to 4 target genes for CKD-associated genetic signals, including a previously published gene, CASP9, and others including MANBA and ALMS1. To examine the functional role of the newly identified gene, MANBA, we used Danio rerio as a model system. eQTL analysis showed decreased MANBA expression in kidneys of subjects with risk alleles. Expression of MANBA was also decreased in kidneys of patients with CKD. Manba knockdown in zebrafish resulted in pericardial edema, a phenotype seen with kidney developmental defect.

Conclusions: Integrative analysis of genetic and transcript level data is critical to understand genes' functionality to specific trait development. Our integrative analysis identified novel genes for CKD.

Funding: Private Foundation Support

FR-PO585

Rare Genetic Variants That Segregate with Familial IgA Nephropathy Belong to a Single Happernently Modulated Immune-Related Network Sharon N. Cox,1,2 Francesco Pesce,1,2 Julia Sarah El-Sayed Moustafa,1,3 Fabio Sallustio,1,2 Grazia Serino,1,2 Charalampos Kkoufou,4 Annalisa Giampetruzzii,1,2 Nicola Ancona,1,2 Mario Falchi,1,2 Francesco Paolo Schena.1,2 1Univ of Bari, Italy; 2Ca.R.S.O. Consortium, Italy; 3Imperial College London, United Kingdom; 4King’s College London; 1IBBCS, Italy; 2ISSIA, CNR, Italy.

Background: The pathogenesis IgA nephropathy (IgAN) is still not clear but familial clustering demonstrates a strong genetic involvement. Aim of our study was to find rare, high penetrant risk variants, combining family-based linkage analysis (LA) with whole exome sequencing (WES).

Methods: Genotyping and LA were performed on 16 families of South Italian ancestry. Eight informative IgAN families containing 2 affected individuals and the most genetically informative family-based control selection were controlled for WES. Variant calling and annotation were performed with GATK high standard procedures. High priority variants in linked regions were identified and validated using Sanger sequencing. Their frequency was evaluated in external databases and with TaqMan Asays on an independent cohort of 240 IgAN patients and 113 controls. The connectivity between genes containing variants was evaluated with IPA network analysis.

Results: We found suggestive linkage signals to multiple loci. Our WES study identified 24 validated linked variants segregating with IgAN status. They were confirmed to be private or very rarely seen (MAF<0.0003) and were present within coding or regulatory regions of 23 genes that merged into an IgAN-related network. The genes were interconnected by AKT, CTNNB1, NFKB, MYC and UBC, key modulators of WNT-b-catenin and PI3K/AKT pathways, notably implicated in IgAN pathogenesis. Overlapping publicly available expression data on this network, genes/proteins whose expression is notably altered in IgAN were included. A central role in this network was ascribed to the glucocorticoid receptor, a target of corticosteroid therapy and recommended by the KDIGO guidelines in the treatment of IgAN.

Conclusions: Our study suggests that disease could be influenced by multiple rare variants acting in a common immune related network. The analysis of IgAN related network could identify novel drug-targets for personalized therapy.

Funding: Government Support - Non-U.S.

FR-PO586

rs2576178 in Renalase Gene Is Associated with Hypertension in Type 2 Diabetic Nephropathy with Overt Albuminuria Patients Limei Liu,1 Xiaoxue Ge,1 Rong Zhang,1 Ming Li,1 Weijiao Zhao,1 Feng Wang,2 Niansong Wang.3 1Dept of Endocrinology & Metabolism, Shanghai Jiaotong Univ Affiliated Sixth People's Hospital, Shanghai Diabetes Instit; 2Dept of Nephrology, Shanghai Jiaotong Univ Affiliated Sixth People's Hospital, Shanghai, China.

Background: The renalase expression is related to plasma norepinephrine, systolic blood pressure (SBP) and proteinuria and renolase gene (RNLS) polymorphism is correlated with essential hypertension, type 2 diabetes and heart failure have been reported. We performed a case-control study to investigate if the rs2576178 in RNLS is associated with hypertension in type 2 diabetic nephropathy (DN) with overt albuminuria patients in Chinese.

Methods: The study population consists of unrelated 226 type 2 diabetic nephropathy with overt albuminuria patients (DN group) and 251 diabetes without nephropathy subjects (Control group). According to the hypertension (HTN) status, the DN group was further divided into DN-HTN (+) group (n=169) and DN-HTN (-) group (n=56). Genotypic and allelic frequencies of rs2576178 as well as clinical characteristics were compared among groups. Taqman PCR assay was performed for the genotyping of all subjects.

Results: 1) Three genotypes (GG, GA and AA) of rs2576178 (G/A) were detected. The genotype distribution of rs2576178 (G/A) was in consistent with Hardy-Weinberg equilibrium. AA genotypic and A allelic frequencies were decreased in DN group when compared with Control group (P<0.05 for each). 2) AA genotype of rs2576178 is significantly associated with preventing hypertension in all subjects, by multiple logistic regression analysis, adjusted for sex, age, and BMI with OR(95% CI) of 0.48 (0.28-0.81).

Conclusions: AA genotype carriers of rs2576178 in RNLS may decrease the risk of hypertension in overt albuminuria of type 2 diabetic nephropathy when adjusted for sex, onset-age and BMI.

Funding: Government Support - Non-U.S.

FR-PO587

O-Glycosylation of IgA1 Is Associated with Genetic Variation of CIGALTI Daniel P. Ogle,1,2 David Harry John Wimbury,1,2 Fieran Yin,1,2 Patricia Higgins,1,2 Robert Klett,1,2 Xueqing Yu,1,2 Karen Molyneux,1 Jonathan Barratt.2 1UCL Centre for Nephrology, Univ College London, London, London, United Kingdom; 2Dept of Infection, Immunity & Inflammation, Univ of Leicester, Leicester, United Kingdom; 3Inst of Nephrology, The First Affiliated Hospital, Sun Yat-Sen Univ, Guangzhou, China.

Background: IgA nephropathy (IgAN) is associated with abnormal glycosylation of the IgA1 molecule. We sought factors determining IgA1 glycosylation in cohorts of patients and healthy controls.

Methods: Levels of Galactose-deficient IgA1 (Gd-IgA) were measured by lectin binding assay in a discovery cohort of 503 UK patients with biopsy-proven IgAN with >5 year follow-up data and 250 of their healthy parents in 137 complete trios, all genotyped using a 300,000-marker array. Findings were replicated in 309 UK patients with Membranous Nephropathy (MN) genotyped on a different 330,000-marker array. Further replication was performed in 690 Chinese patients with biopsy-proven IgAN genotyped at 38 markers across the locus.

Results: Gd-IgA levels were higher in IgAN patients with progressive kidney damage (p<0.01). Heritability (h2) was 0.28. Linear regression genome wide association study in 613 founder members of the discovery cohort identified alleles at a single locus, spanning the CIGALTI gene, that were strongly associated with Gd-IgA level (p<10^-10), with no other hits across the genome.

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

497A

J Am Soc Nephrol 27: 2016 Genetic Epidemiology and Other Genetic Studies of Common Kidney Diseases Poster/Friday
C1GALT1 encodes an enzyme important in galactosylation of O-linked glycoproteins. The association was replicated in separate cohorts of UK patients with MN (p<10⁻⁹), combined cohorts p<10⁻¹⁰) and Chinese patients with IgA GN (p<10⁻¹⁰). The same extended haplotype was associated with elevated Gd-IgA levels in all cohorts studied, with a frequency of 0.26 in Caucasians but only 0.02 in Chinese people.

**Conclusions:** In addition to providing robust validation of the assay, we conclude that genetic variation at C1GALT1 affects Gd-IgA level in the population.

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

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**FR-PO590**

GWAS for Serum Galactose-Deficient IgA1 Implicates Critical Genes of the O-glycosylation Pathway

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

**Poster/Friday**

**Background:** IgA1-glycosylation disorders are universally detected among patients with IgA nephropathy (IgAN). Serum level of galactose-deficient IgA1 (Gd-IgA1) represents a known heritable biomarker for IgAN, but specific genetic factors involved in its determination are not known.

**Methods:** We performed a quantitative GWAS for serum Gd-IgA1 in 2,633 individuals (IgAN cases and controls). In the discovery phase, we used HAA-lectin ELISA to profile sera of 1,195 individuals of European and Asian ancestry genotyped by Illumina 610q and 550v3 platforms. The association analysis of each cohort was adjusted for age, sex, ancestry and case status. Suggestive loci were followed by targeted genotyping in 1,438 additional individuals. Subsequently, all cohorts were meta-analyzed to identify novel genome-wide significant loci.

**Results:** The strongest association signal was mapped to chr.7p21.3 (P=3x10⁻⁹). The top SNP interacts a B-cell specific enhancer of C1GALT1, the key enzyme of the O-glycosylation pathway. This variant exhibits a significant cis-eQTL effect in which the Gd-IgA1-increasing allele is associated with lower C1GALT1 mRNA levels (P=4x10⁻⁶). The second significant locus mapped to chr.Xq24 containing C1GALT1 (P=3x10⁻⁹). This gene encodes Cosmc, the molecular chaperone of C1GALT1 protein. We confirmed the role of these two genes in the product of Gd-IgA1 by iRNA knock-down experiments in IgA1-secreting cell lines. Jointly, the new loci have large effects and explain up to 7% of the overall variability in the circulating level of Gd-IgA1.

**Conclusions:** In the first GWAS for serum levels of Gd-IgA1, we discovered two genome-wide significant loci encoding enzymes involved in the key step of O-glycosylation. Our findings provide new insights into the genetic regulation of O-glycosylation and are relevant to IgAN as well as other human diseases, including IBD, hematologic disease, and cancer.

**Funding:** NIDDK Support

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**FR-PO588**

Linking Tagging SNPs with Regulatory Information in Idiopathic Membranous Nephropathy

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

**Poster/Friday**

**Background:** Genome-wide association studies have identified an association of two single nucleotide polymorphisms (SNPs) in the introns of PLAR2 and HLA-DOA1 with idiopathic membranous nephropathy (IMN, Stanescu et al., 2011). We hypothesize that IMN SNPs with below genome wide significances can provide information on IMN disease pathways.

**Methods:** An integrative strategy was devised linking less stringently (p<10⁻³) selected SNPs associated with IMN to underlying mechanism. Utilizing ENCODE, HaploReg and RegulomeDB potentially regulatory SNPs (rSNPs) patterns were evaluated for their cis-trantcript impact using genomatix variant analyzer and mRNA levels from 28 IMN and 6 living donor biopsies.

**Results:** Starting with 525 SNPs genome-wide suggestive variants associated with IMN HaploReg identified 7,956 SNPs in linkage disequilibrium. RegulomeDB retrieved 512 potential rSNPs overlapping TF binding sites. In proximity to these 512 rSNPs we identified 127 transcripts. Nineteen of those 127 genes were differentially regulated in glomeruli of IMN patients versus 6 living donors. A strong functional concept among these 19 genes was the Antigen-presentation pathway with non-classical human leukocyte antigen complexes (HLA-F, HLA-G) and superfamily receptors modulating T cell function (BTN3A). Consistent with this concept several members of Antigen-processing pathways like PSMB9, an immunoproteasome subunit or CLC15 regulating macrophage phagosomal functions were identified.

**Conclusions:** A systems genetics approach can generate a testable hypothesis of additional molecular mechanisms in IMN by integrating GWAS and gene expression information.

**Funding:** NIDDK Support

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**FR-PO589**

Bi-Ethnic GWAS Refines Genetic Architecture of Membranous Nephropathy

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

**Poster/Friday**

**Background:** Idiopathic membranous nephropathy (IMN) is the leading cause of nephrotic syndrome worldwide. Common variants at PLAR2 and HLAI loci have previously been associated with MN in Europeans, but these signals have not yet been fine-mapped. Notably, PLAR2 (encoded by PLAR2) represents a known target of pathogenic autoantibodies in up to 70% of MN cases.

**Methods:** We performed a GWAS discovery in 1,465 East Asians and 1,685 Sardinians (543 cases and 2,496 controls). The Asian cohort was genotyped with Omni2.5–8 chip while the Sardinian cohort with OmniExpress. Following stringent QC, genotype data were imputed using 1000G reference. Imputation of classical HLA alleles was performed using SNP2HLA. Ethnicity-specific results were meta-analyzed using METAL.

**Results:** We replicated the HLA signal on chr.6p21 (OR=5.56, P=9.86E-65) and PLAR2 locus on chr.2q33 (OR=3.23, P=2.2E-24). We also confirmed a significant association between these two loci (P=1.4E-3). We next performed conditional haplotype analyses and defined a single genome-wide significant PLAR2 haplotype and 3 independent HLA haplotypes.

**Conclusions:** We confirmed the previously implicated variants with large effects on the risk of MN, fine-mapped the HLA signal to a single gene, demonstrated that the association at the PLAR2 locus can be explained by a single risk haplotype, and identified several novel suggestive loci. Our genetic results confirm that the interaction between the antigen (PLAR2) and HLA-DOA1 is critical for the development of MN, confirming strong immune component to the disease pathogenesis.

**Funding:** NIDDK Support
Conclusions: Our study provides new links between BP and immune, kidney and cardiovascular pathways, and illustrates the advantage of using hypertension susceptible populations of African ancestry to identify novel pathways for BP regulation.

Funding: Other NHIS Support - NHIIB, NIHES

FR-PO592

Pregnancy Outcomes in a Racially Diverse Patient Cohort with Lupus Nephritis

Megan A. Jobson, 1 Michelle M. O’Shaughnessy, 2 Katy Sims, 3 Scarlett Murphy, 3 William Franklin Pendergraft. 1

1Div of Nephrology and Hypertension, UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC; 2Div of Nephrology, Stanford Univ, Palo Alto, CA.

Background: Prior studies examining pregnancy outcomes in patients with lupus nephritis are generally restricted to white, non-US populations.

Methods: We examined maternal and fetal outcomes among patients enrolled in the US Renal Disease Collaborative Network who received obstetric care at the UNC Hospitals between 1995 and 2015, either within the year prior to or any time after their lupus nephritis diagnosis, prior to end-stage renal disease. Our primary outcome was fetal loss (stillbirth ≤ 20 weeks). Secondary outcomes included: premature birth (<37 weeks), fetal weight and maternal outcomes (e.g. pre-eclampsia, disease flare). Categorical variables were compared using Fisher exact testing and continuous variables using Wilcoxon rank sum testing.

Results: We identified 32 pregnancies in 24 women with lupus nephritis. Forty-two percent were black, 34% were white and the remaining 25% were other. Average age was 25 (SD 5.4) with black mothers being younger than white mothers (p=0.001). At baseline, mean serum creatinine was 0.92 mg/dL (SD 1.2) and urine protein 1.4 mg/24hrs (SD 2.2). There were 4 fetal losses, all between 20-24 weeks of gestation, 3 spontaneous and one elective due to disease severity. There were no differences based on race for multiple variables including low birth weight (<2.5), preeclampsia (0.07), prematurity (0.03), having a pediatrician present at birth (0.01), NICU admission (0.004), renal flares in pregnancy (0.008) and IgG (0.04), which were seen more often in black mothers compared to other racial groups. The median gestation was 35 weeks (IQR 34, 37). Sixteen pregnancies (50%) developed pre-eclampsia, 8 were black, and 88% were non-white. Four required dialysis during pregnancy (3 black).

Conclusions: We identified a high frequency of adverse fetal and maternal outcomes in women with lupus nephritis, especially in black patients. We plan to evaluate this further in a multi-site study that includes lupus patients without nephritis as a control for effects seen in black and other non-white pregnancies.

FR-PO593

A Clinical Research of the Effect of LEF as an Induction Treatment for Proliferative Lupus Nephritis

Feng, Daping, Hong, Li Wang, Renal Div and Inst of Nephrology, Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: To assess the efficacy and safety of LEF (LEF) as an induction treatment for proliferative lupus nephritis (PLN).

Methods: Thirty biopsy-proven PLN patients were included and randomized to LEF treatment group (LEF group) and cyclophosphamide (CTX) group with prednisolone (CTX) for 24 weeks. Urine routine, blood routine, blood biochemistry, quantitation of anti-ds-DNA, compliment C3, T-cell subsets and SLEDAI scoring were measured and all adverse reactions were assessed during the study.

Results: Proteinuria and SLEDAI score was reduced, and hemoglobinuria, serum albumin was increased significantly after 24-week treatment (p<0.001). At baseline, the LEF group had significantly higher levels of serum creatinine than the CTX group (p=0.02). After treatment, the difference was eliminated (p=0.11). The LEF group had a higher rate of complete response (p=0.003) and a trend toward a lower rate of renal flares (p=0.05) compared to the CTX group.

Conclusions: LEF has a good efficacy as an induction treatment for PLN. LEF has the equivalent efficacy to that of CTX at the end of the induction treatment but lower adverse reactions and better patient compliance than that of CTX, indicating its further use in the treatment of PLN patients.

FR-PO594

Comparison of Clinical and Histologic Changes in Kidney Biopsies for Lupus Nephritis (LN) Repeated Early and Late after Induction Therapy

Ana Malvar, 1 Valeria Gabriela Alberton, 2 Cecilia Recalde, 1 Bruno Jorge Lococo, 1 Brad H. Rovin. 1 Nephrology, Fernandez Hospital, Buenos Aires, Argentina; 2Pathology, Fernandez Hospital, Buenos Aires, Argentina; 3Nephrology, Ohio State University, Columbus, OH.

Background: Repeat kidney biopsies (Bx) done 6-9 months after starting treatment for LN in females persistently positive for nucleic acid-dependent complement receptor(CR1). We postulated that expanding the interval between repeat Bx may demonstrate more complete histologic resolution and a better correlation to clinical findings. To test this hypothesis we examined histologic and clinical responses at 7 and 14 months after initiating LN therapy.

Methods: 34 patients (9 LN) were biopsied at first presentation of kidney involvement(Bx1) and again (Bx2) either 7 (n=30) or 14 months (n=23) after starting therapy with steroids+MMF. NIH activity(AI) and chronicity(CI) indices, proteinuria (UP) and serum creatinine(SCR) were compared. Complete Response was defined as normal SCR and prot ≤ 0.5 g/d.

Results: Clinical and histologic data are shown in the Table presented as median(range). Final prot was determined after a mean follow-up of 55±12 months. Conversely, proteinuria at Bx2-7 months did not reflect long-term outcome, but at 14 months the association appeared to be better.

FR-PO595

Characteristics and Outcomes of Males with Lupus Nephritis in a Racially Diverse Patient Cohort

Stephen A. Proctor, Megan A. Jobson, Caroline J. Poulton, Keisha L. Gibсон, William Franklin Pendergraft. Div of Nephrology and Hypertension, UNC Kidney Center; Univ of North Carolina, Chapel Hill, NC.

Background: Prior studies examining lupus nephritis (LN) in males have been limited to small racially homogenous cohorts or cohorts outside of the US. Little information exists on the differences between disease in males and females and in white males compared to black males.

Methods: We evaluated disease history and outcomes among patients enrolled in the Glomerular Disease Collaborative Network who were diagnosed with biopsy proven LN. Our primary outcome was end stage renal disease. Secondary outcomes include death and transition from biopsy. Categorical variables were compared using Fisher exact testing and continuous variables using a Mann Whitney test.

Results: A total of 125 male patients with biopsy proven LN were included in the study. Forty-two percent were black, 39% were white and 19% were other. Sub-stratification by race revealed black race to be associated with positive anti-RNP (p=0.004), SSA (p=0.006), SSB (p=0.03), and Smith (p=0.01) antibodies, and present with serositis at presentation (p=0.05) compared to white males. White males had more intense C1q staining compared to black males (p=0.05) and males had more intense C1q staining compared to females (p=0.001). There was no difference in rates of ESRD, time from biopsy to ESRD and mortality in black patients when compared to white male counterparts; however, males time to ESRD from biopsy was shorter compared to females (2.8 vs 4.2 years, p=0.05). Males were more likely to die (0.008) compared to females, but time to death was similar between the two groups (males 4.9 years, females 4.7 years, p=0.4).

Conclusions: We identified that male patients with lupus nephritis have higher mortality rates compared to females. Further understanding of why male presentation and serological markers vary by race and why males have a higher mortality rate need to be elucidated further to provide optimized interventions and therapeutic plans.

FR-PO596

Correlation between Trough Levels of Mycophenolic Acid and Area under the Curve in Patients with Lupus Nephritis

Nippon Pournashr, Rajesh Chandhas, Eric S. Sobel, Westley Reeves, Xuexong Wen, Mark S. Segal. Univ of Florida, Gainesville, FL.

Background: Mycophenolate motefil is the mainstay of induction as well as maintenance therapy for lupus nephritis. Monitoring trough levels of mycophenolic acid (MPC) is particularly important in this population of patients for effective dosing and prevention of toxicity due to the high pharmacokinetic variability, however whether trough levels are the acceptable method of monitoring, remains debatable. We hypothesized that trough levels of MPC might be a poor predictor of Area Under the Curve (AUC) of mycophenolic acid in patients with lupus nephritis.

Methods: 31 patients with lupus nephritis were included in this study. We measured fasting trough levels of mycophenolic acid. Patients were then given the usual dose of oral mycophenolic acid. Mycophenolic acid levels were measured at 0(C0), 1(C1) and 2(C2) hours. The MPA-AUC values were calculated using the linear trapezoidal rule. Pearson or Spearman correlations were used to look for correlations. Multiple linear regression and logistic regression analyses were employed to examine significant predictors of continuous and categorical dependent variables, respectively.

Results: There was a statistically significant correlation between trough levels of mycophenolic acid and area under the curve (P=0.002). However linear regression showed an R² of only 0.55. Demographic, clinical or laboratory variables did not identify subgroups in which trough levels were predictive of AUC. We were able to show that MPA trough level has a significant but moderate correlation (r² = 0.55, P = 0.002) and a positive linear relationship with MPA AUC.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
The occurrence of adverse events was higher in the CYC than in MMF group (56 vs. 15 non-infection related and 10 vs. 7 infection related events).

Conclusions: Present study found that MMF is equally effective in inducing remission with reduction of proteinuria and improvement of kidney function with lesser adverse events than CYC in proliferative lupus nephritis in 6 months therapy.

FR-PO595
Steroid-Treatment Promotes a M2 Pro-Fibrotic Macrophage Phenotypic in Lupus Nephritis
Yohji Kezumi,1 Yuji Matsumoto,1 Takeshi Yamada,2 Hiroya Hasegawa,3 Ichiei Narita,4 David J. Nikolic-Paterson,5 Dept of Pediatrics, Fujita Health Univ School of Medicine, Toyoake, Japan; 1Dept of Nephrology, Niigata Univ Medical and Dental Hospital, Niigata, Japan; 4Dept of Nephrology, Niigata Univ Medical and Dental Hospital, Niigata, Japan; 5Dept of Medicine, Monash Univ, Clayton, Victoria, Australia.

Background: M1 pro-inflammatory macrophages (M0) promote glomerular injury in lupus nephritis (LN). However, it is unclear whether steroid therapy affects macrophage phenotype in these patients. We examined the effect of steroid treatment on M0 phenotype in LN.

Methods: 46 patients with LN were divided in 2 groups; N group, underwent biopsy before steroid-treatment (N=24, 20.0±9.2 years at biopsy); S group, underwent steroid treatment (2 to 6 months) before biopsy (N=19, 20.1±9.2 years at biopsy). Macrophage number and phenotype was assessed by immunofluorescence. In vitro studies used monocyte-derived M0 from healthy human volunteers.

Results: Urine findings were comparable between the two groups, but the S group had a significantly lower eGFR (104±34 vs 125±22 ml/min/1.73m²; p<0.05). Biopsies revealed les endocapillary proliferation (p<0.05) and greater glomerular matrix expansion (p<0.01), glomerulosclerosis (p<0.001) and interstitial fibrosis (p<0.05) in the S group. The total CD68+ M0 infiltrate was comparable between N and S groups. However, the N group had fewer M1 (CD68+CD86+) cells (p<0.05) and more M2 (CD68+CD163+) cells (p<0.05), giving a 6-fold increase in the M2/M1 ratio in S vs N groups. In addition, M2 M0 correlated with glomerular matrix expansion and interstitial fibrosis (p<0.001). Steroid (dexamethasone) treatment of cultured M0 induced up-regulation of CD163 expression, increased production of anti-inflammatory (IL-10 and pro-fibrotic factors (TGF-β), CTGF), and up-regulated the scavenger receptor, stabilin-1. We confirmed up-regulation of stabilin-1 in CD163+ M0 M0 in biopsy from the S group.

Conclusions: Initial steroid treatment induces a M0 phenotypic change from pro-inflammatory M1 to pro-fibrotic M2 in LN with acute/active lesions. Promotion of fibrotic lesions via M2 M0 is a potential downside of steroid single therapy in LN.

FR-PO600
Clinical Features of Metabolic Indices Patients with Lupus Nephritis
Hui Zhou, Lizi Li, Congcang Jiao, Di Li, Kong Weimei, Lining Wang. The First Hospital of China Medical Univ, China.

Background: Lupus Nephritis (LN) is an autoimmune mediated disease. Metabolic disorders often occur in chronic kidney diseases. We aim to investigate clinical features of metabolic indices in LN patients.

Methods: 194 patients with LN proven by renal biopsy were treated with steroid and immunosuppressants at China Medical University from 2007 to 2015. 24h total urinary protein (uTP), hematuria (uRBC), estimated glomerular filtration rate (eGFR-EPI), systemic lupus erythematosus disease activity index (SLEDAI), complement (C), immunoglobulin (lg), and serum metabolic indices including uric acid (UA), low-density lipid cholesterol (LDL-C), and calcium (Ca) were observed up to 18 months. The correlations between pretreated metabolic indices and severity of LN before and after treatment were analyzed.

Results: After 18 months’ treatment, uTP, uRBC, SLEDAI, and IgG decreased (uTP 4.3±0.3 vs 0±0.7 g/24hr, p<0.01; uRBC 50±10 vs ≤5±2/hp, p<0.01; SLEDAI 17.3±0.6 vs 5±3.0/p, p<0.01; IgG13.2±0.6 vs 9.9±0.4 g/L, p<0.01; C3: 0.5±0.2 vs 0.9±0.4 g/L, p<0.01; C4: 0.1±0.01 vs ≥0.2±0.2 g/L, p<0.01). The pretreated metabolic indices significantly correlated with the activity of systemic and renal disease before and after treatment (table).

FR-PO597
Treating Lupus Nephritis with Rituximab and Mycophenolate Mofetil (RituxiRescue Regimen) without Increasing Maintenance Oral Steroids Leads to Sustained Disease Remission and Steroid Reduction
Camilla Pilay, Megan Griffith, Jeremy B. Levy, Tom Cairns, Liz Lightstone. Imperial College Lupus Centre, London, United Kingdom.

Background: To the morbidity caused by high-dose and long-term steroids we have used rituximab as a steroid-sparing agent in patients on maintenance steroids who develop active lupus nephritis (LN). The RituxiRescue regimen (2 × 1g rituximab ± 125-500mg methylprednisolone) at d1 and 15, maintenance mycophenolate mofetil + ↑ in bline steroid dose) led to steroid cessation at 1 year in 18 patients with LN (NDT, 2009).

Methods: Inclusion: 38 patients with class III/IV-VN on biopsy, on steroids ≥ 4 weeks at bline, ↑ in 5 years Fup, Dec 2005-Mar 2016. Exclusion: Requirements for dialysis or cerebral/or other life-threatening lupus features. Treatment: Complete (CR) or PR ≤ 50, eGFR ≥ 60 or ≤ 20% ↓ if > 60 at bline. Partial (PR): uPCR < 50% + ↑ in bline steroid dose ≤ 20% (not nephrotic) + ↑ in bline steroid dose ≤ 300 (if nephrotic) from bline. Relapse (from CR/PR): uPCR > 50% ↑ in CR/PR + ≤100 + eGFR ≥ 60% ↓ from bline.

Results: Outcomes in 38 patients by 1 and 5 years, 4 lost to Fup.

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>5 years</th>
<th>Median time to event (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR</td>
<td>23(62.3)</td>
<td>33(93.9)</td>
<td>13.0(4.8-33.5)</td>
</tr>
<tr>
<td>No response</td>
<td>12(32.4)</td>
<td>8(24.2)</td>
<td></td>
</tr>
<tr>
<td>Relapse from CR/PR</td>
<td>2(5.4)</td>
<td>7(21.2)</td>
<td>28.4(10.4-80.8)</td>
</tr>
<tr>
<td>↓ in eGFR ≥ 50%</td>
<td>3(8.1)</td>
<td>3(8.1)</td>
<td>13.2(7.1-54.6)</td>
</tr>
<tr>
<td>Mean steroid dose (mg)</td>
<td>7.5</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Off oral steroids</td>
<td>7(18.9)</td>
<td>13(34.5)</td>
<td></td>
</tr>
</tbody>
</table>

1 death (28 y/o male, non-adherent) at 21.9 months. 2.37 with ↓ in eGFR ≥ 50% at 1 year progressed to ESRD (from no response). By 5 years: 13/33 had not responded/relapsed before CR/PR with no reccomendation ↑ in oral steroid dose from baseline. Median time to steroid cessation: 21.4 months (10.4-46.8). Adverse events: 19/21 episodes of infection (21 patients) required hospitalisation, 23.8% by 1 year. 42% (16/38) patients had evidence of steroid toxicity, 62.5% (10/16) bone related.

Conclusions: The RituxiRescue regimen led to sustained disease remission and a significant ↓ in steroid dose/cessation by 5 years. Poor renal outcomes were rare + adherence related. The data suggest that it is safe not to ↓ baseline oral steroids at relapse.

FR-PO598
Effect of Cyclophosphamide versus Mycophenolate Mofetil in Induction Therapy of Lupus Nephritis in Nepalese Population
Arun Sedhain, Rajani Hada, Rajendra Kumar Agrawal, Anil Baral, Gandhi R. Bhattarai. Nephrology, National Academy of Medical Sciences (NAMS), Kathmandu, Nepal.

Background: Management of SLE and lupus nephritis (LN) comprises timely and coordinated management consisting of induction phase followed by maintenance phase. This study aimed to evaluate and compare the effectiveness and safety profile of mycophenolate mofetil and intravenous pulse cyclophosphamide in induction therapy of proliferative LN in Nepalese population.

Methods: A prospective open label randomized control trial was conducted in a tertiary hospital at Kathmandu, Nepal for a period of one and half year from January 2014 to June 2015. Fifty two patients with biopsy proven proliferative lupus nephritis were screened and 49 patients were randomized out of which only 42 patients could complete the study period of six months. Monthly intravenous injection of pulse cyclophosphamide (CYC) was given to one group and daily oral mycophenolate mofetil (MMF) to the other. Participants were followed up monthly and the results were analysed at the end of 6 months.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO601

Urinary Levels of TWEAK as a Biomarker of Lupus Nephritis in Hispanic Populations

Fabiola Reyes,1 Monserrat M. Perez-Navarro,2 Adrian Rodriguez Mattas,1 Virgilia Soto3 Gabriela Gutierrez,1 Zaira Valdez-Anaya,1 Rafael Valdez-Ortiz.1 1Servicio de nefrología, Hospital General de México, Mexico, Mexico; 2Dept of Pathology, Hospital General de México, Mexico, Mexico; 3Dept of Experimental Medicine, Univ Nacional Autónoma de México, México, Mexico.

Background: Urinary levels of TWEAK (uTWEAK), may be correlated with the degree of lupus nephritis (LN) activity. Our objective was to determine the sensitivity and specificity of uTWEAK in Hispanic patients with active lupus nephritis.

Methods: A clinical study was performed. Four groups of patients were analyzed as follows: 1) patients with systemic lupus erythematosus (SLE) without renal activity (SLE-LN), 2) patients with SLE with renal activity (SLE+LN), 3) patients with other types of glomerulopathies (GMN), and healthy patients (controls).

Results: In all, 44 patients, with an average age of 35.9±11.5 years, were evaluated. uTWEAK levels were higher in patients with SLE+LN compared with patients in the other groups: SLE+LN 12.88±8.33, SLE-LN 3.12±2.31, GMN 4.36±3.21 and controls 2.41±1.94 pg/mgCr (p=0.007). A total of 72.7% of the cases had renal activity index scores above 12, and 90.4% of the cases had scores of chronicity below 6 points. Receiver Operating Characteristic (ROC) curve analysis revealed that uTWEAK levels above 2.0 pg/mgCr had a sensitivity of 90 % and a specificity of 60% for the diagnosis of renal activity due to lupus, with an area under the curve of 0.876 (IC 0.75 to 0.98). There was a significant correlation of uTWEAK with serum levels of IgG (r=0.4(p<0.01)) and IgM (r=0.4(p<0.01)) and serum levels of eGFR (r=−0.4(p<0.05)).

Conclusions: Our study revealed that uTWEAK can adequately distinguish renal activity due to lupus, but cannot predict the degree of histological activity in Hispanic patients with active lupus nephropathy.

FR-PO602

Using Hazard Functions to Predict Outcomes in Lupus Nephritis: A Novel Way to Assess New Therapies

Brad H. Rovin,4 Megan Mackay,5 Joanna Stein Fishbein,2 Kenneth Kazer,2 Maria Dall’Era.1 1Ohio State Univ, Columbus; 2Feinstein Inst; 3UCSF; 4UCSD.

Background: The goal of therapy in lupus nephritis (LN) is long-term preservation of renal function. In clinical trials of drugs to treat LN, treatment success is evaluated by the proportion of patients achieving complete remission 6-12 months after starting therapy. However, short-term remission does not necessarily equate to sustained long-term kidney function. The present work was undertaken to establish novel endpoints for LN clinical trials that predict long-term kidney health.

Methods: A database of 944 patients with extended follow-up was established from 15 clinical centers/trials. This analysis sought predictors of new or worsening CKD with an area under the curve of 0.876 (IC 0.75 to 0.98). Two variables significantly (p<0.01) associated with CKD were then tested by Cox proportional hazards regression, and using stepwise selection methods included in a final multivariable model if p<0.05.

Results: A total of 558 LN patients had all the required data and were included in the analysis. Variables significantly associated with CKD on univariate regression were race (binary variable, Black/non-Black), urine RBCs at baseline and 12 months, proteinuria at 12 months, Scr at baseline and 12 months, and % change in proteinuria and Scr from baseline to 12 months. The final multivariable model included log (% change proteinuria, p<0.0001), log (Scr) at 12 months, p<0.0001) and race (p<0.04). The hazard ratios (HR) for CKD were 1.86 (95% CI: 1.52, 2.25) for log (% change proteinuria), 5.11 (3.40, 8.58) for log Scr and 1.65 (1.003, 2.70) for race. These variables were combined into a hazard function (HF) for CKD. HF=0.062*log(% change proteinuria)+1.63*log(Scr)+0.49*X3 where X3=1 if black, 0 if non-Black.

Conclusions: The HF can be used to evaluate new LN drugs for superiority in preventing future development of CKD.

Funding: Private Foundation Support

FR-PO603

Medication Adherence, Depression, and Disease Activity among Patients with Systemic Lupus Erythematosus

Adbukareem Alsowaida,1 Nada S. Alsowaida,2 Meshael M. Alrasheed,1 Ahmed Y. Mayet,3 Mohammed A. Omaan.1 1Dept of Medicine, King Saud Univ, Riyadh, Saudi Arabia; 2College of Medicine, King Saud Univ, Riyadh, Saudi Arabia; 3Dept of Clinical Pharmacy, King Saud Univ, Riyadh, Saudi Arabia.

Background: There are only a few studies that correlate adherence problems to disease progression among systemic lupus erythematosus (SLE) patients. The aim of this study is to assess the prevalence of medication adherence and depression among Saudi SLE patients, and to explore the impact of depressive symptoms on patient’s adherence to the treatment regimen.

Methods: In a cross sectional study of 140 outpatients with SLE, we assessed the prevalence of medication non-adherence and severity of depression using paper questionnaires that contain a number of questions based on Morisky Medication Adherence Scale (MMAS-4) and Beck’s Depression Inventory (BDI). The disease activity was assessed using the SLE Disease Activity Index (SLEDAI).

Results: None adherences were reported in 62.1 % and depression was noted 35% (49 patients). Moderate and severe depression were significantly associated with medium and high non adherence (p<0.04) but not with disease activity. There is a significant correlation between disease activity and severity of depression (r=0.31, p<0.003). The logistic regression showed only moderate to severe depression is associated with non-adherence (OR 2.62; 1.02-6.71) and disease activity is the predictor of depression.

Conclusions: SLE patients should be routinely assessed for medication non-adherence and the factors behind that especially depression. Interventions aimed at alleviating depressive symptoms, which are quite common, could result in significant improvements in patient adherence and disease response in patients with SLE.

FR-PO604

24 Hour Protein:Creatinine Ratio (24 PCR), Not Spot PCR (Spot PCR), Should Be Used to Monitor the Treatment of Severe Lupus Nephritis (LN):

The Experience of ACCESS

Ganeesh B. Shidham,1 Daniel J. Birmingham, Brad H. Rovin, Lee A. Hebert. Nephrology, Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: It is well established that in proteinuric renal disease urine PCR varies greatly during any given 24 hour period. Spot urine (single void) PCR reveals this variability; rather than 24 PCR, might lead to serious errors in management of LN because spot PCR are unreliable. Overall spot PCR was Unreliable in 35%, problematic in 24% and Reliable in only 41%. Baseline demographics and clinical measures did not distinguish between Reliable/Unreliable. However, those with Unreliable PCRs were more likely to experience Treatment Failure and less likely to experience Complete Remission than those whose spot PCRs were Reliable (p = 0.024).

Results: The results shows a representative patient in whom spot PCR was deemed Unreliable. Overall spot PCR was Unreliable in 35%, problematic in 24% and Reliable in only 41%. Baseline demographics and clinical measures did not distinguish between Reliable/Unreliable. However, those with Unreliable PCRs were more likely to experience Treatment Failure and less likely to experience Complete Remission than those whose spot PCRs were Reliable (p = 0.024).

Conclusions: Spot PCRs were Reliable (p = 0.024).
**FR-PO606**

**Molecular Imaging of Treatment Naïve and Treatment-Experienced Kidneys in Lupus Nephritis**

Samir Parikh, Ana Malvar, Huijuan Song, Valeria Gabriela Alberton, Jianying Zhang, Lianbo Yu, Brad H. Rovin, 
Nephrology, The Ohio State Univ Medical Center, Columbus, OH; Nephrology, Hospital Fernandez, Buenos Aires, Argentina.

**Background:** Lupus nephritis (LN) frequently relapses, and often shows the same histologic class at each flare. It is not clear whether the kidneys of patients who had LN flares after successful treatment show a similar molecular profile as kidneys from the first presentation of LN. This study was done to investigate the similarities and differences in LN flares at the molecular level.

**Methods:** Molecular profiling of the kidney was done on one SLE patient who had a biopsy at their first presentation of LN (Bx1, treatment naïve), and a second biopsy when the disease relapsed on maintenance immunosuppression after 1.5 years of remission. Both biopsies showed class IV LN. RNA was extracted from each biopsy and the expression of 511 immune-response genes was compared using Nanostring technology.

**Results:** Bx1 and Bx2 showed significant differences in pro-inflammatory transcript profiles. Genes with increased expression at Bx2 compared to Bx1 included: CD79a (12.7-fold >Bx1), CCL19 (10.3-fold), CXCR6 (4.5-fold), CXCL12 (3.6-fold), IL17F (3.1-fold), CXCL11 (2.6-fold), CCL13 (2.3-fold), and CXC19 (2.2-fold). Transcripts with increased expression at Bx1 compared to Bx2 included: CCL23 (3.5-fold), CCL16 (3.3-fold), CCL22 (2.7-fold), and CCBP2 (2.7-fold).

**Conclusions:** These data show that LN flares of the same class and within the same patient can demonstrate different renal molecular profiles. Despite similar histology, the dominant inflammatory signature, especially among chemokine family member genes, is different in a treatment naïve flare compared to a flare that occurs on immunosuppression. These data suggest that relapses of LN may need to be treated differently than the first flare, and may explain why relapses often are more treatment resistant.

**Funding:** NIDDK Support

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**FR-PO607**

**Lupus Podocytopathy: Comparison of Clinical Features and Renal Outcomes with Primary Forms**

Eduardo J.D. de Sa Carneiro Filho, Marcella Pigozzi Veloso, Marcella Martins Frediani, Leticidia Jorge, Cristiane B. Dias, Luis Yu, Viktoria Wortonik, Nephrology Div, Univ of Sao Paulo, Brazil.

**Background:** Lupus podocytopathy (LP) is characterized by diffuse foot process effacement without peripheral capillary wall immune deposits and glomerular proliferation. It has been described in Systemic Lupus Erythematosus (SLE) patients with distinct features from classic proliferative nephritides, sharing similar characteristics with primary podocytodisorders. This study aimed to compare clinical-morphologic features and renal outcomes between primary and lupus forms of focal Segmental Glomerulosclerosis (LPFSGS).

**Methods:** Retrospective unenricent analysis of 24 SLE patients who fulfilled the following 3 criteria were included as LP:[1] morphologic pattern resembling minimal change disease, mesangial proliferation or FSGS by light microscopy with negative immunofluorescence or only mesangial immune deposit;[2] absence of LN class III, IV or V; [3] PBT or intravenous pulse methylprednisolone. LP and FSGS cases were randomly matched with 32 primary FSGS, NOS variant, according to age, gender and eGFR baseline clearance (MDRD simplified formula). Baseline, one year and final follow-up results were analyzed in both groups. Treatment proposed was based on KDIGO guidelines.

**Results:** At baseline LP global group showed an average age of 35 years, proteinuria 4.2±2 g/day, albumin 2.3±0.8 g/dl, Hb 11.8 g/L, C3 103 mg/dl, C4 20 mg/dl, creatinine 1.1±0.5 mg/dL and MDRD 84.9±38.8 mL/min/1.73 m2. FSGS subgroups clinical features and renal outcomes are summarized below.

**FLD (32)**

<table>
<thead>
<tr>
<th>Baseline Features</th>
<th>LP/FLDS (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>31±14.9</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>8.3±0.98</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>1.28±0.9</td>
</tr>
<tr>
<td>Alb (g/dl)</td>
<td>2.0±0.9</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>13±1.93</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>98</td>
</tr>
<tr>
<td>Remission</td>
<td>7(57)</td>
</tr>
<tr>
<td>Partial(%)</td>
<td>8(25)</td>
</tr>
<tr>
<td>No response(%)</td>
<td>7(22)</td>
</tr>
</tbody>
</table>

**p<0.05**

**Conclusions:** Despite there was no difference regarding age, sex, fibrosis, albumin or treatment between subgroups, primary forms presented higher proteinuria (8.3±0.9 vs 4.6±0.7 p<0.01), while LP group lower Hb levels (11.4±0.3 vs 13.1±0.3 p<0.004) with similar renal outcomes.

**Funding:** Other NIH Support - National Institute of Allergy and Infectious Diseases
renal disease (2/20, 10%) (p<0.0001). In IgA disease, drusen occurred more often in ESRD. One CFH SNP (p=0.03) and the CD46 S13F variants (p=0.01) were more common in IgA gn and ESRD than in FSGS or diabetic renal disease. There is a possible increase with ESRD in IgA gn. GWAS suggest associations with Complement loci, and a CFH SNP was more common in patients with IgA disease and ESRD. Other drusen-associated SNPs may be important too.

Funding: Clinical Research Support

FR-PO609

Genetic Markers to Predict Progression of IgA Nephropathy in Caucasians

Tarak Onur Tirvaki,1 Ege Sinan Torun,1 Sonay Temurhan,2 Sebahat Akgul,2 Serra Arsan,1 Yasar Caliskan,1 Mehmet S. Sever.1

1Dept of Internal Medicine, Istanbul Univ Istanbul Faculty of Medicine, Istanbul, Turkey; 2Dept of Medical Biology, Istanbul Univ Istanbul Faculty of Medicine, Istanbul, Turkey:

Background: Genome–wide association studies indicate that IgA Nephropathy (IgAN) has a complex genetic architecture. In this study, we aimed to evaluate 4 tag single-nucleotide polymorphisms (tSNPs) in 129 patients with IgAN. Although these SNPs were found to be associated with risk of IgAN in Chinese cohort, the association signal has not been uniformly replicated in Turkish population.

Methods: A total of 129 IgAN patients (77 (59.7%) male, mean age: 36±13 years, median follow up of 25 months) were evaluated. The relationship between genetic markers (tSNPs; rs3803800, rs2738048, rs2412971, rs6677664) in 4 IgAN-associated genes (TNFSF13, DEFA, HORMAD2, CFH, respectively) and progression to kidney failure [category 5: chronic kidney disease (CKD)] were assessed.

Results: Kidney failure developed in 34 (26.4%) patients after a median follow up time of 25 months. Using the recessive model, we found that the genotype “AA” rs3803800 in TNFSF13 was associated with an increased risk of kidney failure in IgAN (OR = 2.52, 95% CI = 1.15–5.7, p = 0.018). Although not reaching statistically significance, the genotypes “GG” rs6677664 and “GG” rs2412971 were also associated with increased risk of kidney failure. The genotype “GG” rs667764 and was also found to be associated with higher T scores according to Oxford-MEST classification (p=0.04). The genotype “AA” rs3803800 was also found to be associated with higher S scores (p=0.04).

Conclusions: A new progression risk score for IgAN can be calculated based on these genetic markers including tSNPs in TNFSF13 and CFH genes to predict the risk of progression to kidney failure.

FR-PO610

Serum IgA/C3 Ratio: A Marker of Disease Activity in Patients with IgA Nephropathy

Kazuaki Tomoko,1 Tominari Endo,2 Hiroi Suzuki,2 Tatsu Tsukamoto,1 Eri Muso,2 Takashi Yasuda,1 Yoshinari Yasuda,1 Tetsuya Kawamura,2 Seiichi Matsuo,1

1Nephrology and Dialysis Center for Clinical SLE, IgA, C3 Glomerulonephritis, Osaka Hospital, Osaka, Japan; 2Dept of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan:

Background: Serum levels of high IgA and low C3 through lectin and alternative pathway activation might relate the progression and exacerbation of IgA nephropathy (IgAN). The aim of this study was to examine 1) whether the serum IgA/C3 ratio serve as a marker of the progression in patients with IgAN and 2) the effect of tansslecytosis on renal outcome.

Methods: 1) This nationwide multi-center retrospective study included 718 patients with biopsy-proven IgAN in Japan (mean follow-up of 6.5±2.9 years). The patients with doubling of serum creatinine at the time of renal biopsy were defined as progression. 2) After excluding those with insufficient serum IgA and C3 data at the end of observation period, 63 patients were subdivided either into 4 groups by therapy (control, tansslecytosis, and renal and tansslecytosis and steroid pulse (TSP) group) or into 2 groups according to the change of IgA/C3 ratio from the biopsy to the end of observation (6.1±2.8 years) (<15% decrease (improved) and >15% decrease (improved)).

Results: 1) Kaplan-Meir analysis of the patients with IgAN revealed that the group with high serum IgA/C3 (3.3 and above) had a significantly poorer renal outcome (p=0.05, log-rank test). In multivariate analysis of more than 4.45 years observation periods, renal end point of IgAN was associated with proteinuria (OR = 2.52, 95%CI = 1.09–4.08), eGFR<60 (RR=7.30, 95% CI=3.40–15.6) and serum IgA/C3 ratio (3.3 (RR=2.07, 95% CI=1.02–4.22). 2) Among the 4 groups divided by therapy, the serum IgA/C3 ratio and proteinuria were reduced only in the TSP group at the end of observation. The 2 groups divided along the change of ratio showed significantly higher percentage of complete remission of proteinuria in improved group than in non-improved (log-rank=0.035).

Conclusions: The levels of serum IgA/C3 might reflect the disease activity and be a potential surrogate marker of the disease in patients with IgAN.

Funding: Government Support - Non-U.S.

FR-PO611

IF27/1SG12A in Peripheral White Blood Cells is a Useful Marker for IgA Nephropathy

Yasuaki Nagasawa,1 Ryohiei Yamamoto,2 Eri Muso,2 Maki Shizawa,2 Kiyoko Yamamoto,1 Tomoko Kimura,1 Hirotsugu Iwatani,2 Takahiro Kuragano,1 Yoshitaka Isaka,1 Takeshi Nakanishi.1

1Dept of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan; 2Dept of Nephrology, Osaka Univ, Suita, Japan; 3Dept of Nephrology, Kitano Hospital, Osaka, Japan.

Background: IgA Nephropathy is most common primary glomerular nephritis not only in Asian, but also in Caucasians. The methods to identify IgA nephropathy without hospitalization had been required. DNA microarray analysis is useful to comprehensively identify up- or down-regulated genes in PBMCs of patients. To identify a useful marker for IgA nephropathy, we explore the peripheral white blood cells by DNA microarray methods.

Methods: Sequenali 137 patients who underwent kidney biopsy and blood samples were collected from Osaka University Hospital or Kitano Hospital. These patients had been diagnosed totally by kidney biopsy, medical history and blood examinations. Peripheral white blood cells samples from first fifteen IgAN and eight MN patients were provided for DNA microarray compared with healthy volunteers. And other samples were provided for extended qRT-PCR analysis. The study was reviewed and approved by the Research Ethics Committee of Osaka University and Kitano Hospital. Written informed consent was obtained from all participants.

Results: IF27/1SG12A (IFN-alpha inducible protein 27 gene = interferon-stimulated gene 12a protein (ISG12A) gene was identified as the gene which decreased in all 15 IgA nephropathy patients along with 8 membranous nephropathy (See Figure1). Then, extended quantitative RT-PCR revealed the gene expression decreased in 44 IgA patients out of 48 IgA nephropathy patients. Median expression levels of IF27 gene in IgA nephropathy patients (see Figure group 2) significantly reduced than those in immune disorder diseases (group 3) including myeloma kidney (<p=0.019). The expression levels in IgA nephropathy patients were marginally less than those in other primary glomerular nephritis patients (group 2) (P = 0.079). These results suggest that reduced IF27 mRNA level is a useful gene marker that can be measured using RNA from PBMCs.

Conclusions: We propose that IF27 may serve a useful genetic marker to diagnose IgA nephropath using peripheral blood.

FR-PO612

Successful Rituximab Treatment for Adult Patients with Severe IgA Vasculitis-Henoch-Schoenlein Purpura Nephritis (HSPN)

Robert Fontogho, Dario Roccaccia. Nephrology and Dialysis Unit and Center of Research of Immunopathology and Rare Diseases (CMI), San Giovanni Hospital, Turin, Italy.

Background: Corticosteroids alone or in combination with Immunosuppressive agents has been suggested to be effective in IgA vasculitis (IgAV)- Henoch-Schoenlein Purpura Nephritis (HSPN). However, optimal treatment remains controversial. Due to the putative role of B lymphocytes in the pathogenesis of IgAV, Rituximab (RTX) appears a potential therapeutic tool. We report a monocentric experience on the use of RTX in severe adult IgA-vasculitis with biopsy-proven nephritis.

Methods: Our series includes 5 adult patients (3 males and 2 females), age 21-70 years.

Results: The diagnosis was achieved according to EULAR criteria. RTX (lymphoma protocol) was administered as a rescue therapy in 3 patients, previously given a similar immunosuppressive therapy without benefits. Two patients received RTX as a frontline treatment. All had a severe cutaneous and kidney involvement (diffuse intra- and extracapillary proliferation with fibrinoid necrosis). Three patients had abdominal pain (in two cases associated with bleeding) and 2 severe arthritis.

Results: All patients achieved a complete renal remission. One needed a maintenance RTX therapy due to cutaneous relapses. The follow-up ranged from 6 months to 8 years. No clinically relevant adverse events have been observed.

Conclusions: This is the first case series describing successful RTX treatment of adult HSPN, and underlines the role of B lymphocytes in the pathogenesis of IgAV. This is consistent with previously reported benefits of RTX in other forms of vasculitis, and emphasized the role of B lymphocytes in the pathogenesis of IgAV.

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

503A
Can Serum Levels of Galactose-Deficient IgA and IgG Autoantibodies Predict the Course of Disease in Czech Patients with IgA Nephropathy? Dita Maiナーová,1 Chuyun Ling,2,3 Stacy D. Hall,4 Colin Reilly,5 Rhubert T. Brown,6 Michaela Neprasonová,7 Jelena Skibova,8 Miloslav Suchanek,9 Jan Novák,10 Vladimir Tesar,11 1Dept of Nephrology, General Univ Hospital, Brno, Czech Republic; 2Dept of Nephrology, Charles Univ, Prague, Czech Republic; 3Longth hospital, Shanghai Univ of Traditional Medicine, Shanghai, China; 4Dept of Microbiology and Medicine, Univ of Alabama at Birmingham, Birmingham, AL; 5Statistical Unit, Inst of Clinical and Experimental Medicine, Prague, Czech Republic; 6Univ of Chemical Technology, Prague, Czech Republic.

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis with serious prognosis leading to end-stage renal disease in 30-50% of patients. The diagnosis requires renal biopsy. Due to its inherent risks, non-invasive approaches are needed.

Methods: We examined 96 patients with biopsy-proven IgAN who were assessed at the time of diagnosis for renal function, proteinuria, microscopic hematuria, and hypertension, and followed-up clinically since then. Using serum samples collected the time of diagnosis, we determined levels of galactose-deficient IgA1 (Gd-IgA1) and IgG autoantibodies specific for Gd-IgA1 (Gd-IgAb) using lectin and immunodetection methods. Spearman correlation coefficient was used for statistical analysis.

Results: Higher serum levels of Gd-IgA1 were associated with worse renal function (elevated serum creatinine) at the time of renal biopsy and during follow up (r=0.223 and r=0.246, respectively; p<0.05 for both). Higher serum levels of Gd-IgAb correlated with higher degree of microscopic hematuria at the time of renal biopsy (r=0.244, p<0.05) and with worse renal function during the follow-up and at the end of the follow-up (r=0.254 and r=0.338, respectively; p<0.05 for both).

Conclusions: Elevated serum levels of Gd-IgA1 and Gd-IgAb may provide diagnostic as well as prognostic information, enable monitoring of disease activity, and/or responses to treatment.

FR-PO614

IgAN Nephropathy Is Associated with Elevated Levels of Renal BAFF and APRIL. Deepak Kumar,1 Rui Chang,2 Chia Chi Sun,3 Ivy A. Rosales,4 A. Bernard Collins,5 Rex Neal Smith,6 Herbert Y. Lin,7 Ravi I. Thadhani,8 Julie Demartino,9 1TIP Immunology, EDM Serono Inc, Billerica, MA; 2Div of Nephrology, Massachusetts General Hospital, Boston, MA.

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis, with up to 40% of patients progressing to end stage renal disease. Studies have shown that elevated levels of serum BAFF (B cell activating factor) and APRIL (A Proliferation Inducing Ligand) in IgAN are associated with severity of clinical and pathological disease features. Biologically, these cytokines also play a role in IgA class switch recombination in B cells. Further, a recent report showed that sera from IgAN patients can induce proliferation of renal mesangial cells, providing a mechanism for the pathogenesis of IgAN. However, the expression levels of BAFF and APRIL and their cognate receptors in the kidney during IgAN is not known.

Methods: Immunofluorescence (IF) staining was performed on kidney biopsies from 15 IgAN, 3 diabetic glomerulonephropy (DG), 4 Minimal Change Disease (MCD). 1 with no diagnostic abnormality (NDA). We report increased expression of APRIL by IF staining in both the glomerulus and tubular epithelial cells, and for BAFF in the glomerulus in kidney biopsies showing IgAN compared to biopsies showing DG, MCD and NDA. APRIL and BAFF staining in IgAN was also evident in interstitial CD68+ macrophages. Moreover, IF analysis of cognate receptors for BAFF and APRIL, such as B cell maturation antigen (BCMA), transmembrane activator and CAML interactor (TACI) and BAFF-R, also showed increased expression in both tubular epithelial cells and glomerular parietal epithelial cells in IgAN compared to MCD. BCMA, TACI and BAFF-R staining was also evident in the interstitial CD20+ B cells.

Conclusions: Taken together, these data showed increased tissue expression by immunohistochemical studies of BAFF, APRIL and their cognate receptors in kidney biopsies showing IgAN. Given the roles of BAFF and APRIL in autointenigen and/or autobody production in IgAN, this demonstrates the potential of BAFF and APRIL blockade in the treatment of IgAN.

Funding: Pharmaceutical Company Support - EDM Serono Research and Development Inst. Inc.

FR-PO615

Long Term Renal Survival in IgA Nephropathy with Crescents Kendral R. Knight, Dustin J. Little, Stephen W. Olson. Walter Reed National Military Medical Center, Bethesda, MD.

Background: The Oxford Classification (MEST criteria) established an explanation of mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy/intertstitial fibrosis (T) histopathology on renal survival for IgA nephropathy (IgAN). Outcomes have been reported for Asian patients with >55% crescents, but there are no data on implications of glomerular crescents (including 1-50% crescents) in an ethnically diverse population have not been reported.

Methods: We performed a retrospective cohort study of 136 biopsy confirmed IgAN cases identified in the military electronic medical record system from 2000 - 2015. The renal survival, defined by the absence of renal replacement therapy (RRT), of IgAN with 1-50% crescents was compared to both IgAN with >50% crescents, and IgAN without crescents. For secondary analysis, the incidence of a >25% decline in eGFR and progression to stage IV CKD were compared between IgAN cases with 26%-50% crescents and IgAN cases with 1-25% crescents.

Results: Renal survival of IgAN with 1-50% crescents was superior to IgAN with >50% crescents (89%; 49/55 vs. 25%; 3/12, p<0.001), and equivalent to IgAN without crescents (89%; 52/59 vs. 87%; 66/79, p=0.79) over a median (IQR) follow up period of 61 (24,110) months. There was no statistically significant difference between these groups for any component of the MEST criteria. A greater proportion of subjects with 26-50% crescents experienced a ≥25% decline in eGFR (44%; 7/16 vs. 13%; 5/39, p=0.02) and progressed to stage IV CKD (13% vs. 3%, p=0.006) than those with 1-25% crescents.

Conclusions: In this comprehensive analysis of the prognostic value of crescents, independent of MEST criteria, for renal outcomes in IgAN patients followed for median 5 years, IgAN with<50% crescents had a renal survival superior to IgAN with >50% crescents and similar to IgAN without crescents. The subgroup of IgAN with 1-25% crescents experienced a more favorable renal survival. In GFR of eGFR and further often reached stage IV CKD than IgAN with 1-25% crescents. Future prospective immunosuppression therapy trials could be considered for IgAN patients with 26-50% crescents.

Funding: Other U.S. Government Support

FR-PO616

Renal Outcomes in Patients with IgA Nephropathy (IgAN) Undergoing Liver Transplant (LT) Musah S. Hommed, Ziad El-Zoghby. Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: Liver cirrhosis is the most common cause of secondary IgAN. Renal IgA deposition is thought to be a consequence of impaired removal of IgA-containing immune complexes by Kupffer cells following liver injury. If this hypothesis is correct, IgAN should have favorable renal outcomes following liver transplant.

Methods: Included are 11 patients (9 males) with biopsy proven IgAN. 6 patients underwent LT and 5 patients underwent combined liver-kidney transplant (CLKT) with a mean interval of 8.3 years at transplant time (Tx). We collected the level of proteinuria, hematuria, GFR at time of transplant, 12 and 60 months after Tx. We also reviewed any kidney biopsy done after Tx.

Results: Results are summarized in Figure 1. All patients had hematuria prior to Tx. Patient 2 progressed to end stage renal disease 5 years post Tx. Patient 9 had historical recurrence of IgAN found on protocol kidney allograft biopsy done 4 months post CLKT without clinical features of IgAN. Patient 10 had recurrent IgAN 2 months post CLKT associated with high proteinuria of 2640 mg/day, but that resolved with the addition of angiotensin-converting enzyme inhibitor (ACEI) and GFR remained stable at 60 mg/min.

Conclusions: Previous reports suggest that IgAN in liver cirrhosis patients has a benign course following LT. However, our data shows that IgAN can progress to end stage renal disease following LT and have early recurrence in kidney allograft following CLKT. It is possible that some patients with progressive disease have primary rather than secondary IgAN. Persistent hematuria and/or proteinuria > 1000 mg/day post-transplant may indicate recurrent or persistent IgAN and may identify patients who would benefit from aggressive supportive therapy, including treatment with ACEI to prevent poor renal outcomes.

FR-PO617

Clinical Presentation of IgA Nephropathy Is Changing Toward More Aggressive Forms Affecting Older Patients: Data from the Spanish Registry of Glomerulonephritis Eduardо Gutiérrez-Martínez,1 Manuel Praga,1 Francisco Moro,2 Juan Manuel Lopez Gomez.3 Nephrology, Hospital Univer. 12 de Octubre, Madrid, Spain; 2Nephrology, Hospital General de Ciudad Real, Ciudad Real, Spain; 3Nephrology, Hospital Gregorio Marañón, on Behalf of All Members of the Spanish Registry of Glomerulonephritis, Madrid, Spain.

Background: IgA nephropathy (IgAN) is the most common glomerulonephritis in the world, but there are few epidemiological data about possible changes in its presentation over the years. Also, available information about the influence of age on the form of clinical presentation is scarce.

Methods: Aim of the study was to analyze all renal biopsies performed between 1994 and 2013 and recorded in the Spanish Registry of Glomerulonephritis with histological diagnosis of IgAN. The study was divided into five 4-year periods (1994-97, 1998-2001, 2002-2005, 2006-2009 and 2010-2013) and patients were divided into 4 age groups: children (<17 years), adults: (17-45 years) and (46-65 years), and elderly (>65 years).

Conclusions: Previous reports suggest that IgAN in liver cirrhosis patients has a benign course following LT. However, our data shows that IgAN can progress to end stage renal disease following LT and have early recurrence in kidney allograft following CLKT. It is possible that some patients with progressive disease have primary rather than secondary IgAN. Persistent hematuria and/or proteinuria > 1000 mg/day post-transplant may indicate recurrent or persistent IgAN and may identify patients who would benefit from aggressive supportive therapy, including treatment with ACEI to prevent poor renal outcomes.
FR-PO618

Association of Recurrent Proteinuria Related to IgA Nephropathy with the Mesangial Hypercellularity Score and Grade of Proteinuria at Diagnosis

Takayuki Fuji, Satoshi Suzuki, Mizuki Shinozaki, Kaiti Saito, Mayu Morimoto, Noriko Terasaki, Tanaka Hiroaki.
Kidney Center, Seirei Sakura Citizen Hospital, Sakura City, Japan.

Background: The grade of proteinuria is important for predicting the renal prognosis of patients with IgA nephropathy. The renal prognosis of those with the remission of proteinuria is favorable. However, even when treatment leads to the remission of proteinuria, recurrence is often observed. Currently, there are no global guidelines defining the remission or recurrence of IgA nephropathy. We examined recurrence-associated factors, regarding patients with a urinary protein level of ≥0.3 g/day as achieving remission and those in whom remission could not be maintained for 6 months or more as showing recurrence.

Methods: Of 313 patients who were diagnosed with IgA nephropathy based on kidney biopsy findings, with an eGFR of ≥30 mL/min/1.73 m² and an unequivocal disappearance of proteinuria for 2 years, we conducted a retrospective cohort study in 155 with the remission of proteinuria. Regarding recurrent proteinuria as an outcome, we examined recurrent proteinuria-associated clinical/pathological data and treatment using Cox’s proportional hazard model.

Results: The mean follow-up period was 16.5±7.7 years. The mean daily urinary protein level on kidney biopsy was 1.0±0.9 g/day. The mean eGFR was 78.1±23.2 mL/min/1.73 m². Of the 155 patients with remission of proteinuria, recurrent proteinuria was noted in 68. Recurrent proteinuria was associated with a urinary protein level of ≥1 g/day (HR: 2.78, 95% CI: 1.40-5.47) and mesangial hypercellularity score (M) =1 according to the Oxford classification (HR: 1.99, 95% CI: 1.06-3.58). On the other hand, steroid therapy was useful for maintaining the remission of proteinuria (HR: 0.37, 95% CI: 0.18-0.75).

Conclusions: Recurrent proteinuria in patients with IgA nephropathy was associated with a urinary protein level of ≥1 g/day at diagnosis and M1 according to the Oxford classification.

FR-PO619

The Clinical and Histopathological Difference of IgA Dominant Infection-Related Glomerulonephritis from Those of IgA Nephropathy: A Single Center Study


Background: IgA dominant infection-related glomerulonephritis (IgA-IRGN) is a unique form of IRGN histologically resemble to IgA nephropathy (IgAN). However, IgA-IRGN should be discriminated because of the difference of the clinical course. We compared both using a database of our hospital.

Methods: We extracted 15 patients with IgA-IRGN, whose clinical and pathological findings were matched the previous paper (Kidney Int2013;83,792-803), and 122 patients with IgAN as control from 1788 patients who underwent kidney biopsy from 2000 to 2015 in our hospital. To rise the characteristic surface of IgA-IRGN, we took several clinical and pathological parameters, including age, laboratory findings, and histological observation with light microscopy, immunofluorescence, and electron microscopy, and compared these with those of IgAN. We further examined the prognosis of IgA-IRGN by the all-cause mortality and end stage renal disease.

Results: IgA-IRGN showed higher proportion of elderly (26.7±5.9%,p<0.05), lower eGFR (53.8±22.5 vs 74.7±24.9 mL/min/1.73 m²;p<0.05), heavier proteinuria (5.1±6.0 vs 1.1±2.2 g/day;p<0.05), and lower serum albumin (3.1±0.7 vs 3.9±0.4 g/dl;p<0.05). Endocapillary proliferation was common (93% vs 86%;p<0.05), and immunoglobulins(IgG, IgA and IgM) and complements(C3, C1q and C4c) were detected along the glomerular capillary more frequently(p<0.05) consistent with the dense deposits at both subendothelial and subepithelial sites more frequently (p<0.05). IgA-IRGN patients were more susceptible to acute kidney injury (54% vs 4%, p<0.01). The prognosis of IgA-IRGN patients was poorer than IgAN patients. Using multivariate analysis, the risk factors of IgA-IRGN were past history of diabetic mellitus, heavy proteinuria (>3.0 g/day), IgG and C1q deposition along the glomerular capillary.

Conclusions: IgA-IRGN and IgAN showed different clinical course and histological findings with a high degree of differentiation. Involvement of glomerular capillary lesion and activation of multiple complement pathway might influence on the prognosis of IgA-IRGN.

FR-PO620

Complement Factor H Gene Polymorphism rs6677604 and the Risk, Severity and Progression of IgA Nephropathy: A Systematic Review and Meta-Analysis

Cheng-Ye Ye, Xinyang Liu, Adrian Liew. Renal Medicine, Tan Tock Seng Hospital, Singapore.

Background: Several studies reported an association between rs6677604 polymorphism and susceptibility to IgA nephropathy (IgAN), but attempts at validating this finding yielded inconsistent results.

Aim: We seek to clarify the association between complement factor H gene rs6677604 polymorphism and IgAN susceptibility, severity and progression.

Methods: Eligible studies were identified by a comprehensive database search. Meta-analyses were performed for rs6677604 allele frequency and the association with IgAN susceptibility. Subgroup analyses, publication bias, and sensitivity analyses were also conducted.

Results: 10 studies were included in the systematic review. Among them, four studies containing 10 datasets (15,617 IgAN-cases and 31,947 controls) were included in the meta-analyses. The overall association between rs6677604 polymorphism and risk of IgAN – AA vs. GG, odds ratio (OR)=0.58, 95% confidence interval (CI) [0.48, 0.69] in stratification by ethnicity, significant association between AA vs. GG and IgAN susceptibility was observed in European (OR=0.56, 95% CI: 0.46-0.69) but not in Asians (OR=0.66, 95% CI: 0.46-0.94). No publication bias was observed. Systematic review did not reveal any association between rs6677604 polymorphism and IgAN severity/progression.

Conclusions: rs6677604-A allele was more prevalent in Europeans than in Asians. The presence of rs6677604-A allele significantly decreased IgAN susceptibility in Europeans, but no association was observed in Asians. Not enough clinical evidence was found between rs6677604 polymorphism and IgAN severity/progression. Further functional studies are needed to validate the findings.

FR-PO621

First 1-Year GFR Decline Slope Can Identify High-Risk Patients in IgA Nephropathy

Kyungho Lee, Eun Jeong Lee, Jung-Ho Shin, Hye Ryoung Jang, Jung Eun Lee, Wooseong Huh, Yoon-Goo Kim, Dae Young Kim, Han Young Oh. Div of Nephrology, Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Korea.

Background: IgA nephropathy (IgAN) is the most frequent primary glomerular disease and the leading cause of end-stage renal disease. This study investigated clinical and histopathological predictors for renal outcome in patients with IgAN with a focus on glomerular filtration rate (GFR) slope decline.

Methods: We screened all patients who diagnosed with primary IgAN between 1995 and 2012. Renal prognosis was defined as creatinine doubling. Using serial measurements of serum creatinine during the first year, we calculated the GFR slope declines. Then, we defined the patients with the steepest quartile of GFR slope as rapid decliner, those with the 2nd quartile of GFR slope as slow decliner and the others as non-decliner.

Results: Among 214 subjects, the age was 37 (28, 46), and baseline GFR was 81 (62, 100) mL/min/1.73 m². Both of them did not differ between the 3 groups. Rapid decliner and slow decliner had higher levels of protein/creatinine ratio (0.88, 0.89, and 0.58 g/g Cr respectively, P< 0.001) and higher score of tubular atrophy/interstitial fibrosis compared with non-decliner; 20.8%, 16.7%, and 6.5% in each groups showed score ≥1 (P = 0.007). Renal progression at 5 year was 76 % in rapid decliner, 91 % in slow decliner, and 100 % in non-decliner (P< 0.001, rapid or slow decliner vs non-decliner). After adjustment for sex, blood pressure, GFR, proteinuria, and histologic findings, slow decliner was associated with a 7.3-fold higher risk of progression (P = 0.017) and rapid decliner was associated with a 9.6-fold increased risk of progression (P = 0.008) compared with non-decliner. GFR slope value was also negatively associated with renal progression after adjustment for aforementioned covariates (P = 0.005).

Conclusions: First 1-year GFR slope was a predictor of renal progression, independently of proteinuria amounts and histologic findings. GFR slope can be incorporated to identify high-risk patients who need more aggressive treatment.

FR-PO622

Clinical Usefulness of the Oxford Classification in Determining Immunosuppressive Treatment in IgA Nephropathy

Min-uk Cha, Chanyang Yoon, Changhae Park, Seokho Han. Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Although the Oxford classification has been widely used in IgA nephropathy, its clinical usefulness of determining immunosuppression is unknown. Here, we conducted an observational study to investigate whether the Oxford-MEST could predict the development of persistent proteinuria and worsening kidney function. We also evaluated the clinical effectiveness of corticosteroid treatment by the Oxford classification.

Methods: We studied 44 patients with early-stage IgA nephropathy who had proteinuria ≥1.0 g/g Cre and estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73 m². The study endpoints were the development of a random urine protein-to-creatinine ratio of ≥1 g/g Cre and a 30% decline in eGFR during follow-up.

Results: The Oxford-MEST only, M1 predicted the risk of the development of proteinuria ≥1.0 g Cr compared to other lesions in a
time-varying Cox model adjusted for multiple confounding factors. In addition, the risk of reaching a 30% decline in eGFR was significantly higher in patients with M1 than in those with M0. However, steroid treatment in M1 lesion was not associated with improved clinical outcomes in the unmatched and propensity score matched cohort.

Conclusions: The results showed that among the Oxford-MEST lesions, only M1 predicted the risk of the development of proteinuria ≥1 g/d against other lesions in a time-varying Cox model adjusted for multiple confounding factors. In addition, the risk of reaching a 30% decline in eGFR was significantly higher in patients with M1 than in those with M0. However, steroid treatment in M1 lesion was not associated with improved clinical outcomes in the unmatched and propensity score matched cohort.

FR-PO623
Response of Patients with IgA Nephropathy to High Doses of Lisinopril and Omacor

Background: For treatment patients (pts) with IgA nephropathy (IGAN) using angiotensin converting enzyme inhibitors (ACEi) or omega-3 fatty acids (O3FA) has been described previously, but there are limited data describing results obtained when the two are combined in high doses.

Methods: Lisinopril 10-80mg, as tolerated, and O3FA (Omacor®) 4gm (EPA 1.88 g, DHA 1.48 g), were given daily to 79 IGAN pts with urine protein to creatinine ratios (UP/C) ≥0.35 g/g (males) 0.58 g/g (females) who were enrolled in a multicenter prospective clinical trial. We evaluated the efficacy of the therapy after 3-6 months in 29 pts who were not receiving pre-study ACEi and/or O3FAs. Complete remission (CR) of proteinuria = UP/C ≤0.05 g/g. Partial remission (PR) = UP/C < 0.5 (males), < 0.8 (females).

Results: The UP/C fell from 1.94±1.3 to 0.88±0.75 in the 29 pts. The decrease in UP/C was correlated with decrease in systolic BP (−4.4±1, p=0.02) and diastolic BP (−4.83, p=0.01). Seventeen of the 29 pts had a CR (n=5) or PR (n=12) after 3 months; an additional 3 pts had a PR after 6 months. The UP/C fell from 1.91±1.26 to 0.42±0.15 in these 20 pts. Three of the pts who did not have a PR at 3 months were randomized to mycophenolate and subsequent UP/C results were censored. The overall rate of CR or PR after 3 or 6 months was significantly higher in patients with M1 than in those with M0. Furthermore, patients with M1 had a greater decline of eGFR than patients with M0. However, steroid treatment in M1 lesion was not associated with improved clinical outcomes in the unmatched and propensity score matched cohort.

FR-PO624
Clinicopathological Features and Outcomes of IgA Nephropathy with Mild Proteinuria

Background: Information about the outcomes of IgA Nephropathy is mostly based on patients in whom proteinuria are higher than 1–2 g/d at renal biopsy time. The clinicopathological features and outcomes of IGAN patients presenting with mild proteinuria are not well described. Therefore we conducted a study to investigate the clinicopathological features and outcomes of IGAN patients with mild proteinuria.

Methods: Primary IGAN patients with proteinuria less than 1 g/d in our hospital from January 1995 to December 2014 were retrospectively reviewed. The clinical and pathological data at renal biopsy and follow-up collections were identified and analyzed. Results: 510 IGAN patients with mild proteinuria were enrolled in this study. At biopsy, 32.7% of the patients were found to have hypertension and 32.3% had a history of macroscopic hematuria. Lee’s Grade III was observed in 73.1% of the patients. Lee’s Grade IV-V was observed in 7.7% of the patients. Of the Oxford Classification, M1 was observed in 30.4% of the patients, E1 was observed in 5.1% of the patients, S1 was observed in 69.6% of the patients, T1 was observed in 14.9% of the patients, and T2 was observed in 1.6% of the patients. After a median follow-up of 50 months, 40.8% patients developed ESRD, 22 (5.85%) presented proteinuria levels ≥1 g/24 h, 316.1% patients had a eGFR decline ≥50% of the baseline(not including ESRD), 45(8.8%) patients presented proteinuria ≥1 g/d, only 82 (16.1%) patients had complete clinical remission. Logistic regression revealed that time-average-proteinuria(TA-P)(RR31.85, P=0.000) was the risk factor of renal function deterioration and ESRD. Age(RR1.53, P=0.022) and proteinuria(RR1.61, P=0.001) were the risk factors of sustained proteinuria ≥1 g/d after biopsy.

Conclusions: Severe renal pathological lesions may be observed in some IGAN patients with mild proteinuria. Renal outcome is dismal in IGAN patients with mild proteinuria. Life-long follow-up with regular monitoring of proteinuria, blood pressure and renal function is essential for older patients with more proteinuria.

FR-PO625
Mycophenolate Mofetil Treatment for Henoch-Schonlein Purpura Nephritis with Nephrotic Range Proteinuria

Background: We present our experience with Mycophenolate Mofetil (MMF) as an adjuvant agent for treatment of severe childhood HSP nephritis with nephrotic range proteinuria.

Methods: A retrospective chart review was performed on all patients (N=65) referred to our clinic for HSP Nephritis 01/01/2001 - 12/31/2015. Patients with confirmed nephrotic range proteinuria (>3 mg/mg creatinine) who were treated with MMF (N=9) were included in analysis. Biases were classified according to Oxford MEST scores. MMF mean dosage was 1251 mg/m²/day, median follow up was 115 weeks.

Results: Demographic characteristics, treatment, and response to therapy are summarized below.
FR-PO627
Clinicopathological Characteristics and Prognosis of IgA Nephropathy Patients with Hepatitis B Virus Infection
Hongrui Shi, Mengjun Liang, Jiafan Zhou, Ning Su, Jiang Zongpei. Dept of Nephrology, The Six Affiliated Hospital, Sun Yat-sen Univ; Guangzhou, China.

Background: Some studies had found HBV played an important role in IgA nephropathy(IgAN). The aim of our study is to investigate clinicopathological characteristics and prognosis in IgA nephropathy patients with HBV infection.

Methods: We conducted a cohort study enrolling primary IgAN patients diagnosed by renal biopsy in our Hospital from Jan 2013 to Feb 2016. We compared clinicopathological characteristics between IgAN patients with or without HBV infection. Then the HBV-positive group was followed for a median of 14.2 months. Primary outcome was the decline of eGFR<25%. Secondary outcomes were remission of proteinuria and hematuria (defined as decline of proteinuria or hematuria>50%) and reactivation of HBV replication.

Results: There were 46 patients eligible in our study, including 29 patients with HBsAg positive(9.1%). Patients in HBV+IgAN group were older(40.90±10.05y vs.34.50±12.05y, p=0.007),and had higher ALT level (26.38±14.72U/L vs 22.90±21.91U/L, p=0.020),higher AST level (21.21±7.82U/L vs 18.64±9.90U/L, p=0.010), worse pathological grade (Lee IV:7,72.8% vs. 49.4%,p=0.040) and more thickness of vessel wall (100% vs. 81.9%,p=0.040)23 HBV+IgAN patients were followed up 10 patients (43.5%) had met the primary outcome,who had more serious renal injury (CKD4-5,50% vs. 0, p=0.007),more proteinuria in 24h(2.60±1.98g vs. 1.19±1.10g, p=0.017) and more interstitial infiltration than the other groups (55% vs. 15%, p=0.017). The reactivation rate of HBV replication in GC group and CV group were 44.4% and 57.1% (p=0.68).was 50.0%(p=0.67),30.8%(p=0.38) and 42.9%(p=0.018),respectively.

Conclusions: HBV+IgAN patients were 19.9% in our center. After follow-up, 43.5% of the HBV+IgAN patients had met primary outcome. Glucocorticoid or immunosuppressant therapy may improve renal outcome of HBV+IgAN patients without obvious effect on reactivation of HBV replication.

FR-PO628
Long-Term Study of Cyclophosphamide, Leflunomide, Glucocorticoids and ACE-Inhibitors Treatment in IgA Nephropathy
Shasha Chen, Li Wang, Guisen Li. Renal Div and Inst of Nephrology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.

Background: Few studies are currently available about the efficiency and renal survival of IgA nephropathy (IgAN) treated with immunosuppressive agents. We retrospectively analyzed data from Chinese patients with IgAN to study long-term efficacy with different therapies, and explore the prognostic factors for recovery of renal function in patients with declining renal function.

Methods: 311 cases of biopsy-proven IgAN were retrospectively studied in this study. Outcome was renal function recovery (defined as improvement of creatinine by at least 30% or back to normal range), declining renal function. Results: Cyclophosphamide group had a higher level of Scr (P<0.001) than other groups. Leflunomide group had a lower level of SCR (P<0.001), a lower eGFR (P<0.001), a lower proteinuria level (P<0.001), and better renal outcomes (P<0.001) than cyclophosphamide group. Glucocorticoids group had worse outcomes than the other groups. Conclusions: We found that leflunomide was superior to cyclophosphamide in terms of renal function recovery and has a significantly lower reactivation rate of HBV replication. Leflunomide can be the first choice of immunosuppressive therapy in IgAN.

FR-PO629
Alternative Pathway Activity in IgA Nephropathy
Raid B. Chowdhury,1 Magdalena Riedl,2 Ping Lam,1 Jennifer Gommerman,1 Jan Novak,2 Krzysztof Kirdyuk,1 Stuart Yang,1 Sean Barbour,1 Daniel C. Cattran,1 Michelle A. Hladunewich,2 Rulan S. Parekh,2 Elisa Porfido,2 Bryan Coburn,2 David Guttman,2 Scott Gray-Owen,3 Harinda Rathajeikan,1 Christopher Licht,1 Heather N. Reich.1 1UHN, Univ of Toronto; 2Univ of Alabama at Birmingham; 3Univ of British Columbia; 4Dept of Pediatrics.

Background: A hallmark of IgA nephropathy (IgAN) is mesangial and circulating immune complexes containing aberrantly glycosylated IgA1 an anti-glycobody antibody and C3. Recent data suggests a common depletion of CFBH1 and CFHRI1 as protective variant in IgAN. Deficiency of CFHRI1 results in functional surplus of CFH, key regulator of the complement alternative pathway (AP), suggesting a functional role for the AP in IgAN pathogenesis. We evaluated functional differences in systemic AP activity in patients with IgAN hypothesizing that AP activity is increased in IgAN due to CFH dysfunction.

Results: 52 IgAN and 38 healthy subjects were examined. AP activity was quantified via ELISA (Wieslab) detecting terminal C5b-9 generation after pathway-specific activation. CFH function was evaluated via hemolysis assay using sheep erythrocytes. Complement activity was correlated with clinical measures of disease activity including proteinuria and renal function.

Methods: We did not observe an increase in systemic AP activity in IgAN compared with healthy controls with the Wieslab ELISA nor the hemolysis assay (p<0.05). In IgAN AP activity was inversely correlated with renal function (eGFR) (Pearson r=-0.35, p=0.01). There was no correlation with proteinuria.

Conclusions: We did not observe an increase systemic AP activity in our IgAN cohort although we did find an inverse correlation with kidney function. If studies in a larger cohort confirm these results it is possible that AP dysregulation in IgAN is more important locally (at the cell surface) than systemically (fluid phase). Genotype and measures of AP proteins will be evaluated next.

FR-PO630
Altered Expression of O-Glycan Biosynthetic Enzymes in IgA1-Producing Cell Lines from Patients with IgA Nephropathy (IgAN) and Their Family Members
Hiroyuki Ueda,1 Yoshimi Ueda,2 Colin Reilly,1 Zina Molodecarbon,1 Stacy D. Hall,3 Karen Hart,1 Dana Rizk,1 Krzysztof Kirdyuk,1 Ali G. Gharavi,2 Takashi Yokoo,2 Bruce A. Julian,1 Jan Novak.1 1Univ of Alabama at Birmingham; 2The Jikei Univ School of Medicine, Japan; 3Columbia Univ College of Physicians and Surgeons.

Background: Familial (F) and sporadic (S) IgAN patients (IgANP) have elevated levels of serum galactose-deficient IgA1 (Gd-IgA1). Moreover, 50% of the first-degree relatives of F-IgANP have high serum Gd-IgA1 levels, ≥95th percentile of healthy controls (HC) without any clinical sign of IgAN. These serum Gd-IgA1 levels are longitudinally stable in most individuals. We have previously generated immortalized IgA1-producing cell lines (IgAPC) from S-IgANP and HC as a model system for analysis of IgA1-O-glycosylation pathways. Cells from IgANP secrete more Gd-IgA1 than do the cells from HC. This aberrant O-glycosylation is associated with aberrant expression of key glycosyltransferases (GTs) involved in the biosynthesis of O-glycans. Here, we generated IgAPC from a pedigree with F-IgAN and characterized their gene-expression patterns for C1GALT1 and O-glycan branching enzymes (GCNTs).

Methods: The pedigree includes 4 IgANP. We generated IgAPC from blood relatives of F-IgANP to study long-term efficacy with different therapies, and explore the prognostic factors for recovery of renal function in patients with declining renal function. Conclusions: Immunosuppressants (cyclophosphamide and leflunomide) played an important role in increasing renal recovery in IgAN nephropathy patients with impaired renal function, especially in patients with crescents, vasculitic lesions on renal biopsy or important role in increasing renal recovery in IgAN patients with impaired renal function, especially in patients with crescents, vasculitic lesions on renal biopsy.

FR-PO631
Clinical Significance of Histopathology in C3 Glomerulopathy (C3G)
Pietro A. Canetta,1 Dominick Santorillo,2 Andrew S. Bomback,1 Rupali S. Avassare,1 Viette D. A’Agati,2 Glen S. Markowitz,2 Gerald B. Appel,1 Nephrology Div, Columbia Univ; New York, NY; 2Renal Pathology Div, Columbia Univ, New York, NY.

Background: C3G is defined by glomerular lesions containing C3 with little or no immunoglobulin (Ig). The relationship between histology, clinical features, and prognosis has not been studied in a large US series.

Methods: We examined histologic and clinical features of 66 patients (pts) with biopsy (bx) and followup data at our center. Each initial bx was re-scored for light microscopic
(LM) pattern of injury, immunofluorescent (IF) staining, and deposition location by electron microscopy (EM). The combined endpoint of 2x creatinine, GFR <15 or transplant was studied by logistic regression.

**Results:** Median GFR at bx was 62 ml/min (IQR: 39-135) and proteinuria was 2.8 g/gCr (1.2-5.4). LM patterns included membranoproliferative (MP, 55%), mesangial-proliferative (MP, 23%), diffuse proliferative (12%), and diffuse sclerotic (11%). MP GN pts were youngest (22±16y); Mes GN pts were older (45±25y, P<0.01) and had the least proteinuria (median 1.3 vs 3.2 g/gCr, P<0.01). By IF, CF3 was the only immunoreactant in 47%; these pts were older than pts with any Ig (37±23 vs 23±14y, P<0.01). Mem and MP CF3 were lowest (15% and 37%, respectively). Mes GN pts had diffuse C3 glomerulonephritis (DDD). DDD pts were older than C3GN (39±21 vs 26±18, P<0.01) and had a suggestion of lower GFR (P=0.07) but similar proteinuria. Rare variants of C3, CFH, CFHR5, or CF5 were found in 11 and 48% (5/147 and 7/67 CFHR5, respectively). A paraprotein was found in 12/25 (48%) and was always low (<12%). Common HLA and EM, 28% had EM and DDD (DDD) and 72% had C3 glomerulonephritis (C3GN). C3GN pts were younger than DDD pts (median 41 vs 54y, P=0.01) and had lower GFR (median 41 vs 54 ml/min/1.73m², P=0.01) and had a suggestion of lower GFR (P=0.01) but similar proteinuria. Rare variants of C3, CFH, CFHR5, or CF5 were found in 7/25 (28%) and 2/25 (8%). Proteinuria was not associated with LM/IF/EM pattern. A paraprotein was found in 12/25 and when present was associated with DDD (OR 6.7, P<0.01). Over a median 38 months (13-117), 35% reached the endpoint. Univariable outcome predictors included GFR at bx, global and segmental glomerulosclerosis, and IFTA. Achieving a 50% fall in proteinuria lowered the risk of the endpoint (OR 0.11, P<0.01). Mes GN had marginally lower significant risk (OR 0.22, P=0.07). In multivariable analysis, only GFR was significant.

**Conclusions:** C3GN histology had important associations with age onset, disease severity, and other clinical features (such as DDD with paraproteins), but for predicting the effect of GFR dominated.

**FR-PO632**

**Recurrent C3GN and Dense Deposit Disease (DDD) in the Renal Allograft**

Woon Ahn, Renu Regunathan-Shenk, Rupali S. Avassare, Pietro A. Canetta, Andrew S. Bombback, Gerald B. Appel. Internal Medicine, Columbia Univ Medical Center, New York, NY.

**Background:** C3 glomerulopathy (C3G) is a GN associated with dysregulation of the alternative complement pathway, histologically categorized as either DDD or C3GN. There are few studies of transplantation in C3G, none comparing C3GN to DDD, and little data on the effect of eculizumab in recurrent C3G.

**Methods:** We retrospectively reviewed the charts of 19 patients (pts) with biopsy-diagnosed C3GN evaluated at Columbia University Medical Center, who’d received a renal transplant (txp). We analyzed their clinical and laboratory presentation, and post-txp outcomes.

**Results:** Of the 19 pts receiving allografts 12 had C3GN and 7 DDD. There were 14 males and 5 females with a median age at diagnosis of 27(range 17-70) and at transplantation 24 yrs (15 – 43). Median creatinine was 1.27 mg/dl (0.8 – 2.0). Median proteinuria was 2.8 g/gCr (1.5 – 5.1). Of 74 patients with whole exome sequencing or complement-cascade specific testing, 14 (19%) had rare variants in the C3 cascade specific testing, 14 (19%) had rare variants in C3, CFH, MCP, CFHR5, or CF5 genes, although some variants were of unknown significance. Seven of 35 (20%) and two of 24 (8%) patients had C3 nephritic factor and CFH Ab, respectively. Nineteen of 32 (58%) patients had a monoclonal protein. Median follow-up time was 3.2 yrs (1.3 – 8.5). Therapies included steroids (n=65) and other immunosuppression (n=49). Forty-two patients reached the endpoint of doubling Scr, ESRD, or death: 32.78 (41%) in the C3GN group and 10/25 (42%) in the DDD group (p=0.6).

**Conclusions:** In 100 US patients, we found no major differences in clinical presentation, diagnostic workup, or outcomes between C3GN and DDD. Our detection rate for mutations and autoantibodies was lower than in previous reports. C3GN and DDD share not only a common pathogenesis but also a common course. The value of distinguishing between the two should be examined in future studies.

**FR-PO634**

**Clinicalopathological Features in Patients with Amyloidosis and Low Serum C3 Level**

Bernardo V. Reichert, Leticia Jorge, Preci Diego Miranda de Menezes Neves, Cristiane B. Dias, Luis Yu, Viktoria Woronik. Nephrology, Univ of São Paulo, São Paulo, SP, Brazil.

**Background:** The complement system play an important role in the pathogenesis of different glomerulopathies. Recently, we have observed patients with amyloidosis and low serum C3 level as we are very interested in studying the complement levels in patients with amyloidosis. The aim of this study was to describe subjects with kidney amyloidosis and low serum C3 as well as compare them with those who present normal levels of C3.

**Methods:** We performed a retrospective study by reviewing clinical and histological data of amyloidosis patients submitted to renal biopsy at our center from 1999-2016. Decreased serum C3 levels (hypoC3) was defined as C3<90mg/dl. Of 47 patients, 9 were excluded by insufficient data.

**Results:** Of the patients, there were 9 patients with hypoC3(24%). In hypoC3, the type of amyloid was Ig amyloidosis in 6 patients(67%), AA amyloidosis in 2 patients(20%); AA amyloidosis in 2 patients(20%); other amyloidosis in 1(11%). The type of amyloid was Ig amyloidosis in 20 patients(69%), AA amyloidosis in 2(7%), familiar amyloidosis in 2(7%) and unclassified in 5(17%). The data are summarized in table 1.

**FR-PO635**

**Myophenolate Mofetil in C3 Glomerulopathy: Is It Really Effective?**

Ege Sinan Torun,1 Tarik Onur Tiryaki,1 Aysegul Oruc,1 Yasemin Ozluk,1 Halil Yazici,2 Mehmet S. Sezer,1 Yasar Caliskan.1 1Dept of Internal Medicine Div of Nephrology, Istanbul Univ Istanbul Faculty of Medicine, Istanbul, Turkey; 2Dept of Internal Medicine Div of Nephrology, Uludag Univ Faculty of Medicine, Bursa, Turkey; 3Dept of Pathology, Istanbul Univ Istanbul Faculty of Medicine, Istanbul, Turkey.

**Background:** This study aimed to evaluate the effect of immunosuppressive treatment on C3 glomerulopathy (C3G) progression.

**Methods:** A total of 68 patients [37 male, mean age:36±16 years] with C3G were enrolled. Patients with a baseline GFR value ≥30 ml/min and a minimum follow up of 6 months were assigned to myophenolate mofetil (MMF) based (n=22) or non-MMF based (cyclophosphamide or azathioprine) (n=18) or conservative care (ACE inhibitors or ARBs) (n=12) treatment groups. The study groups were similar regarding age, gender, systolic blood pressure (BP), hemoglobin, serum albumin, proteinuria and eGFR at the time of biopsy. Patients in the MMF or non-MMF based groups received low-dose daily corticosteroids. The relationship between study groups and composite kidney failure events (defined as ESRD or a two-fold increase in serum creatinine level as compared to baseline) was assessed.

**Results:** Composite kidney failure events developed in 13 (25%) and ESRD developed in 10 (20%) patients after a mean follow-up of 40 months. The number of patients developing composite kidney failure events were similar among the study groups (MMF based group: 22.7%, non-MMF based group: 16.7%, conservative care group: 41.7%, p=0.29). In Cox
Regression analysis, age (HR:0.863, p<0.003), proteinuria at the time of biopsy (HR:1.86, p=0.005) and GFR (HR:0.922[0.860]) at baseline were the clinical markers and the presence of crescents was the histopathological marker (HR 1.41, p=0.002) which predicted the composite kidney failure events.

Conclusions: In the present study, immunosuppressive treatment, particularly MMF baseline use was not found to be superior to conservative care in delaying the progression of CGG. Age, proteinuria and eGFR at the time of biopsy as clinical markers and the presence of crescents as a histopathological marker predicted the progression to ESRD.

FR-PO636
Progression of Chronic Kidney Disease in Alport Syndrome: Interim Data from the Athena Study
Oliver Gross,1 Gerard B. Appel,2 James F. Simon,3 Bertrand Knebelmann,4 Paul C. Grint,1 Jacqueline Blem,1 Michael Huang,5 Michelle N. Rheault.1 1Univ Medicine Goettingen, Goettingen, Germany; 2Columbia Univ Med Center, NY; 3Cleveland Clinic, Cleveland; 4Hospital Necker, Univ Paris Descartes, Paris, France; 5Regulus Therapeutics, San Diego; 6Regulus Therapeutics, San Diego; 7Regulus Therapeutics, San Diego; 8Univ Minnesota Masonic Children’s Hosp, Minneapolis.

Background: Alport syndrome (AS) is a genetic kidney disorder resulting in capillary glomerular basement membrane defects, leading to end stage renal disease. The natural progression of chronic kidney disease (CKD) in AS is not well studied and biomarkers to predict CKD progression are lacking. The current study characterizes the natural decline in renal function in AS patients over 120 weeks.

Methods: ATHENA (NCT01213682) is a non-interventional, global, multicenter study enrolling 250 AS patients. Eligibility criteria include: ≥12 years of age, confirmed diagnosis of AS, and glomerular filtration rate (GFR) between 30-90 ml/min/1.73 m2. Patients with previous renal transplantation are excluded. Renal biomarkers and estimated GFR (eGFR) are assessed at baseline and every 12 weeks. mGFR is assessed at baseline and every 24 weeks.

Results: Interim analysis included 113 enrolled patients, with 69 and 33 patients through 24 and 48 weeks of follow-up, respectively. At baseline, mean age was 44.8 years (SD 15.2), 65% of patients were female, and 82% were white. Genetic analysis revealed 65% had X-linked AS. Baseline mean mGFR and eGFR (MDRD) were 55.2 and 58.5 ml/min/1.73 m2, respectively. At week 24 and 48, mean mGFR change from baseline was -0.61 and -2.19 ml/min/1.73 m2 and mean eGFR (MDRD) change from baseline was -1.27 and -2.03 ml/min/1.73 m2, respectively, compared to baseline. No clear trends in other blood or urine biomarkers were observed during 24 weeks and 48 weeks of follow-up.

Conclusions: In this first prospectively designed natural history study of AS, interim data show a measurable decline in GFR by 24 and 48 weeks. With no currently approved therapeutic clinical trials. Enrollment and analysis of ATHENA is ongoing.

Funding: Pharmaceutical Company Support – Regulus Therapeutics

FR-PO637
Rates of Kidney Transplantation across Glomerulonephritis Subtypes in the United States
Michelle M. O’Shaughnessy,1 Sai Liu,2 Maria E. Montez-Rath,3 Richard A. Lafayette,4 Wolfgang C. Winkelmayer.1 1Stanford Univ, Palo Alto, CA; 2Univ of North Carolina, Chapel Hill, NC; 3Regina Margherita Hospital, Turin, Italy; 4Vanderbilt Univ Medical Center, Nashville, TN.

Background: Whether access to kidney transplantation differs by cause of ESRD, and specifically by glomerulonephritis (GN) subtype, has rarely been explored.

Methods: Using the US Renal Data System, we identified all adult patients with ESRD attributed to 1 of 6 GN subtypes or 1 of 2 non-GN comparator groups (see table) who initiated dialysis in the US (1996-2011). Using Cox proportional hazards regression, with death as a competing risk and follow-up to end of 2011, we estimated hazard ratios [HRs (95% confidence intervals)] for first kidney transplantation (IGAN-reference) across GN subtypes were adjusted for baseline demographics, comorbidities, and socioeconomic factors, as well as Organ Procurement Organization (OPO; actual or geographically most proximate).

Results: Among 632,908 patients, considerable heterogeneity in transplant rates across GN subtypes existed:

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Median Fu yrs</th>
<th>Decreased Donor TX, %</th>
<th>Living Donor TX, %</th>
<th>Death before TX, %</th>
<th>Censored, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSGS</td>
<td>n=27,036</td>
<td>2.7</td>
<td>22.9</td>
<td>11.7</td>
<td>32.6</td>
</tr>
<tr>
<td>IgAN, n=9,882</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN, n=5,356</td>
<td></td>
<td>2.0</td>
<td>17.9</td>
<td>11.3</td>
<td>38.2</td>
</tr>
<tr>
<td>MPGN, n=3,977</td>
<td></td>
<td>2.7</td>
<td>19.3</td>
<td>12.7</td>
<td>39.6</td>
</tr>
<tr>
<td>LN, n=14,161</td>
<td></td>
<td>2.4</td>
<td>17.6</td>
<td>11.7</td>
<td>36.7</td>
</tr>
<tr>
<td>Vasculitis, n=5,277</td>
<td></td>
<td>2.4</td>
<td>18.7</td>
<td>8.8</td>
<td>47.2</td>
</tr>
<tr>
<td>DN, n=540,755</td>
<td></td>
<td>2.4</td>
<td>6.0</td>
<td>3.0</td>
<td>61.4</td>
</tr>
<tr>
<td>ADPKD, n=26,429</td>
<td></td>
<td>2.5</td>
<td>30.0</td>
<td>11.8</td>
<td>26.8</td>
</tr>
</tbody>
</table>

Conclusions: Patients with these biopsy proven glomerular diseases appear to have reduced creatinine generation. The reasons are unclear, but reduced muscle mass related to CKD likely plays some role. These results have implications for interpretation of both random and timed urine collections.

Funding: NIDDK Support, Private Foundation Support

FR-PO638
 Unexpectedly Low 24-Hour Creatinine Excretion amongst Patients with Biopsy-Proven Glomerular Diseases

Background: Urine creatinine excretion (Ucre) is often used to assess accuracy of timed urine collections. Urinary analytes are also often normalized to Ucre concentration.

Methods: Data from 666 unique 24 hr urine collections of 226 adults collected at personal visits in the NEPTUNE cohort were available for analysis (minimal change 60, Focal sclerosis 91, membranous 60, other 91). Ucre was analyzed in batches in a centralized laboratory by enzymatic creatinine assay.

Results: Total Ucre was systematically lower than typical reference ranges independent of weight (Figure). Overall among NEPTUNE adult patients, the measured Ucre was systematically 50% lower than predicted by a recently published equation (lx and Wassel; JASN 6:184-191,2001). A model using repeated measures ANOVA for 48 patients with 3 or more available values supported internal consistency of Ucre by subject (p<0.50). CKD stage influenced creatinine excretion with 37% at CKD stage 1 within the predicted Ucre range while only 24% were at CKD stage 4 (p<0.001). Ucre did not associate with serum albumin, but correlated with baseline steroid exposure (OR=1.5; p=0.02). However, when Ucre was stratified by exposure (on steroids one, both, or neither collection) intra-patient correlations did not vary.

Figure. Correlation of individual patients’ 24-hour urine creatinine excretion (mg/weight kg) for all adult NEPTUNE samples (n=226 patients/ 666 observations). Reference lines denote published 96% reference ranges for Ucre (Junge et al. Clin Chim Acta 344: 137-148, 2004).

Funding: NEPTUNE, Grants from the US National Institutes of Health; Private Foundation Support

FR-PO639
Glomerular Disease Frequency Distributions by Continent - Results from the International Kidney Biopsy Survey
Michelle M. O’Shaughnessy,1,2 Susan L. Hogan,3 Bavana Donna Thompson,2 Rosanna Coppo,2 Agnes B. Fogo,4 J. Charles Jennette.1 1Stanford Univ, Palo Alto, CA; 2Univ of North Carolina, Chapel Hill, NC; 3Univ Florida, College of Medicine, Gainesville, FL; 4Vanderbilt Univ Medical Center, Nashville, TN.

Background: Large-scale studies comparing glomerular disease frequencies across continents are lacking.

Methods: We surveyed 29 nephropathology laboratories in 4 continents using a standardized form to obtain kidney biopsy diagnosis frequencies in recent consecutive years, along with population demographics for each diagnosis. If a specimen had multiple diagnoses, each was coded separately. This report focuses on glomerular disease frequencies by region and race/ethnicity. Cooperation was received from ASN-GDAG, RPS, and ERA-EDTA Immunohemopathology Working Group.

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

509A
Results: Diagnosis frequencies differed significantly by continent:

<table>
<thead>
<tr>
<th>Glomerular disease frequencies by continent (n=41,527)</th>
<th>USA/Canada (18 centers) n=23,189</th>
<th>Europe (14 centers) n=15,042</th>
<th>Asia (2 centers) n=1,609</th>
<th>Latin America (3 centers) n=1,687</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal Segmental GN1</td>
<td>19.4</td>
<td>14.9</td>
<td>6.9</td>
<td>21.8</td>
</tr>
<tr>
<td>IgA nephropathy2</td>
<td>11.7</td>
<td>22.1</td>
<td>39.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Diabetic GN1</td>
<td>19.0</td>
<td>7.6</td>
<td>10.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Membranous GN3</td>
<td>11.7</td>
<td>12.5</td>
<td>10.1</td>
<td>14.1</td>
</tr>
<tr>
<td>Lupus GN</td>
<td>9.7</td>
<td>10.1</td>
<td>10.8</td>
<td>20.0</td>
</tr>
<tr>
<td>Fibrinolytic immune GN1</td>
<td>5.2</td>
<td>8.0</td>
<td>2.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Minimal change disease1</td>
<td>4.2</td>
<td>6.4</td>
<td>3.4</td>
<td>10.0</td>
</tr>
<tr>
<td>Malignant GN/CMGN3</td>
<td>2.6</td>
<td>3.7</td>
<td>1.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Amyloidosis1</td>
<td>2.2</td>
<td>4.4</td>
<td>0.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Thrombotic microangiopathy1</td>
<td>2.8</td>
<td>2.2</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Thin basement membrane GN1</td>
<td>2.2</td>
<td>1.4</td>
<td>3.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Other1</td>
<td>9.5</td>
<td>7.3</td>
<td>4.2</td>
<td>8.7</td>
</tr>
</tbody>
</table>

1Chi-square p<0.004 (0.05/12). GS, glomerulosclerosis; GP, glomerulopathy; GN, glomerulonephritis.
2Focal segmental GN
3Diabetic GN

After stratifying by race/ethnicity, diabetic GS was more (17% vs 2%, p=0.001) and lupus GN less (16% vs 28%, p<0.001) frequent among Latinos in USA/Canada vs Latin America, while focal segmental GS was more (13% vs 7%, p=0.001) and IgA nephropathy less (27% vs 41%, p<0.001) frequent among Asians in USA/Canada vs Asia.

Conclusions: Glomerular disease frequencies differed by continent, even among patients of similar race. Environmental factors or local biopsy policy may influence regional glomerular disease epidemiology independently from race.

FR-PO640
Temporal and Demographic Trends in Glomerular Disease Epidemiology in the United States, 1986-2015

Michelle M. O’Shaughnessy,1 Susan L. Hogan,1 Caroline J. Poultou,1 Ronald J. Falk,2 Harshendar Kaur Singh,2 Volker Nickel,1,2 J. Charles Jennette.1 1Stanford Univ, Palo Alto, CA; 2Univ of North Carolina, Chapel Hill, NC.

Background: Large-scale, contemporary, US studies exploring temporal trends in glomerular disease epidemiology by patient age, sex, and race are lacking.

Methods: In this cross-sectional, observational study, we examined glomerular disease subtype frequencies among all patients whose native kidney biopsy specimen was referred to the University of North Carolina (UNC), Chapel Hill, Nephropathology Laboratory (1986 to 2015), and who received a first biopsy confirmed diagnosis of a primary or secondary glomerular disease. Biopsy era (1986-1995, 1996-2005, 2006-2015) was the primary predictor. Patient age, sex, and race were secondary predictors. Relative biopsy frequencies were the primary outcomes.

Results: Among 23,959 cases of biopsy confirmed glomerular disease, the frequency of diabetic glomerulosclerosis increased dramatically over the 3 decades (4.4%, 10.0%, and 17.6% of cases, respectively, p<0.002). The frequency of FSGS increased initially but subsequently declined (18.0%, 23.8%, and 22.1%, respectively, p<0.002), whereas the frequency of other common glomerular disease subtypes remained stable (IgA nephropathy, pauci-immune glomerulonephritis, lupus nephritis) or declined (minimal change disease, membranous nephropathy). These temporal trends were observed within all major sex, race, and age groups, with the exception of children, although substantial variation in glomerular disease subtype frequency distributions were observed across demographic groups cross-sectionally, Figure 1.

Conclusions: We identified significant changes in the relative frequencies of many glomerular disease subtypes over the past 30 years. We propose that exploration of behavioral and environmental exposures that likely underlie these findings should be the focus of future hypothesis-driven studies.

FR-PO641
B7.1 and suPAR Fail as Potential Biomarkers to Detect Podocyte Injury and Focal Segmental Glomerulosclerosis in Kidney Biopsies
Zoltan G. Laszik,1 Flavio Vincenti.2 1Pathology, UCSF, San Francisco, CA; 2Transplant Service, UCSF, San Francisco.

Background: The mechanism of injury to podocytes in focal segmental glomerulosclerosis (FSGS) remains unclear. Both B7.1 (CD80) and suPAR have been proposed to cause FSGS but the findings have not been validated. To survey these markers as potential mediators of podocyte injury and as an aid to histologic diagnosis of FSGS we evaluated the expression of B7.1 and suPAR in native and transplant (Tx) kidney biopsies (Bx), and the expression of suPAR in mice injected with suPAR.

Methods: Study groups included Bx with FSGS (n=10), early post-Tx recurrent FSGS prior to (n=15) and post-plasmapheresis (n=7). Native Bx with membranous nephropathy (MN) (n=10) and minimal change disease (MCD (n=5), and normal 6 month post-Tx protocol Bx [n=10] served as controls. Immunostains were performed on formalin-fixed paraffin-embedded (FFPE) and frozen tissues for B7.1 and suPAR. B7.1 mRNA expression was also assessed by next generation in situ hybridization (ISH) on FFPE. Signal co-localization was evaluated via co-stain with the podocyte marker synaptopodin. In addition, suPAR immunohistochemical expression was also evaluated in the kidneys of wild type and suPAR−/− mice infused with recombinant suPAR. Electron microscopy was used in the next generation to assess foot process effacement in conjunction with renal functional studies.

Results: B7.1 protein and mRNA were not expressed in native kidneys with FSGS or MCD in or transplant kidneys with recurrent FSGS. In MN, B7.1 was localized only to the immune deposits. No apparent suPAR immunoreactivity was present in native kidneys or recurrent FSGS. SuPAR infusion did not produce proteinuria or effacement of podocytes in wild type or suPAR deficient mice. SuPAR was detected along the glomerular endothelial cells but not in podocytes in wild type mice while suPAR stain remained negative in uPAR deficient mice even after suPAR injection.

Conclusions: The data suggest that B7.1 and suPAR may not play a significant role in podocyte injury in native and transplant kidneys with FSGS. B7.1 and suPAR immunostains and ISH seem to have a limited value as diagnostic markers in kidney Bx with FSGS and recurrent FSGS post-transplant.

Funding: Pharmaceutical Company Support - AbbVie

FR-PO642
Urinary Monocyte Chemotactic Protein 1 as a Predictive Marker of Steroid Responsiveness in Children with Idiopathic Nephrotic Syndrome
Yui Matsumoto, Yohei Ikezumi, Tomomi Kondo, Yoko Nakajima, Tetsuya Ito, Tetsushi Yoshikawa. Pediatrics, Fujita Health Univ, Toyoake, Aichi, Japan.

Background: We have previously reported that CD36 (low-density lipoprotein scavenger receptor) macrophage (MQ) contributed in the pathogenesis of refractory nephrotic syndrome (NS). To elucidate the mechanism of MQ accumulation and to identify a predictive biomarker of steroid responsiveness, we compared differences in cytokine and chemokine levels in serum and urine between steroid-sensitive (SSNS) and steroid-resistant (SRNS) children.

Methods: In this study, 20 children with NS (7.1 ± 4.3 years; male-to-female ratio, 13:7) were enrolled. They were divided into a steroid-sensitive group (SSNS; n = 15) and a steroid-resistant group (SRNS; n = 5) according to their clinical course. Serum and urinary samples were collected at the time of onset and remission. Control serum and urine samples were also collected from age-matched healthy children (n = 15). Cytokines and chemokines were measured by using a cytometric bead array kit.

Results: The levels of several cytokines and chemokines in the urinary samples were significantly higher at onset than at remission (IP-10: p = 0.001, MCP-1: p = 0.001, MIG: p = 0.012, RANTES: p = 0.003) and those in the control samples (IL-6: p = 0.026, IP-10: p < 0.001, MCP-1: p = 0.032, MIG: p = 0.001, RANTES: p = 0.005). However, serum cytokine and chemokine levels did not significantly differ among the three groups. At onset, the urinary MCP-1 level was significantly higher in the SRNS group than in the SSNS group (p = 0.044).

Conclusions: The present study demonstrated that urinary cytokines and chemokines might be associated with the pathogenesis of NS. In particular, increased urinary excretion of MIP-1 in SRNS children was a potent predictive biomarker of steroid responsiveness in idiopathic NS. MCP-1, a chemokine recruiting macrophage, may play an important role in the pathogenesis of steroid resistance. Further histological studies warrant elucidation of the mechanisms of steroid resistance in refractory NS.

Funding: Clinical Revenue Support
FR-PO643

Biomarkers to Predict the Development of Glomerulosclerosis
Nina A. van de Lest,1 Malu Zandbergen,1 Ingeborg M. Bajema,1 Jan A. Bruijn,1 Reinhold Kreutz,2 Marion Scharpenecker.1 Pathology, Leiden Univ Medical Center, Leiden, Netherlands; Clinical Pharmacology and Toxicology, Charité Universitätsmedizin, Berlin, Germany.

Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are two common causes of the nephrotic syndrome. Some patients with biopsy-proven MCD have been shown to progress to FSGS. Early biomarkers indicating potential development of glomerulosclerosis before it becomes detectable by histology could help to discriminate between MCD patients that do or do not progress to FSGS. We previously described early changes in nephrin and segmental changes in desmin and podoplanin in a rat model for proteinuria and glomerulosclerosis (MWF rats). The aim of this study was to investigate whether changes in these markers are predictive for the development of glomerulosclerosis in MWF rats and patients with MCD.

Methods: 20 kidney sections of MWF rats and the non-proteinuric SHR strain were stained for desmin, podoplanin and nephrin at 4, 8 and 24 weeks of age. Quantification was performed using ImageJ. For a pilot study, renal biopsy samples of 10 MCD patients and 15 primary FSGS patients, diagnosed between 2001 and 2016, were stained for desmin, podoplanin and nephrin.

Results: In MWF rats, desmin expression in glomeruli was significantly increased at 8 and 24 weeks of age (p<0.0001), whereas it remained stable in SHR. Moreover, at 8 and 24 weeks, MWF rats showed segmental loss of podoplanin, which co-localized with de novo expression of desmin in podocytes. At 24 weeks of age, MWF rats developed segmental glomerulosclerosis, which was associated with segmental loss of nephrin in podocytes and loss of podoplanin at the site of sclerosis. Confirming other studies, in biopsies of patients with MCD, the expression pattern of nephrin was granular and in FSGS, segmental loss of nephrin was observed. However, we also detected segmental loss of nephrin in patients with MCD.

Conclusions: Loss of podoplanin expression and de novo expression of desmin in podocytes predict development of segmental sclerosis in MWF rats. We also show segmental loss of nephrin in patients with MCD, which suggests that this marker may predict progression to FSGS.

FR-PO644

Minimal Change Disease and Focal Segmental Glomerulosclerosis Patient Subgroups Using Cluster Analysis of Morphologic Descriptors: Early Findings from the Nephrotic Syndrome Study Network
Laura H. Marijanic,1 Jacry Zee,2 Jeffrey B. Hodgkin,1 Matthias Kretzler,1 Brenda W. Gillespie,1 L. Barisoni,1 Lawrence H. Holzman,1,4 U. Michigan; 1Arbor Research; 2U. Miami; 4U. Pennsylvania.

Background: Conventional classification of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) is based on qualitative interpretative pathology and does not capture disease heterogeneity. To overcome this problem, the descriptor-based NEPTUNE Digital Pathology Scoring System (NDPSS) was developed to assess multi-level, annotated whole slide images of renal biopsies.

Methods: To explore whether the NDPSS can identify patient subgroups, we used unsupervised cluster analysis of 68 MCD and 110 FSGS patients using the percent of global scores below the median level, annotated whole slide images of renal biopsies.

Results: 3 clusters were found. Patients with a conventional diagnosis of MCD and FSGS were distributed among all 3 clusters, although FSGS patients represented 25% of Cluster 1. Cluster 1 patients had the highest rates of the composite outcome and lowest remission rates compared to the other two (p<0.001). Cluster 2 patients had higher rates of remission compared to Cluster 3. Cluster 2 patients were younger, had higher baseline eGFR, and lower baseline urine protein creatinine ratio (p<0.001).

Conclusions: Clusters of patients with similar glomerular descriptor profiles had different clinical characteristics and outcomes. Therefore, given that the clusters do not match conventional morphologic classifications, there may exist previously undiscovered patient subtypes with different disease phenotypes. Further studies using the NDPSS are ongoing. The NDPSS is thus a useful methodology for diagnostic and prediction medicine.

FR-PO645

Simple and Rapid Identification of Podocyte (Podo) Injury Using Anti-Podocalyxin (PCX) Antibody-Bound Latex Beads and Urine Sediments
Masanori Hara, Dept of Pediatrics, Yoshida Hospital, Tsuabame, Niigata, Japan.

Background: The urine sediments from patients with Podo injury contain numerous PCX positive structures as a form of granules trapped in the casts, in addition to Podo(es).

Methods: In order to get the antibody-bound latex we have newly developed monoclonal antibodies designing to trap the PCX positive granules or Podo(es). PCX expressing cell line (NCIT) was used as positive control to search for the optimal reaction condition or requirements. Various approaches were tried and examined for requirements positive for Podo injury in this assay. The time needed for entire procedure was 1.5ml was mixed with 10 ul of 0.2 % antibody-bound latex and centrifuged using swing type at 1500 G for 15minutes and then the mixtures was gently suspended and served for light microscopic examination. The presence of latex-bound cells or casts was evaluated as positive for Podo injury in this assay. The time needed for entire procedure was ~30 minutes. The good sensitivity (0.71) and specificity (0.96) was obtained.

Conclusions: We have developed a new method to detect podocyte injuries using antibody-bound latex beads and urine sediments that is simple and rapid without use of immunofluorescent microscope. This new approach might offer great advantages for the screening of podocyte injury in the practice of clinical nephrology.

FR-PO646

Proteomic Analysis Identifies Candidate Biomarkers of Steroid Resistance in Pediatric Glomerular Disease
Michael Merchant,1 Shipra Agrawal,2 William E. Smoyer,3 Jon B. Klein,4 1Medicine, Univ of Louisville; 2CCTR, The Research Inst at Nationwide Children’s Hospital, Columbus, OH; 3Pediatrics, The Ohio State Univ, Columbus, OH; 4Robley Rex VAMC, Louisville, KY.

Background: Glomerular disease is the third leading cause of ERD in the US. Immunosuppressive drugs are the primary therapies for most glomerular diseases, but ~20-50% of patients fail to achieve a remission and can be deemed steroid resistant. No biomarkers exist to predict treatment responsiveness, leaving patients at high risk for both toxic side effects and disease progression. Prognostic biomarkers to prevent drug-induced toxicity, and to identify more targeted and effective treatments for glomerular disease represents an urgent need.

Methods: Paired plasma samples (n=30) were collected from 15 patients with nephrotic syndrome (NS) (steroid sensitive, SSNS; n=7 and steroid resistant, SRNS; n=8) and low abundant serum proteins were enriched by FPLC based immunodepletion of high abundant proteins. These paired samples were collected 6-8 weeks apart and corresponded to entry into a study (pre-steroid treatment) and a follow-up period at which time the clinical determination of steroid responsiveness was known. Samples were trypsinized, LCMS data (Orbitrap ELITE) collected and analyzed with Mascot/Sequest search strategy. Scaffold 4 was used for false discovery rate control, and ANOVA analysis was used to determine differences in protein abundances between SSNS and SRNS patient samples at pre- and follow-up time points.

Results: 45 of 223 protein clusters were differentially expressed (p-value <0.05) by ANOVA, 21 proteins remained significantly different following Benjamini-Hochberg multiple comparison correction (*p-value< 0.003). Unique protein abundance observations were discovered; 1) the mixture of 4 different antibodies (clones; 4A2, 4A7, 4D2 and 4E5) was required. 2) size and color of the latex should be 1.0 um and blue, 3) the sediments after centrifugation of starting urine volume of 1.5ml was mixed with 10 ul of 0.2 % antibody-bound latex and centrifuged using swing type at 1500 G for 15minutes and then the mixtures was gently suspended and served for light microscopic examination. The presence of latex-bound cells or casts was evaluated as positive for Podo injury in this assay. The time needed for entire procedure was ~30 minutes. The good sensitivity (0.71) and specificity (0.96) was obtained.

Conclusions: We have developed a new method to detect podocyte injuries using antibody-bound latex beads and urine sediments that is simple and rapid without use of immunofluorescent microscope. This new approach might offer great advantages for the screening of podocyte injury in the practice of clinical nephrology.
FR-PO647

Regulatory T-Cells Dynamics Predicts Clinical Response to Rituximab in Patients with Severe Primary Membranous Nephropathy

Michelle Rosenzwieg,1,2 Eva Langille,1,2 Hanna Debec,2 Joana Hygino,3 Karine Daham,4 David Klattmann,5,6 Pierre M. Ronco,4,7 Sorbonne Unives, UPMC Univ Paris 06, UPMC Univ Paris 06, Paris, France; 4UMR S 1155, F-75020, INSERM, Paris, France; 6Biotechnology (CIC-BIT) and Inflammation-Immunoopathology-Debiexy Dept (12B), AP-H, Hôpital Pitié-Salpêtrière, Paris, France; 5UM S 959, F-75005, INSERM, Paris, France; 7Dept of Nephrology and Dialysis, AP-H, Hôpital Tenon, Paris, France.

Background: Little is known about cellular immune responses in primary membranous nephropathy (PMN). We aimed to characterize lymphocyte populations and cytokines/chemokines in patients with severe PMN at baseline and after rituximab infusion added to non-immune-suppressive anti-proteinuric treatment (NIAT) or under NIAT alone in the first rituximab-based RCT.

Methods: Twenty-five patients were enrolled in this study as well as 27 age-matched healthy donors. We investigated the dynamic changes of 33 lymphocyte subpopulations and cytokines/chemokines in patients’ peripheral blood. Twenty-one patients had PLAR2-related MN and one had anti-THSD7A antibodies.

Results: At baseline, the most significant changes between PMN patients and controls were (i) increased percentages of naive B-cells with decreased switched and non-switched memory B-cells; (ii) overall decrease of NK cells percentage, contrasting with an increase of the CD56dimCD16- NK subset; (iii) decreased percentage of regulatory T cells (Tregs). This was associated with an increase of the plasma concentration of TNF-alpha, IL-5 and IL-2RA. After rituximab treatment, B-cell recovery was still incomplete at 6 months, with persistent alterations of B-cell subsets, overall increase of Treg and NK cell percentages and decrease of CD56dimCD16- NK subset and TNF-alpha levels. Noteworthy, the patients who responded to rituximab had a lower percentage of Tregs at baseline and a significant Treg increase at day 8 after rituximab. In contrast, Tregs remained unchanged in non-responders and in patients not treated with rituximab.

Conclusions: Altogether, these delineate subgroups of PMN patients and is a potential predictive biomarker of rituximab efficacy.

Funding: Pharmaceutical Company Support - Hoffman-La Roche

FR-PO648

Rituximab Residual Levels and Neutralizing Anti-Rituximab Antibodies (Ab) Are Associated with Response to Treatment in Patients with PLAR2-Related Membranous Nephropathy (MN)

Barbara Seitz-Polski,1 Hanna Debec,2 Karine Daham,2 Sylvia Bentzenk,1 Pierre M. Ronco,1,3 'Nice Univ Hospital, France; 3Tenon Univ Hospital, France.

Background: The anti-CD20 monoclonal antibody rituximab can induce remission of membranous nephropathy. Rituximab levels were measured in the plasma at follow-up to investigate its effects on prognosis.

Methods: Twenty-five patients were enrolled in this study as well as 27 age-matched healthy donors. Anti-rituximab antibodies at months 3 and 6 after each rituximab course, and searched for a neutralizing effect of anti-rituximab antibodies in 15 patients from Nice (1g at day 0 and 500mg at week 2 and 4). Rituximab-induced 10 remissions at month 6 in patients from Nice. Residual anti-rituximab levels at months 3 and 6 after rituximab infusion were significantly different (p=0.03) and associated with higher residual rituximab level at month 3 (p=0.002) and achieved remission at month 6 (p=0.003) while baseline proteinuria and PLA2RAb titer seemed unrelated with clinical relapse at month 6 (p=0.35) in patients with anti PLAR2 antibodies.

Conclusions: Altogether, these delineate subgroups of PMN patients and is a potential predictive biomarker of rituximab efficacy.

FR-PO650

Clinical and Pathological Spectrum of THSD7A Positive Membranous Glomerulopathy

Shree G. Sharma, Christopher Patrick Larsen. Nephropathology, Arkana Laboratories, Little Rock, AR.

Background: Thrombospondin type 1-domain containing 7A (THSD7A) is a recently described antigenic target in primary membranous glomerulopathy (MG). In the initial report, anti-THSD7A antibodies were identified in approximately 10% of the patients negative for PLAR2 antibodies.

Methods: All non-SLE associated MG cases (n=107) were stained for PLAR2 and THSD7A in a laboratory for a 30 month period. THSD7A-positive MG cases were selected for study. Serum samples were available from 18 THSD7A positive cases at the time of biopsy and tested by IFA for the presence of THSD7A antibodies (Euroimmun).

Results: The cohort consisted of 28 patients (17 males and 11 females). The mean age was 66 years (range 17 to 91 years). Twenty five (25) patients presented with full nephrotic syndrome and 3 patients with proteinuria with a mean proteinuria of 10 grams/day (range: 1.1-15 grams/day). The mean serum creatinine was 1.3 mg/dL (range: 0.6-3.3; n=25) and serum albumin was 2.0 g/dL (range: 1.3-2.1; n=18). On renal biopsy, all the cases had positive THSD7A staining and two cases were also positive for PLAR2. Serum samples of five patients available for study at the time of biopsy were positive for THSD7A antibodies (1:10-1:500) for THSD7A antibodies. Follow up data was available in 18 patients. The mean proteinuria on follow up was 7.5 grams/day (range: 0.06 – 9.9; n=13), creatinine was 1.3 mg/dL (range 0.5-3.2; n=17) and albumin was 2.5 g/dL (range 1.2-4.1; n=14).

Conclusions: We present the largest cohort to date of THSD7A-associated MG. In our patient population, THSD7A-associated MG accounts for 2.6% of non-SLE associated MG. Biopsy staining correlates well with the presence of serum antibodies at the time of diagnosis. Ongoing studies are underway examining the prognostic significance of serum antibody level.

FR-PO651

Analysis of PLAR2 Sequence Variants in Japanese Patients with Idiopathic and Secondary Membranous Nephropathy

Hajime Koga, Hideki Wakuji, Atsushi Komatsuda, Naoto Takahashi. Hematology, Nephrology, and Rheumatology, Akita Univ Hospital, Akita City, Japan.

Background: Phospholipase A2 receptor (PLAR2) was found to be the major target antigen of autoantibodies in idiopathic membranous nephropathy (IMN) [N Engl J Med. 361: 11-21, 2009]. The prevalence of anti-PLAR2 antibodies in Japanese patients with IMN is lower than that of any other countries [Clin Exp Nephrol. 19: 653-60, 2015]. Several reports showed PLAR2 sequence variants are associated with IMN. However, genetic background of PLAR2 in Japan has not been studied. Also genetic backgrounds of PLAR2 in IMN and secondary MN are unclear in Japanese patients.

Methods: A total of 50 patients with IMN, 23 patients with sMN, and 50 patients with other renal diseases as a control admitted to our hospital and affiliated hospitals between January 2005 and November 2017 were enrolled in this study. Coen et al. reported that single nucleotide polymorphisms (SNPs) in exon 1, 1.2, 5.1, 15.6 and 24 of PLAR2 gene are significantly associated with IMN [J Am Soc Nephrol. 24: 677-83, 2013], we selected reported six SNPs, and then sequenced directly five exons of PLAR2, using genomic DNA prepared from peripheral lymphocytes in patients with IMN, sMN, and controls. The differences in these SNPs allele frequency among three groups were analyzed by Kruskal-Wallis test or χ2 test. We also analyzed the relationship between clinical parameters (urinary protein, serum albumin, and serum creatinine) and genotypes of PLAR2 by Kruskal-Wallis test.

Results: Four of six SNPs, rs35771919, rs35771917, rs35771982, and rs2715918 were significantly associated with sMN (p=0.0566, p=0.0001, p=0.0001, and p=0.0001, respectively). Only rs35771982 was significantly but weakly associated with sMN (p=0.0405). Between IMN and sMN, there were significant differences in allele frequency in rs3749117 and rs2715918 (p=0.0439 and p=0.0291, respectively). There were no correlations between PLAR2 genotypes and clinical parameters.
**FR-PO652**

**Changes of Lymphocytes Profile in Patients with Severe Systemic Lupus Erythematosus Treated with an Intensified B-Cell Depletion Therapy with Rituximab**

Dario Roccatello, Savino Sciscia. Nephrology Dept, San Giovanni Bosco Hospital.

**Background:** In this study we aim to prospectively investigate the differentiation and phenotypic changes of peripheral B cells and T regulatory lymphocytes (Treg) in patients with systemic lupus erythematosus (SLE) after an intensified B-Cell depletion therapy with Rituximab (RTX).

**Methods:** Ten patients with severe SLE (2males, mean age 41.6 yrs (25–57)) with severe multigorgan involvement have been prospectively treated with IBCDT protocol due to their resistance or intolerance to previous therapy. Protocol: RTX 375 mg/m² on days 1,8,15,22, and 2 more doses after 1 and 2 months, associated with 2 IV administrations of 10 mg/kg of cyclophosphamide and 3 methylprednisolone pulses (15mg/kg) followed by oral prednisone (0.8 mg/kg/day, rapidly tapered to 5mg/day by the end of the 3rd month after RTX). No further immunosuppressive maintenance therapy has been given. Circulating B cells and Treg in the peripheral blood were investigated by flow-sometry (with monoclonal antibodies against CD45,CD3,CD4,CD19,CD20,CD25,FOXP3) at baseline, month 1, month 2, and every other month thereafter up to 1 year. Response was evaluated by assessing the changes in clinical/laboratory parameters and SLEDAI score.

**Results:** All patients had complete peripheral blood B cell depletion after IBCDT and the CD20+B cells were not detectable in the circulation by the 12th month (detection limit of 0.005x10⁹/l). Upon detection of B cell depletion, we observed in 12 months a 4-fold increase in the circulating Treg (CD4+CD25+FOX3+) (2% at baseline, 3% after 1 month, 4,5% at 6 month, 8% at 12 months). All patients achieved clinical remission after IBCDT and no flare were observed during the one-year follow-up. IBCDT resulted in a decrease of median global SLEDAI from 14.6 [11–23] to 4 [1–5] at 12 months (p<0.01).

**Conclusions:** Our results suggest a phenotypic change of peripheral T lymphocytes as a result of B cells depletion obtained with IBCDT. Treg considered being essential in the maintenance of peripheral self-tolerance, progressively increased after B cell depletion. Such immunological re-assessment was observed in association with clinical remission in the absence of further disease flare.

**FR-PO653**

**Monocyte Chemotactic Protein-1, Fractalkine, and Receptor for Advanced Glycation End Products in Different Pathological Types of Lupus Nephritis and Their Value in Predicting the Treatment Prognosis**

Lan Lin, Jianghua Chen. Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.

**Background:** Early diagnosis is important for the outcome of lupus nephritis (LN), and the pathological type of LN is closely related to the clinical manifestations and treatment prognosis.

**Methods:** In the patients included in this study, through renal biopsy, class III and class IV were defined as proliferative group, class V as nonproliferative group, class V+III and class V+IV as mixed group. During the follow-up, 40 of the 178 enrolled patients were found to have poor response to standard immunosuppressant therapy. The level of urine and serum MCP-1, Fractalkine, and Receptor for Advanced Glycation End Products (RAGE) in the different groups was tested. Underline represents presenting author.

**Results:** The concentration of cytokines MCP-1, Fractalkine, and RAGE may be correlated with the nuclear factor-kappaB pathway. The cytokines may help in predicting the prognosis before standard immunosuppressant therapy.

**Funding:** Clinical Revenue Support

**FR-PO654**

**Zonal Cortical Scarring and Tubular Thyroidization in Biopsies of Patients with SLE - Indicator for Anti-Phospholipid Antibodies?**

Anjali A. Satoskar,1 Robin Shah,2 Sergey V. Brodsky,1 Lee A. Hebert,2 Brad H. Rovin,2 Tibor Nadasdy.1 Pathology, Ohio State Univ Wexner Medical Center, Columbus, OH; 1Internal Medicine Nephrology Div, Ohio State Univ Wexner Medical Center, Columbus, OH, United Kingdom.

**Background:** Anti-phospholipid antibody syndrome (APS) can be primary or secondary to other autoimmune diseases, most commonly systemic lupus erythematosus (SLE). Among SLE patients, prevalence of anti-phospholipid antibodies (aPL) ranges from 30 to 40% and approximately 50% of these develop APS sometime during their disease course. Thrombotic microangiopathy (TMA) is a well-known complication of APS. We have encountered many kidney biopsies in SLE patients with zonal scarring and tubular thyroidization and positive aPL without evidence of ongoing TMA. Therefore we systematically studied the relevance of this association.

**Methods:** We searched our Pathology database for kidney biopsies from patients with SLE. Laboratory testing results for aPL were assessed based on a combination of tests (Staclot, dilute Russel viper venom test [DRVVT], and anti-cardiolipin antibodies). Biopsies were screened for presence/absence of zonal cortical scarring with tubular thyroidization.

**Results:** We identified 114 patients with SLE and kidney biopsy over a period of 9 years and 46 (40%) had at least one laboratory test indicating presence of aPL. Of the 46 patients with aPL, 15 (33%) had zonal scarring, 31 (67%) did not. Of the 68 patients without aPL, only 5 (7.3%) had zonal scarring and 63 (92%) did not. Therefore, sensitivity was calculated to be 33%, specificity 92%, positive predictive value 73% and negative predictive value 67%. TMA-like changes were seen only in 7/15 biopsies with zonal cortical scarring and aPL.

**Conclusions:** Presence of zonal scarring and tubular thyroidization in kidney biopsies from patients with SLE, is a specific indicator for presence of aPL. Sensitivity of this feature is expectedly low because of its zonal nature and biopsy sampling issue. It may be the only morphologic indicator for the presence of aPL because TMA changes are frequently absent. The association of zonal renal cortical scarring with aPL is important to recognize because anti-coagulation therapy may be warranted.
FR-PO655

Proteome Analysis for Identification of Biomarkers for Accurate Diagnosis and Classification of Lupus Nephritis Patients in Saudi Arabia
Khadloun Al-Romaie, 1 Zakia M.Anwar Shinwari, 1 Maram Alwahebi, 2 Basma Mohammed Alhadeh, 1 Menah Allah Ahmed Safari, 2 Turki Al-Hussain, 2 Maged H. Hussein, 2 Ayodele Aliaya, 1 Stem Cell and Tissue Re-Generation Projects, 1 2Nephrology, Department of Medicine, 1 2King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Background: Lupus Nephritis (LN) is one of the most common causes of renal failure in Saudi Arabia. Treatment and prognosis in lupus nephritis are based mainly on the findings in renal histopathology obtained by renal biopsy, which is non-specific, invasive and does not account for disease mechanism. Most proteomic studies to date used either serum or urine samples in studying renal biomarker, making identifying potential biomarkers cumbersome and difficult to trace back to its own origin.

Methods: Kidney tissue biopsy, urine and Peripheral Blood Plasma (PPB) samples from biopsy proven lupus nephritis patients were subjected to expression-proteomics using quantitative label-free liquid chromatography tandem mass-spectrometry (LC-MS/MS).

Results: Approximately 785 & 225 differentially expressed proteins were identified from kidney tissues & peripheral blood samples respectively. About 5% of the identified proteins from the plasma samples were also among the identified proteins from the tissue samples. Some of the differentially expressed proteins in kidney as well as peripheral blood are LGALS3BP, GCK, FN1, IGHM, GHG1, and HBB1. This indicates the likelihood to identify disease-associated biomarkers seen in kidney tissue as well as in plasma. This would subsequently allow monitoring of such biomarker proteins in peripheral blood, demanding less invasive procedures against kidney biopsy for objective classification and prognostic monitoring of LN patients.

Conclusions: The result demonstrates the potential of proteomics as a powerful tool for discovery of reliable diagnostic markers for lupus nephritis and other kidney diseases. The proteins with differential expression in both kidney tissues and corresponding plasma are potential targets for future discovery in larger sample cohorts. Funding: Government Support - Non-U.S.

FR-PO656

Clinical and Histopathologic Determinants of Renal Outcome in Lupus Nephritis - Starting from Scratch
Emilie Rijnink, 1 Yoe Kie Onno Teng, 1 Suzanne Wilhelms, 1 Ron Wolterbeek, 2 Karlien Cransberg, 1 Jan A. Brujin, 1 Ingeborg M. Bajema, 1 Leiden Univ Medical Center; 2Erasmus Univ Medical Center.

Background: Controversy surrounds the prognostic significance of various lesions forming the basis of the IRS/NPS 2003 classification of lupus nephritis (LN). To improve evidence-based patient prognostication, we analyzed individual clinical and histopathologic parameters for their potential to predict renal outcome in LN outside the framework of the classification.

Methods: We included 105 patients with LN biopsied between 1987-2011. Fifty histopathologic and 10 clinical variables were determined as candidate predictors of outcome. We tested these baseline variables for their potential to predict eGFR trajectories during follow-up (registrations at 1, 5, and 10 years) in mixed and linear regression models, and progression to renal flare and end-stage renal disease (ESRD) in Cox regression models.

Results: The mean adjusted decline in eGFR was -0.75 (95% CI -1.46, -0.04) mL/min per year. The change in the level of eGFR was best predicted by %smear glomerulonephritis (2.67 mL/min/10%; 95% CI 0.25, 4.81), %cellular/fibrillary crescents (-3.76 mL/min/10%; 95% CI -6.62, -1.25), %fibrous crescents (-13.47 mL/min/10%; 95% CI -24.20, -2.75), interstitial fibrosis/tubular atrophy (IF/TA) -2% (-39.26 mL/min; 95% CI -21.70, -56.82), age (+0.67 mL/min/yr; 95% CI 0.26, 1.09) and non-Caucasian ethnicity (-13.85 mL/min; 95% CI -2.06, -25.63). Renal flare was best predicted by %fibronud sclerosis (HR 1.48 per 10%; 95% CI 1.00, 2.16) and non-Caucasian ethnicity (HR 2.26; 95% CI 1.25-4.10). The end-point ESRD was predicted by %fibronud sclerosis (HR 2.16 per 10%; 95% CI 1.34, 3.71) %fibrous crescents (HR 2.50 per 10%; 95% CI 1.20, 5.19), IF/TA >25% (HR 3.64; 95% CI 1.18, 11.25), eGFR at baseline (HR 0.98 per mL/min; 95% CI 0.96, 1.00); and non-Caucasian ethnicity (HR 7.21; 95% CI 2.33, 22.27).

Conclusions: Prognostication in LN may benefit from the assessment of specific lesions currently obscured in the classification. These prognosticators necessitate validation in future studies.

FR-PO657

Idiopathic Non-Lupus Full House Nephropathy: Is Associated with Poor Renal Outcome
Emilie Rijnink, 1 Yoe Kie Onno Teng, 1 Timene Kraaij, 2 Ron Wolterbeek, 3 Jan A. Brujin, 1 Ingeborg M. Bajema, 1 1Pathology, Leiden Univ Medical Center; 2Nephrology, Leiden Univ Medical Center; 3Epidemiology, Leiden Univ Medical Center.

Background: Full house immunofluorescence in combination with various histopathologic lesions in the renal biopsies of patients without overt systemic lupus erythematosus (SLE) poses a diagnostic challenge. In this setting, the biopsy findings are sometimes termed non-lupus “full house nephropyhosis” (FH). It is presently unknown whether non-lupus FH is distinct from lupus FH.

Methods: We included non-lupus FHN patients and controls with lupus FHN according to ≥2 of the SLICC criteria who were biopsied between 1987-2011. All non-lupus FHN patients were compared to lupus FHN patients.

Results: Of 149 included patients, 32 had non-lupus FHN. Twenty of the non-lupus FHN patients had idiopathic non-lupus FHN, and the remainder had membranous nephropathy (anti-PLA2R-positive, n=1; paraneoplastic, n=3), IgA nephropathy (n=4), infection-related glomerulonephritis (n=2), and ANCA-associated vasculitis (n=2) with FHN. Idiopathic non-lupus FHN patients were more often male (P<0.001) than lupus FHN, and their renal biopsies more often showed a mesangial (P<0.004) and less intense C1q staining (P<0.002). Clinically, they presented with significantly lower-range erythrocyturia (P<0.04), more proteinuria (P<0.01), and less complement consumption in the classical pathway (P<0.001) than lupus FHN patients.

Conclusions: Our results show that idiopathic non-lupus FHN is clinically and biopathologically distinct from lupus FHN. Importantly, idiopathic non-lupus FHN is associated with a poor renal outcome, warranting (early) recognition and urging future studies to elucidate therapeutic options.
FR-PO660

Comprehensive Aptamer-Based Screening of 1,129 Proteins Reveals Novel Urinary Biomarkers of Lupus Nephritis
Samantha Stanley,1 Huihua Ding,1 Claudia Pedroza,2 Ramesh Saxena,4 Michelle Petri,3 Chandra Mohan,1
1Biomedical Engineering, Univ of Houston, Houston, TX; 2Center for Clinical Research, UT Health Science Center, Houston, TX; 3Rheumatology, John Hopkins Univ Medical School, Baltimore, MD; 4Clinical Research and Evidence-Based Medicine, Univ of Texas Health Science Center, Houston, TX.

Methods: An aptamer-based screen of 1,129 proteins in 24 human urine samples (8 active lupus nephritis (LN), 8 inactive LN, 8 healthy controls (HC)) revealed 281 proteins were significantly elevated in both SLE patients relative to healthy controls and in active LN relative to inactive LN.

Results: Ingenuity Pathway Analysis revealed the upregulated proteins belong to known inflammatory, fibrosis and chemokine/cytokine networks. In an independent cohort of 93 subjects (16 active LN, 52 inactive LN, 25 HC), urine ALCAM, BFL1, calpastatin, hemopexin, PRX6, PF4, properdin, e-selectin, TFPI and VCAM1 were ELISA-validated and shown to be once again significantly elevated in active LN compared to disease HC (Fig 1), they also correlated strongly with many clinical/laboratory parameters, including renal-sLEDAI, PGA, eGFR, ESR and C3/C4. In ROC curve analysis, several proteins exhibited significant AUC in distinguishing active LN: ALCAM [0.89], calpastatin [0.82], FcgRIIBC [0.70], hemopexin [0.76], PRX6 [0.67], PF4 [0.77], properdin [0.71], TFPI [0.77], and VCAM1 [0.81]. Lasso logistic regression analysis identified a 4-marker-panel (PF4, TFPI, PRX6, VCAM1) as the best discriminator of active LN, with an AUC value of 0.93. A longitudinal cohort study of 18 LN patients with an average of 3 visits per patient showed these markers to vary substantially in their ability to track conventional disease indices.

Conclusions: Urine ALCAM, BFL1, calpastatin, FcgRIIBC, hemopexin, MCP1, PRX6, PF4, properdin, e-selectin, TFPI and VCAM1 arise as potential urinary biomarkers of LN; further studies are needed to establish their biomarker potential and pathogenic role.

Funding: NIDDK Support

FR-PO661

Cryofibrinogen Associated Glomerulonephritis
Marian P. Alexander,1 Ralph Yachou,2 David L. Murray,1 Jai Radhakrishnan,1 Sanjeev Sethi,1 1Mayo Clinic, Rochester, MN; 2Marshfield Clinic, Marshfield, WI; 3Columbia Univ Medical Center, New York, NY.

Background: Cryofibrinogen is a cryoprotein that precipitates after refrigeration of plasma, but not serum. While cryofibrinogenemia (CF) may be asymptomatic, it can manifest with thrombosis, often involving skin. Renal involvement by CF is rarely reported. We present 2 cases of CF related membranoproliferative glomerulonephritis (MPGN) that were initially misdiagnosed as immunotactoid glomerulopathy (IG) and cryoglobulmin GN (CGN).

Methods: The clinical presentation, lab results, renal biopsy (BX) morphology as assessed by light (LM), immunofluorescence (IF) and electron microscopy (EM) of 2 patients (pt) is presented. The cryoprecipitate (CRP) was isolated and studied ultrastructurally. The proteomic profile of the CRP was determined by mass spectrometry.

Results: Pt 1 was a 66yr old man who had cold induced skin eruptions. An initial BX due to hematuria & proteinuria was diagnosed as CGN. He was treated with cyclophosphamide & high-dose steroids. A second BX a few years later for declining renal function was also diagnosed as CGN. Lab investigations: CF, present; CG, negative; normal complements, negative viral and autoimmune serology. Pt 2 was a 70yr old man with hematuria & proteinuria. He was a Hepatitis B carrier. He had no cutaneous eruptions. A BX was diagnosed as immunotactoid GN. Lab investigations: creatinine, 2.2mg/dL, 24 hr urine protein, 8 g; SPECT, negative; CG, negative; CF, positive. Both biopsies showed a membranoproliferative GN (MPGN) with rare subendothelial & intraluminal deposits. IF showed no immunoglobulin deposition. EM showed intraluminal, subendothelial and rare subepithelial deposits which had a multilayered tubular structure. The mean luminal diameter was 158 nm. CRP isolated from the plasma showed identical ultrastructure. Mass spectrometry confirmed the peptide profile of the CRP was fibrinogen. Both BX diagnoses were confirmed by CF-GN. At our institution therapy was started with therapy.

Conclusions: Familiarity with the unique ultrastructural appearance of CFG averts erroneous diagnosis, prompts appropriate evaluation for CF & permits accurate & timely initiation of therapy.

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

FR-PO662

Renal Dysfunction and Pathology Evaluation with Contrast-Enhanced Ultrasound
Yao Xu,1 Hongli Li,1 Shan Mou.1 1Nephrology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong Univ, Shanghai, China; 2Ultrasonic, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong Univ, Shanghai, China.

Background: The number of people with renal dysfunction due to CKD is increasing worldwide. The potential application of CEUS in nephrology has been proposed as a novel non-invasive imaging technique. We performed a prospective study to evaluate the ability of contrast-enhanced ultrasound (CEUS) in chronic kidney disease (CKD) progression and its correlation with renal pathological changes.

Methods: CEUS was performed after an intravenous bolus injection of 1.5 ml Sonovue (BR1; Bracco Milan, Italy). Time-intensity curves (TICs) and quantitative indexes were calculated on each kidney. Risk factors related to kidney survival were investigated using a binary logistic regression model. All biopsies were analyzed with Masson’s trichrome stain and α-SMA immunohistochemistry. Spearman correlation analysis was used to determine correlations.

Results: A total of 167 patients with CKD were enrolled in the study and followed for a mean period of 13.95 months. In total, seven (4%) patients exhibited composite kidney failure events (glomerular filtration rate (GFR) halving or end-stage renal disease (ESRD)). A significant difference in derived peak intensity (DPI) was noted among groups in different CKD stages. Multivariate logistic regression analysis revealed that the DPI was independently associated with progression of kidney disease. Patients with a DPI > 9.63 db were less likely to recover from kidney disease progression. DPI levels were highly correlated with the degree of renal fibrosis. The area under the curve (AUC) for DPI and pathology combined was 0.895 (P=0.03), with a sensitivity of 75% and a specificity of 81%, which is greater than the AUC of pathology alone (0.829, P>0.05).

Conclusions: In patients with CKD, a high correlation exists between the DPI value and renal fibrosis. The DPI might be the most valuable CEUS parameter for the evaluation of renal function and fibrosis. It could be rapidly and continuously used for the diagnosis and prognosis of renal dysfunction.

Funding: Government Support - Non-U.S.

FR-PO663

Urine miR-21 Abundance Increases with Decreasing Renal Function
Markus Bitzer,1 Klaas E.A. Max,4 Jian Shi,1 Iddo Z. Ben-Dov,4 Beatrice Goila,1 1The Neptune Consortium,1 Thangamani Muthukumar,2 2Univ of Michigan; 3Weill Cornell Medicine, Cornell Univ; 4Albert Einstein College of Medicine; 5The Rockefeller Univ.

Background: MicroRNAs (miRs) are implicated as regulators and markers of kidney disease. We explored the role of urinary miRs as candidate markers for clinical outcomes in samples of two independent clinical studies.

Methods: Cell-free urine supernatant from 99 subjects with glomerular disease collected at time of enrollment into the Nephrotic Syndrome Study Network (NEPTUNE) was used to isolate RNA using a novel protease/nuclease-based isolation method which allows extraction of RNA tightly bound to proteins, including Argosomes. Small RNA-seqencing was performed using Illumina platform, sequence reads were mapped to the human genome and relative read-frequencies were associated with clinical, laboratory and structural parameters. 161 cell-free and equally processed urine samples of kidney transplant recipients enrolled in the Clinical trials in Organ Transplantation (CTOT) study were used for validation.

Results: Small-RNAs that were detected included microRNAs, tRNAs, ribosomal RNA, mRNA fragments and non-human RNAs. The 300 miRs with the highest mean abundance across all samples were used for further analysis. After correction for multiple testing, only miR-21 was significantly inversely associated with cross-sectional eGFR (r = -0.60; Bonferroni-adjusted p < 0.01), and future development of ESRD (Bonferroni-adjusted p < 0.05). Urinary miR-21 abundance was positively associated with scores for interstitial fibrosis (IF; r = -0.50; Bonferroni-adjusted p < 0.01) and tubular atrophy (TA; r = -0.47; Bonferroni-adjusted p < 0.01) but not with future eGFR decline in 77 samples for which these data were available. No association of urinary miR-21 abundance with diagnosis, age, albuminuria or BMI was detected. In the independent CTOT cohort, miR-21 was also negatively correlated with cross-sectional eGFR (r = -0.42; Bonferroni-adjusted p < 0.01), but not with other available parameters.

Conclusions: The association of higher urinary miR-21 abundance with increased IF/TA scores and lower renal function suggests that urinary miR-21 is a marker of renal fibrosis independent from disease category.

Funding: NIDDK Support, Other NIH Support - NCATS

FR-PO664

Negative Staining for COL4A5 Correlates with Worse Prognosis and More Severe Ultrastructural Alterations in Alport Syndrome
Samantha M. Said,1 Matthew D. Raptis,1 Anthony A. Voigt,1 Lynna M. Corrado,1 Marian P. Alexander,1 Ahmed Mansour Alkuhnazi,1 Anne S. Salyer,1 Carl H.ramer,1 Marc C. Hogan,1 Samih H. Nasr.1 1Mayo Clinic, Rochester, MN; 2Columbia Univ, New York, NY; 3Johns Hopkins Aramco Healthcare, Dhahran, MN, Saudi Arabia; 4Permanent Medical Group, Oakland, CA.

Background: Alport syndrome (AS) is a genetic disorder characterized by progressive hereditary nephropathy with or without sensorineural hearing loss and ocular lesions. Previous studies on AS included mostly children. In this renal biopsy-based study, we seek...
to determine the prognostic value of loss of staining for COL4A5, its value in elucidating the mechanisms of inheritance and its relationship with the ultrastructural glomerular basement membrane (GBM) alterations.

**Methods:** We performed direct immunofluorescence using a mixture of FITC-conjugated and Texas-red conjugated antibodies against COL4A5 and COL4A2, respectively, on renal biopsies of 58 patients with a pathologic diagnosis of AS (including 38 who were diagnosed in adulthood).

**Results:** The cohort consisted of 60% males and 40% females. All patients showed normal positive staining of GBM and tubular basement membranes for COL4A2. Of the 58 patients, 21 showed heavy staining for COL4A5, with an expression pattern consistent with X-linked AS in 65% of cases and autosomal AS in 35% of cases. The remaining 41 (71%) had intact staining for COL4A5. Compared to patients with intact staining for COL4A5, those with loss of staining had more prominent ultrastructural GBM alterations, were younger at biopsy, were more likely to be males, and had a higher incidence of gross hematuria. By Kaplan-Meier survival analysis and Cox regression analysis, loss of staining for COL4A5 predicted earlier progression to overt proteinuria, CKD stage 2 or worse, and ESRD. By multivariate Cox regression analysis, loss of staining for COL4A5 and the severity of ultrastructural GBM alternations were independent predictors of the development of overt proteinuria and CKD stage 2 or worse.

**Conclusions:** COL4A5 expression pattern has an important prognostic value, it can unravel the mode of inheritance, and it correlates with the severity of ultrastructural GBM alterations.

**FR-PO665**

**Podocyte Detachment Rate in Alport Syndrome**  
*Larysa T. Wickman,* Fangrui Ding,† Su Qing Wang,‡ Roger C. Wiggins,§ Jie Ding.¶ University of Michigan, Ann Arbor, MI; ¶Peking Univ First Hospital, Beijing, China.

**Background:** Alport Syndrome (AS) is an important cause of End Stage Kidney Disease recognized as a contributor to global disease burden. We previously reported that podocyte detachment rate measured non-invasively in urine is increased and degree of podocyte detachment in renal biopsies is related to degree of proteinuria and glomerular sclerosis in AS. Podocyte detachment play a role in progressive loss of kidney function in AS. Podocyte detachment rate assay might therefore help guide treatment and assess novel therapies.

**Methods:** Alport Syndrome Prevention of Progression Project is an integration of a large well-characterized cohort of genetically-defined AS patients managed at Peikung University First Hospital in Beijing with novel podometric technology developed to identify and prevent progression of glomerular diseases at University of Michigan in Ann Arbor. Podocyte detachment rate was measured as the urine podocin mRNA in ng/ml/creatinine using TaqMan assay.

**Results:** A total of 169 urine samples were collected for cross-sectional analysis, including from 132 AS patients with a clinical phenotype ranging from hematuria alone through nephritis with and without abnormal kidney function, and 37 age-matched controls. Control values from China and the US were not different. Urine samples from all AS patients contained an average 21-fold elevated amounts of podocin mRNA vs controls (P<0.01), compared with 23-fold increase previously reported for AS patients in the US. AS patients with hematuria alone (without proteinuria) as a group had a 4.1-fold (range undetectable to 230-fold) increased rate of podocyte detachment vs controls (P<0.01), suggesting that individuals with high levels may be identifiable at an early stage as at risk for progression while those with normal levels may be identifiable as at low risk for progression.

**Conclusions:** Initial cross-sectional data in a large Chinese AS cohort are compatible with the concept that podocyte detachment rate measured non-invasively in urine might contribute useful information towards AS management. Further longitudinal studies are therefore warranted.

**FR-PO666**

**Characteristics of Podocytes in the Urine in Pregnancy Using Flow Cytometry**  

**Background:** Podocytes may be useful to predict high risk pregnancy. Detection of podocytes is currently technically complex requiring a high level of expertise for interpretation. Flow cytometry is a sensitive technique that allows immediate study of cells shed into the urine. We describe the characteristics of podocytes detected in the urine of high-risk pregnancies using flow-cytometry and how they differ from their non-pregnant counterparts.

**Methods:** Urine pellets from 11 patients attending high-risk obstetric clinic and 7 non-pregnant healthy subjects at various stages of pregnancy were compared to non-pregnant controls (n=10). Flow cytometry analysis was performed using 7-color flow cytometry. Podocytes were identified as DAPI-CD45+ cells for human Nephron and/or podocalyxin. Appropriate isotype and fluorescence minus one was used for controls. Expression of CD80 and HLA-DR on podocytes was assessed using flowcytometry for CD80 and CD80 on urine cell pellets was used to confirm flow-cytometric findings.

**Results:** Podocytes were detected in the urine of all subjects. Podocytes per ml of urine was higher in high-risk pregnancy compared to healthy pregnancy and non-pregnant individuals, respectively. 205 vs. 22.01 x 10^6/ml, P<0.05 and p<0.001 vs. high risk pregnancy.

**Conclusions:** Podocytes can be detected in the urine using flow cytometry. Low levels of podocytes were detected in non-pregnant individuals suggesting turnover of podocytes occurs in healthy individuals. The number of neprhin/podocalyxin+ cells was higher and the proportion co-expressing CD80 was lower in high-risk pregnancy. Alteration in phenotype of detached podocytes may be a feature of high-risk pregnancies.

**Funding:** Private Foundation Support

**FR-PO667**

**Localization of Kidney Injury Markers TIMP-2 and IGFBP7 in Human Kidney Biopsies**  
Martin Kimmel,† Moritz Schanz,‡ Mark Dominik Alschler,§ Kerstin U. Amann,¶ Christoph Daniel.¶* Internal Medicine, Robert-Bosch-Hospital, Stuttgart, Germany; ¶Nephropathology, FAU Erlangen-Nürnberg, Erlangen, Germany.

**Background:** Tissue inhibitor of matrixmetalloproteases 2 (TIMP-2) and Insulin-like growth factor-binding protein 7 (IGFBP7) are markers of cell cycle arrest and urinary {TIMP-2}[^2] was recently cleared by the FDA for risk assessment of acute kidney injury. However, studies describing the localization or expression profiles of TIMP-2 and IGFBP7 in human renal tissue in patients with glomerular or tubular damage are lacking.

**Methods:** We analyzed n=38 kidney biopsies of patients with renal disease and n=10 control biopsies immunohistochemically. Changes in glomerular morphology were evaluated by a semi-quantitative glomerulosclerosis score (GSI) and tubular interstitial changes were graded by the tubular injury score (TSI) using PAS-stained paraffin sections and interstitial fibrosis and tubular atrophy (IFTA) was graded according to BANFF classification. In addition, co-localization studies were performed using confocal laser scanning microscopy.

**Results:** In healthy control biopsies both TIMP-2 and IGFBP7 are rarely expressed with minimal tubular and glomerular compartment. However, co-localization to these controls both antigens are at least 2-fold significantly upregulated in biopsies from patients with kidney disease. TIMP2 is predominantly expressed in aquaporin 2 positive collecting ducts and to a lesser degree in the glomeruli. In contrast, IGFBP7 is expressed in both the glomerular and tubular compartment with comparable intensity. IGFBP7 expression could be detected in glomerular endothelial cells and podocytes as well as distal tubules and parts of the thick ascending limb. There were significant correlations for the tubular injury score (TSI) with tubular TIMP-2 (r=0.403, p<0.005) and IGFBP7 (r=0.521, p<0.0002). In addition, glomerular sclerosis score (GSI) correlated with glomerular TIMP-2 (r=0.347, p<0.02) and IGFBP7 (r=0.341; p<0.03).

**Conclusions:** The immunohistological examinations of TIMP-2 and IGFBP7 in human kidney biopsies underline the role of these markers especially in tubular damage.

**FR-PO668**

**A New Therapeutic Strategy in IgA Nephropathy with CKD Using Methylprednisolone Pulse Therapy and Autologous Adipose Derived Stem Cells (Stromal Vascular Fraction)**  

**Background:** As yet there is no specific therapeutic means to treat IgAN especially when associated with CKD, but giving RAAS blocker etc., almost all cases of IgAN with CKD eventually progress to ESRD and need RRT.

**Methods:** Cell therapy is extensively evaluated as an alternative therapeutic modality for many kinds of diseases with no other options. Recently human MSCs prevent podocyte apoptosis and injury and other reports have shown to reduce glomerulosclerosis and oxidative stress in animal model. We tried MP pulse therapy and autologous SVF in IgAN with CKD or with moderate degree glomerulosclerosis and followed up for 2 years.

**Results:** Case 1: A 26-year-old male was diagnosed as IgAN with 24% glomerulosclerosis. Follow up renal biopsy showed markedly decreased immune deposits without lesions of glomerulosclerosis. Laboratory results showed BUN/Creatinine 6.9 mg/dl / 1.08 mg/dl, IgA 363 mg/dl, C3 159 mg/dl. urine protein/creatinine ratio 0.974, Ccr 82 ml/min. Follow up laboratory data showed BUN/ Creatinine 9.2 mg/dl / 0.75 mg/dl, normal urinalysis, GFR, spot urine protein/creatinine ratio 0.090, GFR 131 ml/min. Case 2: A 44 years old female was diagnosed as IgAN stage IV (HSLee class.) with 61% glomerulosclerosis. Follow up renal biopsy showed 41% sclerosis with disappearance of IgA and C3 deposits. serum creatinine and GFR before therapy was 1.77 mg/dl and 35 ml/min and however follow up after 27 months was 0.99 mg/dl and 65 ml/min. Case 3: A 35 years old female was diagnosed as IgAN grade V with 67% glomerulosclerosis. Follow up renal biopsy showed IgAN stage IV with 33% glomerulosclerosis. Initial creatinine was 1.39 mg/dl and GFR was 43 ml/min, and follow up serum creatinine 1.21 mg/dl and GFR 53 ml/min.

**Conclusions:** Although further studies are needed, MP pulse therapy and autologous SVF therapy in intractable severe IgAN showed dramatic improvement not only laboratory data but also pathological findings. Therefore MP pulse therapy followed by autologous SVF therapy might be a promising new therapeutic strategy without noticeable side-effects or complications.
Value of Biological Markers for Kidney Involvement and Outcome in Henoch Schönlein Purpura Nephritis: A Prospective Cohort Study

Evangelie Pillebout,1,2 Laureline Berthelot,1 Hamza Ayari,3 Agnès Jamin,1 Jonathan M. Chemouny,1 Pierre Housett,1 Virginie Sauvaget,1 Denis Viglietti,2 Margarita Hurtado-Nedelec,1 Renato C. Monteiro,1 INSERM1149, Paris, France; Nephropathy Unit, St. Louis APHP, Paris, France.

Background: Henoch-Schönlein purpura (HSP) is a systemic vasculitis characterized by immunoglobulin A (IgA) deposits in skin, joints, kidneys and other organs. The current diagnosis and prognosis markers used in HSP assessment lack accuracy to estimate the risk of nephritis occurrence and its long-term outcome.

Methods: This French multicenter study prospectively enrolled 135 patients at the time of HSP diagnosis. All patients were evaluated for clinical and biological parameters, cytokines, immunoglobulins, Neutrophil Gelatinase Associated Lipocalin (NGAL), immune complexes and IgA glycosylation in serum and urine. They were followed 1 year for renal outcome. Poor renal outcome was defined as proteinuria/creatinine ratio >0.5g/l and/or decrease of eGFR or death.

Results: Among the 135 HSP patients, 93 had HSP-related nephritis (HSPN) and 42 did not. At the time of diagnosis, patients HSPN, compared to HSP without nephritis, exhibited higher serum levels of Galactose-deficient IgA1 and higher urinary concentrations of IgA, IgG, IgM, IgA, IgG1, IgA, IgG1 and IgA-sCD95 complexes. Among those, urinary IgA had the highest AUC. After one year of follow-up, 23/93 patients showed a poor renal outcome. Clinical factors associated with poor renal outcome were age, diabetes, hypertension and eGFR decline. Among all biological parameters, determinants of poor renal outcome were urinary IgA, IgM, IgA-IgG and IgA-sCD95 complexes. They showed an accurate discrimination ability to identify patients with poor renal outcome.

Conclusions: This large prospective cohort study, with both adults and children, included at the onset of the disease, bring a better understanding of the pathophysiology of HSP. We defined new biomarkers able to segregate patients initially with or without nephritis (HSPN). Our previous study revealed that Gd-IgA1-specific monoclonal antibody was specifically detected in all patients with IgAN, but not in those with other renal diseases. Gd-IgA1 could not be detected even in patients with nephritis accompanied by glomerular IgA deposition. In patients with IgAN, Gd-IgA1 was localized predominantly in the mesangial region as IgA deposition. Importantly, KM55 mAb was also positive in patient with HSPN as similar to those in IgAN.

FR-PO672
Production of Aberrantly-Glycosylated IgA1 and the Corresponding Autoantibodies Is Elevated in Patients with Henoch-Schönlein Purpura Nephritis

Hitoshi Suzuki,1 Zina Moldoveanu,2 Bruce A. Julian,3 Zina Moldoveanu,1 Hiura,1 Pillebout,1 Chemouny,1

Background: Patients with Henoch-Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) are known to be associated with deposition of IgA1 in glomeruli. Galactose-deficient IgA1 (Gd-IgA1) has been proposed as one of the candidate therapeutic agents for IgAN due to dysfunction of those enzymes under pathophysiological condition. Our previous study revealed that Gd-IgA1-specific monoclonal antibody KM55 mAb against Gd-IgA1 could be a powerful tool to detect nephritogenic IgA in patients with IgAN and HSPN.

Methods: Serum Gd-IgA1 level is significantly high in patients with IgAN, approved by Gd-IgA1 production of Aberrantly-Glycosylated IgA1 and the corresponding autoantibodies is elevated in patients with HSPN due to dysfunction of those enzymes under pathophysiological condition.

Results: IgA1 secreted by cells from HSPN patients had Galactose-deficient O-glycans, whereas IgA1 from HSP patients and healthy controls was normally galactosylated. This finding was consistent with lower expression of B1,3-galactosyltransferase observed in cells from HSPN compared to cells from HSP patients. Levels of Gd-IgA1-specific IgG in sera and cell-culture supernatants of IgA1-secreting cells were higher in HSPN than in HSP patients or healthy controls (P<0.01). Serum levels of Gd-IgA1 and Gd-IgA1-specific IgG were elevated in HSPN patients with active disease, manifested by hematuria/proteinuria (P=0.01). We also found that the production of IgG1 and IgG4 in HSPN patients related to nephritis and hematuria was accompanied by reduction of serum levels of Gd-IgA1 and Gd-IgA1-specific IgG (P<0.001).

Conclusions: Gd-IgA1 and Gd-IgA1-specific autoantibodies are elevated in patients with HSPN, supporting the hypothesis that HSPN and IgAN have common pathogenic components.

FR-PO673
Regional Variations in the Clinical Characteristics at Diagnosis in Japanese Patients with IgA Nephropathy: An Analysis of the Japan Renal Biopsy Registry (J-RBR)

Yusuke Okabayashi,1 Nobuo Tsuboi,1 Yoichi Miyazaki,2 Tetsuya Kawamura,1 Makoto Obara,2 Ichiei Narita,2 Toshiharu Nimitomo,2 Hitoshi Yokoyama,3 Takashi Yokozaki.3

Background: Age, hypertension, renal impairment, and heavy proteinuria at diagnosis are known to be poor prognostic indicators of immunoglobulin A nephropathy (IgAN). Previous studies have shown the remarkable regional differences in the incidence of ESRD within Japan, which has an ethnically homogeneous population (JAMA, 2000). This study examined the regional differences in these clinical features at biopsy and the relevant factors associated with such differences among Japanese IgAN patients.

Methods: The Japan Renal Biopsy Registry registration facilities were divided into 10 regions. The clinical features at biopsy were compared among the groups, which was divided based on the factors that may be associated with regional differences.
Results: A total 7177 patients were analyzed. In each region, the sex ratio was almost the same, but there were significant regional variations in age, eGFR, and urinary protein excretion. Distributions of clinical features were closely associated with the number of the Japanese Society of Nephrology (JSN) members per population, while, the regional variations in the clinical features did not correlate with the distributions of the elderly populations.

Conclusions: There are significant regional differences in the clinical features at diagnosis among Japanese IgAN patients. Social factors, such as an uneven distribution of nephrologists, may influence the timing of diagnosis and contribute to such differences.

FR-PO674
Prognostic Impact of Deleted Variants in Complement Factor H-Related Protein Genes, CFHR3 and CFHR1, in IgA Nephropathy on a Caucasian Population
Perrienne Jullien, Blandine Laurent, Christopher R. Mariat, Eric Alamertine, Nicolas Maillard. Nephrology, Dialysis, Transplantation, CHU de Saint Etienne, Saint Etienne, France.

Background: Activation of complement through the alternative pathway plays a key role in the pathogenesis of IgA nephropathy. Large international genome–wide association studies have identified a deletion of complement factor H–related genes 1 and 3 (CFHR1/3) associated with a lower risk of IgA nephropathy, but the prognosis value of these deletions in IgA nephropathy in Caucasian remains unknown. This study aims to compare the renal outcomes according to the CFHR1/3 genotype.

Methods: This study was retrospective monocentric including only Caucasian patients with biopsy proven primary IgA nephropathy since 1979, with available DNA samples and informed consent. Quantitative PCR was used to determine the presence of deletions of the genes CFHR1/3 (CFHR1-3A, standardized on the RNAs P gene. Clinical and biological data were collected by reviewing subject’s medical records.

Results: A total of 727 patients were included, with an age of (median [IQR]) 38 [28-51] years at diagnosis and a follow up of 11.4 [5-18.1] years. So far, copy number analysis data were collected by reviewing subject’s medical records. Five percent of the whole cohort and evolution of renal function will be available for the ASN meeting.

Conclusions: There is no trend of association between CFHR1 gene deletion and renal outcomes in this intermediate analysis. Complete results concerning CFHR1/3 genotype will be presented at the ASN meeting

FR-PO675
Repeat Renal Biopsy Improves Oxford Classification-Based Prediction of IgA Nephropathy Outcomes
Perrienne Jullien, Blandine Laurent, Christopher R. Mariat, Eric Alamertine, Nicolas Maillard. Dept of Nephrology, Dialysis, Transplantation, CHU Saint Etienne, Saint Etienne, France.

Background: The prognosis of IgA nephropathy is heterogeneous, and its prediction is crucial to refine patient’s treatment. It remains unknown whether a repeat pathological evaluation is useful to refine renal death prediction. The aim of this study was to evaluate the prognostic impact of an Oxford classification-based repeat kidney tissue evaluation to predict end stage renal disease (ESRD).

Methods: Patients with biopsy-proven primary IgAN who underwent 2 renal biopsies in the histo-clinical evaluation at baseline and even from the clinical evolution between the biopsies.

Results: A total of 7177 patients were analyised. In each region, the sex ratio was almost the same, but there were significant regional variations in age, eGFR, and urinary protein excretion. Distributions of clinical features were closely associated with the number of the Japanese Society of Nephrology (JSN) members per population, while, the regional variations in the clinical features did not correlate with the distributions of the elderly populations.

Conclusions: There are significant regional differences in the clinical features at diagnosis among Japanese IgAN patients. Social factors, such as an uneven distribution of nephrologists, may influence the timing of diagnosis and contribute to such differences.
in IgANnp (p=0.057). Expression levels were comparable in the MN and TM. miR135a displayed higher interstitial expression in IgAmp (p=0.02) while IgANp, MN and TN showed no statistical difference in distribution.

Conclusions: These data suggest that a glomerular preference for miR-150 may indicate progressive disease, raised glomerular levels of miR155 may be associated with the IgAN phenotype and increased interstitial expression of miR135a may indicate a lower risk of progression. In conclusion these data provide us with a platform to robustly test miR5, 150, 155 and 135a as potential biomarkers of IgAN progression and to investigate in vitro and in vivo the functional roles of these miRs in the pathogenesis and progression of IgAN nephropathy.

FR-PO678
Gene-Specific DNA Methylation Changes Predict Stable Remission in ANCA-Associated Vasculitis Patients

Britta E. Jones,1,2 Jia Jin Yang,1 Akhil Muthigi,1 Susan L. Hogan,1 Yichun Hu,1 Joshua Starmer,1 Caroline J. Poulton,1 William Franklin Pendergraff,1,2 Charles Jennette,1,2 Ronald J. Falk,1 Dominic J. Ciavatta,1,3 UNC Kidney Center, Dept of Medicine, UNC, Chapel Hill, NC, 3Dept of Genetics, UNC, Chapel Hill, NC.

Background: Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is an autoimmune condition characterized by vascular inflammation and organ damage. Pharmacologically induced remission is complicated by relapses. Potential triggers of relapse are immunological challenges and environmental insults, both of which are associated with changes in epigenetic silencing modifications.

Methods: To establish a link between DNA methylation, a model epigenetic gene silencing modification, and autoantigen gene expression and disease status in AAV, we measured gene-specific DNA methylation of the autoantigen genes, myeloperoxidase (MPO) and proteinase 3 (PRTN3), in leukocytes of AAV patients followed longitudinally (n=82) and healthy controls (n=32).

Results: Patients with active disease demonstrated hypomethylation of MPO and PRTN3 and increased expression of the autoantigens. Longitudinal analysis divided AAV patients into two groups based on DNA methylation change from active disease to remission. In patients with increased DNA methylation, MPO and PRTN3 expression correlated with DNA methylation. Patients who increased DNA methylation at the PRTN3 promoter had a significantly greater probability of a relapse-free period, independent of ANCA serotype; patients with decreased DNA methylation were more likely to relapse with a hazard ratio of 4.55 (95% CI, 2.09 to 9.91).

Conclusions: Changes in the DNA methylation status of the PRTN3 promoter predict likelihood of stable remission and may explain autoantigen gene regulation.

Funding: NIDDK Support

FR-PO679
Gremlin, a New Potential Urinary Biomarker of Crescentic Glomerulonephritis

Alejandra Droouget,1,2 Daniel Carpio,1 Carolina Lavoz,1 Maria Eugenia Burgos,1 Graciela Valderrama,1 Jesus Egido,1 Marta Ruiz-Ortega,2 Sergio A. Mezzano.1 Nephrology, Univ Austral, Valdivia, Chile, 2Fundación Jiménez Diaz, Univ Autónoma, Madrid, Spain.

Background: Crescentic glomerulonephritis (CG) require immediate accurate diagnosis and appropriate therapeutic decisions. The pathogenesis of crescent formation still is debated. We have previously described that Gremlin, a BMP antagonist, is highly expressed both in cellular and fibrocellular crescents, corresponding to proliferating parietal epithelial cells (PECs) and monocytes and we proposed that Gremlin could act as a mediator of this damage and be a urinary biomarker of crescent formation.

Methods: We here studied urinary Gremlin by ELISA test in samples from 94 patients with crescentic glomerulonephritis compared with healthy donors and with patients with other glomerular diseases (CG: 347.8 μg/gCr vs 9.16 in non-crescentic GN and 11.3 in healthy controls, P<0.001) (figure). Furthermore, we aimed to determine the potential colocalization of Gremlin with these proteins by immunohistochemistry and in situ hybridization.

Results: Urinary Gremlin levels were markedly augmented in patients with crescentic glomerulonephritis compared with healthy donors and with patients with other glomerular diseases (CG: 347.8 μg/gCr vs 9.16 in non-crescentic GN and 11.3 in healthy controls, P<0.001) (figure), and were correlated with the percentage of crescents (R=0.5, P<0.004) and tubulointerstitial fibrosis (R=0.5, P<0.02).

Conclusions: In conclusion, GPA patients that have a higher percentage of PB are at increased risk to experience a disease flare. The percentage of PB might be a potential biomarker for relapse and a novel monitoring and therapeutic target in AAV.

Funding: Government Support - Non-U.S.
FR-PO681
International Validation Study for the Histopathological Classification of ANCA-Associated Glomerulonephritis (AAGN) Emma Van Daalen,1 Laure-Hélène Noel,1 Kensuke Joh,1 Yayoi Ogawa,2 Suzanne Wilhelmus,3 Andreas Kronthaler,2 Renate Kain,1 Steven Salvatore,1 Xavier Puechâel,1 Wladimir M. Szpirt,1 Jan A. Brujin,1 Ingeborg M. Bajema,1 Pathology, Leiden University Medical Center, Nephropathology, San Gerardo Hospital, Monza; 1Pathology, Hôpital Necker, Paris; 2Pathology, Tohoku Univ Sendai; 3Renal Pathology Center, Hokkaido; 3Internal Medicine, Medical Univ of Innsbruck; 3Pathology, Medical Univ of Vienna; 4Pathology and Laboratory Medicine, Weill Cornell Medical College, New York; 5Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris; 6Nephrology, Rigshospitalet, Copenhagen.

Background: In the original validation study for the histopathological classification of AAGN, the order of classes from focal to sclerotic corresponded to increasing severity of renal function loss. Subsequent validation studies (N=15) disagreed on outcomes in crescentic and mixed class. We here present an international validation study done by the original investigators.

Methods: This interim analysis included 104 patients from centers in the U.S., Europe, and Asia. Each case was scored at a secured website by 2 pathologists from a group of 6; a 3rd pathologist gave the final conclusion in case of disagreement. Outcome at 1 and 5 years follow-up was based on KDOQI classification (eGFR>60/15-60/<15 or on dialysis/death).

Results: The distribution of the histopathological classes was 41% focal, 18% crescentic, 27% mixed, 14% sclerotic Mean eGFR, differed between classes (P<0.001), but was similar in crescentic and mixed class. The order of classes corresponded to outcome at 1 and 5 years (P<0.001, resp. P=0.016). Renal survival after 5 years was 95% in focal, 89% in crescentic, 96% in mixed, and 71% in sclerotic class. In the original study, renal survival after 5 years for respective classes was 93%, 76%, 61%, and 50%.

Conclusions: In this international validation study for the histopathological classification of AAGN, the classification predicted outcome at 1 year and 5 years with crescentic and mixed class lumped together. Interestingly, in all classes renal survival was much higher than in the original report, possibly due to improvements in therapy.

FR-PO682
Measuring Complement Activation in ANCA-Associated Vasculitis Sonia Brigitte Boyer1 Eve Wu,1 Elizabeth Alderman McMinn,2 Lydia Aybar,3 Carmen E. Mendoza,4 Yichun Hu,1 Susan L. Hogan,1 Ronald J. Falk,1 Patrick H. Nachman,1 J. Charles Jennette,2 Donna O. Bunch.4 UNC Kidney Center, Chapel Hill, NC; 2Pathology, Univ of North Carolina, Chapel Hill, NC.

Background: Investigating complement activation in ANCA-associated vasculitis (AAV) remains important. Cleavage of complement proteins in vitro despite using EDTA has been reported, thus accurate measurement of complement activation requires careful sample processing to avoid in vitro complement activation. We studied the effect of futhan (FU), a broad-spectrum protease inhibitor, on measured complement activation in patients with AAV and healthy controls (HC).

Methods: 61 blood samples (15 active, 26 remission and 20 HC) were drawn into EDTA tubes and put on ice immediately. Paired samples were processed without or with 100mg/ml FU within 30 minutes and stored at -80°C until use. Plasma concentrations of properdin (Hycult), Bb, C3a, Cs and sC5b-9 (Quidel) were measured by ELISA. Differences in quantitative parameters between groups were assessed using a paired signed rank test. The relationship between two continuous variables was analyzed using Pearson’s correlation. Results: Bb levels were higher in plasma processed without than with FU (P<0.0001) for all sample groups (Table); however, the difference was systematic (r=0.83). Levels of sC5b9 also consistently trended higher (r=0.8) in samples processed without than with FU, but were different in one group (p=0.02). C3a, C5a and properdin did not differ with or without FU (data not shown). C3a and Cs in samples strongly correlated with those without FU (r=0.94 and 0.94 respectively).

Analyte Group No FU (median) +FU (median) P
Bb (gg/ml) Act 0.88 0.69 <.0001
Rem 0.85 0.69 <.0001
HC 0.70 0.58 <.0001
CsC5b-9 (ng/ml) Act 203.2 181.3 0.07
Rem 134.7 126.5 0.02
HC 123.6 114.5 0.29

Conclusions: Addition of FU may be required to accurately measure Bb and sC5b-9, but not properdin, C3a or Cs. Further study is required, but our data suggests standardized processing methods including FU will improve measurement of complement activation.

Funding: NIDDK Support

FR-PO683
Significance of Immune Complex Deposition in Antineutrophil Cytoplasmic Antibody Associated Glomerulonephritis Ravi Agrawal,1 James R. Taylor,2 Pranay Kathuria.1 1Div of Nephrology, Univ of Oklahoma, School of Community Medicine, Tulsa, OK; 2Northeast Pennsylvania Nephrology Associates, Scranton, PA; 3Pathology Laboratory Associates, Tulsa, OK.

Background: Antineutrophil Cytoplasmic Antibody (ANCA) associated glomerulonephritis is characterized by findings of a pauci-immune necrotizing and crescentic glomerulonephritis. In a small percentage of cases, immune complex deposition may be seen and in various studies have been associated with more severe disease.

Methods: A retrospective study of 43 ANCA positive patients with necrotizing/ crescentic glomerulonephritis. Using data from the electron microscopy, patients were categorized into those with or without immune complex deposits. The presence and absence of deposits was correlated with age, ethnicity, clinical data, histologic (percentage of crescents and glomerular cellularity score) and immunofluorescence findings.

Results: Thirteen patients (30.2%) had immune deposits on electron microscopy. Immune deposits were seen significantly more in males (p=0.019) and in African-American ethnicity (p=0.023). The presence of immune deposits was associated with significantly more crescents (52.9±19.8 % Vs 31.9±27.4%, p=0.017) and more glomerular cellularity score (p=0.020). The mean serum creatinine but not the cGFR(calculated using Modification of Diet in Renal Disease equation) was significantly higher in the group with immune complex deposits. There was no significant difference between the two groups in terms of comorbid conditions and the amount of proteinuria. Immunoglobulins IgG and IgA were significantly more in patients with immune deposits (p=0.0004 and p=0.025, respectively).

Conclusions: Immune complex deposition in ANCA glomerulonephritis is seen significantly more in males and in African-American ethnicity. It is associated with significantly more crescents and higher glomerular cellularity score indicating more severe glomerular damage.

FR-PO684
Thrombotic Microangiopathy Associated with a Monoclonal Gammopathy Aishwarya Ravindran, Ronald Go, Fernando C. Fervenza, Sanjeev Sethi. Mayo Clinic, Rochester, MN.

Background: Thrombotic microangiopathies (TMA) comprise a heterogeneous set of conditions linked by a common histopathologic finding of endothelial damage resulting in microvascular thrombosis. Monoclonal gammopathy may act as a potential trigger in the pathogenesis of TMA. We performed a retrospective, single institution study to determine the prevalence of monoclonal gammopathy in patients with TMA.

Methods: We included adults (&gt; 18 years) from 2000-2016 with a clinical diagnosis of TMA who met the following criteria: i) microangiopathic hemolytic anemia and thrombocytopenia or histologic evidence of TMA ii) absence of a coagulopathy and a negative direct antiglobin test, iii) screened for monoclonal gammopathy. Monoclonal gammopathy was defined as the presence of monoclonal Ig in the serum/urine.

Results: 146 patients met the study criteria. Monoclonal Ig was detected in 20 patients (13.7%). The median age at diagnosis of TMA in patients with monoclonal Ig was 63 years (range: 19-80) and the majority were males (12; 57.1%). Among patients &gt;50 years, the prevalence of monoclonal gammopathy was 19.7% (n=16), which is approximately 5-fold higher than the expected rate in this population (4.2%). Among the 20 patients with Ig the majority were classified as thrombotic thrombocytopenic purpura (ADAMTS13 activity &lt;10%), 10 (50%) as atypical hemolytic uremic syndrome (clinical/pathologic findings), and the remaining 8 (40%) could not be classified. The median serum creatinine at time of TMA diagnosis was 3.5 mg/dl (range: 0.7-14). Renal failure was categorized into those with deposits and those without deposits. The presence and absence of deposits was correlated with age, ethnicity, clinical data, histologic (percentage of crescents and glomerular cellularity score) and immunofluorescence findings.

Conclusions: Similar to C3 glomerulopathy, our study shows an unexpectedly high prevalence of monoclonal gammopathy in patients with TMA suggesting a potential association of TMA with monoclonal gammopathy. Further studies are required to determine the underlying mechanisms of TMA associated with monoclonal gammopathy.

FR-PO685

Background: Thrombotic microangiopathies (TMA) are a heterogeneous group of conditions characterized by microangiopathic hemolytic anemia, thrombocytopenia or histologic evidence of TMA ii) absence of a coagulopathy and a negative direct antiglobin test, iii) screened for monoclonal gammopathy. Monoclonal gammopathy was defined as the presence of monoclonal Ig in the serum/urine.

Results: 23 out of 696,438 patients received a primary diagnosis of TMA (prevalence rate 3.3 per 100,000). In univariate analyses, indirect bilirubin (odds ratio
FR-PO687 Assessment of Renal Response in Immunoglobulin Light Chain (AL) Amyloidosis by Urinary Exosomes Nelson Leung,1,2 David R. Barnidge,3 Angela Dispenzieri,2 Christopher J. Dick,4 Shawna A. Cooper,4 Samih H. Nasr,3 Christopher J. Ward,3 Marina Ramirez-Alvarado,4,6 1Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Hematology, Mayo Clinic, Rochester, MN; 3Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; 4Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN; 5Nephropathology and Hypertension, Kansas Univ Medical Center, Kansas City, KS; 6Hematology, Mayo Clinic, Rochester, MN.

Background: Immunoglobulin light chain (AL) amyloidosis is a fatal disease caused by the overproduction of a monoclonal immunoglobulin light chain (LC). Accurate assessment of response is crucial for successful treatment. Urinary exosomes (UEX) have demonstrated different characteristics in AL amyloidosis vs multiple myeloma. This study explores the use of UEX to assess the renal response after treatment in AL amyloidosis.

Methods: Western blot was performed on the UEX of 4 patients with different hematologic status.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hematologic status</th>
<th>Current proteinuria (g/d)</th>
<th>Proteinuria reduction</th>
<th>Renal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ND</td>
<td>9.7</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>Treated to CR</td>
<td>0.7</td>
<td>93.6%</td>
<td>CR</td>
</tr>
<tr>
<td>3</td>
<td>Treated to CR</td>
<td>3.4</td>
<td>61.2%</td>
<td>CR</td>
</tr>
<tr>
<td>4</td>
<td>Treated to CR</td>
<td>3.4</td>
<td>76.5%</td>
<td>ESRD</td>
</tr>
</tbody>
</table>

From newly diagnosed (ND) patients to those treated to a hematologic complete response (CR).

Results:

The UEX of Patient 1 showed oligomeric LC bands > 25 kDa. Patient 2 and 3 had only monomeric LC bands (~25 kDa) often seen in multiple myeloma. Oligomeric (50 - 250 kDa) bands (similar to patient 1) were present in the UEX of patient 4 indicating active amyloid formation despite achieving a hematologic CR.

Conclusions: The oligomeric LC bands in UEX appear to be a good marker of renal response in AL amyloidosis. If confirmed, UEX may offer a great advantage over proteinuria in the assessment of renal response in AL amyloidosis.

Funding: Private Foundation Support

FR-PO688 Intratubular Amyloid: A Significant Pathological Finding during Myeloma Cast Nephropathy Jean-Baptiste Gibier,1 Viviane Gnenmi,1 Marie-Christine Copin,1 Francois Glowacki,1 Raymond Azar,4 Maxime Hoffmann,3 Thomas Guinestcr, Xavier Lelevu,9 David Buob,2 1Pathology, CHRU Lille, Lille, France; 2Pathology, Tenon Hospital, Paris, France; 3Nephropathology, CHRU Lille, Lille, France; 4Nephrology, Dukenque General Hospital, Dunkerque, France; 5Nephropathology, Hopital Victor Provo, Roubaix, France; 6Hematology, CHU Poitiers, Poitiers, France; 7Nephropathology, La Louviere Hospital, Lille, France.

Background: Cast nephropathy (CN) is the most common form of kidney disease in patients with multiple myeloma. Occasionally, casts may show amyloid staining properties i.e. green birefringence in Congo red. The frequency and signification of such intra tubular amyloid (ITAM) are poorly understood. In particular the link between ITAM and systemic amyloidosis has never been investigated.

Methods: A retrospective analysis with clinico-pathological correlation was performed of all cases of CN diagnosed at our institution between 2002 and 2012. Renal pathological findings and Congo red staining were reviewed. Each patient was also screened for extra renal samples and if available a Congo red staining was performed. Treatment and clinical follow up data were obtained.

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

Underline represents presenting author.
FR-PO689
Beta Trace Protein Does Not Outperform Cystatin C or Creatinine in Estimating GFR in Older Adults
Natalie Ebert,1 Peter Martus,2 Camilla Koep,1 Olga Jakob,1 Elke Schaefernc,1 1Institut of Public Health, Charité, Berlin, Germany; 2Dept of Nephrology, Antwerp Univ Hospital, Antwerp, Belgium.

Background: Despite a lot of research the optimal endogenous biomarker for GFR estimation in the elderly has not been identified. We sought to analyse if beta trace protein (BTP) improved GFR estimation in older adults.

Methods: In 570 older adults with iohexol clearance measurement (BIS) creatinine, cystatin C, and BTP were measured. In a double logarithmic linear model prediction of mGFR by BTP was assessed. Analyses with BTP only and combined with serum creatinine and cystatin C were performed (all analyses adjusted for age and gender).

Results: Table 1 documents seven regression models including either single biomarkers or combinations.

<table>
<thead>
<tr>
<th>Regression Model (including age and gender)</th>
<th>corrected R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>- BTP</td>
<td>0.671</td>
</tr>
<tr>
<td>- CysC</td>
<td>0.781</td>
</tr>
<tr>
<td>- CysC + BTP</td>
<td>0.789</td>
</tr>
<tr>
<td>- Crea</td>
<td>0.739</td>
</tr>
<tr>
<td>- Crea + CysC</td>
<td>0.787</td>
</tr>
<tr>
<td>- Crea + CysC + BTP</td>
<td>0.840</td>
</tr>
<tr>
<td>- Crea + CysC + BTP</td>
<td>0.845</td>
</tr>
</tbody>
</table>

In terms of best r² the combination of all three biomarkers shows the best prediction of mGFR (r²=0.828), although the combination of creatinine and cystatin C provided only a minimally diverging result (0.82). The single usage of BTP showed the worst prediction (r²=0.671) within the models with one biomarker. In subgroup analysis (ADT, DM, BMI≤23 and BMI>30) there was no relevant additional benefit of including BTP into the prediction model (data not shown).

Conclusions: BTP alone or the addition of BTP does not outperform current biomarkers such as creatinine and cystatin C for GFR-estimation in older adults. Especially the use of cystatin C renders the addition of BTP unnecessary. Also, BTP did not show additional benefit in hypertensive, diabetic, lean or obese elderly patients.

Funding: Private Foundation Support

FR-PO690
Diagnostic Value of Normalized Beta Trace Protein for Estimating GFR in Older Adults
Natalie Ebert,1 Elke Schaefernc,1 Hans Pottel,1 1Pub. Health, Charité, Germany; 2Pub. Health, KU Leuven, Belgium.

Background: BTP as a novel biomarker has emerged as alternative to creatinine (Scr) and cystatin C (Scys). The recently published Full Age Spectrum (FAS)-eGFR equation has been developed by normalizing Scr with mean Scr of large healthy cohorts. We investigate whether this concept is also valid for BTP in elderly indiv. and compare it to Scr and Scys.

Methods: We used data from the Berlin Initiative Study (BIS), a pop-based cohort with mGFR (iohexol) examined KF in indiv. aged ≥70y. The fixed form of the FAS-equation was applied with normalized single (Scr, Scys, BTP) or combined (average of Scr and ScysC or Scr, Scys and BTP) biomarkers and performance statistics were calculated: constant bias (FAS - mGFR), proportional bias (FAS/mGFR), root mean square error of prediciton (rmse), Lin’s concordance corr. coefficient, P10 and P30 (percentage of predictions within 10% or 30% of mGFR).

Results: Based on the distribution of BTP in n=566 BIS participants (mean age 78.5y), the peak-value is ≤0.60 mg/L. Using the fixed form of the FAS equation and rephrasing it with BTP leads to: FAS[BTP]= 107.3/[(BTP/0.60)x0.988]mm, Fig 1 shows FAS-prediction of single BTP versus mGFR.

In both HD and PD pts, the reproducibility over time was excellent with intraclass correlation coefficient of 0.962 (0.928-0.983) and 0.923 (0.858-0.987) respectively.

Conclusions: BTP-based equations are a promising tool for estimations of RRF in pts on conventional HD or PD while in pts receiving HDF, plasma levels of BTP should be interpreted with care.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO692

Urinary β-Trace Protein – A Unique Biomarker to Screen Early Glomerular Filtration Rate Impairment Carlo Donadio. Clinical and Experimental Medicine, Univ of Pisa, Pisa, Italy.

Background: The screening for chronic kidney disease (CKD) patients needs the measurement of serum markers. Our previous results indicated that urinary excretion of β-trace protein (BTP) (23-29 kDa), is increased in CKD patients from stage 2. The aim of this study was to assess the major determinants of urinary excretion of BTP and to evaluate its feasibility as non invasive marker of glomerular filtration rate (GFR) impairment.

Methods: We studied 355 CKD patients (198 males), 15-83 years, in stable clinical conditions, at the different stages of CKD on the basis of GFR (23-120 ml/min). BTP and albumin excretion were expressed as mg/g creatinine. The fractional clearance of BTP was calculated as ratio of BTP clearance to creatinine clearance (%).

Results: Urinary excretion of BTP is mainly determined by its serum concentration and by the level of GFR, and to a lower extent by urinary albumin excretion. In fact, U-BTP and fractional clearance of BTP progressively and significantly increased along with the reduction of GFR and the concurrent rise in serum BTP. The relationship of U-BTP with GFR was very similar to that of S-BTP with GFR: urinary BTP mirrors serum BTP. The accuracy of U-BTP to screen patients with GFR<90 ml/min/1.73 m² was good (AUC: 0.833), its sensitivity was 76.9%, specificity 80% and PPV 84.9%. Sensitivity of U-BTP was similar to that of S-BTP and S-Cr.

Conclusions: The major determinants of urinary excretion of BTP are S-BTP and GFR. U-BTP may be a suitable non invasive marker to screen the general population for detection of GFR<90 ml/min/1.73 m².

Funding: Government Support - Non-U.S.

FR-PO693

Urinary Creatinine Excretion and Creatinine Clearance Can Be Predicted in Severely Obese Patients by the Measurement of Body Cell Mass Carlo Donadio. Clinical and Experimental Medicine, Univ of Pisa, Pisa, Italy.

Background: In obese patients the accuracy of prediction of renal function by formulas based on serum creatinine (PCR) and anthropometric data is quite low. The aim of this study was to evaluate if the value of body cell mass (BCM) allows to predict urinary creatinine excretion (UCE) and creatinine clearance (CCr).

Methods: Seventy-four patients (54 women), 19-66 years, BW 82.5-210 kg; BMI 3.5-45 kg/m²; PCR (0.57-1.06 mg/dL). Measured parameters: PCR; UCr (urine collection 2 hrs); CCr measured (m-CCr) with the standard formula; CCr predicted by CG formula (CG-CCr) and by Salazar&Cocoran formula (S&C-CCr). GFR was predicted using MDRD formula (IDMS) and CKD-EPI formula. BCM was measured using a single frequency impedance analyzer. Renal dimensions were evaluated by bidental ultrasound scanning.

Results: 24h-UCr was 976-3684 mg, m 1809; BCM was 25-74 kg (m 49.3 kg men, 31.6 kg women). A strict linear correlation was found between 24h-UCr and BCM (r=0.79), closer than between 24h-UCr and BW (r=0.65). 24h-UCr and CCr were predicted from the individual values of BCM (BCM-CCr) (Donadio C. Kidney Int 63: S166-S168, 1997). Total variation of CCr was only moderate correlation in the change in renal function using eGFRcreat and eGFRcys.

Conclusions: In this cohort, use of eGFRcys resulted in minimal reclassification from CKD 3a to disease free. Baseline estimates of eGFR were significantly different and there was only moderate correlation in the change in renal function using eGFRcys and eGFRcys. Whilst eGFRcys may have a place in selected patients with extremes of body habitus, these results do not show significant benefit to support its widespread application in primary care.

Funding: Private Foundation Support

FR-PO694

Do Cystatin C Based Estimates of GFR Add Value in CKD Management in Primary Care? Adam Shardlow,1-4 Natasha Juliette McIntyre,1 Simon D.S. Fraser,2 Paul J. Roderick,2 Richard J. Flack,2 Christopher W. McIntyre,2 Maarten W. T. Zaaijer,3,4 Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; 1Univ of Southampton, Southampton, United Kingdom; 2Univ of Western Ontario, London, ON, Canada; 3Centre for Kidney Research and Innovation, Univ of Nottingham, Nottingham, United Kingdom.

Background: Cystatin C has been proposed as a filtration marker and a risk factor in people with CKD. KDIGO guidelines suggest using a cystatin C based estimate of GFR (eGFRcys) in defining those with disease. Cystatin C has not yet been widely adopted in clinical practice and to do so would require significant expense and education. We investigated the use of eGFRcys in 5 year follow-up of people with CKD stage 3 prospectively recruited from primary care.

Methods: 1741 people were recruited from primary care. All participants had an eGFR 30-60 ml/min on two occasions more than 90 days apart prior to study entry. Participants were assessed at baseline, 1 and 5 year follow-up visits. CKD EPI equations were used to calculate creatinine-based (eGFRcreat), cystatin C-based (eGFRcys) and combined (eGFRcre+cys) estimates of GFR. Multivariable regression models were used to predict CKD progression and mortality.

Results: At baseline, mean eGFRcre+cys was 53.5, mean eGFRcys 45.1 and mean eGFRcre 48.3 ml/min (p<0.001 for all). Of 784 participants with eGFRcre+cys 45-60 ml/min, only 57 (7%) had eGFRcre+cys <60 ml/min and 488 (62%) had eGFRcre+cys <45ml/min. Greater difference between eGFRcre+cys and eGFRcre+cys was associated with higher eGFRcre+cys. eGFRcre+cys was higher in women than men (3.8%), and only 51 (6.7%) had eGFRcre+cys <60 ml/min and 448 (58%) had eGFRcre+cys <45ml/min. eGFRcre+cys was lower in people from deprived areas (7.8%) and agreed better with eGFRcre (r=0.76, p=0.00001) and the concordance was similar for all values of renal function.

Conclusions: In severely obese patients urinary creatinine excretion and creatinine clearance can be more accurately predicted from the measurement of body cell mass combined with serum creatinine, than with other formulas.

Funding: Government Support - Non-U.S.

FR-PO695

Glomerular Filtration Rate in Healthy Living Potential Kidney Donors: A Meta-Analysis Hans Potte1, Liesbeth Hoste1, Pierre Delanaye.1 1Nephrology, Univ of Liege, CHU Sart Tilman, Liege, Belgium; 2Dept of Public Health and Primary Care, KU Leuven Campus Kulak, Kortrijk, Belgium.

Background: Normal kidney function, or more specifically, normal glomerular filtration rate (GFR), in males and females, and its decline with age, is still much debated today. Most estimating GFR-equations have gender (and ethnicity) multiplication factors, account for a decline that starts at very young age, and assume that GFR is as high as 120-130ml/min/1.73m² at young age, a reference value that dates back to the work of Homer Smith in the 1950s. The aim of this research study was to give more insight into normal GFR-levels and the physiological decrease of kidney function with age and to test if the mathematical construction of eGFR-equations holds true in healthy kidney donors.

Methods: We conducted a meta-analysis of published GFR-measurements in healthy living potential kidney donors (n=7,076, 46.7% males). Only publications dating from after the year 2000 were selected to avoid the possible influence of body surface area changes in the last decades on the indexed GFR, expressed in ml/min/1.73m², and involving only Caucasian subjects.

Funding: Private Foundation Support
**FR-PO696**

**Associations between Iohexol Clearance Measurement and Outcomes**

Maylies Noordzij,1 Kitty J. Jager,1 Marie Evans,2 ERA-EDTA Registry, Medical Informatics, AMC, Amsterdam, Netherlands; 1Nephrology, CLINTEC, Karolinska Inst, Stockholm, Sweden.

**Background:** In Sweden, the preferred method to determine GFR is measuring plasma iohexol clearance (IC). However, the safety of IC measurement has been questioned. We aimed to evaluate whether demographic and medical factors play a role in the decision to perform an IC measurement, and to assess the associations between IC measurement and timing of start of RRT for ESRD, and all-cause mortality.

**Methods:** We included adult patients from the Swedish Renal Registry of Chronic Kidney Disease with a first visit between 2005-2011. By logistic regression we assessed which factors influenced the likelihood of IC measurement. To analyse time until start of RRT and death, Cox regression was performed. All multivariate models included age, sex, primary renal disease, and eGFR at inclusion in the registry. Propensity score matching was applied to control for confounding by indication in the comparison of patients with and without IC measurement.

**Results:** From a total of 13,570, there were 1,705 patients (12.6%) with IC measurement at least once during follow-up. The likelihood of receiving an IC measurement was significantly lower in patients aged ≥75 years (Odds Ratio [OR]: 0.79, 95% confidence interval [CI]: 0.69-0.91) when compared to those aged 45-64 years, in those with a higher eGFR (OR: 0.98, 95%CI: 0.97-0.98 for every ml/min/1.73m² increase) or with glomerulonephritis (OR: 0.64, 95% CI: 0.51-0.79) compared to those with diabetes as cause of renal failure. Cox regression based on the propensity matched cohort (N=2,966) showed that the risk of starting RRT was not different between patients with and without IC measurement.

**Conclusions:** We found that the oldest patients, those with higher eGFR and with glomerulonephritis were less likely to receive an IC measurement. Exposure to IC measurement was neither associated with higher risk of starting RRT for ESRD, sex, nor with higher mortality risk. Based on these findings IC measurement seems to be safe for assessing GFR. Nevertheless, further research in other study populations is warranted to confirm our findings.

**FR-PO697**

**Measurement of Glomerular Filtration Rate by Plasma Iohexol Clearance: Single versus Multiple Samples Method**

Pierre Delany,1 Etienne Cavalier,2 1Nephrology, Univ of Liège, Belgium; 2Clinical Chemistry, Univ of Liège, Belgium.

**Background:** Iohexol plasma clearance is considered as a reference method to measure glomerular filtration rate (GFR). However, different methodologies, have been developed regarding the number of plasma samples needed. In the current study, we tested the concordance between the simple single sample (SS) versus the multiple samples (MS) method.

**Methods:** We considered the patients referred to our university center for GFR measurement. In all patients, 5 ml of iohexol (Omnipaque®240; 240 mg/mL) were intravenously injected. Iohexol was measured by High Performance Liquid Chromatography. MS plasma clearance were obtained by calculating the clearance from slope calculated with four samples at 120, 180, 240 and 300 min. The result was then corrected by the Brochner-Mortensen equation. SS plasma clearance was calculated at every time with only one concentration and applying the Jacobson equation. We studied the concordance within ±10%. We tested if the concordance was influenced by the timing of the SS method.

**Results:** One hundred and twelve patients have been included in the study (52 females): mean age 59±13 years, BMI 27±7 kg/m², GFR 84±29 ml/min (range from 17 to 158 ml/min). If the SS method was considered as the reference, results with SS method at 120, 180, 240 et 300 min had a concordance ±10% of 73, 91, 92 and 70%, respectively. For patients with GFR≥50 ml/min (n=13), concordances were 15, 54, 77 and 92%, respectively. For patients with GFR<30 ml/min (n=99), concordances were 80, 96, 94 et 67%, respectively.

**Conclusions:** We showed a good concordance between iohexol plasma clearance obtained with two methodologies, (MS and SS). This is especially concordant if the timing of the SS method is adapted to the expected GFR (180 min if normal GFR and 300 min if lower GFR). In large epidemiological studies, iohexol plasma clearance with SS is a validated and simplified alternative to measure GFR. The timing of this SS strongly influences the results and must be adapted to the GFR level.
Precise Estimation of GFR from Multiple Markers in Clinical Trials
Lesley Inker,1 Ronald D. Perrone,1 Andrew S. Levey,1 Hocine Tighiouart,1 Frank S. Czerwiec,2 Jaime Blais,2 Sharin Roth,2 Lucas Westcott-Baker,2 Regis Perrichon,1 Josef Corensh,4 Tufts Medical Center; 2Otsuka Pharmaceuticals; 1Metabolon; 4Johns Hopkins Univ.

Background: We showed that a panel of filtration markers (peGFR) can improve precision of estimated GFR compared to creatinine (eGFRcr). Improved ascertainment of endpoints can enhance conduct of clinical trials. As proof of concept, we evaluated the use of peGFR to detect treatment (Tx) effects of tolvaptan in a subset from the TEMPO-3 pivotal trial (Torres NEJM 2012) compared to eGFRcr.

Methods: 42 (21 tolvaptan and 21 placebo) subjects matched by CKD stage, Mayo imaging classification, sex, age, race, region, hypertension status, and total kidney volume were included. Samples were assayed by Metabolon using LCMS methods for targeted metabolites. eGFRcr was computed using CKD-EPI equation. We examined treatment effects in acute phase after Tx initiation (baseline-week 3), chronic phase on Tx (week 3-month 36), and acute phase after Tx discontinuation (month 36-6 weeks post discontinuation). Tx effect was assessed as the difference in the slope of eGFR between Tx arms using a random effect mixed model with a three piece wise linear spline with knots at week 3 and month 36.

Results: The mean age was 39y and 48% were female. Mean baseline eGFRcr was 78 mL/min/1.73m². In the acute phases before or after Tx initiation, there were no differences between tolvaptan and placebo using peGFR or eGFRcr. In the chronic phase, tolvaptan slowed the decline in GFR compared to placebo using peGFR but not using eGFRcr.

Conclusions: In a small subset of TEMPO trial, peGFR appears to enhance discrimination of the treatment effect seen in the overall population. This example provides preliminary support for test of the hypothesis that more precise estimates of GFR could increase efficiency of clinical trials.

Funding: Pharmaceutical Company Support - Otsuka

FR-PO701

Creatinine-Based Renal Function Assessment Underestimates Chronic Kidney Disease (CKD) Prevalence: The Northern Manhattan Study (NOMAS) Syed Ali Husain1, Joshua Z. Willey,1 Yeseon Park Moon,1 Mitchell S.V. Elkind,1 Ralph L. Sacco,2 Myles S. Wolf,2 Ken Cheung,1 Clinton Wright,2 Sumit Mohan,1 1Columbia Univ; 2Univ of Miami; 3Northwestern Univ.

Background: Accurate glomerular filtration rate estimation (eGFR) informs drug dosing, risk stratification, and prognosis. Body composition heterogeneity influences creatinine production and the precision of creatinine-based eGFR (eGFRcr) is the elderly. We compared CKD categorization using eGFRcr and cystatin C-based eGFR (eGFRcys) in an elderly cohort.

Methods: NOMAS is a predominantly elderly, multi-ethnic cohort (n=3298) with a primary aim to determine stroke and vascular disease risk factors. We included participants with concurrent measured creatinine and cystatin C. eGFRcr was calculated using CKD-EPI 2009 and eGFRcys used CKD-EPI 2012 (cystatin). Logistic regression was used to estimate odds ratios (OR) for correlates of reclassification from eGFRcr<60 to eGFRcys<60mL/min.

Results: Participants (n=2988, mean age 69±10yrs) were predominantly >65 years old (61%), Hispanic (53%), female (63%), former/current smokers (53%), and overweight/obese (BMI >25Kg/m² 61%), of those, 64% had eGFRcr≥60 mL/min, discordant cystatin C-based CKD diagnosis (eGFRcys<60 mL/min) was more likely in those with age>65 (OR 5.68, 4.61-6.99), obesity (OR 2.06 vs BMI≤30, 1.64-2.59), current smokers (OR 1.87 vs non-smokers, 1.41-2.48) and females (OR 1.47, 1.19-1.92).

Conclusions: In a large, multiethnic, elderly cohort with a high BMI, we found a higher prevalence of CKD using eGFRcys. Use of eGFRcys may underestimate CKD prevalence, particularly among the elderly, obese, smokers and women. Determining the best method to estimate renal function in elderly populations needs further study.

Funding: Other NIH Support - National Institute of Neurological Disorders and Stroke

Conclusions: Renal clearance of “cold” iothalamate by LCMS is comparable to renal clearance of “hot” iothalamate by GAMC and offers a safer, less cumbersome option for GFR measurement.

FR-PO700

Creatinine-Based Renal Function Assessment Underestimates Chronic Kidney Disease (CKD) Prevalence: The Northern Manhattan Study (NOMAS) Syed Ali Husain,1 Joshua Z. Willey,1 Yeseon Park Moon,1 Mitchell S.V. Elkind,1 Ralph L. Sacco,2 Myles S. Wolf,2 Ken Cheung,1 Clinton Wright,2 Sumit Mohan,1 1Columbia Univ; 2Univ of Miami; 3Northwestern Univ.

Background: Accurate glomerular filtration rate estimation (eGFR) informs drug dosing, risk stratification, and prognosis. Body composition heterogeneity influences creatinine production and the precision of creatinine-based eGFR (eGFRcr) is the elderly. We compared CKD categorization using eGFRcr and cystatin C-based eGFR (eGFRcys) in an elderly cohort.

Methods: NOMAS is a predominantly elderly, multi-ethnic cohort (n=3298) with a primary aim to determine stroke and vascular disease risk factors. We included participants with concurrent measured creatinine and cystatin C. eGFRcr was calculated using CKD-EPI 2009 and eGFRcys used CKD-EPI 2012 (cystatin). Logistic regression was used to estimate odds ratios (OR) for correlates of reclassification from eGFRcr<60 to eGFRcys<60mL/min.

Results: Participants (n=2988, mean age 69±10yrs) were predominantly >65 years old (61%), Hispanic (53%), female (63%), former/current smokers (53%), and overweight/obese (BMI >25Kg/m² 61%), of those, 64% had eGFRcr≥60 mL/min, discordant cystatin C-based CKD diagnosis (eGFRcys<60 mL/min) was more likely in those with age>65 (OR 5.68, 4.61-6.99), obesity (OR 2.06 vs BMI≤30, 1.64-2.59), current smokers (OR 1.87 vs non-smokers, 1.41-2.48) and females (OR 1.47, 1.19-1.92).

Conclusions: In a large, multiethnic, elderly cohort with a high BMI, we found a higher prevalence of CKD using eGFRcys. Use of eGFRcys may underestimate CKD prevalence, particularly among the elderly, obese, smokers and women. Determining the best method to estimate renal function in elderly populations needs further study.

Funding: Other NIH Support - National Institute of Neurological Disorders and Stroke

Most (78%) had eGFRcr≥60 mL/min; of those, 64% had eGFRcys<60 mL/min. Among participants with eGFRcr≥60 mL/min, discordant cystatin C-based CKD diagnosis (eGFRcys<60 mL/min) was more likely in those with age>65 (OR 5.68, 4.61-6.99), obesity (OR 2.06 vs BMI≤30, 1.64-2.59), current smokers (OR 1.87 vs non-smokers, 1.41-2.48) and females (OR 1.47, 1.19-1.92).

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Funding: Other NIH Support - National Institute of Neurological Disorders and Stroke
The eGFRcreat, eGFRmdrd and eGFRbs1 equations had increased hazards for mortality above the reference eGFR ("J-curve"). This was not seen with cCcr or FAS eGFR equations, which were better calibrated with the Incident Rate Ratio curve above the reference eGFR, while eCcr was better calibrated than FAS eGFR below the reference eGFR value.

**Conclusions:** None of the current models optimize both estimation of measured GFR and risk assessment. The FAS eGFR equation parallels the Relative Risk curves below the reference eGFR; a simple linear adjustment should improve its calibration. In contrast, the "J-curves" for the other eGFR equations cannot be resolved with simple linear adjustments of the hazard ratios above the reference eGFR value.

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**FR-PO703**

**Formulas Do Not Reflect Renal Function Decline in CKD:**

**The Nephrologist in the Mist**


**Background:** The error of estimated GFR (eGFR) may jeopardize clinical trials designed to prevent CKD. However, the agreement between eGFR and measured (mGFR) decline has been seldom analyzed.

**Methods:** NEFROVID clinical trial (NCT01442272) evaluates the impact of calcifediol, paricalcitol or standard therapy in reducing proteinuria in CKD. mGFR was measured (mGFR) in all patients by a gold standard, th iohexol plasma clearance. Subjects were divided in those with proven evidence of renal disease, from the outpatient clinic, and those without evidence of renal disease, referred from general practitioners.

**Results:** 20 subjects had no evidence of renal disease and 11 had CKD of diverse causes: unknown (n=1), CKD (n=5), lupus nephropathy (n=1), tubulointerstitial nephritis (n=1), diabetic nephropathy (n=3).

The difference between eGFR and CrCl was about 40%, and CrCl was frequently higher than eGFR. Of note, mGFR showed values in between eGFR and CrCl. Renal echography was normal in subjects with no history of renal disease.

**Conclusions:** mGFR is restricted to clinical research. However, the use of mGFR may have important consequences in clinical practice, which needs further study. *p<0.05.

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

**FR-PO705**

**Prevalence of Chronic Kidney Disease According to eGFR Derived from Standardized Serum Creatinine: A Population-Based Study**

**Anar Jon Jonsson,** Sigrun Helga Lund, Runolfur Palsson, Olafur S. Indridason. Landspitali - The National Univ Hospital of Iceland, Reykjavik, Iceland; Uni of Iceland, Reykjavik, Iceland.

**Background:** Standardization of serum creatinine measurements (SCr) has improved the use of mGFR for estimating glomerular filtration rate (eGFR). The purpose of this study was to estimate the prevalence of chronic kidney disease (CKD) in Iceland based on eGFR derived from standardized SCr.

**Methods:** In this retrospective study, we obtained all SCr values from all clinical laboratories in Iceland for the years, 2008-2013. Information on age and sex was also obtained. We used computerized algorithms, which excluded SCr values during episodes of acute kidney injury. eGFR was calculated using the CKD-EPI equation. CKD was defined as eGFR <60 mL/min/1.73 m² for more than 3 months and staged according to the KIDIGO classification system. Period prevalence of CKD stages 3-5 was calculated based on the population of individuals aged 18 years or above in Iceland, which numbered 245,631 on December 31, 2013.

**Results:** We retrieved 1,523,914 SCr values for 198,289 individuals aged 18 years and older. The median age was 60 years and 46% were male. The crude prevalence was in men and women. The age-adjusted prevalence rate per 100,000 in men was 975 for CKD 3A, 269 for CKD 3B, 86 for CKD 4, and 33 for CKD 5. In women, the age-adjusted prevalence rate per 100,000 was 1314 for CKD 3A, 382 for CKD 3B, 86 for CKD 4, and 21 for CKD 5. The prevalence of CKD stages 3-5 increased with advancing age, from 31/100,000 in the age group 18-39 years, 261/100,000 in the age group 40-59 years, 1761/100,000 in the age group 60-69 years, 6003/100,000 in the age group 70-79 years and 12116/100,000 in those who were 80 years of age or older.

**Conclusions:** This nationwide study, which included standardized SCr measurements and comprises a large proportion of the Icelandic population, demonstrates lower prevalence of CKD stages 3-5 compared with previous studies in Iceland.

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

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

**Underline represents presenting author.**
Effect of Large Weight Reductions on Measured and Estimated Kidney Function

Background: In patients undergoing gastric bypass surgery and subsequently experiencing fast and large weight loss, muscle mass may be affected followed by changes in plasma creatinine (pCr). The MDRD and CKD-EPI equations for eGFR include creatinine. Serum creatinine C levels provide alternative GFR estimates not linked to muscle mass. We determined the effects of large weight loss after gastric bypass surgery on measured GFR and compared these changes with changes in eGFR.

Methods: Prospective, intervention study including 19 patients. All attended a baseline visit before gastric bypass surgery followed by a visit 6 months post-surgery. Renal function (mGFR) was assessed during four hours plasma 51Cr-EDTA measurement by standard methods. pCr and cystatin C (cysC) were measured and GFR estimated by four different equations (MDRD, CKD-EPI-pCr, CKD-EPI-cysC and CKD-EPI-pCr-cysC) (ClinicalTrials.gov NCT02156563).

Results: Patients were (mean±SD) 40.0±9.3 years, 14 (74%) were female and 5 (26%) had type 2 diabetes. Baseline weight was 127±21 kg, BMI 42±6 kg/m² and mGFR 88±17 ml/min/1.73m². At baseline, mGFR correlated with all estimates of GFR (R=0.50, p<0.025), except MDRD (p=0.093). Six months post-surgery weight loss was 27 (95% CI, 23, 31) kg, mGFR changed -9 (-17) to 122 from 113 ml/min (p=0.024); adjusted for body surface area (BSA) mGFR was insignificantly changed +2 (-5) to 114 ml/min/1.73m² (p=0.52). CKD-EPI-pCr eGFR increased by 12 (6, 17) (p<0.001) and MDRD eGFR by 13 (8, 18) (p<0.001), while CKD-EPI-cysC eGFR was changed by -2 (-8, 4) ml/min/1.73m² (p=0.51). Post-surgery mGFR correlated with all GFR estimates (R=0.60, p=0.008). Change in mGFR correlated with change in MDRD eGFR (R=-0.50, p=0.030), but not with changes in other eGFR measures (p>0.08).

Conclusions: A weight loss of 27 kg achieved after gastric bypass surgery was associated with a reduction in mGFR of 9 ml/min but unchanged after adjustment for BSA. CKD-EPI-pCr and MDRD eGFR were increased, whereas CKD-EPI-cysC eGFR reflected the unchanged mGFR. eGFR equations based on creatinine should be carefully interpreted in patients experiencing large weight reductions, likely due to muscle mass change affecting creatinine.

FR-PO707 Clinical Impact of Nutritious Status to Estimate GFR among Japanese Health-Check Subjects

Background: Accurate estimation of GFR is essential in diagnosis and severity classification of CKD. Utility of various GFR equations based on sCr and cystatin C (Cys) were analyzed in this study.

Methods: The subjects were 6,635 health-check subjects (3,234 females) in a single center in Aichi prefecture, Japan. IDMS-traceable sCr values were measured by enzymatic method and standardized Cys values were measured by immunonephelometry. Estimated GFR was calculated by Japanese GFR equations based on age, gender and sCr (Eq1) or Cys (Eq2), and by Eq3 based on age, gender, sCr, albumin and UN, estimated glomerular filtration rate (eGFR), 50 ± 26.5 ml/min/1.73 m² were recruited for this study. CKD patients were classified into four groups: The chronic glomerulonephritis group (CGN; n=34), the diabetic nephropathy group (DN; n=19), the nephrosclerosis group (BNS; n=15), and others (n=17). All patients underwent noncontrast-enhanced SSFP MRI with spatially selective IR pulse. The coronal sectional areas of kidney cortex, medulla and the maximum and minimum cortical thickness were measured.

Results: eGFR was positively correlated with coronal sectional areas of kidney cortex (R=0.53, P<0.001), medulla (R=0.28, P<0.001) and maximum cortical thickness (R=0.36, P<0.001) and minimum cortical thickness (R=0.47, P<0.001). Among DN and BNS, the correlation efficiency of GFR with area of medulla (R²=0.66, P<0.001; R²=0.63, P<0.001) was significantly higher than with other compartments. By contrast, in CGN, eGFR had no correlation with the area of medulla (R²=0.06, P=0.07) and highest correlation was observed with the area of cortex (R²=0.40, P<0.001).

Conclusions: Two-dimensional quantitative assessment of kidney compartments by noncontrast-enhanced SSFP MRI with spatially selective IR pulse significantly correlates with renal function and could provide specific information for differentiating the etiology of CKD.

FR-PO708 Coronal Sectional Areas of the Kidney Components Measured by Noncontrast-Enhanced Steady-State Free Precession Magnetic Resonance Imaging with Spatially Selective Inversion Recovery Pulse and Their Association with Chronic Kidney Disease

Background: Kidney imaging by magnetic resonance imaging (MRI) has been expected as a powerful tool to diagnose renal lesions. However, without contrast agents, it has been difficult to distinguish renal compartments clearly such as renal cortex or medulla region. Recently, noncontrast-enhanced steady-state free precession (SSFP) MRI with spatially selective inversion recovery (IR) pulse was reported to improve the visibility of renal corticomedullary differentiation in patients with renal insufficiency. Using this method, we investigated the correlations between renal function and segmental areas of the kidney compartments.

Methods: A total of 85 patients (aged 64±17 years) with CKD (mean estimated glomerular filtration rate [eGFR], 54.0±26.5 ml/min/1.73 m²) were recruited for this study. CKD patients were classified into four groups: The chronic glomerulonephritis group (CGN; n=34), the diabetic nephropathy group (DN; n=19), the nephrosclerosis group (BNS; n=15), and others (n=17). All patients underwent noncontrast-enhanced SSFP MRI with spatially selective IR pulse. The coronal sectional areas of kidney cortex, medulla and the maximum and minimum cortical thickness were measured.

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Conclusions: Two-dimensional quantitative assessment of kidney compartments by noncontrast-enhanced SSFP MRI with spatially selective IR pulse significantly correlates with renal function and could provide specific information for differentiating the etiology of CKD.

Table 1. Prevalence of eGFR<60 and ACR≥30.

<table>
<thead>
<tr>
<th>Data and Model</th>
<th>%</th>
<th>95% CI</th>
<th>%</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td><strong>NHANES</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6.72</td>
<td>6.29-7.16</td>
<td>9.25</td>
<td>8.33-9.77</td>
<td></td>
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<tr>
<td>KEEP Weighted</td>
<td>8.01</td>
<td>7.62-9.12</td>
<td>8.07</td>
<td>7.25-8.97</td>
</tr>
</tbody>
</table>

Figure 1. Prevalence of eGFR<60 ml/min/1.73 m² (A) and ACR>30 mg/g (B) by year for KEEP and NHANES.

Conclusions: Selection models may be used to address participation bias in large community detection programs. This makes it possible to substantially enhance inputs for future CKD surveillance systems that provide spatio-temporal maps of CKD hotspots in the community.

Funding: Private Foundation Support
FR-PO710

Secular Trends in Increase in the Prevalence of CKD in Diabetics Tracks the Secular Trends in Lower Systolic and Diastolic Blood Pressures in the U.S. Śrini Beddhu,1,2 Alfred K. Cheung,1,2 Guo Wei,3 R. E. Boucher,1 Rabia Nadecm Kiani,1 Tom Greene.1 1‘Univ of Utah, SLC, UT; 2‘VA, SLC, UT.

Background: Recent studies indicate intensive BP control might ↑ the incidence of CKD, yet ↓ the risk for mortality in those with established CKD. Hence, greater BP control might result in ↑ prevalence of CKD at the population level. Methods: Using 1988-1994 (National Health And Nutrition Examination Survey) NHANES III as the reference, survey weight adjusted secular trends in prevalence of CKD (eGFR < 60 ml/min/1.73 m³) in diabetics in 1999-2002, 2003-2006 and 2007-2010 NHANES were examined. Similarly, trends in SBP and DBP in diabetics with and without CKD were examined. Using median SBP or DBP as the reference, the odds of CKD in diabetics in the entire cohort were related to SBP or DBP in natural cubic spline regression models in svy suite using STATA 14.

Results: The prevalence of CKD in diabetics in the US has increased. In parallel, there has been a drop in SBP and DBP in diabetics without and with CKD but the drop has been more pronounced in CKD.

Conclusions: Secular trends in increase in the prevalence of CKD in diabetics track the secular trends in drop in both SBP and DBP in the US population. This might reflect hemodynamic effects of intensive BP lowering that increases CKD incidence, practice patterns of more intensive BP lowering in CKD or decreased mortality with intensive BP lowering in CKD.

Funding: NIDDK Support, VA Support

FR-PO711

Prediction of Pathologic Proteinuria by Dipstick Albuminuria and the Specific Gravity Hajoeong Lee,1 Hee Gyueng Kang.2 Internal Medicine, Seoul National Univ Hospital, Korea; 2Pediatrics, Seoul National Univ College of Medicine, Korea.

Background: Proteinuria is essential to diagnose kidney disease. Urine dipstick test is easy to recognize pathologic proteinuria with lower cost, so usual health examination programs use it for screening of kidney diseases. However, spot urine dipstick albumin (DSA) is affect by urine specific gravity (USG). The impact of USG on estimation of the diluted urine with USG ≤1.010, more than 80% of patients with dipstick albuminuria was validated in the remaining 40%. Samples were stratified according to DSA and SG values. A DSA versus SG matrix was created, and each sample was allocated to a discrete pattern. The model was applied to 430 transplants performed at SGPGIMS during Jan 2008 to Dec 2013. The creatinine level within 20 days of discharge was considered as baseline. A rise of at least 30% to this baseline was considered as critical level of creatinine. The model has been applied to recipients within the first year of follow up.

Results: The model explained the data set (R²=0.90). The estimate of parameters is: Π=0.5797, λ₁=0.0403 and λ₂=0.2427. About 40% of transplant cases belonged to high risk group, while 60% to low risk group.

Conclusions: The frequency and pattern of creatinine rise may help in formulating more precise and patient centered management strategy in post-transplant period.

Funding: Government Support - Non-U.S.

FR-PO712

A Stochastic Model for the Waiting Time of Creatinine Rise to a Critical Level in Post Renal Transplant Period Chandra M. Pandey,1 Sonam Bedi,1 Raj K. Sharma,2 Sada Nand Dwivedi.1 1‘Biostatistics and Health Informatics, Sanjay Gandhi Postgraduate Inst of Medical Sciences, Lucknow, Uttar Pradesh, India; 2Nephrology, Sanjay Gandhi Postgraduate Inst of Medical Sciences, Lucknow, Uttar Pradesh, India; ‘Biostatistics, All India Inst of Medical Sciences, New Delhi, Delhi, India.

Background: Elevated creatinine is a signal to poor functioning of allograft. There is a need to estimate the risk of rise in creatinine to a critical level, which is not observable directly.

Methods: A stochastic model with varied risk of creatinine rise is proposed to estimate the above risk. The underlying assumptions are: time to achieve the critical level in days was taken as random variable. Π (1-Π) is the proportion of transplant cases whose creatinine rise to critical level in a small length of time t to Πt is λ₁Δt and λ₂Δt; where λ₁<λ₂. The probability density function of duration derived follows multinomial distribution with parameters λ₁, λ₂ and Π. The parameters are estimated using Maximum Likelihood Estimation method. The pilot values were given as an initial input. The estimates produced by previous iteration was given as input for subsequent iteration. The iteration process was repeated till the convergence was achieved and output at this level was taken as final estimate of these parameters. The variances and co-variances of the estimates are also obtained.

Results: The model was applied to 430 transplanted performed at SGPGIMS during Jan 2008 to Dec 2013. The creatinine level within 20 days of discharge was considered as baseline. A rise of at least 30% to this baseline was considered as critical level of creatinine. The model has been applied to recipients within the first year of follow up.

Funding: Government Support - Non-U.S.

FR-PO713

Facebook® Can Be Used to Reach a Target Audience to Screen for CKD Risk Using the QKidney®-2014 Risk Calculator Eric E. Gheuens, Koenraad Peter Bouman, Ronald Daelmans. ZNA Kidney Clinic, Ziekenhuis Netwerk Antwerpen, Antwerpen, Belgium.

Background: On World Kidney Day (WKD) 2015 we launched the QKidney®-2014 risk calculator (www.qkidney.org) to screen for CKD risk in the general population, aged between 35 and 75 years.

Methods: A webpage was created (wereldnierdag.zna.be) and launched on WKD 2015 using different traditional campaigns. In February 2016 we launched a Facebook® advertising campaign targeting users in the desired age group.

Results: The first weeks after the launch the risk calculator was used by about 5000 people. In the proceeding year a steady activity on the website created about 30,000 records. In February 2016, almost a year after the launch, the Facebook advertising campaign was active during two weeks. The website was viewed almost 600,000 times by about 350,000 unique users. 329.000 views were on desktops and 270.000 on mobile devices. Around 30.000 new records were created in this short time span.

Conclusions: There was a need to monitor the Facebook® page on a daily basis, since many messages were posted and discussions ensued that needed to be moderated. All in all the atmosphere on the page was very positive and very few negative reactions were posted.

Funding: Research Foundation - Flanders.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-P0714
Chronic Kidney Disease (CKD) in HIV-Infected Patients: Relation to Viral Load
Justine Johnson, 1 Eric Joseph Lai, 1 Wadi N. Suki, 1 Duc T.M. Nguyen, 2 Edward Graviss, 2 "Dept of Medicine, Houston Methodist Hospital, Houston, TX; 1Pathology, Houston Methodist Hospital, Houston, TX.

Background: Since the advent of HAART, HIV-associated nephropathy has evolved from a disorder characterized by proteinuria and glomerulosclerosis to one with clinical characteristics more suggestive of tubulo-interstitial disease. The object of this study was to investigate the prevalence of CKD in a large HIV-infected population and viral load and CD4 counts as indices of effective HAART.

Methods: Electronic Medical Records of 3858 HIV-infected patients at a community health clinic were reviewed. Demographic characteristics and laboratory values for serum creatinine (SCr), CD4 count, and viral load were collected. Estimated GFR (eGFR) was calculated from the SCr by the CKD-Epi equation. CKD was considered as eGFR <60 ml/min/1.73m2. Differences across kidney function stages were compared using Chi-square or Fisher’s exact tests for categorical variables and Kruskal-Wallis test for continuous variables as appropriate. Univariate and multivariate ordinal logistic regression models were used to examine the relationship between kidney function stages and potential comorbidity associations.

Results: Patients with CKD represented 4.1% of the population; they were older, and had a higher representation of females. On ordinal logistic regression analysis, there was a highly significant association of CKD with viral load <50 copies/ml (OR+1.73, CI1.46 to 2.05, p<0.001), but not with the CD4 count.

Conclusions: Low or undetectable HIV viral load is generally indicative of a high degree of HAART medication compliance. The association of CKD with very low or undetectable viral load indicates that HAART medications are responsible for the high prevalence of CKD in these patients.

FR-P0715
Identification of Chronic Kidney Disease in the Veterans Affairs Healthcare System
Raivat Saran, 1 Anca Tila, 1 Vahalan B. Shahinian, 1 Aaron Pearson, 2 Jennifer L. Bragg-Gresham, 1 Hal Morgenstern, 1 Brenda W. Gillespie, 1 Alan B. Leichtman, 1 Ann M. O’Hare, 1 John R. Hotchkiss, 2 Daniel F. Balkovetz, 2 Susan T. Crowley, 1 Univ of Michigan; 2VA Healthcare System.

Background: The strict application of the KDIGO definition for CKD surveillance in the VA HCS may miss a core case. More liberal case definition may improve sensitivity. We estimated VA CKD prevalence using two different definitions in existing operational data in the VA Renal Information System (VA REINS).

Methods: CKD prevalence was examined using laboratory data and ICD-9 codes from 2006-2014. Proteinuria was hierarchically categorized using any urine tests for albumin excretion rate (AER), albumin-creatinine ratio (ACR), protein excretion rate (PER), protein-creatinine ratio (PCR), or urine dipstick. GFR was estimated from outpatient serum creatinine. CKD prevalence was assessed using both strict KDIGO-specific criteria (evidence of persistent lab abnormality) and ‘liberal’ definitions of CKD. The denominator was defined operationally as the population of V A HCS ‘users’ (with ≥1 contact with VA in that or 2 previous years).

Results: Among 6,932,278 VA users in 2014, CKD prevalence using KDIGO criteria was 16.4%, whereas the liberal definition increased prevalence to 36.3% (Table). Only 159 (10.98%) were smokers, 611 (42.2%) consumed alcohol regularly, diabetes was diagnosed in 91 (6.29%), hypertension in 427 (29.51%) and overweight and obesity in 653 (45%). The evaluation of GFR for the stages 3A, 3B and V was respectively: 0.76, 0.41 and 0.00 (MDRD); 0.97, 0.14 and 0.07 (CKD-EpiC); 3.32, 1.31 and 0.07 (CKD-EpiC).

Conclusions: The prevalence of CKD in Brazilian Afro-descendant communities, with low age and socially vulnerable, was less than previously reported for others populations and presented wide variation of results according to the GFR measurement method used.

FR-P0716
Prevalence of Chronic Renal Disease in Afro-Brazilian Isolated Communities in Brazilian Northeast
Tania Salgado Filho, 1 Joyce S. Lages, 2 Dyego Jose Araujo Brito, 2 Liaison De Moura Feitoza, 3 Francisco Monteiro Jr, 1 Denizar Viana, 4 Gyl Barros-Silva, 5 Elton Jonh Freitas Santos. 1Federal Univ of Maranhao, Brazil.

Background: In Brazil, there are no consistent studies investigating the prevalence of chronic renal disease in its Afro-descendent population. The objective was to investigate the prevalence of chronic renal disease (CRD) in 32 isolated Afro-descendent communities existing in the state of Maranhao, Northeast of Brazil.

Methods: This study included 1539 individuals living in rural areas. Epidemiological, clinical, and laboratory and anthropometric aspects were evaluated. The glomerular filtration rate (GFR) was estimated using CKD-EPI Creatinine (CKD-EpIC), CKD-EPI Cystatin C (CKD-EpIC), CKD-EPI Creatinine-Cystatin C (CKD-EpICc) and MDRD. For the diagnosis and classification of CRD, the KDIGO (2012) criteria were applied.

Results: The gender most frequent was female (59.5%). The average age was 44.4 (17-96 years; 616 (42.5%) without fixed income, 592(40.9%) have less than three years of study, 159 (10.98%) were smokers, 611 (42.2%) consumed alcohol regularly, diabetes was diagnosed in 91 (6.29%), hypertension in 427 (29.51%) and overweight and obesity in 653 (45%). The evaluation of GFR for the stages 3A, 3B and V was respectively: 0.76, 0.41 and 0.00 (MDRD); 0.97, 0.14 and 0.07 (CKD-EpiC); 3.32, 1.31 and 0.07 (CKD-EpiC).

Conclusions: The prevalence of CRD in Brazilian Afro-descendent communities, with low age and socially vulnerable, was less than previously reported for others populations and presented wide variation of results according to the GFR measurement method used.

FR-P0717
Ovarian Reserve and Fertility Hormonal Profiles in Women with Chronic Kidney Disease
Kate Bramham, 1 Aasmita Gautam, 1 Kate S. Wiles, 1 Lucy C. Chappell. 1Div of Women’s Health, King’s College London, London, United Kingdom; 1Dept of Renal Sciences, King’s College London, London, United Kingdom.

Background: Fertility is reported to be reduced in women with increasing severity of chronic kidney disease (CKD). Improved understanding of fertility assessment in women with impaired renal function will enable women with CKD to make informed choices about planning future pregnancy. Previous studies of reproductive hormones in women with CKD using small and the relationship between these hormones and ovarian reserve, Anti-Mullerian Hormone (AMH) and renal function has not been explored. The objective of this study was to define the relationships between glomerular filtration rate (GFR) and i) reproductive hormones (follicle stimulating hormone (FSH), luteinising hormone (LH), oestradiol, progesterone and prolactin) ii) AMH, in women with CKD and healthy controls.

Methods: 94 women with CKD (Stage 1: 24 (23.1%); Stage 2: 23 (22.1%); Stage 3: 35 (31.8%); Stage 4 and 5: 14 (13.5%) and 10(9.6%) healthy female controls were recruited. Participants provided a single blood sample for analysis. Fertility hormones were quantified by standard laboratory assays and their relationship with GFR assessed.

Results: AMH was not affected by GFR after adjustment for age. However there was a strong association between maternal age and AMH in women with CKD (R = 0.474, value p<0.005). No significant relationships were identified between GFR and FSH, oestradiol, progesterone or prolactin (i)AMH, in women with CKD and healthy controls.

Conclusions: CKD does not appear to be associated with reduced ovarian reserve, thus AMH could be a useful tool in the assessment of ovarian reserve in women with CKD as its quantification is not affected by renal function. Serum prolactin increases with worsening GFR which is likely to reflect reduced excretion. Another novel finding was the increase in LH with reduced GFR and requires confirmation in a larger cohort.

Funding: Government Support - Non-U.S.

FR-P0718
Antiretroviral Treatment and Chronic Kidney Disease in Urban Zambia: Cohort Characteristics and Association with Chronic Kidney Disease
Martin G. Zeier, 1Div of Nephrology, Heidelberg Univ Hospital, Heidelberg, Germany.

Background: The widespread use of antiretroviral-treatment (ART) increases life span in Sub-Saharan-Africa (SSA). This goes along with an increase in non-communicable diseases, e.g. chronic kidney disease (CKD).

Methods: Study design Retrospective cohort study Setting & Participants Routine data of 1119 HIV patients were assessed for CKD in Lusaka/Zambia between 2011 and 2013 in a quasi-random sample. Inclusion criteria were at least one serum creatinine measurement and 90 days on ART. Predictor OR Factor HIV-infection, high blood pressure, ART-medication Outcomes We compared patients’ conditions prior to ART initiation and at the last observation and applied multivariate models to assess the association between ART and eGFR. The CKD-Epi-Equation was used to estimate the glomerular filtration rate (eGFR) without the correction factor for African Americans.

Results: Ultimately, 28.2% of patients had eGFR category 2-5 (5.5% <60 ml/min), compared to 24.8% (4.8%) prior to ART initiation. Hypertension was recorded in 26% of patients, 35.3% ever received antihypertensive treatment (12% less than eleven, 13% 11-35, 12% 36-59, 14% ≥60). In ART-naive patients the change in eGFR from baseline to TDF-free ART (TscART) had baseline eGFR categories 3-5, eGFR deteriorated in 41% of
Glomerular Filtration Rate Is Low in the Inflammatory Arthritis Diseases Compared to Healthy Population: Essential Role of Inflammation

**Background:** Inflammatory diseases are associated with subclinical renal impairment. We aimed at investigating the associations between estimated glomerular filtration rate (eGFR), traditional cardiovascular risk factors, and markers of inflammation and oxidative stress in inflammatory arthritis patients compared to healthy controls.

**Methods:** Participants were recruited from January 2013 to 2016. Healthy subjects recruited from the community. MDRD formula was used to get eGFR. t-test was used to compare the laboratory values and renal function parameters between two groups. Linear regression analysis was used to look for the correlation between eGFR and each of traditional cardiovascular risk factors and inflammatory markers.

**Results:**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Frequency</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>128</td>
<td>51</td>
</tr>
<tr>
<td>Female</td>
<td>121</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Frequency</th>
<th>Percentage %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>103</td>
<td>41</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>170</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Diabetes and hypertension</td>
<td>85</td>
<td>34</td>
<td></td>
</tr>
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<td>61</td>
<td>25</td>
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</tr>
</tbody>
</table>

**Conclusions:** 25% of the subjects had neither DM nor HTN, a 16.8% came from three towns located on the Pacific Coast and the mean age was statistically significantly different between both groups, these findings may indicate evidence of MeN in Guatemala. Additional studies are recommended to establish the extent of MeN in Guatemala.

**Funding:** Private Foundation Support

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Rapid Loss of Kidney Function amongst Apparently Healthy Young Adults from Communities at Risk of Mesoamerican Nephropathy

**Background:** Mesoamerican Nephropathy (MeN) is killing thousands of young adults across rural Central America, where intensive agricultural work is the dominant occupation. MeN is a form of chronic kidney disease (CKD) characterised by minimal proteinuria and interstitial scarring on biopsy. The aetiology and natural history of MeN are unknown.

**Methods:** In partnership with 9 affected communities in Leon and Chinanique regions, Nicaragua, we are (to our knowledge) undertaking the first community-based longitudinal study investigating MeN. We invited all men and a random sample of women (ratio 3:1), aged 18-30, without a history of CKD to take part. Questionnaire data and biosamples have been collected at baseline and at 6-monthly intervals. Estimated glomerular filtration rate (eGFR) was calculated by CKD-EPI, and the slope estimated using a multilevel model. This abstract describes the eGFR decline to the halfway point of the 2-year study.

**Results:** 16 potential participants had a diagnosis of CKD and were not included. 350 of 360 eligible participants consented to take part and 94% have attended ≥2 of the 3 visits studies to date. Mean baseline eGFR was 125.5mL/min/1.73m² and mean decline in eGFR was 19.0mL/min/1.73m² (95%CI: 16.5-21.5) over the first year with no difference between sexes (Figure).

Conclusions: The average annualised loss of >15% of kidney function in unselected, apparently healthy, young adults is consistent with the devastating effects of this disease that are reported. Questionnaire data and biosamples should allow us to go on to uncover associations between potential causal exposures and eGFR decline in MeN.

**Funding:** Private Foundation Support

---

**Table 1. Demographic Characteristics (n=249)**

<table>
<thead>
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</tbody>
</table>

**Table 2. Age difference between those without traditional risk factors and those with traditional risk factors**

<table>
<thead>
<tr>
<th>Category</th>
<th>Without traditional risk factors</th>
<th>With traditional risk factors</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean±SD</td>
<td>35±18.5</td>
<td>50±17.3</td>
<td>&lt;0.001</td>
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Conclusion: 25% of the subjects had neither DM nor HTN, a 16.8% came from three towns located on the Pacific Coast and the mean age was statistically significantly different between both groups, these findings may indicate evidence of MeN in Guatemala. Additional studies are recommended to establish the extent of MeN in Guatemala.

**Funding:** Private Foundation Support

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**Table 3. Age difference between those without traditional risk factors and those with traditional risk factors**

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**FR-PO720**

**Chronic Kidney Disease of Unknown Origin-Possible Link to Mesoamerican Nephropathy in Guatemala**

**Background:** Several epidemiological studies have described a high prevalence of Chronic Kidney Disease of unknown etiology (CKDu) along the Pacific Coast of Central America. This particular disease presentation is known as Mesoamerican Nephropathy (MeN). A definitive study has not been conducted to confirm the presence of MeN in Guatemala.

**Methods:** This cross sectional study was conducted in the largest referral center in Guatemala. All the patients who presented with ESRD during a period of 6 months were interviewed. We looked for “traditional” risk factors (diabetes and/or hypertension) and lack of “traditional” risk factors of CKD.

**Results:** A total of 249 patients were interviewed. 51% were males and 49% females, 54% of the patients lived in Guatemala City and 16.8% along the Pacific Coast. A total of 68% of the subjects had hypertension (HTN), 41% had diabetes mellitus (DM), and 25% did not present with DM or HTN. The subjects without DM and HTN were younger (35 ± 18.5) than the subjects with DM and/or HTN (50±17.3, p<0.001).

**Conclusions:** The average annualised loss of >15% of kidney function in all selected, apparently healthy, young adults is consistent with the devastating effects of this disease that are reported. Questionnaire data and biosamples should allow us to go on to uncover associations between potential causal exposures and eGFR decline in MeN.

**Funding:** Private Foundation Support

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**FR-PO719**

**Glomerular Filtration Rate Is Low in the Inflammatory Arthritis Diseases Compared to Healthy Population: Essential Role of Inflammation**

**Background:** Inflammatory diseases are associated with subclinical renal impairment. We aimed at investigating the associations between estimated glomerular filtration rate (eGFR), traditional cardiovascular risk factors, and markers of inflammation and oxidative stress in inflammatory arthritis patients compared to healthy controls.

**Methods:** Participants were recruited from January 2013 to 2016. Healthy subjects recruited from the community. MDRD formula was used to get eGFR. t-test was used to compare the laboratory values and renal function parameters between two groups. Linear regression analysis was used to look for the correlation between eGFR and each of traditional cardiovascular risk factors and inflammatory markers.

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**Conclusions:** 25% of the subjects had neither DM nor HTN, a 16.8% came from three towns located on the Pacific Coast and the mean age was statistically significantly different between both groups, these findings may indicate evidence of MeN in Guatemala. Additional studies are recommended to establish the extent of MeN in Guatemala.

**Funding:** Private Foundation Support
FR-PO722

A Comparison between the First-Degree Relatives of IgAN Patients and General Population: Prevalence, Risk Factors and Relative Risk of Chronic Kidney Disease

Ye Bao, Xin Wei, Jing Zhou. Nephrology, The First Affiliated Hospital of Nanchang Univ, Nanchang, China.

Background: Primary IgA nephropathy (IgAN) is the commonest type of primary glomerulonephritis worldwide, which is a major cause of leading to ESRD in China. However, it is well unclear whether the first-degree relatives (FDRs) of IgAN patients underwent a higher risk with CKD or renal damage than the general population. The aim of our study was to investigate the familial clustering of IgAN in southern China, and estimated the relative risk of CKD comparing with matched controls.

Methods: A total of 634 FDRs of 295 IgAN patients were reviewed from November 2007 to March 2009 in southern China, and a random sample of 1167 age-, gender-, and region-matched controls without family history of CKD were included. Information on questionnaire, anthropometric measurements, laboratory examination results, and hypertension history were recorded. CKD risk factors, including age, gender, BMI, hypertension and etc were investigated. The odds ratio (OR) was used to estimate the relative risk of CKD between FDRs of IgAN patients and controls.

Results: There was a significant difference in prevalence of CKD (31.3% vs. 11.3%, P < 0.001) between the FDRs of IgAN patients and matched controls. After adjusting confounders, female gender (OR=2.02, P=0.008), hypertension (OR=2.14, P<0.001) and etc were independently associated with increased risk of CKD. The adjusted relative risk of 4.03 for CKD was obtained among the FDRs of IgAN patients and matched controls, and the adjusted relative risk for hematuria, albuminuria and reduced eGFR were 6.61, 3.32 and 4.00, respectively.

Table 1: The risk analysis of CKD, hematuria, albuminuria and reduced eGFR in IgAN patients’ first-degree relatives comparing with controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>P</th>
<th>Adjusted OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>3.71 (1.07, 1.84)</td>
<td>0.013</td>
<td>4.03 (3.08, 5.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haematuria</td>
<td>6.59 (4.60, 9.43)</td>
<td>&lt;0.001</td>
<td>6.61 (4.59, 9.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>4.00 (2.10, 4.48)</td>
<td>&lt;0.001</td>
<td>3.32 (2.26, 4.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduced eGFR</td>
<td>2.92 (1.65, 5.16)</td>
<td>&lt;0.001</td>
<td>4.00 (2.17, 7.37)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions: The study revealed the FDRs of IgAN patients experienced a higher risk with CKD than the general population. Furthermore, hypertension, female gender, hypertriglyceridemia and overweight are independent risk factors of CKD for this special population.

FR-PO723

Renal Interstitial Fibrosis: An Imperfect Prognostic Indicator in Chronic Kidney Disease

Hanni Menn-Joseph, Carol S. Lee, Angela Nolin, Marta Christov, Denis Rybin, Janice Weinberg, Joel M. Henderson, Ramon G. Bonegio, Andrea Havassy, Medicine Renal Section, Boston Univ School of Medicine, Boston, MA. 1Renal Div, New York Medical College, Valhalla, NY.

Background: It is well unclear whether the first-degree relatives (FDRs) of IgAN patients have a higher risk of CKD or renal damage than the general population. The aim of our study was to investigate the familial clustering of IgAN in southern China, and estimated the relative risk of CKD comparing with matched controls.

Methods: A total of 634 FDRs of 295 IgAN patients were reviewed from November 2007 to March 2009 in southern China, and a random sample of 1167 age-, gender-, and region-matched controls without family history of CKD were included. Information on questionnaire, anthropometric measurements, laboratory examination results, and hypertension history were recorded. CKD risk factors, including age, gender, BMI, hypertension and etc were investigated. The odds ratio (OR) was used to estimate the relative risk of CKD between FDRs of IgAN patients and controls.

Results: There was a significant difference in prevalence of CKD (31.3% vs. 11.3%, P < 0.001) between the FDRs of IgAN patients and matched controls. After adjusting confounders, female gender (OR=2.02, P=0.008), hypertension (OR=2.14, P<0.001) and etc were independently associated with increased risk of CKD. The adjusted relative risk of 4.03 for CKD was obtained among the FDRs of IgAN patients and matched controls, and the adjusted relative risk for hematuria, albuminuria and reduced eGFR were 6.61, 3.32 and 4.00, respectively.

Table 2: Multivariate logistic regression analysis of associated risk factors of CKD in the first-degree relatives with IgAN patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>20–39</td>
<td>1.14 (0.73–1.77)</td>
<td>0.586</td>
</tr>
<tr>
<td>40–59</td>
<td>2.35 (1.37–9.05)</td>
<td>0.033</td>
</tr>
<tr>
<td>60–69</td>
<td>6.62 (2.26–15.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td>2.02 (1.20–3.40)</td>
<td>0.008</td>
</tr>
<tr>
<td>BMI</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1.30 (0.81–2.05)</td>
<td>0.281</td>
</tr>
<tr>
<td>Obese*</td>
<td>1.91 (1.07–3.41)</td>
<td>0.028</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.61 (1.11–2.96)</td>
<td>0.018</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.89 (0.52–1.52)</td>
<td>0.675</td>
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<tr>
<td>Hypertension</td>
<td>0.91 (0.55–1.52)</td>
<td>0.721</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.14 (1.25–3.79)</td>
<td>0.026</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.00 (1.13–3.60)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Conclusions: The study revealed the FDRs of IgAN patients experienced a higher risk with CKD than the general population. Furthermore, hypertension, female gender, hypertriglyceridemia and overweight are independent risk factors of CKD for this special population.

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

531A
Low Serum Magnesium and Incident Chronic Kidney Disease in the Dallas Heart Study
Javier A. Neyses, Silvia Ferré, Xiaolin Li, Beverly Adams-Huey, Orson W. Moe. UT Southwestern, Dallas, TX.

Background: CKD is highly prevalent in the US adult population and carries increased mortality risk. Low magnesium has been associated with higher inflammatory cytokines in endothelial cells, which may contribute to kidney function decline. In this study, we aim to examine the association of serum magnesium (SMg) with incident CKD in the multiethnic population-based Dallas Heart Study (DHS) cohort.

Methods: DHS participants without prevalent CKD (eGFR-EP1 ≥ 60 and absence of microalbuminuria) were included in the study (n = 3146). The independent variable was SMg measured at the beginning of the study period, both as a continuous variable and divided into tertiles (low-medium-high). The primary outcome was incident CKD, defined as eGFR <60 and ≥25% reduction from baseline and/or de novo microalbuminuria (doubling of urinary albumin-to-creatinine ratio [ACR] from <10 mg/g to ≥10 mg/g). Multivariable Cox regression hazard models included demographics, comorbidity, anthropometric and biochemical parameters including albumin, phosphorus, and PTH; use of diuretics; and their interactions.

Results: Mean (SD) age was 44 (10) years, eGFR 102 (18) ml/min/1.73 m², and ACR 4.4 (4.4) mg/g. 44% were men, 52% African American, 29% Caucasian and 17% Hispanic. Mean SMg was 2.07 (0.18) mg/dL. Incident CKD occurred in 123/467 (26%) in the low, 177/884 (20%) in the medium, and 83/619 (13.4%) in the high SMg tertile groups, after a median follow-up of 7.1 years. SMg was independently associated with incident CKD-adjusted HR 1.5 (95% CI, 1.1–2.0) for low vs high tertile. Every 0.2 mg/dL increment in SMg was associated with an adjusted hazard for incident CKD by 63%. There was a negative correlation between SMg and high-sensitivity C-reactive protein (hs-CRP) at the time of CKD diagnosis (r = -0.11, p < 0.001).

Conclusions: Low SMg was independently associated with incident CKD and had an inverse correlation with hs-CRP in the DHS cohort. Whether Mg deficiency contributes to the occurrence of CKD require further investigation.

Funding: Other NIH Support - P50 DK079328-06; UL1 TR001055

Lesser Renal Function Is Associated with Higher Aldosterone and High Blood Pressure in Chronic Kidney Disease, Irrespective of RAAS Inhibition
Christina M. Gant, MD,1 Guzewsijn Dirk Lavereman,1 Liffert Vogt,1 Hiddo Jan Lambers Heerspink,2 Marc H. Hermelink,2 Gerjan Navis,2 Femke Waanders,2 1Internal Medicine, ZGT Hospital, Almelo, Netherlands; 2Nephrology, Univ Medical Centre Groningen, Groningen, Netherlands; 3Nephrology, Academic Medical Centre Amsterdam, Amsterdam, Netherlands; 4Clinical Pharmacy and Pharmacology, Univ Medical Centre Groningen, Groningen, Netherlands; 5Internal Medicine, Isala Hospital, Zwolle, Netherlands; 6Internal Medicine, Medical Centre Leeuwarden, Leeuwarden, Netherlands.

Background: Aldosterone is elevated in chronic kidney disease (CKD) and may be involved in hypertension. The determinants of aldosterone and its association with blood pressure (BP) in CKD are yet to be studied in CKD patients. We studied the determinants of the plasma aldosterone concentration (PAC) and its association with BP in CKD, untreated and during renin-angiotensin-aldosterone system inhibition (RAASi).

Methods: We performed a post-hoc analysis on data from a randomized controlled cross-over trial in non-dialysis CKD patients (n = 32, creatinine clearance (CCr) 85 (75-95) ml/min, proteinuria 3.2 (2.5-4.0) g/d). The 6-week study periods were placebo, losartan 100mg (ARB) and ARB+hydrochlorothiazide 25mg (HCT), during both a normal (200±10 mmHg Na+/d) and low (89±8 mmHg Na+/d) dietary sodium intake (LS).

Results: Plasma aldosterone concentration

<table>
<thead>
<tr>
<th>Condition</th>
<th>PAC (ng/L)</th>
<th>ARB</th>
<th>HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>75±63</td>
<td>68±44</td>
<td>73±66</td>
</tr>
<tr>
<td>Losartan</td>
<td>52±45</td>
<td>44±31</td>
<td>51±37</td>
</tr>
</tbody>
</table>

Aldosterone-to-renin ratio

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ratio</th>
<th>ARB</th>
<th>HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.58±0.09</td>
<td>0.52±0.08</td>
<td>0.56±0.08</td>
</tr>
<tr>
<td>Losartan</td>
<td>0.55±0.08</td>
<td>0.50±0.07</td>
<td>0.54±0.08</td>
</tr>
</tbody>
</table>

Lower CrCl was associated with higher PAC (left panel) and ARR (right panel), similarly during placebo (black line) and during ARB (grey dotted line; ARR line shifted down). Patients with baseline PAC above the median had higher BP during most study periods. Only during maximal treatment with ARB+HCT+LS, BP was no longer different.

Conclusions: In CKD patients with mild renal function impairment, lower CrCl is associated with higher PAC, irrespective of RAASi. Also, high PAC is associated with higher BP. It is important to test the implications of our study on BP treatment in patients with function impairment.

Funding: Pharmaceutical Company Support - Merck Sharp & Dohme

FR-P0728
Hyperuricemia as a Risk Factor for Proteinuria in Japanese General Population
Tadasu Toyama, Shinji Kitajima, Akikuni Harada, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Kengo Furuchi, Takashi Wada. Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan.

Background: Chronic kidney disease (CKD) is a risk factor for end-stage kidney disease and cardiovascular disease. Proteinuria consists the definition of CKD and is a known risk factor for progression of kidney dysfunction. Recent studies showed that hyperuricemia is one of the risk factors for loss of GFR and end-stage kidney disease; however, few studies have focused on the relationships of the development of proteinuria.

Methods: A historical Japanese cohort who underwent annual medical check-up between 1998 and 2007 and met the eligible criteria were included in the analysis. Participants aged ≥ 18 years and without CKD (eGFR was ≥60 ml/min/1.73 m³ and urinary protein was minus or trace) were included in the analysis. Participants with CKD at baseline, without baseline status, or aged < 18 years were excluded from the analysis. Hyperuricemia was defined as uric acid ≥ 7 mg/dL for male and ≥ 6 mg/dL for female. Outcome was defined as development of dipstick proteinuria 1+ or more. Cox proportional hazard model was used to estimate risks for proteinuria.

Results: A total of 58,563 subjects satisfied inclusion criteria. Mean follow-up period was 4.4 years. During the follow-up period, 2,285 (3.90%) subjects developed proteinuria. Compared with reference group, hyperuricemia was a significant risk factor for development of proteinuria (hazard ratio [HR] 1.64, 95% confidence interval [CI] 1.19–2.26) in female. These relationships were not found in male (HR 0.98, 95% CI 0.83 – 1.16).

Conclusions: Stratified with male and female, hyperuricemia was a significant risk factor for development of proteinuria in females in the general Japanese population. Intervventional studies are required to define the relationships.

Funding: Government Support - Non-U.S.

FR-P0729
Hyperuricemia out of Proportion to Renal Dysfunction in a Hotspot of Mesoamerican Nephropathy
Joseph Kupferman,1 Juan Jose Amador,2 Katherine E. Lynch,1 Rebecca L. Law,3 Damaris A. Lopez Pilar,4 Daniel R. Brooks,2 David J. Friedman,1 1Dept of Medicine, Beth Israel Deaconess Medical Center, Boston, MA; 2Dept of Epidemiology, Boston Univ School of Public Health, Boston, MA; 3Dept of Environmental Health, Boston Univ School of Public Health, Boston, MA.

Background: An epidemic of CKD of unknown etiology, termed Mesoamerican Nephropathy (MeN), is a major cause of morbidity and mortality in parts of Central America. Previous research has found hyperuricemia in some patients, and suggested that uric acid may play a role in disease pathogenesis. To probe deeper into this question, we compared the relationship between uric acid and kidney function in MeN cases to that in patients with CKD of traditional etiology.

Methods: In a community in northwestern Nicaragua with very high CKD prevalence, we identified 24 families with multiple members affected by MeN. We also studied unrelated

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

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former sugarcane workers with CKD of unknown cause. We compared the relationship of serum uric acid and eGFR between males with CKD from 3 NHANES cycles (n=253) and MeN patients from each of our two groups (n=99 and 237 for related and unrelated cases, respectively).

Results: Hyperuricemia, often severe, was common among MeN patients, whose uric acid levels were higher than of NHANES participants despite more frequent use of uric acid-lowering medications in the NHANES subjects (mean 9.8 and 9.6 mg/dL in unrelated and related patients, respectively, vs. 7.2 mg/dL in NHANES subjects). In multivariable linear mixed-effects regression analysis, uric acid levels were 2.0 mg/dL (95% CI 1.0-3.0; p=0.001) higher in MeN cases with familial clustering compared to NHANES subjects, adjusting for age, eGFR, and hypouricemic therapies. Mean serum uric acid was higher in unrelated MeN cases than in the NHANES group by 1.8 mg/dL (1.0-2.6; p<0.001), after adjustment for age and eGFR.

Conclusions: Serum uric acid may be important in MeN pathogenesis.

FR-PO730
Heart Rate Variability and Its Relation to Renal Disease: Longitudinal Results from the PREVEND Study
Chris H.L. Thio,1 Ariët M. Van Roon,2 Ron T. Ganseroovert,1,4 Harold Snieder,1 Epidemiology, UMC Groningen (UMCG), Groningen, Netherlands; 2Vascular Medicine, UMCG; 3Nephrology, UMCG; 4Prevention of Renal and Vascular End-stage Disease (PREVEND) Cohort Study, Groningen, Netherlands.

Background: In the general population, autonomic dysfunction (reflected by low heart rate variability, HRV) has been associated with cardiovascular disease. However, little is known about its relation to renal disease. We therefore examined the association between low HRV and renal outcomes.

Methods: In the population-based PREVEND Cohort Study, HRV measures (among which SDNN, standard deviation of normal-to-normal RR-intervals) were calculated from time-series of beat-to-beat blood pressure recordings at baseline. The lowest quartile was considered the risk group of interest and compared to the upper three quartiles combined. Cox-regression was performed to assess difference in incidence of chronic kidney disease (CKD: de novo: eGFR<60ml/min/1.73 m2 and/or urinary albumin excretion, UAE≥30mg/24h). Using mixed effects modelling we examined the effect of SDNN on levels and slopes of eGFR and UAE in the total population and in CKD patients.

Results: Included were 4605 subjects (49% males, age range 33-80). During a median follow-up time of 7.3 years we identified 341 new cases of CKD. Low SDNN was not associated with de novo CKD. We found low SDNN to be associated with levels but not with steeper decline of eGFR in a stratified based on annual rate of decline of eGFR in 3 categories: < 1 ml/min/1.73 m2, 1 to 4 ml/min/1.73 m2, and > 4 ml/min/1.73 m2. A mixed effects model with no compared to covariance structure was used to model eGFR over time, measured quarterly. Two-way interactions of time by comorbidities, time by lab scores, time by proteinuria status, as well as time by stage and time by age were included.

Conclusions: In our study, low SDNN was not associated with de novo CKD. We found low SDNN to be associated with levels but not with steeper decline of eGFR in a subgroup of subjects with baseline CKD. Our findings suggest that autonomic dysfunction is a complication of CKD rather than a causal factor.

FR-PO731
Progression of Kidney Disease in Stage 3 and 4 Chronic Kidney Disease Elderly Patients
Pradeep Arora,1 Kabir Jalal,2 Anu Gupta,3 James W. Lohr.4 1Div of Nephrology, Richmond VA Medical Center, Richmond, VA; 2Dept of Biostatistics, SUNY at Buffalo, Buffalo, NY; 3Div of Nephrology, Buffalo VA Medical Center, Buffalo, NY.

Background: The prevalence of chronic kidney disease is rising in the elderly population. We studied the rate of progression of CKD in this population and the factors associated with progression of CKD.

Methods: 4,562 patients > 65 years with 2 outpatient eGFRs < 60 ml/min/1.73 m2, at least 90 days apart with no intervening eGFR > 60 ml/min/1.73 m2 (March 1, 2001 and March 31, 2008) in VISN2 network. Patients with eGFR<15 ml/min/1.73 m2 were excluded. Data obtained included demographics, comorbidities, and laboratory variables. Patients were stratified based on annual rate of decline of eGFR in 3 categories: < 1 ml/min/1.73 m2, 1 to 4 ml/min/1.73 m2, and > 4 ml/min/1.73 m2. A mixed effects model with no compared to covariance structure was used to model eGFR over time, measured quarterly. Two-way interactions of time by comorbidities, time by lab scores, time by proteinuria status, as well as time by stage and time by age were included.

Results: Mean age was 77.2 years. 24.3% were diabetics, 4.3% had proteinuria. In univariate comparison of different rates of progression, 54.2% patients had an annual rate of progression < 1 ml/min/1.73 m2. Multivariable Mixed Model analyses revealed that increasing age, BMI, presence of CVD, DM and proteinuria were associated with significantly increased rate of progression of CKD. Serum albumin and hemoglobin level were inversely associated with progression of CKD.

Conclusions: Lower urine NH4+ excretion may associate with death and CKD progression among African Americans with hypertensive CKD, however, this did not reach statistical significance.

FR-PO732
Association of Urine Ammonium with Death and Kidney Outcomes in Hypertensive Chronic Kidney Disease
Kalani L. Raphael,1 David J. Carroll,2 Jennifer L. Murray,2 Thomas H. Hostetter,3 John R. Asplin,4 Sriini Beddhu,1 1Univ of Utah; 2Colorado College; 3Case Western Reserve; 4Litholink, Inc.

Background: High renal NH4+ promotes tubulointerstitial fibrosis in animal models of chronic kidney disease (CKD); however, low NH4+ excretion was associated with CKD progression in a prior clinical study. We examined the association between urine NH4+ excretion, CKD progression, and death in the African American Study of Kidney Disease (AASK).

Methods: Baseline urine [NH4+](mEq/L) was measured by the glutamate dehydrogenase method (n=1057). Participants were divided into tertiles of urine NH4+ excretion (meq/day). Cox and spline regression models related baseline urine NH4+ excretion to the AASK primary composite outcome (death, dialysis or GFR reduction by 50%). Models were adjusted for demographics, randomized group, protein intake, urine potassium excretion, body mass index, measured GFR (mg/dL), proteinuria, and [bicarbonate] at baseline. The lowest tertile served as the reference group in Cox model. The median NH4+ excretion value was the reference in the spline model.

Results: Baseline characteristics were: age 54 years, 61% male, meGFR 47 ml/min per 1.73m2, median proteinuria 81 mg/gm, and urine NH4+ excretion rate 19.5 (95% CI 6.5-44.3) meq/day. After adjustment, the hazard ratios of the composite outcome were 0.93 (95% CI 0.71-1.22) in the middle tertile and 0.89 (95% CI 0.65-1.21) in the highest tertile compared to the lowest tertile of NH4+ excretion. The results were similar after including blood pressure, heart disease, and smoking status at baseline in the model. Adjusted spline regression models showed a trend towards higher risk of the composite outcome with urine NH4+ excretion below the median value.

Death, dialysis, or 50% GFR decline

FR-PO733
Glycosuria and Renal Outcomes in Patients with Nondiabetic Chronic Kidney Disease - Is Glycosuria or Proximal Tubulopathy Renoprotective? Chi-Chih Hung,1 Shang-Jyh Hwang.2 Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung Medical Univ.

Background: Sodium glucose cotransporter 2 inhibitors have shown a potential for renoprotection beyond blood glucose lowering. Glycosuria in nondiabetic patients with chronic kidney disease (CKD) is sometimes noted. Whether glycosuria in CKD implies a...
channelopathy or proximal tubulopathy is not known. Theoretically, proximal tubulopathy could prevent protein reabsorption and damage in proximal tubular cells. The consequence of glycosuria in CKD is also not studied.

Methods: We performed a cross-sectional study for the association between glycosuria and urine electrolyte excretion in 208 nondiabetic patients and a longitudinal study for the consequence of glycosuria, defined by dipstick, in 783 nondiabetic patients with stage 4-5 CKD and urine protein-to-creatinine ratio >500 mg/g.

Results: In the cross-sectional study, fractional excretion (FE) of glucose >4% was 3.4%, 6.3% and 62.5% in CKD stage 3, 4 and 5, respectively. Log-transformed FE glucose correlated with FE sodium, FE potassium, FE urea, and log-transformed eGFR in multivariate linear regression. In the longitudinal study, 279 (35.6%) patients had glycosuria. Glycosuria was associated with a decreased risk for end-stage renal disease (adjusted hazard ratio: 0.77; CI: 0.62-0.97; p=0.024) and for rapid renal function decline (adjusted odds ratio: 0.63; CI: 0.43-0.95; p=0.02); but glycosuria was not associated with all-cause mortality or cardiovascular events. The results were consistent in the propensity score matched cohort.

Conclusions: Glycosuria or proximal tubulopathy becomes frequent with renal function decline and is related to favorable renal outcomes in nondiabetic patients with stage 4-5 CKD.

Funding: Private Foundation Support

FR-PO734

Health Literacy and Clinical Outcomes in Adults with Chronic Kidney Disease

Background: In the general population, limited health literacy has been associated with increased risk for hospitalization and death. These associations have not been well evaluated in pre-dialysis chronic kidney disease.

Methods: We conducted a prospective study of 2,392 non-Hispanic white and black adults enrolled in the Short Test of Functional Health Literacy (STOFHLA) starting in 2008 (median: 4.7 years post-CRIC enrollment). Limited health literacy was defined as STOFHLA score ≤22.

Results: Five percent of non-Hispanic whites and 28% of non-Hispanic blacks had limited health literacy. Compared to participants with adequate health literacy, individuals with limited health literacy were more likely to be older (66 vs. 61 years), have income <$20,000 (51 vs. 19%), and less than high school education (44 vs. 7%). Over a median follow-up of 3.5 years, 229 developed STOFHLA, 206 experienced an atherosclerotic event, the overall hospitalization rate was 64 per 100 person-years, and 265 died. Table 1 summaries multivariable analyses.

Table 1. Adjusted Hazard Ratio or Rate Ratio for Participants with Limited vs. Adequate Health Literacy (N=2,392)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident STOFHLA</td>
<td>1.09 (0.74, 1.60)</td>
</tr>
<tr>
<td>Atherosclerotic event</td>
<td>1.68 (1.10, 2.58)</td>
</tr>
<tr>
<td>Hospitalization rate</td>
<td>1.40 (1.28, 1.53)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1.10 (0.72, 1.67)</td>
</tr>
</tbody>
</table>

* Adjusted for clinical center, age, gender, race, education, smoking, body mass index, systolic blood pressure, diabetes, HgA1c, baseline eGFR, urine protein, ACEi/ARB use

Conclusions: Limited health literacy was associated with higher risk of atherosclerotic events and hospitalization than in those not with incident STOFHLA or death. Future work is needed to better understand these associations.

Funding: NIDDK Support

FR-PO735

T2* Values Are Better Than ADC Values for Functional MRI Evaluation to Accurately Predict CKD Progression
Kee Sugiyama,¹ Tsutomu Inoue,¹ Eito Kozawa,² Masahiro Ishikawa,² Naoki Kobayashi,³ Hirokazu Okada.¹
¹Nephrology, Saitama Medical University, Iruma-gun, Saitama, Japan; ²Radiology, Saitama Medical University, Iruma-gun, Saitama, Japan; ³Biomedical Engineering, Saitama Medical University, Hidaka, Saitama, Japan.

Background: Blood oxygen level-dependent (BOLD) and diffusion-weighted (DW) magnetic resonance imaging (MRI), can non-invasively assess oxygen bioavailability and fibrosis in the kidney (Inoue T, et al. JASN 22: 1429; 2011). To extend their clinical utility, in this study, we investigated the relationships among the parameters from these two functional MRI modalities and the clinical course of chronic kidney disease (CKD).

Methods: This was a single center, retrospective observational study. Participants consisted of CKD stage G1-4 patients who had regularly visited our outpatient clinic. MRI was performed using a 1.5 T imager. Age, gender, history of diabetes, proteinuria level, estimated glomerular filtration rate (eGFR), as well as T2* and apparent diffusion coefficient (ADC) values from both BOLD and DW MRI, were examined. Multiple regression analysis was performed using a multivariable-adjusted logistic regression model to test the association of uC3a with subsequent CKD progression.

Results: Among 388 CRIC participants, uC3a was above the detection limit (0.026 ng/mL) in 45%. Logistic regression models adjusted for age, sex, race, clinical center, proteinuria, and eGFR, we detected no association between tertiles of uC3a and risk of CKD progression (adjusted OR 2.02-1.00; odds ratio 0.96, 95% CI 0.55 – 1.66; tertile 3 vs tertile 1: odds ratio 1.24, 95% CI 0.64 – 2.40).

Conclusions: Readily implemented modifications of a commercial C3a assay eliminated analytical interference when used in urine. We found no evidence that uC3a levels can be used to identify CKD progression among CRIC Study participants.

Funding: NIDDK Support

FR-PO736

The Ambulatory Arterial Stiffness Index Is an Independent Predictor of Accelerated Age-Related GFR Decline in the General Middle-Aged Population

Background: Arterial stiffness measured as aortic pulse wave velocity predicts cardiovascular disease and incident chronic kidney disease. However, the role of arterial stiffness as a predictor of age-related GFR decline in the general population is unresolved due to the difficulty of measuring arterial stiffness and GFR with sufficient precision in population studies. The ambulatory arterial stiffness index (AASI) is a validated indicator of arterial stiffness easily calculated from ambulatory blood pressure measurements. We investigated whether AASI could predict iohexol clearance decline in a cohort representative of the general population.

Methods: We calculated the AASI from baseline ambulatory blood pressure measurements and measured iohexol clearance at baseline and follow-up in the Renal iohexol Clearance Survey Follow-Up Study (REINS-FU). The AASI was defined as 1 minus the regression slope of diastolic over systolic blood pressure. The REINS cohort included a representative sample of the general middle-aged population without self-reported diabetes, cardiovascular, or kidney disease at baseline (n=1627). The age was 50 to 62 years at baseline, and the median observation time was 5.6 years.

Results: The mean (standard deviation) of the GFR decline rate was 0.95 (2.23) ml/min/year of the AASI 0.38 (0.13). Baseline ambulatory systolic blood pressure did not predict a steeper GFR decline. In multivariable-adjusted linear mixed regression analysis, one standard deviation increase in baseline AASI was associated with a 0.12 (0.02) ml/min/year increase in GFR. This effect was independent of baseline ambulatory systolic and diastolic blood pressure and antihypertensive medication. The same finding was made in a subgroup with baseline hypertension (p=0.05).

Conclusions: We conclude that increased arterial stiffness, measured with the AASI, is an independent risk factor for accelerated age-related GFR decline in the general middle-aged population.

Funding: Government Support - Non-U.S.
FR-P0738
Serum FGF21 and FGF23 Are Associated with the Diastolic and Systolic Functions, Respectively, in Patients with Non-Diabetic Chronic Kidney Disease
Masashi Kitagawa, Hitoshi Sugiyama, Akifumi Onishi, Keiko Tanaka, Toshihiko Yamanari, Tatsuyuki Inoue, Jun Wada. Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Background: Fibroblast growth factor (FGF) 19/21/23 is an endocrine FGF. Besides regulating mineral metabolism, FGF23, with the co-receptor Klotho, plays an important role in cardiovascular conditions including left ventricular hypertrophy. FGF21, a fibroblast growth factor that is crucial in glucose and lipid homeostasis, also has cardioprotective effects.

Methods: FGF21, Klotho and FGF23 influence the systolic and diastolic functions in chronic kidney disease (CKD) patients remain unclear.

Results: The level of serum FGF21 and FGF23 were measured by a sandwich ELISA and the relationship between these biomarkers and the echocardiographic data was examined. Echocardiography was performed to measure the left ventricular mass index (LVMI), peak early diastolic mitral filling velocity (E), peak early diastolic mitral annular velocity (E'), and E/E' and ejection fraction (which represent the diastolic and systolic functions, respectively).

Conclusions: Serum FGF21 and FGF23 concentrations were independently associated with the diastolic and systolic functions, respectively in patients with non-diabetic chronic kidney disease.

Funding: Government Support - Non-U.S.

FR-P0739
Predicting Treatment Response and Renal Survival in Crescentic ANCA Associated Glomerulonephritis
Xia Liu, Ying-Hua Chen, Hai Tao Zhang, Zheng Zhao Liu, ZhiHong Liu, Wei Xin Hu. National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.

Background: Patients with crescentic ANCA associated glomerulonephritis (cre-AAGN) received intensive immunosuppressive therapy still have poor long-term renal survival. In this study, we analyze the factors, which may predict treatment response and long-term renal outcome in Chinese patients with cre-AAGN.

Methods: Sixty patients with biopsy-proven cre-AAGN were included and classified into renal replacement therapy (RRT, n=30) and non-RRT groups (n=30). Treatment response was recorded as good response (GR, the patients got rid of RRT in RRT group, or Scr declined ≥25% of the baseline in non-RRT group) and non-response (NR, the patients needed maintenance RRT in RRT group, or Scr declined <25% of the baseline in non-RRT group) at three months of induction treatment.

Results: At three months treatment, GR was achieved in 53.3% and 80% of patients in RRT and non-RRT groups, respectively. In RRT group, renal disease duration, total crescent percentage, circumferential crescent ratio (circumferential/total crescents) and sclerotic glomeruli (p≤0.01) were significantly lower in GR than that in NR cases. By multivariate Cox regression analysis, the circumferential crescent ratio was the only risk factor predicting not being GR, with the circumferential crescent ratio ³50% been the high factor for not being GR (HR 22.2, CI 2.17-200, P=0.002). In non-RRT group, the normal glomeruli percentage was markedly higher in GR patients than in NR patients (median: 20.4(12.3,29.0)% vs 5.3(2.3,11.5)%, p=0.022), with the normal glomeruli >7% being more likely to be GR (HR 13.3, CI 1.7-107.4, p=0.006). During a median follow-up of 19 (6-58) months, 18 (30%) patients developed to ESRD, the five-year renal survival rate range proteinuria (HR 5.9, CI 1.35-25.88, P=0.019) were the two independent risk factors (6-58 months), 18 (30%) patients developed to ESRD, the five-year renal survival rate was 86.9% and 51.9% in GR and NR patients respectively. For the patients achieved GR, the renal survival rate was 88.5% at 5 years.

Conclusions: The serum FGF21 and FGF23 concentrations were independently associated with the diastolic and systolic functions, respectively in patients with non-diabetic chronic kidney disease.

FR-P0740
Urine Citrate Excretion Might Identify Eubicarbonatemic CKD Patients with Acid Retention and Assess Their Response to Therapy
Nisimori Goraya, Jan Simoni, Jessica Pruszynski, Nicolaos E. Madias, Donald E. Wesson.

Background: Acid retention in eubicarbonatemic CKD patients was higher after dietary acid reduction with F+V. Low urine citrate excretion which increased after dietary acid reduction with F+V. Low urine citrate excretion might identify eubicarbonatemic CKD patients with acid retention and assess their response to therapy.

Methods: We measured acid excretion and urine citrate excretion in CKD stage 2 (n=40) and stage 1 (eGFR >90 ml/min/1.73 m², n=26) eubicarbonatemic patients (TCo2 >24.5 mmol/L) before and after 30 days of dietary acid reduction with baseline-creating foods and vegetables (F+V). Acid retention was measured by comparing observed to expected increase in plasma [TCo2] in response to reduced HC03 (dose -13, pH 7.4) 8 hours after an oral NaHCO3 bolus (0.5 eq/kg bw), assuming 50% loss made, space distribution.

Results: Baseline acid retention was higher in CKD 2 than CKD 1 (28.1±9.4 vs. 5.2±12.0 mmol/L, respectively, P=0.01) but baseline 8 hour urine citrate excretion was lower in CKD 2 than CKD 1 (184±17.4 mmol/L, P<0.01) but not in CKD 1 (4.7±15.6 mmol/L, P=0.88) and acid retention higher in CKD 2 than CKD 1 (P=0.01). By contrast, 30 days of F+V increased urine citrate excretion in both CKD 2 (to 245±70 mg, P=0.01 vs. baseline) and CKD 1 (to 136±25 mg, P=0.02 vs. baseline) yet urine citrate excretion remained lower in CKD 2 than CKD 1 (P=0.01).

Conclusions: Acid retention in eubicarbonatemic CKD patients was associated with low urine citrate excretion which increased after dietary acid reduction with F+V. Low urine citrate excretion might identify eubicarbonatemic CKD patients with acid retention and assess their response to therapy.

FR-P0741
Apolipoprotein L1 Genetic Variants Are Associated with Evidence of Early Kidney Injury in Sickle Cell Disease

Background: Apolipoprotein L1 (APOL1) renal-risk variants prevalent in African-ancestry populations are associated with chronic kidney disease (CKD). APO1 is a major cause of morbidity and mortality in sickle cell disease (SCD) in adults; yet the prevalence and significance of APOL1 renal-risk variants in this population remains unknown. Our objective was to determine expression of biomarkers of early kidney disease in African American youth with SCD, based on their APOL1 genotype.

Methods: We enrolled 40 African American subjects between 5 to 21 years of age with SCD (HB SS or HB Sß thalassemia). Blood and concurrent urine samples were collected. All enrolled subjects underwent APOL1 genotyping by PCR analysis of DNA extracted from whole blood. Presence of two renal-risk variants qualified for APOL1 High Risk (HR) genotype, while presence of zero or one copy of renal-risk variants qualified for APOL1 Low Risk (LR) genotype. Only two subjects (both in APOL1 LR group) were on ACEI/ARB therapy at baseline.

Results: 23% reported prevalence of APOL1 HR genotype in African American adults with CKD (AASK study). Both groups were similar with respect to distribution of age, BMI z-scores, renal function, and urine osmolality. Hyperfiltration was noted in both groups, based on low serum creatinine for age, and elevated eGFR based on creatinine clearance. However, median urine albumin excretion rate was significantly higher in GR group vs. LR group.
FR-P0742
Blood Monocyte Subsets and Neutrophils Increase with CKD Stage and Correlate with Both Renal Function and Inflammatory Cytokines
Serika D. Naicker,1 William P. Martin,1,2 Sarah Cormican,1,2 Thomas P. Griffin,1,2 Matthew D. Griffin,1,2 School of Medicine, Regenerative Medicine Inst (REMEDi), National Univ of Ireland, Galway, Ireland; 1Nephrology Services, Galway Univ Hospital, Saoirse Univ Health Group, Galway, Ireland.

Background: Chronic kidney disease (CKD) is associated with systemic inflammation which may contribute to cardiovascular complications and progression of renal injury. The aims of this study were to examine the relationships between specific circulating leukocyte populations and CKD stage/eGFR as well define the correlations between circulating leukocytes and specific innate cytokines.

Methods: Blood samples were collected from outpatients with CKD stage 2-5 (n=188) and from healthy adult volunteers (Ctrl, n=42). Total lymphocyte, monocyte and neutrophil counts were quantified in whole blood aliquots by flow cytometry. Peripheral blood mononuclear cells were prepared and were analyzed immediately by 8-colour flow cytometry to quantify individual monocyte subsets. Serum cytokines levels were quantified by multi-plex assay. Statistical analyses were performed using GraphPad Prism software.

Results: Total blood monocyte and neutrophil (but not lymphocyte) numbers increased progressively from Ctrl through CKD stages 2-5 and correlated strongly with serum creatinine, eGFR and blood urea nitrogen (BUN). Among the monocyte subsets, intermediate (CD14+CD16-) monocytes demonstrated the strongest relationship with CKD stage, eGFR and BUN. Intermediate monocyte numbers also correlated strongly with neutrophil numbers. Among the serum cytokines analyzed, interferon gamma (IFNγ) and IL-18 were most significantly increased in a CKD stage-dependent manner and also correlated with intermediate monocyte numbers as well serum creatinine, eGFR, BUN and serum albumin levels. Serum concentrations of IFNγ and IL-18 correlated strongly with each other.

Conclusions: Our results demonstrate relationships between circulating innate immune cells (neutrophils/monocytes) and severity of CKD as determined by eGFR. Selective expansion of intermediate monocytes and increases in specific innate cytokines indicate that CKD-associated inflammation has distinct characteristics that may be amenable to intervention.

Funding: Government Support - Non-U.S.

FR-P0743
Implication of the White Blood Cell Count (WBC) in the Progression of IgA Nephropathy
Ricong Xu,1 Qijun Xu,2 Tong Li,1 Yongcheng Liu,1 1Shenzhen Second People’s Hospital; 2Shenzhen Second People’s Hospital; 1Shenzhen Second People’s Hospital.

Background: Inflammatory markers such as serum or urinary interleukin-6 (IL-6) and serum albumin have been shown predicted effect for renal progression in patients with IgA nephropathy (IgAN), however, there are limited data regarding on the relationship between the white blood cell count (WBC) and renal progression in IgAN patients.

Methods: We conducted a retrospective cohort study in 543 biopsy proven IgAN patients in our center to evaluate the association between the WBC and the clinical characteristics and the pathological features in IgAN patients, and analyzed the predictive effect of the WBC on long-term renal progression. The renal progression endpoint was defined as end stage renal disease (ESRD) or the doubling of the baseline serum creatinine concentration. Patients were divided into four groups according to the quartiles of the WBC.

The Cox’s proportional hazards regression models were used to assess the association of WBC with long-term renal progression.

Results: Compared to patients with lower quartiles of the WBC, those with higher quartiles of the WBC were with higher systolic blood pressure, diastolic blood pressure, and higher levels of neutrophils, lymphocytes, eosinophils, triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol, 24 hours proteinuria, complement component 3 and complement component 4, as well as a lower level of estimated glomerular filtration rate (eGFR) (P<0.05). In addition, patients with higher quartiles of the WBC were with higher proportion of sclerosis in renal biopsy (P=0.03). During a median follow up of 50 months, 47 (8.7%) patients were found to achieve renal progression endpoint. The highest quartile of WBC was associated with higher risk of long-term renal progression (HR, 3.90; 95% CI, 1.23 - 12.4) after adjusting for potential confounding factors, and this result was still observed when using WBC as a continuous variable (HR, 1.13; 95% CI, 1.01 - 1.23).

Conclusions: Our results suggest that the higher baseline level of the WBC is associated with the long-term renal progression in IgAN patients.

FR-P0744
Urinary Activin A: A Novel Biomarker Reflecting the Severity of Tubular Damage in IgA Nephropathy
Yoshihito Takei, Akito Maeshima, Shunsuke Takahashi, Masao Nakasatomi, Hidekazu Ikeuchi, Toru Sakairi, Yoriaki Kaneko, Keiji Hiromura, Yoshihisa Nojima. Dept of Medicine and Clinical Science, Gunna Univ Graduate School of Medicine, Maebashi, Gunma, Japan.

Background: Activin A, a member of TGF-β superfamily, is known to regulate cell growth and differentiation in various tissues. It has been reported that activin A modulates ureteric bud branching in kidney development, inhibits tubular regeneration after renal ischemia, and acts as a potent inducer of renal fibrosis in rodents. However, the role of activin A in kidney diseases remains unknown in human. To address this issue, we analyzed renal biopsy specimens and urine from patients with IgA nephropathy (IgAN).

Methods: Ninety-two patients with biopsy-proven IgAN who were treated in our department from 2011 and 2015 were included in this study. Patients were categorized into 4 groups according to estimated GFR (≥60 versus <60 ml/min/1.73m²) and proteinuria (<0.5 versus >0.5 g/gCr). Serum and urine activin A were measured by ELISA. Correlation of urinary activin A with urinary N-gal, urinary KIM-1, renal functions and urinary protein levels were analyzed. The localization of activin A in renal biopsy specimens from IgAN patients was examined by immunostaining. Normal kidney specimens from patients who underwent nephrectomy were used as controls.

Results: Urinary activin A was almost undetectable in healthy volunteers, but was significantly increased in IgAN patients categorized into high-risk group (eGFR<60, U/P-Cr≥0.5 g/gCr) (9.6 ± 2.3 vs. 37.5 ± 9.6 mg/mgCr, p<0.001). There was a significant correlation of urinary activin A level with urinary N-gal and KIM-1. Urinary activin A level was negatively correlated with eGFR, but not with urinary protein level. Activin A was localized in the cytoplasm of distal tubules of normal kidneys. In contrast, activin A was present not only in distal tubules, but also in the apical lumen of proximal tubules in patients with IgAN.

Conclusions: These data suggest that urinary activin A is a new biomarker reflecting the severity of tubular damage in IgAN.

Funding: Pharmaceutical Company Support - Astellas Pharma Inc.
FR-PO746
Low White Blood Cell Count Is Independently Associated with the Progression of Chronic Kidney Disease in the Elderly: The CKD-ROUTE Study
Yohei Araki,1 Eiichiro Kanda,2 Soichiro Iimori,1 Shotaro Naito,1 Yumi Noda,1 Sei Sasaki,1 Eisei Sohara,1 Tomokazu Okado,1 Tatetsumi Rui,1 Shintani Uchida,11 Dept of Nephrology, Graduate School of Medicine, Tokyo Medical and Dental Univ, Tokyo, Japan; 2Dept of Nephrology, Tokyo Kyosai Hospital, Tokyo, Japan; 3Dept of Nephrology, Tohge Memorial Nakanoh General Hospital, Tokyo, Japan.

Background: Elevated white blood cell (WBC) count is a well-known predictor of the progression of chronic kidney disease (CKD). However, particularly in elderly patients, it is not uncommon for them to present with low WBC count rather than developing high WBC count in response to various morbidity states. Therefore, we hypothesized that not only high WBC count but also low WBC count may be associated with the progression of CKD in the elderly.

Methods: A prospective cohort derived from three-year follow-up data of the CKD Research of Outcomes in Treatment and Epidemiology (CKD-ROUTE) study was conducted in the present study. Participants aged over 60 years with pre-dialysis CKD stage G2-G5 were eligible. They were stratified into three groups based on WBC count using tertiles (T). The primary outcome was a composite of end-stage renal disease (ESRD) and 50% reduction in estimated glomerular filtration rate (eGFR). Data were analyzed using Cox proportional hazards model with adjustments for baseline characteristics.

Results: We enrolled 761 patients (males, 69%). Median WBC count was 6100 cells / high-power field (T1: <5000, n = [missing]248; T2: 5000-6900, n = [missing]250; T3: ≥6900, n = 263). During a median follow-up of 854 days, the primary outcome was observed in 181 patients (T1: 86, T2: 61, T3: 34). Not only T3 but also T1 had significantly higher hazard ratios (HR) for the primary outcome than T2 (HR 1.54, 95% confidence interval 1.02-2.33). During a median follow-up of 90.0 months (TQR: 62.1-113.7), Loss of renal function was defined as ≥50% loss of GFR from baseline, doubling of serum creatinine, Dialysis or death. Multivariable associations between crescent and loss of renal function were examined by Cox proportional-hazards regression. Renal survival curves were generated with the Kaplan–Meier method.

Results: Of the 1054 subjects (59.3% women, mean age (33.4±9.9) years, mean proportion of crescent (13.2%±15.7%), mean GFR (98.0±35.5). Pathological indicators of activity indexes such as mesangial proliferation, glomerular sclerosis, tuft necrosis and chronic pathological changes such as tubular atrophy/intertstitial fibrosis showed statistical difference in four groups, with an increasing of crescent proportion, degree of pathological further aggravate (P<0.05). There were significant difference in the Lee’s classification and the Oxford classification (P<0.05). Progression to renal failure was observed in 106 (10.3%) patients. After multivariable adjustment, crescent (≥25%) was significantly associated with an increased risk of developing the loss of renal function (P=0.03). A Kaplan-Meier plot showed statistical difference in four groups in survival rate (P=0.004).

Conclusions: There is a certain correlation between the crescent lesion and the clinical-pathological features, which can reflect the degree of disease progression to a certain extent. Higher proportion of crescent lesion (≥25%) is an independent risk factor for progression to Loss of renal function in IgAN.

FR-PO747
Japanese Histologic Grade but the Oxford Classification Could Predict Renal Outcome in Japanese IgA Nephropathy Patients
Ahmad Basere Khatam, Yoshinori Yasuda, Takayuki Katsuno, Shoichi Maruyama. Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya City, Aichi Prefecture, Japan.

Background: The Oxford classification (Oxford) is globally used, however it has not been fully validated among Japanese patients with IgAN nephropathy (IgAN). The aim of this study is to elucidate utility of Oxford and Japanese histologic grade (JHG), used in nationwide renal biopsy registry by Japanese Society of Nephrology, to predict renal outcome in Japanese IgAN patients.

Methods: This is a retrospective cohort study of 91 adult IgAN patients diagnosed in Nagoya University Hospital between 2001-2009 and followed up 1 year. Five cases with ≤8 glomeruli were excluded. Oxford and JHG were evaluated by 6 independent specialists. In this study, Oxford and JHG were evaluated by 6 independent specialists. In total, 1054 patients were diagnosed with IgAN in Hangzhou hospital, including the last 1054 subjects (59.3% women, mean age (33.4±9.9) years, mean proportion of crescent (13.2%±15.7%), mean GFR (98.0±35.5). Pathological indicators of activity indexes such as mesangial proliferation, glomerular sclerosis, tuft necrosis and chronic pathological changes such as tubular atrophy/intertstitial fibrosis showed statistical difference in four groups, with an increasing of crescent proportion, degree of pathological further aggravate (P<0.05). There were significant difference in the Lee’s classification and the Oxford classification (P<0.05). Progression to renal failure was observed in 106 (10.3%) patients. After multivariable adjustment, crescent (≥25%) was significantly associated with an increased risk of developing the loss of renal function (P=0.03). A Kaplan-Meier plot showed statistical difference in four groups in survival rate (P=0.004).

Conclusions: There is a certain correlation between the crescent lesion and the clinical-pathological features, which can reflect the degree of disease progression to a certain extent. Higher proportion of crescent lesion (≥25%) is an independent risk factor for progression to Loss of renal function in IgAN.

FR-PO748
Clinico-Pathological Characterization and Outcome of IgAN with Crescent
Dong-Rong Yu, Qi-Ke Sun, Yun-Qin Hu, Fei Jiang, Jun Wu, Yong-Jun Wang.1 Hangzhou Hospital of Traditional Chinese Medicine; 2Zhejiang Chinese Medical Univ.

Background: We examined the relations of crescent with clinic-pathological features and loss of renal function in IgAN.

Methods: 1054 patients with IgAN in Hangzhou hospital of traditional Chinese medicine between 2001 and 2007 were retrospectively studied. We divided 1054 patients who were diagnosed with IgAN into three groups based on their having mild (<10%; n = 271), moderate (>10% and ≤25%, n = 182), or severe (>25%; n = 46) proportion of crescent lesion at diagnosis, compared with 555 cases without crescent formation as control group. Ratios of decline in renal function was compared among the four groups during a median follow-up of 90.0 months (IQR: 62.1-113.7). Loss of renal function was defined as ≥50% loss of GFR from baseline, doubling of serum creatinine, Dialysis or death. Multivariable associations between crescent and loss of renal function were examined by Cox proportional-hazards regression. Renal survival curves were generated with the Kaplan–Meier method.

Results: Of the 1054 subjects (59.3% women, mean age (33.4±9.9) years, mean proportion of crescent (13.2%±15.7%), mean GFR (98.0±35.5). Pathological indicators of activity indexes such as mesangial proliferation, glomerular sclerosis, tuft necrosis and chronic pathological changes such as tubular atrophy/intertstitial fibrosis showed statistical difference in four groups, with an increasing of crescent proportion, degree of pathological further aggravate (P<0.05). There were significant difference in the Lee’s classification and the Oxford classification (P<0.05). Progression to renal failure was observed in 106 (10.3%) patients. After multivariable adjustment, crescent (≥25%) was significantly associated with an increased risk of developing the loss of renal function (P=0.03). A Kaplan-Meier plot showed statistical difference in four groups in survival rate (P=0.004).

Conclusions: There is a certain correlation between the crescent lesion and the clinical-pathological features, which can reflect the degree of disease progression to a certain extent. Higher proportion of crescent lesion (≥25%) is an independent risk factor for progression to Loss of renal function in IgAN.

FR-PO749
Associations of Echocardiographic Measures with Rapid Kidney Function Decline among African-Americans: The Jackson Heart Study
Leila R. Zelnick,1 Ronit Katz,2 Bessie A. Young,1 Adolfo Correa,3 Bryan K. Kestenbaum,1 Ian H. De Boer,3 Nisha Bansal.1 Univ of Washington; 2Univ of Mississippi.

Background: Heart failure (HF) is common in African-Americans. Structural cardiac abnormalities precede its clinical presentation, including greater left ventricular mass (LVM), greater pulmonary artery systolic pressures (PASP) and lower ejection fraction (LVEF). These subclinical measures, measured by echocardiogram, may also be associated with longitudinal kidney function decline.

Methods: We studied 2,405 African-American participants in the Jackson Heart Study (JHS) who had available echocardiograms at baseline and longitudinal measures of kidney function. LVM, PASP and LVEF were quantified from baseline echocardiograms. Estimated glomerular filtration rate (eGFR) was calculated from the creatinine-based CKD-EPI equation. Rapid kidney function decline (RKFD) was defined as >30% over a mean of 8 years, and incident CKD was defined as development of eGFR ≤60 ml/min/1.73m² and eGFR decline >1 ml/min/1.73m²/year among CKD-free participants at baseline. Logistic regression models were adjusted for demographics, physical characteristics, comorbidities and medication use.

Results: Of the 1054 subjects (59.3% women, mean age (33.4±9.9) years, mean proportion of crescent (13.2%±15.7%), mean GFR (98.0±35.5). Pathological indicators of activity indexes such as mesangial proliferation, glomerular sclerosis, tuft necrosis and chronic pathological changes such as tubular atrophy/intertstitial fibrosis showed statistical difference in four groups, with an increasing of crescent proportion, degree of pathological further aggravate (P<0.05). There were significant difference in the Lee’s classification and the Oxford classification (P<0.05). Progression to renal failure was observed in 106 (10.3%) patients. After multivariable adjustment, crescent (≥25%) was significantly associated with an increased risk of developing the loss of renal function (P=0.03). A Kaplan-Meier plot showed statistical difference in four groups in survival rate (P=0.004).

Conclusions: There is a certain correlation between the crescent lesion and the clinical-pathological features, which can reflect the degree of disease progression to a certain extent. Higher proportion of crescent lesion (≥25%) is an independent risk factor for progression to Loss of renal function in IgAN.
Mean (SD) age and eGFR were 52.2 (11.9) years and 87.4 (17.1); 37% of participants were male. Higher LVM was significantly associated with RFKD and incident CKD; a sex, LVM interaction was not significant in continuous models. The association with RFKD, but not incident CKD, remained statistically significant after multivariable adjustment. There was no association of LVEF or PASP with either RFKD or incident CKD in multivariable models.

Conclusions: Among African-Americans in a community-based cohort, greater LVM was significantly associated with RFKD. Further studies are needed to determine whether treating risk factors for left ventricular hypertrophy may also reduce risk of progression of kidney disease in this high-risk population.

Funding: NIDDK Support, Other NIH Support - The Jackson Heart Study is supported by contracts HHSN26820130046C, HHSN26820130047C, HHSN26820130048C, HHSN26820130049C, HHSN26820130050C from the National Heart, Lung, and Blood Institute and the National Institute on Minority Health and Health Disparities, VA Support

FR-PO750

Moderate Elevated Blood Selenium Is Associated with Reduced Risk of Renal Function Decline

Hao Zhang, 1,2 Yi Fang, 1,2 Xiayong Zhang, 1,2
1 Dept of Nephrology, Zhongshan Hospital, Fudan Univ, Shanghai, China; 2 Shanghai Inst of Kidney Disease and Dialysis, Shanghai, China; 1 Kidney and Blood Purification Laboratory of Shanghai, Shanghai, China.

Background: Although the benefit of selenium (Se) supplementation for patients with end-stage renal disease was supported by many studies, it is not clear whether elevated blood Se could or could not improve renal function among general people. The purpose of this study is to examine the relationship between Se states and glomerular filtration rate (GFR) among general adults.

Methods: We conducted a cross-sectional analysis using 2011-2012 National Health and Nutrition Examination Survey (NHANES), and a total of 4885 persons 20 years or older were included. Whole blood Se were measured by inductively coupled plasma mass spectrometry. Renal function decline was defined as estimated GFR (CKD-EPI) <60 mL/min/1.73m². Logistic regression was applied to assess the association between blood Se levels and risk of renal function decline.

Results: The mean of blood Se of the all the 4885 participants was 193.3±27.5 μg/L, and all of them were above the Se deficiency, i.e. 98 μg/L. The mean Se concentrations for persons with eGFR≥90, 60-89, 50-59 and <30 mL/min/1.73m² were 193.8±21.4, 194.5±25.8, 186.8±28.5 and 177.3±24.0 μg/L, respectively. Compared to the lowest quintile of blood Se, the age-, gender- and race- adjusted odds ratios (ORs) were 0.88 (95% confidence interval 0.63-1.22) for the 2nd quintile, 0.61 (0.43-0.87) for the 3rd quintile, 0.60 (0.42-0.85) for the 4th quintile and 0.59 (0.41-0.85) for the highest quintile.

Conclusions: Even for the persons with relatively low but normal Se levels, moderate elevated blood Se was associated with reduced risk of renal function decline, but further elevated Se concentration, e.g. > 200 μg/L, may not have additional benefit for renal function.

Funding: Government Support - Non-U.S.

FR-PO751

Elevated Bilirubin Level Is Associated with Better Renal Prognosis

Soo Hwang, 1 Jin Ho Park, 2 Jin Hyuk Kim, 3 Chun Soo Kim, 1 Yon Suk Kim, 1 Jung Pyo Lee, 2 1Dept of Internal Medicine, Seoul National Univ Hospital, Korea; 2 Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Korea; 3 Dept of Internal Medicine, Chung-Ang Univ, Korea.

Background: Protective effect of bilirubin on kidney injury was reported in patients with diabetes mellitus or Gilbert syndrome, and its role as an antioxidant was claimed as the reason. However, whether mildly elevated bilirubin is related to renal prognosis in more generalized population was scarcely described.

Methods: We assessed a cohort with reference range value of total bilirubin which visited for screening coronary artery CT scans. Patients who had major adverse cardiovascular events and follow-up duration less than 1 month were excluded from the study. The primary outcome was 30% reduction of eGFR from baseline, and the secondary outcome was a composition of doubling of serum creatinine, eGFR halving and a start of dialysis. Next, in vivo experiment with C57BL/6 mice was done to investigate the protective effect of intraperitoneal bilirubin treatment on kidney fibrosis by unilateral ureteral obstruction (UUO) model. The relationship between bilirubin treatment and activation of the HIF-1 pathway was also evaluated.

Results: A total number of 1,128 patients were included in our cohort. The study group who had relative hyperbilirubinemia (total bilirubin 0.8-1.2mg/dL) showed better renal prognosis in terms of the primary outcome (adjusted hazard ratio (HR) 0.332, 95% CI 0.162-0.679, P<0.003) and the secondary outcome (adjusted HR 0.141, 95% CI 0.026-0.791, P=0.026). Moreover, mice treated with bilirubin showed less fibrosis in UUO model (P<0.05) and decreased fibrosis markers such as TGF-β or FSP1 (P<0.01). Lastly, intraperitoneal bilirubin treatment led increment in HIF1α (P=0.01) and HIF1β (P<0.05).

Conclusions: Relative hyperbilirubinemia even within reference range level showed a protective effect on renal dysfunction progression. Intraperitoneal bilirubin treatment decreased kidney fibrosis and upregulated HIF-1 pathway in vivo experiment. Therefore, bilirubin could be a potential therapeutic target to ameliorate kidney fibrosis by reducing oxidative stress injury.

Funding: Other NIH Support - NIEHS

FR-PO752

Differential Effects of Nicotine on the Cortical Production of Prostaglandins in Rats with Chronic Kidney Disease

Gabriel Rezonovszky, 1 Philip H. Chumley, 2 Helena Furberg-Barnes, 3 Irene Orlov, 3 Edgar A. Jaimes. 1 Dept of Nephrology, Univ of Alabama at Birmingham; 2 Renal Service, Memorial Sloan Kettering Cancer Center.

Background: Cigarette smoking is a risk factor in the progression of CKD. Nicotine (N), a major component of tobacco, worsens renal injury in 5/6 nephrectomy rats (Nx), a well-validated model of CKD (AJP-12). As we have shown, COX2 inhibition reduces renal injury in Nx rats on nicotine (ASN’13). In these studies we determined the effects of nicotine on the cortical production of prostaglandins (PGs) in normal rats and in rats with CKD.

Methods: Male SD rats were divided in five groups (n=7): Sham (S), S+0.1 g/ml L, DW, S+N=COX-2 inhibitor (NS, 1.5 mg/kg/day, SQ), Nx, Nx+N, Nx+N+NS, Nx+NS for 12 weeks. Rats were euthanized after 12 weeks and kidney cortex snap frozen and saved for PGs measurement by mass spectrometry (ng/g wet weight).

Results: Nicotine increased production of PGE2, PG12 and in sham that was inhibited by NS. Nx resulted in increases in the cortical production of all PGs studied. Nicotine significantly reduced the production of PGE1, PG12 and PG2 in Nx rats but not of TXB2 (Table). NS reduced the production of PGs in Nx groups suggesting COX2 as the is the main source of PGs in this model.

Funding: Other NIH Support - NIEHS

FR-PO753

Association between Gestational Diabetes and Maternal Chronic Kidney Disease

Elizabeth W. Dehner, 1 Milind A. Phadnis, 2 Corna E. Lewis, 3 Holly J. Kramer, 3,1 Erica P. Gundersen, 1 1Univ of North Carolina Gillings School of Public Health; 2Univ of Kansas School of Medicine; 3Univ of Alabama at Birmingham; 4 Loyola Univ Chicago, 5 Kaiser Permanente Northern California.

Background: Gestational diabetes mellitus (GDM) is associated with subsequent type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease for affected women. We analyzed whether GDM was associated with incident chronic kidney disease (CKD), controlling for pre-pregnancy risk factors for both conditions.

Methods: A total of 820 women without diabetes enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study who were nulliparous at baseline in 1985-1986 and reported at least one pregnancy during 25 years of follow-up were studied. GDM was self-reported. CKD was defined as development of estimated glomerular filtration rate < 60 mL/min/1.73m² or urine albumin to creatinine ratio ≥ 25 mg/g. Hazard ratios (HR) for developing CKD were compared between women with and without history of GDM using complementary log log models, beginning with first pregnancy and adjusting for pre-pregnancy age, systolic blood pressure, high density lipoprotein cholesterol, body mass index, smoking, education, kidney function, fasting glucose, and physical activity level as well as race and family history of diabetes. Interaction between race and GDM was also tested.

Results: Over mean follow-up of 20.8 years, N=101 women reported GDM and N=105 (58 black, 47 white) developed incident CKD, predominately confirmed by increased albumin excretion in the urine. The unadjusted HR (95% confidence interval (CI)) for CKD was 1.46 (0.87, 2.45) for women with GDM compared to parous women who did not report a pregnancy with GDM. There was evidence of a GDM-race interaction (Wald interaction p=0.07 in the fully adjusted model). The HR (95% CI) for CKD in the fully adjusted model was 1.96 (1.04, 3.67) for black women with GDM compared to those without GDM. Among white women, the HR (95% CI) was 0.65 (0.23, 1.83).

Conclusions: GDM may be associated with subsequent development of CKD among black women.
FR-PO754
Advanced CKD Is Associated with Higher Use of Insulin, Independent of Hemoglobin (Hb) AIC Levels and Duration of Type 2 Diabetes Mellitus (T2DM)  R. E. Boucher,1 Debra Lynn Simmons,1 Rabia Nadeem Kiani,1 Guo Wei,1 Tom Greene,1 T. S. Bjordahl,1 Linda F. Fried,3 Srinivasa Beddhu,3 1Univ of Utah; 2VA Pittsburgh.

Background: Need for insulin in T2DM might reflect decreased insulin secretion (beta cell dysfunction) and/or insulin resistance. Longer duration of T2DM might also result in exhaustion of beta cell insulin secretion. We hypothesize that more advanced CKD reflects a state of insulin secretion and/or insulin resistance, so that need for use of insulin is higher in more advanced CKD after accounting for T2DM duration and HbA1C.

Methods: We examined a cohort of 592,491 veterans with a diagnosis for T2DM (defined by ICD9 codes) and outpatient serum creatinine measured between 1/1/2010 and 12/31/2013. Data on filled medications were obtained from outpatient pharmacy database. Laboratory data were obtained from routine clinical labs. DM duration was obtained by identifying the first instance of ICD9 codes for DM or HbA1c≥6.5% or use of diabetes medications in the preceding 12 years. In a logistic regression model, eGFR stages, duration of DM and HbA1c levels were related to the use of insulin as the dependent variable adjusted for age, gender, race, CHF, lung disease, cancer, atherosclerotic conditions, SBP, DBP and BMI.

Results: Mean age was 67 ± 11 yrs. 96.6% were males and 16.9% were black. 28.0% were on insulin. Mean BMI was 32 ± 6 kg/m², mean eGFR was 74 ± 22 ml/min/1.73 m², mean HbA1c was 7.4 ± 1.7%, and mean diabetes duration was 5.8 ± 3.8 yrs.

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<th>Associations of eGFR groups, duration of diabetes and Hb1C with the use of insulin in veterans (N = 592,491)</th>
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Diabetes Duration (yrs)
<5 | Reference |
5-9 | 2.05 (2.02, 2.08) |
 ≥10 | 4.00 (3.92, 4.07) |
HbA1c (%)
<7 | Reference |
7.8-8.4 | 3.49 (3.44, 3.55) |
 ≥8.5 | 9.90 (7.93, 10.07) |

Conclusions: Worsening renal function is associated with greater use of insulin. This is observed even at eGFR levels (< 45) at which metformin use is not contraindicated.

Funding: NIDDK Support

FR-PO755
Renal Function in Kidney Cancer Patients: Effects of Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors Brian Charles Bouriquet,1 Emily C. Zabor,2 Ilya Glezerman,3 Edgar A. Jaimes,1 1Stanford Univ School of Medicine, Stanford, CA; 2Dept of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; 3Dept of Medicine, Div of Nephrology & Hypertension, Weill Cornell Medical College, New York, NY; 4Dept of Medicine, Renal Service, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: VEGF tyrosine kinase inhibitors (TKIs) have become first line therapy for metastatic renal cell carcinoma (mRCC). Their use leads to hypertension (HTN) in ≥30% of patients, but their effects on long-term renal function are not known. In addition, it has been suggested that the development of HTN is linked to treatment efficacy. The main objective of this study was to determine whether TKIs affect long-term renal function and the role of HTN on these effects.

Methods: This is a retrospective study of 130 mRCC patients who were treated with TKIs at MSKCC. Longitudinal measurements of serum creatinine were used to calculate the eGFR for each patient over time, for a median of 1.5 years among survivors. New or worsening HTN was defined by documented start or addition of antihypertensives.

Results: Overall, the use of TKIs in patients with eGFR < 60 ml/min or eGFR ≥ 60 ml/min did not result in significant changes in long term renal function.

FR-PO756
Histopathological Findings for Renal Progression Are More Pronounced in Upper Tract Urothelial Carcinoma Than in Renal Cell Carcinoma after Unilateral Nephrectomy Sheng-Wei Niu,1 Peir-In Liang,2 Ming-Yen Lin,1 Wei-Ming Li,1,4 Chun-Nung Huang,3,4 Wen-Jeng Wu,2,4 Li-Tzong Chen,2 Shiang-Jyh Huang,1 1Nephrology, Kaohsiung Medical Univ Hospital; 2Pathology, Kaohsiung Medical Univ Hospital; 3Urology, Kaohsiung Medical Univ Hospital; 4National Inst of Cancer Research; 5Faculty of Medicine, Kaohsiung Medical Univ.

Background: Patients with upper urinary tract urothelial carcinoma (UTUC) had high risk of chronic kidney disease or entering dialysis than renal cell carcinoma (RCC). We studied the pathological changes of renal tissue from nephrectomized kidney of UTUC and RCC, and compared the correlation between renal histopathology and progression to end-stage renal disease in these two groups of cancer patients.

Methods: This study included 132 cases of UTUC post ipsilateral nephrectomy and 61 cases of RCC post radical nephrectomy(RN). All of them were not yet on dialysis before surgery. The renal histopathology was read by 3 specialists: nephrologists or pathologist, independently. Clinical and laboratory data before surgery, whether entering into dialysis eventually, and dialysis-free days from surgery until December 31, 2014 were collected. We used logistic regression for tubulointerstitial (TI) nephropathy score and glomerular sclerosis(GGS) rates respectively, and Cox regression to investigate which factors affect renal survival.

Results: There were significantly higher TI nephropathy scores and greater abnormal GGS rates from nephrectomized kidneys of UTUC than from RCC. Kaplan-Meier survival curve showed five-year dialysis-free survival rate was 0.863 in UTUC group and 0.967 in RCC group. There were two major pathological factors, hypertension [HR(95%CI): 3.03(1.02-9.10), p=0.046] and abnormal GGS rate [HR(95%CI):2.88(1.01-8.17), p=0.047], for dialysis-free survival in UTUC group; but no factor in RCC group.

Conclusions: There were two major pathological factors, hypertension and abnormal GGS rate, for dialysis-free survival within 5 years in UTUC patients post ipsilateral NUX; but no specific risk factor in RCC patients.

Funding: Government Support - Non-U.S.

FR-PO757
The Impact of the Kumamoto Earthquake on Renal Parameters in CKD Patients Yushi Nakayama, Masataka Adachi, Hideki Inoue, Takashige Kusabara, Yuichiro Izumi, Yukata Kakizoe, Masashi Mukoyama.
Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.

Background: Disasters inevitably affect a number of diseases such as hypertension and kidney disease. A series of strong earthquakes attacked Kumamoto in central Kyushu, a southwest part of Japan, in April 2016. In this study, we evaluated the impact of the seismic disaster on CKD states during an early phase.
**Methods:** We analyzed blood and urine data from 225 out-patients with CKD (58±1.2 years), who visited our hospital during four weeks after the main shock. Systolic and diastolic blood pressures (sBP and dBP), pulse rate (PR), and body weight were also evaluated. These data were compared with preceding ones.

**Results:** Percentage of diabetic nephropathy (DN) was 12% and that of nephrotic syndrome was 14%. sBP and dBP did not change significantly (Fig. 1A). However, PR significantly reduced after the disaster (Fig. 1B). In sub-analyses evaluating the changes of each parameter between groups, sBP significantly increased in patients only in whose daily NaCl intake was not monitored (Fig. 2A). For patients under monitoring, NaCl intake before and after the disaster was almost equivalent (Fig. 2B). dBP significantly reduced in DN (−9.5±3.0% vs non-DN; +1.2±1.1%, p<0.01). Urine protein excretion (U-Pro) tended to increase during three weeks (Fig. 3A). U-Pro also tended to increase in male (+22.5±12.3% vs female; +8.7±5.2%, p=0.086) or patients who experienced evacuation (+33.9±24.9% vs no; +5.7±5.2%, p=0.089). Serum creatinine significantly increased in patients with nephrotic syndrome (Fig. 3B).

**Conclusions:** Regular monitoring of urinary NaCl excretion might ameliorate the increase of BP during disaster. Sex, evacuation, and nephrotic syndrome could affect renal parameters after the earthquake. Further analyses are needed to evaluate the long-term impact of earthquake on CKD.

**FR-PO759**

**Haptoglobin Genotype among Patients with IgA Nephropathy: Impact on Disease Progression and Response to Treatment**

Zaher Armaly,1 Nayef Mohamed Habbash,2 Kamal Hassan,2 Rawi Ramadan,2 Raymond Farah,4 Nephrology, E.M.M.S. Hospital, Bar Ilan Univ, Nazareth, Israel; 2Nephrology, Hadassah Medical Center, Jerusalem, Israel; 3Nephrology, Western Galilee Hospital-Nahariya, Israel; 4Nephrology, Rambam Health Campus, Haifa, Israel; 5Internal Medicine, Ziv Medical Center, Safed, Israel.

**Background:** IgA nephropathy (IgAN) is the most common primary glomerulonephritis, may progress to ESRD. Although the pace of decline in kidney function in IgAN is affected by proteinuria, hypertension, and low eGFR at the time of the diagnosis, the exact mechanisms underlying the pace of deterioration is still largely unknown. Recently, the role of genetic risk factors in the pathogenesis of IgAN is being elucidated. However, the impact of haptoglobin (Hp) genotype on the pace of progression of IgAN, is not well defined yet. Therefore, the current study examines whether Hp genotype influences disease progression and response to treatment.

**Methods:** The present study included 28 patients with IgAN (42.5±5.2 years old), 26 non-IgAN chronic kidney disease (CKD), 54 patients on hemodialysis, and 150 healthy subjects. Blood and urine samples were collected at baseline and 6 months after initiation therapy. Serum creatinine (SCr) and total proteinuria, were determined in all IgAN patients. Blood analysis for Hp genotype was performed for all subjects.

**Results:** Twenty nine percent of IgAN patients were Hp 1-1, 36% Hp 1-2, and 36% Hp 2-2. In contrast, in patients with non-IgAN chronic kidney disease the prevalence of Hp 1-1, Hp 2-2, and Hp 2-2 was 8%, 19%, and 73%, respectively. In hemodialytics patients, prevalence of Hp 1-1, Hp 2-1, and Hp 2-2 was 19%, 28%, and 54%, respectively. In healthy subjects, the distribution of Hp 1-1, Hp 2-1, and Hp 2-2 was 7%, 39%, and 54%, respectively. Interestingly, IgAN Hp 2-2 patients were more stable and responded better to treatment with routine therapy (RAS inhibitors or steroid) than other Hp genotype, as was evident by the extent of proteinuria and SCr.

**Conclusions:** Hp 2-1 genotype is more common in IgAN patients as compared with general population in Israel, and even more than CKD patients or subjects on HD. Patients with Hp 2-2 responded better to appropriate therapy. The mechanisms underlying this phenomenon remain to be explored.

**FR-PO760**

**Effects of Uric Acid and Inflammation on the Risk of Developing Chronic Kidney Disease in Female Rheumatoid Arthritis Patients**

Masako Kocchi,1 Kentaro Kohagura,2 Yusuke Ohy,3 1Dept of Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukus School of Medicine, Nishihara, Okinawa, Japan; 2Diaalysis Unit, Univ Hospital of the Ryukus, Nishihara, Okinawa, Japan; 3Dept of Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukus School of Medicine, Nishihara, Okinawa, Japan.

**Background:** Inflammation is a risk factor for progression of chronic kidney disease in the patients with in patients with rheumatoid arthritis as well as general population.Uric acid (UA) is suggested to promote inflammation. However, the combined effects of UA and inflammation on the risk of developing CKD are not known in RA. This study aims to examine the relationship between UA, C-reactive protein (CRP; a marker of inflammation), and the incidence of CKD in female RA patients.

**Methods:** We retrospectively examined a total of 284 female RA patients. The outcome of interest was incidence of CKD which was defined as an eGFR<60 ml/min/1.73 m² and/or positive dipstick testing for proteinuria for ≥3 months. High UA was defined >5.0 mg/dL, based on more than the highest quartile value at baseline and high CRP was defined as >4.9 mg/L, based on more than median value for the baseline CRP Patients were categorized into four subgroups by the presence of high UAand high CRP at baseline: lowUA and low CRP, lowUA and high CRP, highUA and low CRP, and high UA and high CRP.

**Results:** Mean baseline patient age was 57 years, and mean eGFR was 86 ml/minute/1.73 m². Over a median follow-up of 8 years, 41 (14%) patients developed CKD. High UA and high CRP were independently associated with the incidence of CKD, respectively. Subgroup analysis showed that the cumulative incidence of CKD was the highest in patients with high UA and high CRP group compared with all other groups (P = 0.002, log-rank test). In a multivariate analysis, high UA and high CRP was significantly associated with increased risk for incident CKD (adjusted HR, 3.9; 95% confidence intervals, 1.40–9.7; p=0.009) independent of age, eGFR at baseline, classical risk factors and anti-RA drug uses.

**Conclusions:** Independent of confounding risk factors, high UA had an inflammation-augmented association with increased risk of CKD in female RA patients.

**FR-PO761**

**Predictive Factors of Renal Outcome after Heart Transplantation**

Hye Jin Kwon, Subin Hwang, Jae Shin Choi, Jung Eun Lee, Wooseong Huh, Yoon-Goo Kim, Dae Joong Kim, Ha Young Oh, Hye Ryoun Jang. Nephrology Div, Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Korea.

**Background:** Cardiorenal syndrome (CRS) frequently occurs in end-stage heart failure patients waiting for heart transplantation (HT) and combined heart transplantation (CHT) is required in some patients. However, there have been few reports investigating predictive factors of renal outcome in patients receiving HT with no consensus for indication.
of HTK. In this study, we investigated the factors predicting renal outcome after HT in end-stage heart failure patients, focusing on changes in renal function and chronic kidney disease (CKD) evaluated 1 year after HT.

**Methods:** A single-center retrospective cohort study of 182 patients receiving HT from 1996 to 2015 was conducted. A total of 160 patients were followed for at least 1 year after HT. Primary outcomes were eGFR, \%ΔeGFR (100 X post-HT eGFR - pre-HT eGFR)/pre-HT eGFR, and CKD (eGFR < 60 mL/min/1.73m²) prevalence at 1 year after HT. The results of pre-transplant kidney ultrasound (US) images were scored as follows: normal (0), increased echogenicity (1), findings suggestive underlying CKD (2). Old age, preexisting CKD, and high kidney US image score were identified vs. -1 to <0 mL/min/1.73m² (multinomial odds ratios [95% CI] for eGFR slope <-10, -10 to <-5, -5 to <-1, and ≥ 0, respectively). The mean age of the cohort was 57.8 (11.3) years; 19% were African American and 27% were diabetic. Patients who received (vs. those who did not receive) TRT had experienced significantly lower risk of fast and very fast eGFR decline (logistic odds ratio [95% CI] for eGFR slope <-5 vs. >=-5 mL/min/1.73m²/year, 0.84 [0.81, 0.87]) (multinomial odds ratios [95% CI] for eGFR slope <-10, -10 to < -5, -5 to < -1, and ≥ 0, vs. -1 to 0 mL/min/1.73m²/year, 0.68 [0.63-0.73], 0.91 [0.87-0.95], 1.08 [1.06-1.11] and 0.93 [0.93-0.97], respectively) (Figure).

Conclusions: TRT is associated with lower risk of rapid eGFR decline. Further studies are needed to elucidate the underlying mechanisms and to determine whether testosterone replacement therapy could indeed be renoprotective.

**Funding:** NIDDK Support, VA Support

**FR-PO763**

**Diuretic Use and Type on Progression in Chronic Kidney Disease**

Claudia S. Cabrera,1 Jingrong Yang,2 Thida Tan,2 Bargur V. Stefanosson,1 Peter J. Greasley,3 Alan S. Go.2,4 *AstraZeneca; 5Kaiser Permanente Northern California.*

**Background:** Few studies have systematically evaluated medical therapies as potential risk factors for accelerated progression of CKD in “real world” populations. Conflicting data exist about the impact of diuretics outside clinical trials. In a large community-based Stage 3/4 CKD cohort, we evaluated the association between diuretic use and type with CKD progression and development of ESRD.

**Methods:** Within Kaiser Permanente Northern California, we identified adults with eGFR 15-59 mL/min/1.73m² by CKD-EPI between 2008-2012 who had no prior diuretic use or ESRD. Through 2012, we calculated the rate (per 100 P-Y) of the composite outcome of ESRD, reaching eGFR <15 mL/min/1.73m², or >50% reduction from baseline eGFR. New initiation of diuretic therapy and type was identified from comprehensive pharmacy claims and electronic medical records. Clinical and longitudinal medical therapies were obtained from electronic medical records. We used marginal structural models (MSM) with inverse probability weighting (IPW) to evaluate the impact of loop or thiazide diuretics on CKD progression after adjusting for baseline and time-dependent confounders (including heart failure episodes). IPW’s were calculated with and censoring for each 30-day period of follow-up and integrated into pooled logistic regression models to estimate the effect of new use of loop or thiazide diuretics.

**Results:** In 117,728 eligible adults with eGFR 15-59 mL/min/1.73m², mean age was 72 years (SD=13), 24% of persons of color and 25% with diabetes. Over mean follow-up of 3.7±1.3 years, the overall rate of the renal composite outcome was 1.47 per 100 P-Y (95% CI: 1.43-1.50). In MSM models, initiation of diuretics was independently associated with higher rates of CKD progression even after accounting for use of other cardiovascular and renal related medications and time-dependent confounders: thiazide diuretic (adjusted odds ratio [OR] 2.95, 95% CI 2.11-4.12) and loop diuretic (OR 1.47, 95% CI 1.23-1.74).

**Conclusions:** In a large, diverse, community-based Stage 3/4 CKD population, use of diuretics was independently associated with a higher risk of CKD progression, especially thiazide diuretics.

**Funding:** Pharmaceutical Company Support - AstraZeneca

**FR-PO764**

**Long Term Kidney Outcomes among Proton Pump Inhibitors Users with Acute Kidney Injury**

Yan Yan,1 Tingting Li,2 Hong Xian,1 Yan Yan,1 Ziyad Al-Al,1,2,3 *Clinical Epidemiology Center, VA Louis H. Stokes Cleveland HCS; 1Dept of Medicine, Washington Univ School of Medicine, Saint Louis, MO; 2Dept of Medicine, VA Louis H. Stokes Cleveland HCS, Saint Louis, MO.*

**Background:** Proton Pump Inhibitor (PPI) use is associated with increased risk of acute kidney injury (AKI), incident chronic kidney disease (CKD), CKD progression, and end stage renal disease (ESRD). PPI-associated CKD is presumed to be secondary to incomplete recovery of AKI. Whether long term adverse renal outcomes are mediated solely by occurrence of AKI is not known.

**Methods:** We used the Department of Veterans Affairs national databases to build a cohort of 158,574 incident users of acid suppression therapy: 137,310 PPI and 21,264 Histamine H2 receptor antagonists (H2 blockers) users with no history of AKI. Logistic regression models were built to estimate the association of PPI exposure and risk of incident CKD, CKD progression, and ESRD within cohort participants with and without AKI during follow up.

**Results:** After a follow-up of 5 years, among those who developed AKI, and compared to new users of H2 blockers, new users of PPI had 1.29 (1.20, 1.38), 1.24 (1.17, 1.32), and 1.19 (1.03, 1.39) odds of having incident CKD, eGFR decline >30%, and 50% decline in eGFR or ESRD, respectively. Among cohort participants without AKI, and compared to new users of H2 blockers, new PPI users had 1.34 (1.25, 1.42), 1.30 (1.23, 1.37), and 1.31 (1.15, 1.50) odds of having incident CKD, eGFR decline >30%, and 50% decline in eGFR or ESRD, respectively.

**Conclusions:** Our results demonstrate that PPI use is associated with significant higher odds of adverse long term renal outcomes in incident users of acid suppression therapy with AKI and without AKI. The first interventional study that identifies the role of PPI and AKI and long term renal outcomes may not be solely mediated by occurrence of AKI. Other possible pathways may include chronic incident renal damage caused directly by PPI or mechanisms related to PPI-induced hypogammaglobulinemia. Further investigation is necessary to elucidate the mechanisms linking PPI use and CKD.

**Funding:** VA Support

**FR-PO765**

**Red Cell Indices Are Not Indicative of Iron Deficiency in Children with Pre-Dialysis Chronic Kidney Disease**

Abdullahi Mudi,1,2 Cecil S. Levy.1,2 *1Div of Paediatric Nephrology, Univ of the Witwatersrand, Johannesburg, South Africa; 2Dept of Paediatrics, Bayero Univ, Kano, Nigeria.*

**Background:** Iron deficiency is common in children with chronic kidney disease (CKD). Clinicians in developing countries often rely on red cell indices (MCV, MCHC, RBCDw) as a screening tool for iron deficiency because serum iron parameter tests are either expensive or not readily available. We aimed to evaluate the use of red cell indices in screening for iron deficiency in a group of children with pre-dialysis CKD.

**Methods:** Ninety-four children with CKD stage 1–4 were reviewed for age, sex and current medications. Each patient had blood samples sent for FBC and Iron Studies. CRP was simultaneously sent to exclude inflammation.

**Results:** Eleven of the children were on iron supplement and were excluded from the analysis. None of the children had received blood transfusion within the last four months. Median age 10 years (IQR:7-13 years); male to female ratio 1.96:1; 9/83 had low Hb (<12g/dl); 43/83 had a low TSAT (<20%); 32/83 had a low ferritin (<30μg/l) and 20/83 had an absolute iron deficiency (low TSAT and low ferritin). 23/83 had functional iron deficiency (low TSAT and normal ferritin). There was no statistically significant difference in the mean values of the haemoglobin and red cell indices between patients with deplete (low TSAT and low ferritin) and not readily available. We aimed to evaluate the use of red cell indices in screening for iron deficiency in a group of children with pre-dialysis CKD.
FR-PO766
Anemia Prevalence and Treatment in Patients with Non-Dialysis-Dependent Chronic Kidney Disease

Wendy L. St. Peter, 1 Haifeng Guo, 1 Shaum Kabadi, 2 Sean Zhao, 2 David T. Gilbertson, 2 Louise Janice Sargent Heuer, 1 Yi Peng, 1 Trudy Pendergraft, 2 Suying Li 1
1 Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN; 2 AstraZeneca, Wilmington, DE.

Background: Relative little is known about the burden of anemia in stage 3-5 non-dialysis-dependent chronic kidney disease (NDD-CKD) patients. We evaluated anemia prevalence, treatment patterns, and cardiovascular (CV) outcomes in adults with stage 3-5 NDD-CKD.

Methods: We used Medicare and MarketScan® (commercial) claims data (10/1/2011 to 3/30/2012) to identify “older” (65+ yrs) and “younger” (18-64 yrs) CKD-NDD patients, respectively. During the baseline year from 10/1/2011 to 9/30/2012, anemia status (defined by diagnosis codes), patient demographics, and comorbidities were determined. We evaluated anemia treatment patterns [erythropoiesis-stimulating agents (ESAs), intravenous (IV) iron, and red blood cell (RBC) transfusions] after baseline anemia diagnosis. CV outcomes were identified during the 1-y follow-up period.

Results: There were 148,550 (52%) older and 15,716 (28%) younger patients with anemia among stage 3-5 NDD-CKD patients in Medicare and MarketScan databases, respectively. Prevalence increased as CKD stage and age increased and was generally higher among women. The most common form of treatment (at least 1 administration) for anemia was RBC transfusions (22.2% older, 11.7% younger) followed by ESA (12.7% older, 10.8% younger) and IV iron (6.7% older, 9.4% younger). Treatment across all modalities increased by CKD stage and age. Comorbidity burden and inflammatory conditions were more commonly observed among older patients relative to younger patients. Major adverse cardiac events and thromboembolic events (unadjusted) increased by CKD stage and were higher among patients with anemia versus those without.

Conclusions: Approximately half of Medicare stage 3-5 NDD-CKD patients have anemia; RBC transfusion was commonly used to treat anemia. Anemia treatment patterns differ by age; older patients received twice as many RBC transfusions as younger patients and were also more likely to receive treatment with ESAs. Investigation into effects of anemia treatment patterns on CV outcomes is warranted in this population.

Funding: Pharmaceutical Company Support - AstraZeneca

FR-PO767
Anemia Treatment Pattern Changes in Non-Dialysis-Dependent Chronic Kidney Disease Patients before and after Revised Food and Drug Administration Label and New Anemia Guidelines for Erythropoiesis-Stimulating Agents

Wendy L. St. Peter, 1 Haifeng Guo, 1 Shaum Kabadi, 2 Sean Zhao, 2 David T. Gilbertson, 2 Louise Janice Sargent Heuer, 1 Yi Peng, 1 Trudy Pendergraft, 2 Suying Li 1
1 Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN; 2 AstraZeneca, Wilmington, DE.

Background: Anemia in CKD: An Updated Systematic Review and Meta-Analysis

IRMA and Myoglobin stores were major components of oral iron monotherapy costs, as were drug acquisition costs and transport costs. Efficacy was the main driver of CE for all treatments. AE and medical management costs were major components of oral iron monotherapy costs, as were drug acquisition costs for the other treatments.

Conclusions: FER was found to be the more cost-effective treatment strategy for patients with anemia of chronic kidney disease (CKD) not on dialysis. It is not clear which is the best method of iron administration. A previous meta-analysis which included studies through 12/2010 showed a significant improvement in transferrin saturation (Tsat), ferritin, and hemoglobin (Hgb) levels with the use of intravenous (IV) iron. However, further studies addressing this have been inconsistent in showing a benefit of IV iron over oral iron supplementation.

Funding: Pharmaceutical Company Support - AstraZeneca

FR-PO768
Cost-Effectiveness Analysis of Intravenous Ferumoxytol for Treatment of Iron Deficiency Anemia in Adult Patients with Non-Dialysis-Dependent Chronic Kidney Disease (ND-CKD)

Naomi V. Dahl, 1 William Strauss, 1 Robert F. Kaper, 1 Frank A. Corvino, 2 Marko Zirkovic, 1 1 AMAG Pharmaceuticals, Inc., Waltham, MA; 2 Genesis Research, Hoboken, NJ.

Background: Treatment of iron deficiency anemia (IDA) in CKD patients requires oral or IV iron replacement therapy, with or without simultaneous use of erythropoietin stimulating agents (ESAs). Ferumoxytol (FER) has demonstrated superior efficacy to oral iron in clinical trials.

Methods: A previous meta-analysis which included studies through 12/2010 showed a significant improvement in transferrin saturation (Tsat), ferritin, and hemoglobin (Hgb) levels with the use of intravenous (IV) iron. However, further studies addressing this have been inconsistent in showing a benefit of IV iron over oral iron supplementation.

Funding: Pharmaceutical Company Support - AstraZeneca

FR-PO769
Intravenous versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-Analysis

Xavier Perez Hernandez, 1 Sumeet Munjal, 1 James W. Lohr, 1 Pradeep Arora, 1 Irfan Ahmed Moinuddin, 1 Medicine, SUNY at Buffalo, Buffalo, NY; 2 Nephrology, VA Medical Center, Buffalo, NY; 3 Nephrology, VA Medical Center, Richmond, VA.

Background: Iron supplementation is essential for the treatment of patients with anemia of chronic kidney disease (CKD) not on dialysis. It is not clear which is the best method of iron administration. A previous meta-analysis which included studies through 12/2010 showed a significant improvement in transferrin saturation (Tsat), ferritin, and hemoglobin (Hgb) levels with the use of intravenous (IV) iron. However, further studies addressing this have been inconsistent in showing a benefit of IV iron over oral iron supplementation.

Funding: Pharmaceutical Company Support - AMAG Pharmaceuticals, Inc.
Hgb level (RR, 1.44, 95% CI, 1.13 to 1.82). ferritin level (weighted mean difference, 22.2 mg/L, 95% CI, 15.7 to 29.1 L), and Trs level (weighted mean difference, 2.99 mg/dL, 95% CI, 1.49 to 4.49).

Conclusions: Our review shows that CKD patients not on hemodialysis therapy have better Hgb level response when treated with IV iron.

FR-PO770
Serum Level of Soluble Fas Is a Predictor of Need for Red Blood Cells Transfusion in Patients with Chronic Kidney Disease

Methods: We conducted a prospective study with 56 pre-dialysis patients for 144 months (Jan/2004-Dec/2015). Need for RBCs transfusion was the primary outcome. Serum sfas, IL-6, PTH, level, Epo, level, EPO, Hb, Ht, iron status and use of hHuEPO were analyzed at baseline. Correlation between the variables and multivariate regression with Hb-dependent variable were performed on admission and binary logistic regression for RBCs transfusion were performed at the end of follow up with sfas, EPO, ferritin saturation(Tsat), IL-6 and Epo.

Results: Our population at baseline was 56+13 yo, 65,5% (35) males; diabetes and hypertension were the leading causes of kidney failure; HB 12.5±2.3g/dL, Hct 37±7%, Trs 23±14%, ferritin 123±119ng/ml, EPO-CKD 34±14ml/min, sfas 3121±1299pg/ml, Epo 11±10pg/ml, IL-6 7.0 ± 6.4pg/mL, PTH 200 ± 178pg/ml. There was a positive correlation between Hb and EPI-CKD (r=0.35; p=0.009), Hb and Trs (r=0.14; p=0.09) and a negative association between Hb and sfas (r=0.35; p=0.008) and Hb and PTH (r=0.32; p=0.03).

Conclusions: Serum sfas level is associated with anemia and is an independent predictor of need for RBC transfusion in CKD patients.

FR-PO771
Achieving Target Haemoglobin with Single High-Dose Iron Infusion: Predicting the Optimal Approach in Non-Dialysis Chronic Kidney Disease

Methods: This retrospective analysis of 197 patients examined the Hb response to a single infusion of iron isomaltoside. Individual doses were calculated from the Ganzoni equation (with a target Hb set at 110g/L and iron stores set at 500mg) to a maximum single infusion of iron isomaltoside. Individual doses were calculated from the Ganzoni equation.

Of the 197 patients analysed who received high-dose iron infusion between Oct 2012 and Apr 2016, one patient developed an adverse drug reaction (ADR); rash. Subsequent doses in this cohort resulted in 264 infusions with no further reported ADR. No patients had angioedema or required stopping the infusion, hospitalisation or medical intervention. Both ESA and non-ESA treated patients equally achieved aspirational Hb level. We calculated an indicative adjustment to the iron dose that may improve Hb target achievement to direct future dosing decisions. The higher indicative dose in the non-ESA group reflects the lower baseline iron stores (ferritin and TSAT).

Conclusions: A high-dose, low-frequency approach to IV iron can effectively achieve aspirational Hb levels in non-dialysis CKD patients. This is equally achievable in both ESA and non-ESA treated patients. Further analysis of dosing strategies are needed to predict the appropriate IV iron dose to achieve Hb levels and to evaluate the long-term safety of a HDLF approach.

FR-PO772
The Mortality Risk Associated with Functional Iron Deficiency in the U.S. Veterans with CKD

Methods: We performed a historical cohort study using the Veterans Affairs Informatics and Computing Infrastructure. We identified a CKD cohort (MDRD eGFR <60 mL/min/1.73m²) with at least one set of iron indices between 2006-2015. The clinical characteristics were determined from the ICD-9 codes and laboratory data during the baseline period, defined as the year preceding the first available iron indices. Patients with baseline hematologic disorders, ESRD, organ transplantation, and cancer were excluded. The cohort was divided into 4 iron groups based on the joint quantiles (Q) of transferrin saturation (TSat) and ferritin: 1st quartile Q1 = 35%-54%, 2nd quartile Q2 = 55%-71%, 3rd quartile Q3 = 72%-90%, 4th quartile Q4 = 91%-100%

Conclusions: A high-dose,low-frequency approach to IV iron can effectively achieve aspirational Hb levels in non-dialysis CKD patients. This is equally achievable in both ESA and non-ESA treated patients. Further analysis of dosing strategies are needed to predict the appropriate IV iron dose to achieve Hb levels and to evaluate the long-term safety of a HDLF approach.

FR-PO773
Lowering Diastolic Blood Pressure Was Associated with Higher Incidence of Chronic Kidney Disease in General Population Only in Those Using Antihypertensive Medication

Methods: Using national health check-up database from 2008 to 2011 in the general Japanese population aged 39 to 74 years, we evaluated the association between DBP and incidence of CKD 2 years later in 128,005 participants without CKD (proteinuria and/or eGFR <60, ml/min/1.73m²). DBP was categorized by every 5mmHg from the lowest

Conclusions: FID is significantly more prevalent in patients with diabetes and CV disease and is strongly associated with all-cause mortality risk in CKD.

Funding: Private Foundation Support.
(<60mmHg) to the highest category (>100mmHg), and was further stratified into those with (med+) and without antihypertensive medication (med-). We calculated odds ratio (OR) for estimated adjusted risk of developing CKD using logistic regression model.

**Results:** Participants including 62% of female and 25.9% of med+ had mean age of 70.09 years, 54% (371) male, with a mean eGFR of 78.2±13.4 and DBP of 76±11mmHg. Two years later, 12.4% (G1) and 14.1% (G2) had developed CKD. Compared to meds- with DBP 60-64mmHg, multivariate analysis showed no difference in risk of developing CKD among meds-, but significant difference in most DBP category of meds+ especially in the lowest category showing the highest risk (OR 1.51, 95%CI 1.14 to 1.99). The risk decreased as the DBP rose with (meds+) and without antihypertensive medication (meds-). In subgroup analysis, meds+ similarly showed CKD risk reduction as DBP rose (p for trend 0.02), with significant difference among categories in part, but no difference was seen among any DBP in meds-. Analysis of CKD patients who rated their general health as ‘much better’ to ‘much worse’.

**Conclusions:** Lower DBP was associated with higher risk of developing CKD only in those taking antihypertensive medication.

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**FR-PO774**

The Minimum Clinically Important Difference in the Incremental Shuttle Walk Test following a 12 Week Exercise Intervention in Chronic Kidney Disease

**Background:** Chronic kidney disease (CKD) patients have poor cardiorespiratory capacity which limits physical performance and is strongly associated with outcome. The incremental shuttle walk test (ISWT) is a popular and well-defined field test to assess this but has not been validated in CKD. For clinical and research outcome measures, the minimum clinically important difference (MCID) is ‘the smallest change important to patients’ and is more relevant than ‘statistically significant’ changes which merely indicate that a change did not occur by chance. We aimed to establish the MCID in the ISWT after an exercise intervention in non-dialysis CKD.

**Methods:** 23 CKD patients (10 male, mean age 59 (27–80) years, eGFR 25 (8–41) ml/min/1.73m²) undertook 30 minutes supervised aerobic and resistance exercise training thrice weekly for 12 weeks. Participants completed the ISWT at baseline and end of study. MCID was estimated using a patient centred anchor-based approach. Patient’s perception of change of ISWT change using the 36-item Short Form Survey was completed after the exercise programme, patients were asked to identify, on a 5-point Likert scale, their perceived change in general health (‘much better’ to ‘much worse’).

**Results:** Mean baseline ISWT was 431 (SD: 232) m, which increased to 474 (SD: 227) m (+43m (CI: 17–68)) after the exercise intervention (P = 0.002). Using an anchor-based analysis, for participants who rated their general health as ‘somewhat better’, the mean improvement in the ISWT was 60m (CI: 27–93), or 14%. Conversely, in the participants who rated their general health as ‘somewhat worse’, the mean difference was -25m.

**Conclusion:** The MCID in the ISWT following an exercise intervention in CKD is 60m. This corresponds well with the ISWT MCID in patients completing cardiac (70m) and pulmonary rehabilitation (48m). This value will inform the design of clinical trials, and aid clinicians in the interpretation of meaningful ISWT changes in CKD after medical and lifestyle interventions in both clinical and research settings.

**Funding:** Private Foundation Support

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**FR-PO777**

Waist Circumference and LDL-Cholesterol and the Incidence of Chronic Kidney Disease in the Healthy Young- to Middle-Aged Working Men in Japan

**Background:** Identifying modifiable risk factors is crucially important for reducing the burden of chronic kidney disease (CKD) in the working age population. We aimed to examine the association of lifestyle-related clinical parameters with kidney function decline over 5 years in a cohort of healthy young- to middle-aged men with preserved estimated glomerular filtration rate (eGFR).

**Methods:** We enrolled 10,668 adult Japanese men (<60 years) who had worked at the two companies in a retrospective fashion. We selected the subjects whose basal eGFR (ml/min/1.73m²) was more than 60 from 90 to 99. We analyzed medical checkup data 5 years later, and examined changes of those data between the 2 time points. We defined the cut-off values of waist circumference (WC) as below 85 cm and serum LDL-cholesterol (LDL-C) as below 120 mg/dl, according to the definition of the metabolic syndrome in Japan Ministry of Health, Labour and Welfare.

**Results:** Mean age and eGFR were 49.9±10.3 years and 76.2±7.8 at baseline. The 773 males (7.2%) who had developed to CKD 5 years later. There was a significantly higher risk of CKD in men whose WC (OR=1.63, p<0.001) or LDL-C (OR=1.78, p<0.001) remained elevated at the two points. In addition, healthy men whose WC or LDL-C had become elevated over the cut-off value at 5 years later had a higher risk for CKD development (WC: OR=1.53, p<0.001; LDL-C: OR=1.38, p<0.008). There was also a significantly lower rate of eGFR decline in men whose WC and LDL-C levels had been concomitantly normalized at 5 years later than those whose levels had been still elevated (<1.1±1.7 vs. -.3±6.6, 5, p=0.012).

**Conclusions:** These findings show that both WC over 85 cm and LDL-C over 120 mg/dl were risk factors for CKD development in adult men with 60-90 in eGFR. Because normalization of WC and LDL-C were related to a slower rate of eGFR decline, abdominal fatness and disturbed lipid profile could be a potentially modifiable risk factor in preventing CKD development in healthy young- to middle-aged working men.

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**FR-PO775**

Charlson Comorbidity Index - Impact on Hospitalization and Mortality in Chronic Renal Disease

**Background:** Chronic kidney disease (CKD) is a known risk factor for increased morbidity and mortality. Charlson comorbidity index (CCI) is the most extensively studied comorbidity index for predicting mortality and may help improving outcomes by identifying and treating patients earlier and more effectively. In this study we evaluated the correlation between CCI and hospital admissions in patients with chronic kidney disease and the influence of CCI on their mortality.

**Methods:** We included, in a retrospective observational study, 693 patients, with an eGFR <30 ml/min/1.73m², followed in a pre-dialysis clinic between 2008-2012. Four groups were created according to the CCI: G1 (n=172) CCI ≤ 5.2; G2 (n=162) CCI – 5.2-6.4; G3 (n=177) CCI – 6.5-7.4 and G4 (n=182) CCI ≥7.5. Descriptive statistics, ANOVA and chi-square tests were used for comparison between groups. Bonferroni test was used as a post-hoc test. Kaplan-Meier analysis was used to evaluate mortality in each group and Log Rank test for comparison between groups. To evaluate the relationship between CCI and the other variables we used a multivariate logistic regression.

**Results:** The mean age of our population was 70.09 years, 34% (371) male, with a mean eGFR (MDRD) of 20.2±19.2 ml/min. G1 patients were younger (p<0.001) and showed higher hemoglobin (p<0.001), eGFR (p=0.025), calcium (p=0.033) and albumin (p=0.001). In a multivariable logistic regression model adjusted to gender, age, haemoglobin, phosphorus, parathormone, eGFR, albumin and blood pressure, CCI is a risk factor of hospitalization (OR=1.362, CI 95% 1.175-1.580, p=0.001) and death (OR=1.243, CI 95% 1.053-1.467, p=0.010). Survival at 85 months was progressively shorter with higher CCI (G1 = 86.7%, G2 = 65.9%, G3=59.35 % and G4 = 30.4%, Log Rank = 34.46, p<0.001).

**Conclusions:** CCI provides a simple and valid method for classifying comorbidities and can be used as an instrument to predict patient’s survival/mortality as their kidney disease progresses.

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

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

Underline represents presenting author.

544A
Association between Weight, Abdominal Obesity, and Albuminuria: Results from NHANES 2003–2014

**Background:** Many conditions are related to albuminuria. However, the relationship between obesity and albuminuria is controversial. We aim to determine the prevalence of albuminuria by obesity status based on multiple complementary measures of adiposity in U.S. adults and examine the association between weight, abdominal adiposity, and albuminuria.

**Methods:** We analyzed data from U.S. adults aged 18 years and older examined in the National Health and Nutrition Examination Survey (NHANES) from 2003–2014. We excluded persons who were pregnant or had estimated GFR<15 ml/min per 1.73 m². We determined the prevalence of albuminuria (urine albumin-to-creatinine ratio [UACR]≥30 mg/g) among the total sample, and separately within the two BMI classes: normal weight (18.5≤BMI<25) or obesity (BMI≥30), and abdominal obesity status: defined by gender specific waist circumference relationship between adiposity, obesity, and albuminuria were evaluated using multivariable logistic regression.

**Results:** Among 28,468 adults who met inclusion criteria, 8.75% had UACR≥30 mg/g and 1.14% had UACR≥300 mg/g. Prevalence of having UACR≥30 mg/g in obesity, normal BMI, abdominal obesity, and normal waist are 11.43%, 7.32%, 8.75%, and 6.54%, respectively. In univariate model, obesity increases odds of having UACR≥30 mg/g (OR=1.43-1.87), and UACR≥300 mg/g (OR=1.79; 95% CI: 1.38-2.31). Abdominal obesity also increases odds of having UACR≥30 mg/g (OR=1.72; 95% CI: 1.51-1.95) and UACR≥300 mg/g (OR=1.93; 95% CI: 1.53-2.45). After adjusting for age, gender, race, history of hypertension, history of diabetes mellitus, SBP, and DBP, being obese does not having UACR≥30 mg/g (OR=0.91-1.20) or UACR≥300 mg/g (OR=0.87; 95% CI: 0.67-1.4). After adjusting for these factors and obesity, abdominal obesity increases odds of having UACR≥30 mg/g (OR=1.14; 95% CI: 1.01-1.18), but not UACR≥300 mg/g (OR=1.14; 95% CI: 0.73-1.47).

**Conclusions:** Abdominal obesity defined by waist circumference is an independent predictor of having UACR≥30 mg/g. Obesity defined by BMI is not associated with albuminuria.

Sedentary Time and Chronic Kidney Disease: A Cross Sectional Analysis of the Canadian Health Measures Study

**Background:** Low physical activity (PA) levels are associated with adverse outcomes, including mortality in individuals with CKD. To determine the association between PA behavior and CKD using accelerometry data in a Canadian population, we conducted a cross-sectional analysis of data in the Canadian Health Measures Survey (CHMS). We hypothesized that lower kidney function would be associated with low PA levels and increased sedentary time.

**Methods:** The CHMS, a national survey, collects health information about Canadians. Data from adults (>18 years old) in the first three cycles (2007-2013) were analyzed (n=8444). PA monitoring was performed using Actical accelerometers. Primary outcome was proportion of sedentary time by activity quartiles (n=2111 per quartile). Multivariable logistic and linear regression incorporating key modifiers of PA behavior was used to assess the association between kidney function and sedentary time.

**Results:** Mean proportion of weekly sedentary time ranged from 81% (most sedentary quartile) to 58% (least sedentary quartile). CKD prevalence was highest in the most sedentary quartile (6.5%). CKD Stages 3b or higher had a 4.2-fold higher likelihood (95%CI 2.5-7.3) of being in a more sedentary quartile in comparison to gFr=60ml/min/1.73m². CKD Stage 3a was associated with a 1.7-fold (95%CI 1.2-2.3) higher likelihood of being increasingly sedentary. Age, female sex, diabetes, heart disease and increased pulse pressure were significantly associated with increased sedentary time. Linear regression identified that the presence of CKD Stage 3b or higher was associated with an additional 5.41% (95%CI 3.8-7.0) of sedentary time vs. those with gFr=60ml/min/1.73m². Stage 3c CKD was associated with an additional 3.58% (95%CI 1.6-6.5) of sedentary time compared with CKD 3a.

**Conclusions:** In this analysis more advanced CKD was strongly associated with increased sedentary time as measured by accelerometry. The effect of PA promotion and exercise programming on long-term improvement of sedentary behavior and associated adverse outcomes in this population warrants further investigation.

**Funding:** Private Foundation Support, Government Support - Non-U.S.
Conclusions: Daily drinking of two or more cups of coffee may reduce ESRD risk, and this effect is not mediated by the caffeine content. The much stronger association in men suggests that the effect of coffee may be mediated via estrogen-receptors and is more apparent in estrogen deficiency.

Funding: Other NIH Support - National Institutes of Health, USA (R01 CA144034 and UM1 CA182876)

FR-PO782

Prevalence of Medication Non-Adherence and Factors Affecting It in Patients of Chronic Kidney Disease at a Tertiary Care Public Teaching Hospital: A Cross Sectional Study

Sanjay D'Cruz,1 Rajiv Ahlawat, Pramil Tiwari.1 General Medicine, GMCH, Chandigarh, India; Pharmacy Practice, NIPER, SAS Nagar, Punjab, India.

Background: Medication non-adherence in CKD patients leads to adverse outcomes. The two important factors leading to non-adherence to medications are inability to afford the treatment and poor knowledge of the patient. The present study was carried out to study the prevalence of medication non-adherence and the factors influencing it in patients of CKD.

Methods: A cross sectional study was carried out in 600 CKD patients over a period of 20 months from Sept 2014 to April 2016 at our tertiary care hospital. CKD definition of the KDIGO was used. The proportion of covered days (PDC=total days all drugs/available/days in follow-up period) algorithm was used to assess medication adherence in CKD patients. PDC varies between 0 and 1; and it can be converted to percentages. PDC value over 80% is considered adherent. Multivariable logistic regression was used to analyse factors affecting medication compliance.

Results: Out of 600 patients, 69% were non-adherent to prescription. Forgettingness in 30% was found to be most common reason for non-adherence to drug therapy. It was followed by the highest cost of medications (21%), lack of information of medicines (12%) and others in 22%. Medication non-adherence was found highest towards antihypertensive drugs (27%) followed by oral hypoglycemic drugs (21%), insulin (19%), iron injection (11%) and others in 23%. Non-adherence to drug therapy was found significantly higher with pill burden over 5 (OR 1.32, 95% CI 1.06-3.21; P=0.047), illiteracy (OR 3.43, 95% CI 1.43-6.65; P=0.035) and lack of reimbursement (OR 2.17, 95% CI 1.31-3.26; P=0.012). Gender, dialysis, GFR, and duration of CKD did not have any influence on adherence.

Conclusions: 69% of patients were found non-adherent to drug therapy. Medication adherence was found to decrease with increased pill burden, drugs given by caregiver, increased age, lack of reimbursement and illiteracy.

FR-PO783

Effectiveness of Multifaceted Care Approach on Adverse Clinical Outcomes in Non-Diabetic CKD: A Systematic Review and Meta-Analysis

Aminu K. Bello,1 Bilal Qarni,1 Ariam Sammini,1 Julius Oluoch Okel,1 Trish Chatterley,1 Branko Braam.1 Medicine, Univ of Alberta; 1Library Sciences, Univ of Alberta.

Background: The impact of multifaceted interventions as compared to the usual care (ie. single risk factor control) in patients with non-diabetic CKD is unclear. We reviewed the evidence on the impact of multiple interventions on reducing adverse clinical outcomes in non-diabetic patients with CKD.

Methods: We searched MEDLINE, EMBASE, CINAHL and the Cochrane Library databases for published studies up to May 2016 on adult patients with CKD and the Cochrane Specialty Care Group, with ≥2 CKD risk factors, treated with a combination of two or more interventions. We included randomized controlled trials (RCTs) and observational studies with at least 100 participants. The intervention of interest was treatment with a combination of two or more interventions. We included randomized controlled trials and observational studies with at least 100 participants. The intervention of interest was treatment with a combination of two or more interventions. We included randomized controlled trials (RCTs) and observational studies with at least 100 participants. The intervention of interest was treatment with a combination of two or more interventions.

Results: Among 5 studies (2 RCTs and 3 cohort studies). In comparison to the usual care, multifaceted interventions were associated with a lower risk of all-cause mortality: (Risk ratio; [RR] 0.81, 95% confidence interval [CI] (0.63-1.03) and progression to kidney failure requiring dialysis- RR (95% CI): 0.57 (0.35-0.94). Multifaceted interventions did not impact risk of all-cause hospitalization: RR (95% CI): 0.93 (0.71-1.23) and blood pressure control- mean difference (95% CI): -0.48 (-2.5 to 1.55). Only a small number of studies met inclusion criteria. Heterogeneity, small sample sizes, and suboptimal study quality hampered the internal validity and generalizability.

Conclusions: Multifaceted interventions targeting multiple risk factors appeared to reduce the risk for major adverse clinical outcomes in patients with CKD. There is a need for high quality studies that can rigorously evaluate a set of interventions targeting multiple domains of CKD management in the population with non-diabetic CKD.

FR-PO784

Prevalence of Hyperkalemia among Patients with Chronic Kidney Disease

Keith Betts,1 J. Michael Woolley,2 Fan Mu,1 Evangeline McDonald,1 Wenhui Tang,1 Eric Wu.1 Analysis Group, Inc., Boston, MA; 1ZS Pharma, San Mateo, CA.

Background: There are limited published data on the epidemiology of hyperkalemia among patients with chronic kidney disease (CKD). This study estimated the prevalence of hyperkalemia among patients with CKD.

Methods: Adult patients with CKD were selected from a large US commercial claims database (01/01/2011-12/31/2014). CKD and CKD stage were identified by ICD-9 diagnosis codes or estimated glomerular filtration rate. Dialysis was identified by procedure codes. Patients were required to have at least one calendar year of data with continuous enrollment throughout the year and at least one potassium lab result. Hyperkalemia was defined as having at least two serum potassium measurements >5.0 mEq/L or one diagnosis code of hyperkalemia (ICD-9, 276.7) or one prescription fill of a sodium polystyrene sulfonate. Prevalence of hyperkalemia for each calendar year (2011-2014) was calculated as the number of patients with hyperkalemia divided by the total number of eligible patients within the year.

Results: A total of 847,604 CKD patients were included in the analysis. Among all CKD patients, the prevalence of hyperkalemia ranged from 2.2% to 2.7% across calendar years (Figure 1). When stratified by CKD stage, the prevalence of hyperkalemia across calendar years ranged from 40.0% to 43.5% among patients on dialysis, 29.0% to 33.6% for stage 5, 22.1% to 22.6% for stage 4, 4.4% to 5.3% for stage 3, 1.0% to 1.1% for stage 2, 2.3% to 3.4% for stage 1. Among patients with unspecified CKD stage, the prevalence ranged from 3.8% to 5.6%. Figure 1. Prevalence of Hyperkalemia Among Patients with CKD.

Conclusions: The study provided estimates of prevalence of hyperkalemia among patients, stratified by CKD stages across different calendar years. Hyperkalemia is common among CKD patients, and its prevalence generally increased at more advanced CKD stages. Funding: Pharmaceutical Company Support - ZS Pharma

FR-PO785

Cost of Hyperkalemia in Patients with Chronic Kidney Disease

J. Michael Woolley,1 Fan Mu,1 Cheryl Q. Xiang,1 Wenhui Tang,1 Eric Wu.1 Analysis Group, Inc.; 2ZS Pharma.

Background: Healthcare costs in patients with hyperkalemia (HK) have not been well characterized. This study estimated the healthcare costs of HK in patients with chronic kidney disease (CKD).

Methods: Adult patients with CKD, with or without HK (cases vs. controls), were selected from a large US commercial claims database (1/1/2010-12/31/2014). Patients were required to have serum potassium lab results. CKD was identified by ICD-9 diagnosis codes or estimated glomerular filtration rate. Dialysis was identified by procedure codes. HK was defined as having at least two serum potassium measurements >5.0 mEq/L or one diagnosis code of HK (ICD-9, 276.7) or one prescription fill of sodium polystyrene sulfonate. The index date was a randomly selected claim date indicating HK for cases and a randomly selected claim date for controls. Continuous enrollment of at least 6 months before the index date and 12 months after the index date was required. Controls were exactly matched one-to-one to cases on age group, CKD stage, heart failure, and Renin-Angiotensin-Aldosterone-System inhibitor use. 30-day and 1-year total healthcare costs (2015 USD) from the third-party perspective were compared between cases and controls.

Results: A total of 14,689 CKD patients with HK were matched to 14,689 CKD patients without HK. Among all CKD patients, cases had $4,379 higher 30-day costs ($7,241 vs. $2,862) and $19,589 higher 1-year costs than controls ($45,172 vs. $25,583) (both p<0.01). The 30-day cost difference was $5,983 between cases and controls in patients on dialysis, $9,685 for CKD stage 5, $3,730 for CKD stage 4, $3,880 for CKD stage 3, $13,113 for CKD stage 2, $3,075 for CKD stage 1 and $6,706 for unspecified CKD stage (all p<0.01, except for stage 1). The 1-year cost difference was $25,097 in patients on dialysis, $52,795 for CKD stage 5, $16,756 for CKD stage 4, $16,474 for CKD stage 3, $13,964 for CKD stage 2, $6,072 for CKD stage 1 and $27,459 for unspecified CKD stage (all p<0.01, except for stage 1).

Conclusions: The study provided estimates of prevalence of hyperkalemia among patients, stratified by CKD stages across different calendar years. Hyperkalemia is common among CKD patients, and its prevalence generally increased at more advanced CKD stages. Funding: Pharmaceutical Company Support - ZS Pharma
Conclusions: Patients with HK had higher healthcare costs across all CKD stages, with generally higher costs in more advanced disease, supporting the hypothesis that HK imposes a large economic burden on US payers and the healthcare system.

Funding: Pharmaceutical Company Support - ZS Pharma

FR-PO786

Real-World Treatment Discontinuation of Sodium Polystyrene Sulfonate

Keith Betts,1 J. Michael Woolley,2 Lihao Chu,1 Fan Mu,1 Wenxi Tang,1 Eric Wu,1 1Analysis Group, Inc., Boston, MA; 2ZS Pharma, San Mateo, CA.

Background: Sodium polystyrene sulfonate (SPS) has been studied in the context of clinical trials, but there is limited information regarding SPS treatment patterns in the real-world. This study describes the persistence of SPS treatment over time.

Methods: Adult patients who had at least one SPS prescription fill were identified from a large US commercial claims database (01/01/2010-12/31/2014). Patients were required to have at least 31 days of continuous enrollment post SPS prescription fill. SPS discontinuation was defined as having no subsequent SPS prescription refills within 30 days after the end of days of supply of their previous SPS prescription. Patients who did not discontinue SPS treatment were censored at the end of their continuous eligibility. SPS discontinuation was evaluated using the Kaplan-Meier estimator.

Results: A total of 4,559 patients initiated SPS therapy and met the eligibility criteria. Among these patients, the average number of SPS fills was 2.3 and the median time to discontinuation of SPS was 7 days (Figure 1). 49.8% of patients remained persistent with SPS through 7 days, 42.0% through 14 days, 30.7% through 30 days, 7.7% through 60 days, and 5.4% through 90 days, and 2.6% of patients were censored (not observed to discontinue). Figure 1. Kaplan-Meier curve of SPS persistence.

Conclusions: Patient persistence with SPS treatment was low, as the majority of patients discontinued treatment within 7 days and less than 10% remained persistent through 60 days.

Funding: Pharmaceutical Company Support - ZS Pharma

FR-PO787

No Association of Serum Potassium Level with Mortality in Patients with Optimized Chronic Kidney Disease Care - The NephroTest Study

Sandra Wagner,1,2 Marie Metzger,1 Martin Flammant,1 Pascal Houillier,1,3 Jean-Philippe Haymann,1 François Vrtovsnik,1 Eric Thervet,1 Jean-Jacques Boffia,1 Ziad Massy,2,8 Benedicte Stengel,1 Patrick Rossignol,1 1INSERM U1018, Villejuif, France; 2F-CRIN INI-CRCT; 3Bichat APHP; 4INSERM U1138; 5HEGP APHP; 6Touon APHP; 7INSERM UMR5970; 8INSERM CIC 1433, Nancy, France.

Background: Low and high serum potassium (S K) values are often associated with chronic kidney disease (CKD) or its treatments, and with poor outcomes, but their prognostic value in patients with optimized CKD care is uncertain.

Methods: We studied the prevalence of hypokalemia (hypoK) (<4 mmol/L) and hyperK (>5 mmol/L) in 1993 nondialysis patients with stage 1 to 5 CKD who underwent extensive renal tests during a 5-h in-person visit (mean age: 59 ± 15 yrs, 66% men). All had baseline S K and GFR measurements (mGFR; 1Cr-EDTA renal clearance) and 60% at least two. Cox models were used to estimate adjusted hazard ratios (HRs) of end-stage kidney disease (ESKD) and mortality prior to ESKD associated with baseline and time-dependent S K levels.

Results: At baseline, median mGFR was 38.4 ml/min/1.73 m² (IQR: 26.9-53.0); prevalence of hypoK was 26% (3.9% for Sk<3.5), and of hyperK, 6.4%; ACEI or ARBs was used in 77% of patients, thiazide or loop diuretics in 48%, potassium-sparing diuretics in 4%, K-binding resins in 6%, bicarbonates in 4%. At the initial and 2 years visits, 67.1% and 63.9% of the patients were normokalemic. After excluding 94 patients with stage 5 CKD at baseline, there were 376 ESKD events and 219 deaths prior to ESKD (36% from CV death).

Conclusions: Prevalence of hyperkalemia in the US increases substantially with age, and is especially high among persons with CKD or heart failure, and those taking RAASi.

Funding: Pharmaceutical Company Support - ZS Pharma

FR-PO788

Prevalence of Hyperkalemia among U.S. Adults

J. Michael Woolley,1 Derek Weycker,2 Mark Atwood,2 Gerry Oster,1 1ZS Pharma; 2Policy Analysis Inc.

Background: While the underlying causes and clinical consequences of hyperkalemia (HK) are well understood, relatively little is known about the epidemiology of the condition among US adults, especially persons with comorbidities that may predispose them to high potassium (K) levels.

Methods: A retrospective study was undertaken using data from the National Health and Nutrition Examination Survey (NHANES), a large, multi-year, cross-sectional, nationally representative survey of the health and nutritional status of US adults and children based on both interview and physical exam. We identified all persons in NHANES, aged ≥18 years, with valid serum K values between 1999 and 2014; observations across years were pooled to increase precision of analyses. We estimated the point prevalence of HK (serum K level ≥5.0 mEq/L) on an overall basis and within subgroups defined on the basis of age, gender, comorbidity profile, and medication use. Multivariable logistic regression was employed to evaluate the relationship between the demographic and clinical characteristics of study participants and the presence of HK.

Results: We identified a total of 42,083 persons, aged ≥18 years, with valid serum K values between 1999 and 2014. Mean (SD) age of study subjects was 46 (17) years, 52% were women, 29% had hypertension, 10% had diabetes, 7% had chronic kidney disease (CKD), and 13% were taking a RAASi. Prevalence of HK increased approximately 9-fold with age, from 278 per 100,000 persons aged 35-49 years to 2394 per 100,000 persons aged ≥75 years; on an overall basis, the rate was 564 per 100,000 persons. In multivariable analyses, age, CKD, heart failure, and use of RAASi were important predictors of HK.

Conclusions: Prevalence of hyperkalemia in the US increases substantially with age, and is especially high among persons with CKD or heart failure, and those taking RAASi.

Funding: Pharmaceutical Company Support - ZS Pharma

FR-PO789

Prevalence of Hyperkalemia among U.S. Adults

Lindsay Zepel,1 Patrick Robinson,1 Wendy Metzger,1 Stephanie Atwood,1 Marie Oster,2 1ZS Pharma, San Mateo, CA; 2Policy Analysis Inc.

Background: While the underlying causes and clinical consequences of hyperkalemia (HK) are well understood, relatively little is known about the epidemiology of the condition among US adults, especially persons with comorbidities that may predispose them to high potassium (K) levels.

Methods: A retrospective study was undertaken using data from the National Health and Nutrition Examination Survey (NHANES), a large, multi-year, cross-sectional, nationally representative survey of the health and nutritional status of US adults and children based on both interview and physical exam. We identified all persons in NHANES, aged ≥18 years, with valid serum K values between 1999 and 2014; observations across years were pooled to increase precision of analyses. We estimated the point prevalence of HK (serum K level ≥5.0 mEq/L) on an overall basis and within subgroups defined on the basis of age, gender, comorbidity profile, and medication use. Multivariable logistic regression was employed to evaluate the relationship between the demographic and clinical characteristics of study participants and the presence of HK.

Results: We identified a total of 42,083 persons, aged ≥18 years, with valid serum K values between 1999 and 2014. Mean (SD) age of study subjects was 46 (17) years, 52% were women, 29% had hypertension, 10% had diabetes, 7% had chronic kidney disease (CKD), and 13% were taking a RAASi. Prevalence of HK increased approximately 9-fold with age, from 278 per 100,000 persons aged 35-49 years to 2394 per 100,000 persons aged ≥75 years; on an overall basis, the rate was 564 per 100,000 persons. In multivariable analyses, age, CKD, heart failure, and use of RAASi were important predictors of HK.

Conclusions: Prevalence of hyperkalemia in the US increases substantially with age, and is especially high among persons with CKD or heart failure, and those taking RAASi.

Funding: Pharmaceutical Company Support - ZS Pharma

FR-PO790

Higher Phosphorus Is Associated with Lower Hemoglobin in CKD Stages 3-5: Early Results from the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps)

Roberto Pecoco-Filho,1 Charlotte Tu,2 Lindsay Zepel,1 Michelle M.Y. Wong,2 Ronald L. Pisoni,1 Friedrich K. Port,2 Bruce M. Robinson,2 Ziad Massy,2,8 Francesca Tentori,2 1Pontificia Univ Catolica do Parana, Brazil; 2Arbor Research Collaborative for Health; 3Ambroise Paré Univ Hospital, France; 4CESP UFSC, INSEMR U1018, France; 5Vanderbilt Univ; 6On Behalf of CKDopps and CKD REIN Investigators.

Background: High phosphorus (P) and low vitamin D levels, typical manifestations of mineral and bone disorder (MBD), are common in patients with advanced CKD. MBD has been associated with increased inflammation, which may affect normal erythropoiesis. In order to better understand the link between phosphorus and hemoglobin (Hb) levels, we tested this association in the international CKDopps.

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

Underline represents presenting author.

547A
Methods: We evaluated early data from CKDoppins, a prospective study of CKD patients with eGFR <60 ml/min/1.73m² from national samples of nephrology clinics in Brazil, France, Germany, and US. Linear mixed models were used to estimate the effect of P on hemoglobin (Hb), with different levels of adjustment for potential confounders and mechanistic variables.

Results: Data were available from 5,040 patients (mean age: 69 years; 40% female; median eGFR: 28.8 ml/min/1.73m²). eGFR was associated positively with Hb and inversely with P. Higher serum P was strongly associated with lower Hb even after adjustment for demographics, comorbidities, eGFR, labs, and vitamin D therapy (Table 1).

Table 1. Associations of serum phosphorus (per 1 mg/dl higher) with hemoglobin level, by level of adjustment

<table>
<thead>
<tr>
<th>Model</th>
<th>Effect (95% CI on Hgb (g/dL) per 1 mg/dl higher serum P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: adjust for age, gender, black, BMI, diabetes, hypertension, country</td>
<td>-0.60 [-0.70, -0.50]</td>
</tr>
<tr>
<td>Model 2: Model 1 + eGFR</td>
<td>-0.89 [-0.95, -0.83]</td>
</tr>
<tr>
<td>Model 3: Model 2 + albumin</td>
<td>-0.39 [-0.42, -0.30]</td>
</tr>
<tr>
<td>Model 4: Model 3 + PTH+VIT D levels + VIT D therapy</td>
<td>-0.36 [-0.42, -0.30]</td>
</tr>
</tbody>
</table>

Conclusions: In this multinational CKD cohort, higher P was associated with lower Hb, independent of kidney function and other MBD markers/treatments. Further studies will need to explore these mechanistic possibilities (inflammatory, endocrine) for this association and may generate important advances in the management of both anemia and MBD.

FR-PO791
Prognostic Significance of Dysnatremia in the Survival of Chronic Kidney Disease Patients Not on Dialysis

Background: Patients with chronic kidney disease (CKD) show a high prevalence of comorbid conditions that could predispose to dysnatremias. The assessments of dysnatremias are scarce, being less in case of outpatients. In this study, we analyze the prevalence of dysnatremias in patients with CKD not on dialysis and its effect on survival and renal progression.

Methods: Post-hoc analysis of PECERA study(a 3-year follow-up prospective observational multicenter study, in Spanish Nephrology clinics), which included 882 patients, CKD stages 4-5 not on dialysis: 61.6% male, mean age:68±13 years. Baseline data: serum creatinine:3.1±1.1mg/dl; estimated glomerular filtration rate (eGFR) (MDRD):20±5ml/min/1.73m². Mean follow-up:47±30 months.

Results: The prevalence of hyponatremia was 4.1% and hyponatremia 9.6%. The univariate analysis found no differences in age, BMI, GFR, presence of liver disease or use of diuretic therapy among those with hyponatremia and normonatremia. The history of congestive heart failure (CHF)(p=0.034) and proteinuria (p=0.038) were more prevalent in patients with hyponatremia. After adjustment for age, sex, eGFR, CHF, diuretics, phosphatemia and serum albumin, the presence of hyponatremia was independently associated with worse survival (HR 1.97,95% CI:1.06-3.67;p=0.033)

Conclusions: Increased polypharmacy has a negative impact on patient adherence. Low adherence is associated with a poorer quality of life compared with patients who have high adherence. Physicians should therefore aim to prescribe drug regimens with a lower pill count as this could lead to an increase in patient adherence and improved patient outcomes.

FR-PO792
Barrier to Dietary Adherence in Chronic Kidney Disease

Background: Dietary restriction is essential to multidisciplinary chronic kidney disease (CKD) care. Barriers to dietary adherence are poorly understood.

Methods: English and Spanish speaking patients with Stage 4 and 5 CKD were enrolled in a cross sectional study and completed 1) a Short Assessment of Health Literacy (SAHL screen), 2) Newest Vital Sign (NVS), a numeracy screen, 3) a survey evaluating barriers to adherence, 4) a food frequency questionnaire (FFQ), and 5) a knowledge assessment of high potassium and phosphorus foods.

Results: The majority of patients (37/52, 71%) had limited health literacy and numeracy (p=0.003). Patients who did and did not receive dietary counseling. In the total cohort, the mean number of correct answers in identifying the four high potassium and four high phosphorus foods was 2.4 and 1.5, respectively. These numbers were not different among patients with and without dietary counseling. Dietary counseling did not result in better knowledge of restricted foods or differences in intake of restricted nutrients. Methods to improve the efficacy of dietary counseling need to be explored further.

Conclusions: Limited health literacy and numeracy is common among patients with CKD 4 and 5 but there was no difference in dietary intake of restricted nutrients, or knowledge of restricted foods in subjects with and without limited literacy and numeracy. Dietary counseling did not result in better knowledge of restricted foods or differences in intake of restricted nutrients. Methods to improve the efficacy of dietary counseling need to be explored further.

Funding: Other NIH Support - U1L TR000040, Private Foundation Support
FR-PO793
Pharmacological Treatment for Chronic Kidney Disease (CKD) and Associated Outcomes in Medicare Part D Enrollees
Yun Han,1 Steven Erickson,2 R. Hirth,3 Rajiv Saran,1 Rajesh Balkrishnan1 1U of Michigan; 2U of Virginia.

Background: Few studies have assessed the effects of different pharmacological treatment regimens in hypertensive CKD patients. This study aimed to assess the effects of monotherapy with ACEIs/ARBs versus the combination therapies of ACEIs/ARBs plus other blood pressure-lowering agents among Medicare Part D enrollees with hypertension and CKD in the United States.

Methods: We used the Medicare 5% sample claim data (2006-2013) in this retrospective cohort study. Eligible cases were hypertensive patients newly diagnosed with CKD and continuously enrolled in Medicare Part D from 2008-2013. Pharmacologic therapies were assessed using a 3-month period after the date of the first CKD diagnosis. Multivariable Cox proportional hazards regression was used to assess effects of different pharmacologic therapies on progression to end stage renal disease (ESRD) and death.

Results: About 44% of CKD patients used ACEIs/ARBs within three months after the diagnosis of CKD. Compared to therapies without ACEIs/ARBs, combination therapy of ACEIs/ARBs plus statins showed the largest beneficial effect on reducing the risk for ESRD (HR: 0.53, p<0.0001). Combination of statins, ACEIs/ARBs, and other concomitant antihypertensive agents was most significantly associated with reducing the risk for all-cause mortality (HR: 0.45, p<0.0001).

Conclusions: Therapies including ACEIs/ARBs were preferred as initiation therapy in hypertensive CKD patients more than non-ACEIs/ARBs therapies. Combination therapies of ACEIs/ARBs and statins were associated with reduced risk of ESRD, while treatment regimens including ACEIs/ARBs plus statins and other antihypertensive agents were associated with decreased risk of death. These findings may provide additional evidence for the effectiveness of treatment regimens including ACEIs/ARBs in treating elderly patients with hypertension and CKD.

Funding: NIDDK Support

FR-PO794
Intake of Proton Pump Inhibitors Is a Significant Risk Factor for Bacterial Pneumonia in CKD Patients
Takeru Seto,1 Tsutomu Inoue,1 Hiroaki Amano,1 Takeru Kusano,2 Kei Sugiyama,1 Hirokazu Okada.1 1Nephrology, Saitama Medcial Univ, Iruma-gun, Saitama, Japan; 2General Medicine, Saitama Medcial Univ, Iruma-gun, Saitama, Japan.

Background: CKD is a well-known risk factor for cardio- and cerebrovascular diseases, thus many of CKD patients are treated with oral antiplatelet agents together with proton pump inhibitors (PPIs). Recently, an association between the intake of PPIs and pneumonia has received a good deal of attention, particularly among the elderly. In this study, therefore, we investigated whether PPI intake increases the incidence of pneumonia in CKD patients.

Methods: The study was designed as a single center, observational and longitudinal study. Subjects consisted of patients with renal insufficiency equal to or more than CKD stage 3A, who had visited our outpatient clinic. Multivariable logistic-regression models were employed to estimate the risk of hospitalization due to bacterial pneumonia. Independent variables included age, gender, serum albumin, the presence of diabetes mellitus, and the administration of immunosuppressants, statins, PPIs, and H2-receptor blockers (H2RB).

Results: A total of 410 CKD patients were enrolled. Mean age was 60.0 ± 13.1 years, mean estimated GFR was 34.1 ± 16.0 ml/min/1.73m2, and rates of PPI and H2RB intake were 18.0% and 17.8%, respectively. Adjusted odds ratio (aOR) of PPI and H2RB were 7.81 (p=0.01) and 1.01 (p=0.99), respectively. Intake of PPIs was found to be a significant risk factor for hospitalization due to bacterial pneumonia. Additionally, lower serum albumin, the presence of diabetes mellitus, and the administration of immunosuppressants were also significant risk factors, while intake of statin decreased the incidence of pneumonia (OR: 0.20, 95% CI: 0.04).

Conclusions: Intake of PPIs was a marked risk factor for pneumonia. Since there was a significant difference in the incidence of pneumonia between patients receiving PPIs and those receiving H2RBs, mechanisms unique to PPIs, such as their effect on the pH of respiratory secretions, likely contribute to the episodes of pneumonia. We should, therefore, pay attention to the deterioration of defense mechanisms against bacterial infection in CKD patients when we prescribe PPIs with or without antiplatelet agents.

FR-PO795
Increased Urinary Angiotensinogen in CKD Patients with High Salt Diet and Hypertension
Ha Yoan Kim,1 Eun Hui Bae,1 Seong Kwon Ma,1 Kook-Hwan Oh,2 Curie Ahn,2 Soo Wan Kim.1 1Dept of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea; 2Dept of Internal Medicine, Seoul National Univ, Seoul, Korea.

Background: Urinary angiotensinogen is known to be related with intra-renal renin-angiotensin system (RAS) activity. High sodium diet is associated with volume expansion and hypertension. Increased RAS activity is suggested as its common pathomechanism. We investigated whether PPI intake increases the incidence of pneumonia in CKD patients.

Methods: In total, 969 CKD patients were included and divided into four groups according to quartile of their 24h - urine sodium excretion to creatinine ratio and 24h - urine sodium-to-creatinine ratio (24HUNa/Cr): The urine angiotensinogen-to-creatinine ratio (UAGT/Cr) was specifically assessed with a commercially available enzyme-linked immunosorbent assay kit.

Results: Urine angiotensinogen was significantly higher in patients with increased 24hr - urine sodium excretion to creatinine ratio. Univariate linear regression analysis showed that the urine angiotensinogen concentrations were correlated with systolic blood pressure, the albumin-to-creatinine ratio, and 24-hr urine sodium-to-creatinine ratio. Whereas they were negatively correlated with waist hip ratio, the estimated glomerular filtration rate, serum albumin and hemoglobin levels and 24-hr urine potassium-to-creatinine ratio. Multiple regression analysis revealed that 24-hr urine sodium-to-creatinine ratio was specifically assayed with a commercially available enzyme-linked immunosorbent assay kit.

Conclusions: Urine angiotensinogen concentrations are higher in patients with increasing 24hr - urine sodium excretion to creatinine ratio. In a group of 4th quartile systolic blood pressure and 4th quartile 24h - urine-sodium excretion to creatinine ratio, the level of urine angiotensinogen levels (r = 0.35, p =0.021).

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

Background: Hypertension (HTN) is the second most common cause of ESRD. There is scarce information about prevalence of early nephropathy (EN) in patients with essential HTN. Aim: To determine the prevalence of EN and associated risk factors in patients with essential HTN of 9 primary health care units (PHC) in Guadalajara.

Methods: Cross-sectional study in patients with essential HTN, ≥18 yrs, any HTN vintage. Patients with transient albuminuria, diabetes, secondary HTN, other CKD causes and previously known CKD were excluded. Sociodemographic, clinical and biochemical data were collected. Albuminuria/Creatinuria ratio (A/C) in a first void urine sample and eGFR (CKD-EPI) were determined. Kidney function was classified (KDIGO) as normal (Normal: eGFR < 60 mL/min/1.73m² and A/C < 30, mg/g), EN: CKD stages 1 and 2, and overt nephropathy (ON) stage ≥ 3.

Results: Prevalence of CKD was 18% (6% EN and 12% ON). Main results are shown in the table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>NF (N=71)</th>
<th>EN (N=66)</th>
<th>ON (N=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>59±6</td>
<td>62±6</td>
<td>69±5</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>267(31)</td>
<td>294(40)</td>
<td>564(53)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>222(28)</td>
<td>280(30)</td>
<td>431(42)</td>
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<tr>
<td>&lt;6 school yrs (%)</td>
<td>503(60)</td>
<td>456(57)</td>
<td>965(70)</td>
</tr>
<tr>
<td>Systolic blood pressure mmHg</td>
<td>131±16</td>
<td>135±17</td>
<td>137±20</td>
</tr>
<tr>
<td>HTN yst (yrs)</td>
<td>7±34</td>
<td>9±14</td>
<td>10±17</td>
</tr>
<tr>
<td>≥140/90 mmHg (%)</td>
<td>33(40)</td>
<td>34(51)</td>
<td>63(50)</td>
</tr>
<tr>
<td>Body mass index kg/m²</td>
<td>30±5</td>
<td>30±6</td>
<td>29±5</td>
</tr>
<tr>
<td>Antihypertensives (%)</td>
<td>1.5±0.7</td>
<td>1.5±0.7</td>
<td>1.7±0.7</td>
</tr>
<tr>
<td>ACE inhibitors (%)</td>
<td>488±56</td>
<td>40±61</td>
<td>66±55</td>
</tr>
<tr>
<td>Uric acid mg/dL</td>
<td>5.4±1.1</td>
<td>5.6±1.4</td>
<td>6.4±1.3</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>0.80±0.16</td>
<td>0.82±0.20</td>
<td>1.32±0.49</td>
</tr>
<tr>
<td>eGFR ml/min/1.73m²</td>
<td>88±14</td>
<td>88±14</td>
<td>47±10</td>
</tr>
<tr>
<td>AUR mg/dL</td>
<td>75±14</td>
<td>35±17</td>
<td>81±20</td>
</tr>
</tbody>
</table>

Conclusions: Higher SUA in midlife was independently associated with lower eGFR in late life especially in women. The association was confirmed with IPTW which supports causal effect of SUA.

Funding: Private Foundation Support

FR-P0798

The Effect of Early Urate Lowering Therapy on Renal Disease Progression in Hyperuricemic Patients with Chronic Kidney Disease. Sung Joon Shin, Kwanghoon Lee. Nephrology, Dongguk Univ Ilsan Hospital, Goyang-si, Gyeonggi-do, Korea; Rheumatology, Dongguk Univ Ilsan Hospital, Goyang-si, Gyeonggi-do, Korea.

Background: This study aimed to determine whether urate lowering therapy (ULT) could delay renal disease progression in hyperuricemic patients with chronic kidney disease (CKD) according to the baseline stage of CKD.

Methods: We retrospectively reviewed the medical records of patients who were diagnosed as stage 3 and 4 CKD and concurrent hyperuricemia (> 7.0 mg/dL for males and > 5.7 mg/dL for females) from September 2005 to October 2015. The duration of follow-up should be longer than 6 months and the duration of treatment longer than 6 months for ULT group. We defined renal disease progression as follows: decline of eGFR greater than 30% compared to the baseline value, initiation of dialysis or eGFR < 15 mL/min/1.73m².

Results: The uric acid levels markedly decreased from baseline (from 9.2±1.0 mg/dL to 7.5±3.0 mg/dL, p = 0.028) and the degree of decrease was significantly greater in the ULT group (1.9±4.2 mg/dL vs. 0.6±1.8 mg/dL, p = 0.037). The mean decrease of eGFR from baseline tended to be smaller in the group that achieved target uric acid level (−2.8±1.4 mL/min/1.73m² vs. −8.5±7.0 mL/min/1.73m²) and the rate of renal disease progression tended to be lower in the ULT group (33.9% vs. 44.1%). Subgroup analysis showed that the benefit of ULT was most apparent in CKD patients with stage 3a. In the multivariate analysis, the baseline stage of CKD was significantly associated with renal disease progression (p for trend < 0.001) and the adjusted odds ratio for renal disease progression with stage 3a as a reference was 6.5 (95% confidence interval CI) 3.419 – 12.357.

Conclusions: The ULT delayed renal disease progression significantly in hyperuricemic patients with CKD. The baseline stage of CKD was an independent risk factor for renal outcomes in ULT group. So, patients with early CKD stage might gain more benefit from ULT than those with late stage.

FR-P0797

The Association of Midlife Uric Acid with Kidney Function in the General Population after 26 Years of Follow-Up. Anny Ros Gudmundsdottir, Thor Aspelund, Bjorn Odar Eiriksen, Rafn Benediktsson, Margaret B. Andresdottr.

Background: Hyperuricemia has been associated with kidney dysfunction. Proving causation is a challenge because of the renal elimination of serum uric acid (SUA) in addition to the association between SUA and other metabolic factors. In this study we used inverse probability of treatment weighting (IPTW) as an approach to limit confounding.

Methods: Data from 5141 volunteers in the AGES-Reykjavik study who had been followed prospectively for a median of 26 years, were analyzed to examine the association between SUA in midlife and GFR in late life. Estimated GFR (eGFR) was calculated with CKD-EPI creatinine equation. First, a multivariable linear regression model was conducted with SUA as exposure of interest and eGFR as outcome. We adjusted for age, hypertension, erythrocyte sedimentation rate, triglycerides, glucose, BMI and eGFR aturic. Second, a propensity score was calculated based on the variables above. IPTW was used which is based on the propensity scores. The effect on eGFR was then studied with linear regression analysis, with hyperuricemia as exposure.

Results: Average eGFR in late life was 64.6 ml/min per 1.73m² in men and 63.2 ml/min per 1.73m² in women with mean age 76.5±(5.5) and 76.1±(5.5), respectively. Patients with hyperuricemia were 364 in total. Results of the statistical models are shown in table 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.2±0.9</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>73.9±30.8</td>
</tr>
<tr>
<td>C-Reactive Protein (mg/dL)</td>
<td>4.9±(1.5-8)</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.4±0.5</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>3.7±0.4</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.3±1.3</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>170±48</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>129±58</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>91.4±41.9</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>53.1±17.3</td>
</tr>
<tr>
<td>NF-kB mRNA expression</td>
<td>0.83±(0.66 – 1.5)</td>
</tr>
</tbody>
</table>

Only 33% of patients presented high uric acid levels. Linear regression showed that uric acid was an independent predictor for NF-kB mRNA expression (β = 0.35, p = 0.04) after adjustment on age, gender, BMI, GFR and CPR levels.

Conclusions: The results suggest that uric acid levels, even in the normal range, are associated with increased NF-kB expression in CKD patients.
FR-PO800
Uric Acid and Disease Progression and Mortality in CKD
Hernan Rincon-Choles,1 Stacey Jolly,1 Susana Arriagin,2 Victoria Konig,3 Michael Rothberg,2 Jesse D. Schold,2 Sankar D. Navaneethan,2,3 Joseph V. Nally,1 1Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH; 2General Internal Medicine, Cleveland Clinic, Cleveland, OH; 3Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH; 4Nephrology, Baylor College of Medicine, Houston, TX; 5Nephrology, Houston Veterans Affairs Medical Center, Houston, TX.

Background: Various observations associate hyperuricemia (HU) with progression of CKD and mortality. We examined the association of HU with ESRD and mortality in the Cleveland Clinic CKD Registry.

Methods: We included 1,676 patients with CKD stages 3 and 4 from Ohio, without malignancy who had uric acid (UA) measurements a year prior to second eGFR<60/ml per 1.73 m², and some follow up eGFR, between 2005 and 9/15/2009. We ascertained ESRD from the USRDS and mortality from the State Department of Health mortality files. We fitted Cox models of pre-ESRD morality and competing risks model of ESRD with death as a competing risk adjusted for demographics, comorbidities, and laboratory measures including eGFR. Time-dependent uric acid lowering therapy (UALT) was adjusted on mortality models, and baseline UA on ESRD models.

Results: 95 patients reached ESRD and 201 reached pre-ESRD death during a median follow up of 2.8 years. In the adjusted models, neither UA level nor UALT were significantly associated with mortality or ESRD.

Table 1. Associations between uric acid and UA and pre-ESRD mortality and ESRD

<table>
<thead>
<tr>
<th>Model 1 (high/low UA)</th>
<th>Pre-ESRD Mortality**</th>
<th>ESRD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High UA (M=8.0, IQR=3) vs. low</td>
<td>1.15 (0.85, 1.55)</td>
<td>1.25 (0.97, 1.64)</td>
</tr>
<tr>
<td>UA LT vs. No</td>
<td>0.81 (0.60, 1.09)</td>
<td>1.40 (0.92, 2.16)</td>
</tr>
</tbody>
</table>

Model 2 (Quartiles of UA)

| Q1 (1.5-5.9) | Ref | Ref |
| Q2 (6.0-7.3) | 1.07 (0.68, 1.67) | 0.32 (0.19, 1.42) |
| Q3 (7.4-8.8) | 1.24 (0.80, 1.93) | 1.59 (0.72, 3.50) |
| Q4 (9.0-16.6) | 1.20 (0.84, 1.75) | 1.43 (0.65, 3.14) |

Model 3 (continuous UA)

| Uric acid (per 1 mg/dl higher) | 1.05 (0.98, 1.12) | 1.06 (0.97, 1.16) |
| UALT vs. No | 0.81 (0.60, 1.10) | 1.39 (0.91, 2.13) |

*Ajusted for age, sex, race, BMI, SBP quartiles, DM, ACEi/ARB, diuretics, eGFR.**Above variables plus log triglycerides, log cholesterol, CAD

Conclusions: In contrast to some prior reports we found no evidence that hyperuricemia is associated with increased risk of mortality or CKD progression to ESRD in patients with CKD stages 3 and 4, in the adjusted models.

Funding: Pharmaceutical Company Support - Pharmaceutical Company Support-CCF CKD Registry creation was supported by an unrestricted grant from Amgen to the Department of Nephrology and Hypertension at the Cleveland Clinic

FR-PO801
Urine Calcium Excretion and Risk of Chronic Kidney Disease in the General Population
Jacob M. Taylor,1 Lynne M. Kieneker,1 Martin H. De Borst,1 Sipke T. Visser,1 Ido Peter Kema,1 Stephan J.L. Bakker,1 Ron T. Gansvoort,2 1Internal Medicine, Univ of Groningen, UMCG, Netherlands; 2Pharmacoeconomics and Pharmacoepidemiology, University of Groningen, UMCG, Netherlands; 3Laboratory Medicine, Univ of Groningen, UMCG, Netherlands.

Background: Calcium and vitamin D are essential nutrients for human health, and are recommended as part of a healthy diet. However, high urinary calcium excretion (UCaE) has been shown to lead to accelerated renal function decline in individuals with renal tubular calcium nephropathy. It is not known whether this association also exists in the general population. Therefore, we investigated whether high UCaE is associated with risk of developing chronic kidney disease (CKD) in community dwelling subjects.

Methods: Urine samples of 5,491 subjects who were free of CKD at baseline and participated in the PREVEND study (a prospective, observational, general population based cohort of Dutch men and women aged 28-75 years), were examined for UCaE. UCaE concentration was measured in two 24h urine samples at baseline (1997-1998) by indirect potentiometry. UCaE was treated both as a continuous variable and as a categorical variable grouped according to sex-specific quintiles for UCaE. UCaE was compared to de novo development of eGFR <40 ml/min/1.73m² and/or albuminuria >30 mg/24h.

Results: Baseline median UCaE was 166 mg/24h for men (interquartile range [IQR]: 117-220 mg/24h), and 141 mg/24h for women (IQR: 96-193 mg/24h). During a median follow-up of 10.3 years (IQR: 6.2-11.4 yrs), 899 subjects developed CKD. After multiple imputation adjustment for non-missing data, the mortality rates were 4.0%/year for all-cause mortality, 2.0%/year for cardiovascular mortality, and 1.4%/year for non-cardiovascular mortality.

Conclusions: These findings indicate that high levels of UCaE do not increase risk of CKD, but rather that low levels of UCaE may be harmful.

Funding: Private Foundation Support

FR-PO802
Optimal End Stage Renal Disease Starts Are Associated with Less Sepsis, Lower Mortality and Fewer Inpatient Days
Peter W. Crooks,1 Christopher O. Thomas,2 Linda K. Radler,3 1The Permanente Federation, LLC, Oakland, CA; 2Kaiser Permanente Northwest, Portland, OR.

Background: Endorsed by the National Quality Forum, the Optimal End Stage Renal Disease (ESRD) Starts measure assesses the proportion of patients who receive a preemptive kidney transplant or initiate maintenance outpatient therapy on peritoneal dialysis or hemodialysis [HD] via arteriosurgical fistula or arteriosurgical graft. Six Kaiser Permanente Regions have tracked the measure since 2011; this study compares outcomes for patients with and without an optimal ESRD start.

Methods: 2089 patients with an optimal ESRD start were propensity score-matched by demographics, comorbidities, BMI, eGFR before ESRD, and alcohol and tobacco use to 2089 patients starting outpatient HD with a central venous HD catheter. Outcomes included sepsis, mortality and inpatient days for the first 12 months after starting renal replacement therapy. Logistic regression and Cox proportional hazard regression, adjusted for propensity score, were used to calculate odds ratios for sepsis and mortality and the hazard ratio for mortality. The rate ratio for inpatient days was adjusted for prior inpatient use and propensity score.

Results: Among patients with optimal ESRD starts, mean sepsis and mortality rates per person-year were 0.14 and 0.09, mean annual inpatient days were 9.8. Comparable rates and days for patients with nonoptimal starts were 0.19, 0.31, and 25.8, respectively. Odds ratios for sepsis and mortality were 0.29 (95% confidence interval [CI], 0.24 to 0.34) and 0.28 (95% CI, 0.23 to 0.35), respectively, compared to patients with nonoptimal starts; the mortality hazard ratio was 0.36 (95% CI, 0.30 to 0.43). Patients with optimal ESRD starts had 62% fewer inpatient days (rate ratio 0.38, 95% CI 0.31 to 0.46). All ratios were significant at p < 0.001.

Conclusions: Optimal ESRD Starts were associated with substantial reductions in morbidity, mortality, and inpatient days. While it was not possible to match for all patient characteristics, this study supports the use of the Optimal ESRD Starts measure within the U.S. health care system to evolve a more systematic approach to identifying, educating and supporting patients at high risk for ESRD.

Funding: Clinical Revenue Support

FR-PO803
Prediction Model and Risk Stratification Tool of Survival in Patients with CKD
Alexander S. Goldfarb-Rumyantsev,1 Shiva Gautam,2 Robert S. Brown,2 1Personalized Medicine, LLC, Harvard Medical School, Boston, MA; 2Div of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; 3Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background: CKD patients have an increased risk of death. A simple prediction model of CKD patient mortality would be useful. To improve the accuracy and streamline such predictions, we used the Woodpecker™ approach to construct models from reported risks in the literature. The goal of this project was to develop a risk scoring system and prediction model of two-year mortality of patients with CKD of stage 2 and greater.

Methods: A risk indicator (RI) was calculated by starting with 0, add 0.039 for every year of age, add 0.4 for male sex, add 0.4 for every stage of CKD over stage 2, add 0.9 for presence of proteinuria, add 0.6 for smoking history, and add 0.3 for each significant comorbidity up to 5. The result is multiplied by 1.257 to scale RI from 0 to 10. We developed 4 different equations (one linear, two exponential, and a combined one) to estimate the probability of two-year mortality. We used NHANES 1999-2004 data for validation (n=6,057 subjects with CKD stage 2 or above).

Results: The predictions were compared to actual NHANES mortality outcomes by R alone and in patient groups divided by R (0-2, 2-3, 3-4, 4-5, 5-6, >6). This prediction yielded a satisfactory area under an ROC curve of 0.84. We compared the predicted probability of death based on R with the actual two-year mortality using each of the prediction formulae. The combined expression offered predictive results closest to the actual outcomes, particularly in the higher risk groups (R>4).

Conclusions: We propose a practical prediction model that allows estimation of a CKD patient’s relative risk of two-year mortality on a 1 to 10 scale, and a probability of death. This equation can be used in clinical practice to target subjects at risk as well as in clinical research, e.g., to help designing clinical trials.

Funding: Clinical Revenue Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
551A
FR-PO804
eGFR Decline of 40% as an Alternative Endpoint in Clinical Trials: Experience from EMPA-REG OUTCOME

Christoph Wanner, 1 Hiddo Jan Lambers Heerspink, 2 Egon Pfar, 3 Mario Maldonado-Lutomirsky, 4 Audrey Koitka-Weber, 1 Hans-Juergen Woerle, 1 Maximilian von Eynatten, 1 Vladko Perkovic, 4 1 Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany; 2 Dept of Clinical Pharmacy and Pharmacology; Univ of Groningen, Groningen, Netherlands; 3 Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; 4 George Inst for Global Health, Sydney Univ, Sydney, Australia.

Background: Doubling of serum creatinine (DSC) is highly predictive of ESRD but its use as an endpoint in clinical trials requires long duration of follow-up and large samples. The National Kidney Foundation and FDA have proposed the utility of lower thresholds in eGFR decline as alternative renal endpoints.

Methods: In EMPA-REG OUTCOME, 7020 patients with type 2 diabetes and high cardiovascular risk were randomized 1:1:1 to receive empagliflozin (EMPA) 10 mg, 25 mg, or placebo in addition to standard of care. Treatment group differences in the time to first DSC (accompanied by eGFR [MDRD] of ≤45 mL/min/1.73m²) was assessed for EMPA pooled vs placebo using a Cox proportional hazards model.

Results: Incidence rates of DSC were 9.7 and 5.5 events per 1000 person-years with placebo and EMPA, respectively. EMPA reduced DSC risk by 44% vs placebo (p<0.001). Incidence rates of sustained eGFR decline of 40% were 12.4 and 7.0 events per 1000 person-years with placebo and EMPA, respectively. The risk of sustained eGFR decline of 40% was reduced by 45% with EMPA vs placebo (p<0.001, Figure).

Conclusions: EMPA significantly lowered the risk of sustained eGFR decline of 40% and the overall effect size was consistent with the harder endpoint of DSC. Our data support the consideration of a lower threshold in eGFR decline as an alternative renal endpoint for assessing CKD progression in clinical trials.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

FR-PO805
Effect of Empagliflozin on Albuminuria in Patients with Type 2 Diabetes and High Cardiovascular Risk

Christoph Wanner, 1 Bernard Zinman, 2 Silvio E. Inzucchi, 3 Egon Pfar, 1 Audrey Koitka-Weber, 1 Maximilian von Eynatten, 1 Hiddo Jan Lambers Heerspink, 2 David Cherney, 1 1 Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany; 2 Essenfild-Tannenhaus Research Inst, Mount Sinai Hospital, Toronto, Canada; 3 Section of Endocrinology, Yale Univ, New Haven, CT; 4 Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; 5 Dept of Clinical Pharmacy and Pharmacology, Univ of Groningen, Groningen, Netherlands; 6 Toronto General Hospital, Univ of Toronto, Canada.

Background: Short-term treatment with empagliflozin (EMPA) reduced albuminuria in patients with type 2 diabetes (T2D). The present analysis aimed to explore short- and long-term effects of EMPA on albuminuria in EMPA-REG OUTCOME.

Methods: Patients with T2D and high cardiovascular (CV) risk were randomized (1:1:1) to EMPA 10 mg, 25 mg or placebo in addition to standard of care. Changes in urinary albumin-to-creatinine ratio (UACR, log-transformed) from baseline were analyzed for EMPA pooled vs placebo using a mixed model repeated measures analysis.

Results: 7020 patients were treated. At baseline, 59.4%, 28.7% and 11.0% had normo-, micro- and macroalbuminuria, respectively. At Week 12, placebo-adjusted geometric mean ratio of UACR change from baseline with EMPA pooled was -21% (95%CI -31 to -9; p<0.001), -40% (95%CI -51 to -27; p<0.001) and -38% (95%CI -58 to -9; p<0.05) in patients with normo-, micro- or macroalbuminuria at baseline, respectively. At Week 192, placebo-adjusted geometric mean ratio of UACR change from baseline with EMPA pooled was -21% (95%CI -31 to -9; p<0.001), -40% (95%CI -51 to -27; p<0.001) and -38% (95%CI -58 to -9; p<0.05) in these subgroups, respectively (Figure).

For UACR over time:

Conclusions: In patients with T2D and high CV risk, EMPA led to sustained reductions in UACR from as early as Week 12, regardless of baseline albuminuria status. These results support both short- and long-term renal effects of EMPA on UACR.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

FR-PO806
Rapid Onset of Renal Effects with Empagliflozin in Type 2 Diabetes: A Cumulative Renal Event Analysis over Time in EMPA-REG OUTCOME

Christoph Wanner, 1 Guntram D. Scherimhaner, 2 Audrey Koitka-Weber, 3 Michaela Mattheus, 4 Maximilian von Eynatten, 1 Mark E. Cooper, 1 1 Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany; 2 Dept of Internal Medicine, Rudolfstiftung Hospital, Vienna, Austria; 3 Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; 4 Baker IDI Heart and Diabetes Inst, Melbourne, Australia.

Background: Patients with diabetes are at high risk of developing CKD. In EMPA-REG OUTCOME, empagliflozin (EMPA) significantly slowed CKD progression in patients with type 2 diabetes and high cardiovascular risk. To further explore the onset of the observed renal effects with EMPA we investigated hazard ratios (HRs) over time for the composite outcome of incident or worsening nephropathy.

Methods: Patients were randomized to receive EMPA 10mg, 25mg or placebo in addition to standard of care. The cumulative probabilities of experiencing incident or worsening nephropathy (i.e. progression to macroalbuminuria, doubling of serum creatinine...
accompanied by eGFR [MDRD] ≥45 mL/min/1.73m², initiation of renal replacement therapy or death due to renal disease were analyzed for pooled EMPA vs placebo patients treated with ≥1 dose of study drug. HRs and 95% CIs (obtained from Cox regression analyses) were derived at each point following randomization until the last observation of the last patient. All events until the respective cut-off day were considered and patients without events were censored at that day.

Results: A significantly lower risk for the composite renal outcome with EMPA vs placebo was observed within the first 3 months and this effect was maintained throughout the trial (Figure). HRs stabilized as the number of patients with events increased over time.

Figure. Incident or worsening nephropathy. (A) Kaplan-Meier estimates (B) Hazard ratio over time.

Conclusions: Renal effects of EMPA occurred within the first 3 months of treatment. This rapid onset of action may reflect renal hemodynamic changes and reduction of glomerular hypertension.

Funding: Pharmaceutical Company Support - Janssen Scientific Affairs, LLC

FR-PO807

Effects of Canagliflozin versus Glimepiride on eGFR Based on Serum Creatinine and Cystatin C in Patients with Type 2 Diabetes Matthew R. Weir,1 Christian W. Mende,2 Ujjwala Vijapurkar,2 Jimmy Ren,2 Michael J. Davies.3 1Univ of Maryland School of Medicine, Baltimore, MD; 2Univ of California, San Diego, La Jolla, CA; 3Janssen Scientific Affairs, LLC, Raritan, NJ.

Background: Canagliflozin (CAN), an SGLT2 inhibitor, has shown durable glycemic improvement and weight loss versus placebo (GLIM) over 104 weeks in patients with type 2 diabetes mellitus (T2DM) on background metformin; CAN showed a transient improvement and weight loss versus glimepiride (GLIM) over 104 weeks in patients with type 2 diabetes mellitus (T2DM) with moderate or severe renal impairment.

Methods: This post hoc analysis used data for CANA 300 mg (n=252) and GLIM (n=215) from patients in the overall study who completed 104 weeks of treatment without rescue therapy. Correlation in baseline (BL) eGFR using Cr and Cr/CysC equations was assessed based on serum Cr but not Cr/CysC. SGLT2 inhibitors are a newer class of antihyperglycemic agents with hemodynamic effects and ongoing, long-term, renal outcome trials will determine the potential for renoprotection in patients with T2DM.

Table. Change in eGFR at Week 104 Using Cr- and Cr/CysC-Based Equations

<table>
<thead>
<tr>
<th>eGFR (Cr)</th>
<th>CANA 300 mg (n=252)</th>
<th>GLIM (n=215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) baseline, mL/min/1.73 m²</td>
<td>67.5 (16.7)</td>
<td>91.7 (18.1)</td>
</tr>
<tr>
<td>LS mean change (SE) at Week 104</td>
<td>-8.2 (1.0)</td>
<td>-2.7 (0.9)</td>
</tr>
<tr>
<td>Difference (95% CI) Cr/CysC vs GLIM</td>
<td>-4.4 (1.0)</td>
<td>-4.5 (1.0)</td>
</tr>
</tbody>
</table>

Conclusions: There was a modest correlation in BL eGFR calculated using Cr and Cr/CysC equations (R=0.38). Similar eGFR reductions were seen with CANA 300 mg and GLIM after 104 weeks using the Cr/CysC equation, whereas eGFR reduction was larger with GLIM compared to CANA 300 mg using the Cr-based equation (Table).

Conclusions: Differences in eGFR over 2 years were seen with CANA and GLIM when assessed based on serum Cr but not Cr/CysC. SGLT2 inhibitors are a newer class of antihyperglycemic agents with hemodynamic effects and ongoing, long-term, renal outcome trials will determine the potential for renoprotection in patients with T2DM.

Funding: Pharmaceutical Company Support - Janssen Scientific Affairs, LLC

FR-PO808

Clinical Characteristics of Patients with Bullous Pemphigoid Associated with Dipeptidyl Peptidase-4 Inhibitors: Is Chronic Kidney Disease a Risk Factor? Hideaki Oka,1 Shunsuke Yamada,2 Taro Kaminuma,1 Yutaro Hirashima,1 Tomoya Shukuri,1 Seishi Aihara,1 Atsumi Harada,1 Kazuhiro Tsuyru,2,3 Matsuura Red Cross Hospital, Div of Kidney Center; Matsuura, Japan; 2Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ; Fukuoka, Japan; 3Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ; Fukuoka, Japan.

Background: Bullous pemphigoid (BP) is the most commonly acquired autoimmune blistering dermatosis. Its etiology is usually idiopathic but may occasionally be drug-induced. This study assessed the incidence of BP induced by dipeptidyl peptidase-4 inhibitors (DPP4is) and the factors associated with DPP4is-induced BP.

Methods: The present study was a single-center retrospective cohort study that reviewed and examined all patients who were histologically diagnosed with BP at our hospital between 2005 and 2015. We analyzed the incidence of DPP4is-associated BP and compared the characteristics of BP patients who were and were not treated with DPP4is.

Results: Of the 66 patients diagnosed with BP during the study period, 19 were diagnosed during the 5 years before the introduction of DPP4is and 47 during the 6 years after the introduction of DPP4is. Of the latter, nine had been taking DPP4is at diagnosis. There were no significant differences in age, sex, prevalence of anti-BP180 antibody, and BP treatment and outcomes between patients who were and were not treated with DPP4is. By contrast, the prevalence of chronic kidney disease (CKD) was higher in patients who were than were not treated with DPP4is, with rates of stage 5 CKD being 44% (9 of 4) and 4% (2 of 57), respectively.

Conclusions: The incidence of DPP4is-associated BP appears to be increasing. CKD may increase the risk of DPP4is-associated BP. Further large-scale, prospective and case-control studies are required to identify the interactions between CKD and DPP4is-associated BP.
FR-PO810

Omarigliptin, a Novel Once-Weekly Oral Dipeptidyl Peptidase-4 Inhibitor, Is Non-Inferior to Daily Teneligliptin in Controlling Plasma Glucose Fluxuations and Extends Better Medication Adherence in Hemodialysis Patients with Type 2 Diabetes in a Crossover Study: An Assessment by Continuous Glucose Monitoring

**Background:** During hemodialysis (HD), plasma glucose (PG) level drops due to various factors including clearance gap between glucose and insulin, and then rebounds to hyperglycemic state after HD. These PG fluctuations can induce cardiovascular events in HD patients with type 2 diabetes mellitus (T2DM). Omarigliptin (OMG) is a novel long-acting oral dipeptidyl peptidase-4 inhibitor (DPP-4) based in the treatment of T2DM patients with or without renal impairment.

**Methods:** In this study we compared once-weekly OMG to once-daily teneligliptin (TNG) on PG control in a crossover study assessed by continuous glucose monitoring (CGM) in a crossover study. Six adult HD patients with T2D who had been treated with 40mg of daily TNG were switched to once-weekly 12.5mg of OMG for 8 weeks, then to previous dose of daily TNG. All patients were monitored for PG control by 5-day CGM, and the mean amplitude of glycemic excursions (MAGE) calculated before and after switching. OMG was given right after HD treatment in the presence of HD staff, and the medication adherence (total actual number of tablets taken during a period / number of tablet expected to be taken during a period x 100) was calculated at the end time point of each arm.

**Results:**

**Weekly OMG is Non-inferior to Daily TNG in Controlling Plasma Glucose Fluxuations Monitored by CGM**

<table>
<thead>
<tr>
<th>OMG</th>
<th>TNG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose (mg/dL)</strong></td>
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As shown in figure 1, there was no significant difference between once-daily TNG and once-weekly OMG in PG at the start of HD or MAGE. The medication adherence was 100% in OMG and 87% in TNG, respectively.

**Conclusions:** Our results indicate the effects of OMG are non-inferior to TNG, and OMG exerts better medication adherence.

**Funding:** Private Foundation Support

FR-PO811

Linagliptin and Changes in Novel Urinary Biomarker Panels in Type 2 Diabetes: A Predefined Substudy from the MARLINA-T2D™ Trial

**Background:** The DN_Score (from the urinary proteome dataset) is a simple but powerful and clinically relevant biomarker that reflects early kidney injury in the setting of diabetes. It measures the extent of proteinuria, albuminuria, and glycemic control. Linagliptin significantly reduced the DN_Score (%) from baseline to Week 24 vs PBO (p<0.05). Moreover, adjusted mean change in the DN_Score (%) were consistently reduced with linagliptin in subgroups of patients with baseline HbA1C<300, eGFR-Cr<60, HbA1C<8.5%, and age<45 (all p<0.05).

**Funding:** Preventive Medicine Corp., Taiwan; Boehringer Ingelheim Pharma GmbH & Co KG, Germany

FR-PO812

Non-Insulin Glycemia-Lowering Strategies and Mortality in Patients on Chronic Hemodialysis: A EURODOPPS Study

**Results:** Our results suggest a reduced risk of death in patients with diabetes on hemodialysis when non-insulin vs insulin based glycemia-lowering strategies. However, these findings may be subject to residual confounding and require further investigation.

**Conclusions:** Clinical data were obtained from the European Dialysis Outcomes and Practice Patterns Study (EURODOPPS) phases 1-4 (1998-2011) for 5437 diabetic patients (age 40-104 years) on hemodialysis from 7 European countries (Belgium, France, Germany, Italy, Spain, Sweden, and United Kingdom). Patients on non-insulin glycemia-lowering strategies (all classes) were compared with those on insulin containing strategies (all types) for all-cause and cardiovascular mortality. Multivariate Cox regression analysis was conducted in the total sample.

**Results:** After adjusting forage, gender, diabetes vintage, comorbidities, country, EURODOPPS phase, body mass index, albumin, glycated hemoglobin (HbA1c), smoking, Kt/V, residual renal function, and diabetes as a cause or as a comorbidity, patients on non-insulin vs insulin containing glycemia-lowering strategies had a reduced risk of all-cause mortality (HR: 0.74; 95% CI 0.57-0.96) but not of cardiovascular mortality.

**Conclusions:** Our results suggest a reduced risk of death in patients with diabetes on hemodialysis when on non-insulin vs insulin based glycemia-lowering strategies. However, these findings may be subject to residual confounding and require further investigation.

**Funding:** Other NIH Support - The EURODOPPS Initiative is supported by the European Renal Association Dialysis and Transplant Association (ERA-EDTA), and the DOPPS Program. The DOPPS Program is principally supported by Amgen, Kyowa Hakko Kirin, Baxter Healthcare. Additional support for specific projects is also provided by Vifor Pharma, Ltd. Hexal, Deutsche Gesellschaft für Nephrologie (DGN), and Shire in Germany, the Societa Italiana di Nefrologia (SIN) in Italy, Keryx, Japanese Society for Peritoneal Dialysis (JSPD) and Genzyme Corporation. Public support is provided by National Health & Medical Research Council (NHMRC) in Australia, Canadian Institutes of Health Research (CIHR) and Ontario Renal Network in Canada, Agence Nationale de la Recherche in France, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN) in the United Kingdom, and National Institutes of Health (NIH) and Patient-Centered Outcomes Research Institute (PCORI) in the United States. All support is provided without restrictions on publications. The authors alone are responsible for the reporting and interpretation of EURODOPPS data used in the publication and they do not necessarily represent the decisions or policies of the ERA-EDTA or the DOPPS Program.

FR-PO813

Dulaglutide, a Once-Weekly GLP-1 Receptor Antagonist, Is Superior to Daily Liraglutide in Reducing Plasma Glucose Fluxuations in Hemodialysis Patients with Type 2 Diabetes Receiving Insulin Degludec: An Assessment by Continuous Glucose Monitoring

**Background:** Plasma glucose (PG) levels are shown to drop during the course of hemodialysis (HD) but to rebound to a hyperglycemic state following HD. These PG fluctuations place HD patients with type 2 diabetes (T2D) at risk of cardiovascular events.

**Results:** Of 360 patients in MARLINA-T2D™, urine samples for this biomarker study were available for 157 and 161 individuals receiving PBO and linagliptin, respectively. Linagliptin significantly reduced the DN_Score (%) from baseline to Week 24 vs PBO (p<0.05). Moreover, adjusted mean changes in the DN_Score (%) were consistently reduced with linagliptin in subgroups of patients with baseline HbA1C<300, eGFR-Cr<60, HbA1C<8.5%, and age<65 (all p<0.05).

**Funding:** Pharmaceutical Company Support - Boehringer Ingelheim Pharma GmbH & Co KG, Germany

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

Underline represents presenting author.
FR-P0814
Pleiotropic Effects of GLP-1 Treatment on Renal Risk Factors in Type 2 Diabetes: Individual Effects of Treatment

Background: Management of diabetic nephropathy includes reduction of albuminuria, blood pressure, glucose and weight. The GLP-1 receptor agonist liraglutide may possess these pleiotropic effects. We aimed to elucidate the individual treatment response on multiple renal risk factors and determined if high responders (highest reduction) in each risk factor also had the highest response in other renal risk factors (cross-dependency).

Methods: We treated 31 type 2 diabetics with liraglutide for 7 weeks followed by 3 weeks washout. 23 re-started treatment and were followed for 1 year. We evaluated changes in HbA1c, weight, SBP and mGFR. Changes in high (Q4) vs. low responders (Q1-Q3) were compared for each outcome measure. The effects of treatment/offset treatment/re-treatment (the off-on-off-on effect) was evaluated to account for random effects.

Results: After 7 weeks HbA1c was reduced by 6 (95%CI: 3; 9) mmol/mol, weight 2.5 (1.8-3.2) kg, SBP 4 (-1;9) mmHg and mGFR 30 (12;44) mL/min/1.73 m2. Liraglutide treatment reduced HbA1c by 8 (95% CI: 5; 11) mmol/mol (p<0.001) and weight by 1.8 (95% CI: 0.2; 3.4) kg (p=0.032) when compared to placebo. In addition liraglutide treatment reduced UAER by 32 (95% CI: 7; 50) % (p=0.032) compared with placebo. Seven patients (26%) had a reduction in UAER > 50%. Change in GFR (95%CI: -0.15; 1.1) mL/min/1.73 m2 (p<0.017) compared with 24-h systolic blood pressure was -4 (95% CI: -9; 2) mmHg (p=0.16). Change in UAER was associated with change in 24-h systolic blood pressure (p=0.05) but not with change in HbA1c, weight or GFR (p<0.06), overall model R2=0.54.

Conclusions: Our placebo-controlled randomized trial suggests that liraglutide treatment has renoprotective effects on top of multifactorial treatment, including RAS inhibition, in patients with type 2 diabetes and albuminuria.

FR-P0815
Renal Effects of Liraglutide in Type 2 Diabetic Patients with Albuminuria: A Randomized Clinical Trial
Bernt Johan Illum von Scholten, Frederik I. Persson, Signe Rosenlund, Tine Hansen, Peter Rossing.1,2 Steno Diabetes Center; 1Univ of Copenhagen; 2Aarhus Univ.

Background: Patients with type 2 diabetes and albuminuria have high cardiac morbidity and mortality despite multifactorial treatment. We evaluated the renoprotective effect of glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide on top of multifactorial care, including renin angiotensin system (RAS) inhibition.

Methods: Randomized, double-blind, placebo-controlled, cross-over trial including patients with type 2 diabetes and persistent albuminuria (urinary albumin to creatinine ratio (UACR) > 30 mg/g in at least two of three consecutive morning spot urine samples, estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2, and prescribed stable antidiabetic and RAS inhibition > 4 weeks before inclusion. Patients received liraglutide (1.8 mg/day) and matched placebo for 12 weeks in random order. Primary endpoint was change in 24-h urinary albumin excretion rate (UAE) (ClinicalTrials.gov, NCT02545738).

Results: We screened 40 patients, 32 were randomized and 27 completed the study. After placebo treatment, geometric mean (IQ) UAE was 199 (81-531) mg/24-h, mean (SD) measured GFR (95%CI:EDTA) was 75 (36) mL/min per 1.73 m2, 24-h blood pressure 145±80 (15/8) mmHg and HbA1c 61 (11) mmol/mol. Liraglutide treatment reduced HbA1c by 8 (95% CI: 5; 11) mmol/mol and mGFR by 1.8 (95% CI: 0.2; 3.4) kg (p<0.032) compared to placebo. In addition liraglutide treatment reduced UAER by 32 (95% CI: 7; 50) % (p=0.032) compared with placebo. Seven patients (26%) had a reduction in UAER > 50%. Change in GFR (95%CI: -0.15; 1.1) mL/min/1.73 m2 (p<0.017) compared with 24-h systolic blood pressure was -4 (95% CI: -9; 2) mmHg (p=0.16). Change in UAER was associated with change in 24-h systolic blood pressure (p=0.006) but not with change in HbA1c, weight or GFR (p>0.06), overall model R2=0.54.

Conclusions: Our placebo-controlled randomized trial suggests that liraglutide treatment has renoprotective effects on top of multifactorial treatment, including RAS inhibition, in patients with type 2 diabetes and albuminuria.

FR-P0816
Delayed-Release Metformin Targeting the Lower Small Intestine Elicits Minimal Systemic Exposure in Patients with Severe Renal Impairment: Results of Pharmacokinetic Simulation
George L. Bakris, Adekemi Taylor, Brandon Walsh, Colleen Burns, Ralph A. DeFronzo, Mark Fineman.1 Univ of Chicago; 2Certa Strategic Consulting; 3Elcelyx Therapeutics; 4Univ of Texas.

Background: Initiation of metformin is not recommended in patients with chronic kidney disease (CKD) Stage 3B or greater due to lactic acidosis risk secondary to increased systemic metformin exposure. A delayed-release metformin (Met DR) that targets the L-cell in the lower bowel is in development and results in improved potency (e.g., equivalent fasting glucose reduction at daily doses of 600 mg Met DR vs. 1000 mg current metformin), with ~50% less systemic exposure at identical daily doses. Thus, Met DR may provide an alternative to current metformin in subjects with CKD Stage 3B/4. To select appropriate Met DR doses in various CKD stages, we developed a population PK model capable of predicting metformin plasma exposure based on formulation, dose, and CKD stage.

Methods: Metformin exposure predictions from simulations of 3 doses of Met DR (600, 900, 1200 mg) were compared to 1000 and 2000 mg metformin immediate-release (Met IR) in patients with CKD Stage 3A, 3B, or 4. Each simulation consisted of 1000 subjects with varying body weight and eGFR values.

Results: Across CKD Stages 3 and 4, all Met DR doses elicited lower systemic exposure than 2000 mg daily Met IR in Stage 3A patients. In Stage 3B CKD, 1200 mg of Met DR (a dose predicted to elicit similar glycemic effects to 2000 mg Met IR) elicits 40% lower mean exposure than the suboptimal, but recommended, 1000 mg daily Met IR dose.

Conclusions: We conclude that Met DR at doses up to 1200 mg daily may provide a useful alternative for subjects receiving ≤1000 mg Met IR with CKD Stage 3B, or as an option to initiate metformin for patients with CKD Stage 3B/4.
FR-PO817

Metformin Misuse in Chronic Kidney Disease: A Cohort Study

Vladimir Coliche, Laetitia Koppe, Louis De Laforcade, Maurice Laville, Solenne Pelletier, Pierre Trolliet, Denis Fouque. Nephrology, Centre Hospitalier Lyon Sud, Lyon, France.

Background: Metformin is the most widely prescribed oral antidiabetic treatment, and the only one that showed a survival benefit including in chronic kidney disease (CKD) patients. However, metformin has side effects, particularly in these patients. Yet, there is no consensus on metformin optimal dose and withdrawal necessity in severe CKD stages. The aim of our study is to describe the use of metformin in routine practice in patients with CKD.

Methods: We followed 581 patients with type 2 diabetes in the Department of Nephrology at the University Hospital between March 2014 and March 2016. Pts were classified into 6 CKD stages: 45 pts (eGFR<50 ml/min/1.73 m²), stage 1, 72 (stage 2), 117 (stage 3a), 187 (stage 3b), 124 (stage 4), and 36 (stage 5N). All antidiabetic treatments were gathered. Glycated hemoglobin (HbA1c) was recorded in 376 patients. Comparisons were performed by Student’s t test.

Results: Results are shown in Table 1. There was no statistical difference between Met+/− groups for HbA1c. One lactic acidosis episode was recorded over 2 yrs.

FR-PO819

Glycemic Markers and Cardiovascular Events in Hemodialysis Patients from the GIDE Study

Mark E. Williams,1 Neal Mittman,2 Lin Ma,2 Julia I. Brennan,4 Ann Mooney,4 Chinu M. Jani,4 Curtis D. Johnson,4 Eduardo K. Lacson,4 Norma J. Olfshun,2 Franklin W. Maddux,2 Joslin Diabetes Center, Boston, MA;4 Kidney Care of Brooklyn and Queens, Brooklyn, NY;4 Presenius Medical Care North America, Watham, MA;4 Spectra Laboratories, Rockleigh, NJ;4 Tufts Univ School of Medicine, Boston, MA.

Background: The GIDE (Glycemic Indices in Dialysis Evaluation) study is evaluating several glycemic indices including HgbA1c, albumin-adjusted and unadjusted fructosamine (AlbF, F), and glycated albumin (GA) or percent GA (%GA) in hemodialysis (HD) cohorts with and without diabetes. Since cardiovascular events (CVE) are associated with diabetes, we examined the associations between each glycemic indices and CVE risks.

Methods: A combined cohort of 2,501 active HD patients (1,478 with diabetes, 1023 without) from 26 FMCNA facilities had baseline indices measured Jan-Mar 2013 and monthly until March 2016. Poor glycemic controls were based on: HgbA1c >7%, F>285µmol/L, AlbF≥974µmol/g, GA>300µmol/L, and %GA>15.7%. CVE included acute myocardial infarction (AMI), cerebrovascular accident (CVA), and peripheral vascular disease (PVD) which were diagnosed from hospital discharges in 3-years follow up. Times to the first CVE were used for the survival analysis. Standard and time-dependent (TD) Cox models with adjustments for case-mix and albumin level at baseline were utilized to determine associations between each glycemic indices and CVE risks.

Results: In 2,501 HD patients, 179 (7.1%) had at least one CVE during the 3-years follow-up periods; 125 (8.5%) in diabetes and 54 (5.3%) in non-diabetes. The hazard ratios of CVE from standard and time-dependent Cox models were shown in Figure 1.

Conclusions: While most studies in ESRD evaluated for a relationship between poor glycemic control and mortality, the GIDE study also demonstrates an increased risk for CVE associated with elevated levels of multiple glycemic indices.

FR-PO820

Glycemic Control and All-Cause Hospitalization in an Urban Hemodialysis Population

Jeffrey L. Silberzweig,1,2 Thomas Parker,1 Daniel Levine,1 The Rogosin Inst, New York, NY; 2Nephrology and Hypertension, Weill Cornell Medicine, New York, NY.

Background: Data suggests a U-shaped association of mortality with glycemic control in patients with diabetes mellitus treated by hemodialysis (Ricks1, Ramirez2, Rhe3) but limited published data suggest that poor glycemic control is associated with increased risk of hospital admission (Toidle4).

Methods: We evaluated time-averaged glycemic control in a population of 346 in-center hemodialysis patients and assessed its relationship with all-cause hospitalization between January 1, 2014 and July 30, 2015. Data were analyzed using t tests and a multifactorial model of the number of hospitalizations per patient.

Results: We observed close fits between time-averaged serum glucose levels and hemoglobin A1c (r²=0.56). While the risk of hospital admission associated with the diagnosis of diabetes (p < 0.05), it did not associate with either measure of glycemic control (p>0.04 for serum glucose, p=0.7 for mean hgbA1c). These relationships were not changed by inclusion of race, gender, age, duration of dialysis or tobacco use. Both serum albumin (p<0.05) and ferritin (p<0.05) were associated with increased risk of hospital admission.

Conclusions: Glycemic control does not associate with increased risk of hospital admission despite an association with the presence of diabetes. The relationships with markers of inflammation and nutrition suggest that improved glycemic control may associate with poor nutrition, a known risk factor for poor outcomes among patients treated by hemodialysis.
Associations between Mortality and Glycemic Control with Gleycted Albumin and Hemoglobin A1c in Diabetic Patients on Hemodialysis

Junichi Hoshino, 12 Masanori Abe, 1 Takashi Hasegawa, 1 Takayuki Hamano, 1
Atsushi Wada, 1 Yoshifumi Ubara, 2 Kennei Takaichi, 3 Shigeru Nakai, 4 Masashi Inaba, 5 Ikuto Masakane, 6 The Committee of Renal Data Registry, 7,8 The Japanese Society for Dialysis Therapy, Tokyo, Japan; 8Nephrology Center, Toranomon Hospital, Tokyo, Japan; 9Nihon Univ School of Medicine, Tokyo, Japan; 10Showa Univ Fuyagaoka Hospital, Kanagawa, Japan; 11Osaka Univ Graduate School of Medicine, Osaka, Japan; 12Kitasato Hospital, Ashibakawa, Japan; 13Fujita Health Univ, Aichi, Japan; 14Osaka City Univ Graduate School of Medicine, Osaka, Japan; 15Tabi Hospital, Yamagata, Japan.

Background: For glycemic control in diabetic HD patients, it remains unclear what level of glycated albumin (GA) was associated with lower mortality. Here we examined the differences of association between GA and hemoglobin A1c (HbA1c) with 1-year mortality in a cohort of the Japanese Society for Dialysis Therapy.

Methods: We followed 84,282 diabetic patients on maintenance hemodialysis (mean age 67±11.2 years; mean dialysis vintage, 6.4±4.5 years) for a year, 2013-2014, using Cox regression to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (95% CI) for 1-year mortality after adjusting for all potential confounders as age, sex, smoking, diabetes type, etc.

Results: The adjusted HRs of mortality with baseline GA <12.5, 12.5–17.5, 17.5–20.0, 20.0–22.5, 22.5–25.0, 25.0–27.5, 27.5–30.0, and ≥30.0% were, respectively, 2.53 (95% CI, 1.10-5.80), 1.06 (0.68-1.60), 1.00 (reference), 1.22 (0.93-1.58), 1.09 (0.84-1.43), 1.40 (1.07-1.85), 1.31 (0.96-1.79), 1.77 (1.26-2.49), and 1.64 (1.20-2.23); and with HbA1c <4.5, 4.5–<5.0, 5.0–<5.5, 5.5–<6.0, 6.0–<6.5, 6.5–<7.0, 7.0–<7.5, 7.5–<8.0, and ≥8.0%, respectively, 1.04 (0.94-1.04) (97/1-84/1), 1.16 (0.87-1.55), 1.11 (0.83-1.47), 1.09 (0.82-1.45), 1.14 (0.84-1.54), 1.00 (reference), 1.30 (0.89-1.80), and 1.55 (1.11-2.18). Lowest mortality; 12.5-22.5% for GA, 5.0-7.5% for HbA1c. U-shape association of GA and HbA1c was consistent regardless of albumin level, although weakened in cardinal HD patients.

Conclusions: Both GA and HbA1c levels showed U-shape associations with 1-year mortality in diabetic HD patients, lower mortality with GA 12.5-22.5% and HbA1c 5.0-7.5%.

FR-P0824 Urinary Metabolomics Predict Albuminuria Response to Spironolactone Therapy in Type 2 Diabetes

Michelle Pena, 1 Skander Mulder, 1 Paul Pero, 1 Christina Stolzenburg Oxlund, 1 1B A. Jacobsen, 2 Morten Lindhardt, 2 Peter Rossing, 1 Hildo Jan Lambers Heerink. 1 Med University Groningen; 2EmedicareBiodvelopment GmbH; 3Odense Univ Hospital; 4Steno Diabetes Center.

Background: Spironolactone, a mineralocorticoid blocker, significantly reduces albuminuria (UACR) in patients with type 2 diabetes (T2DM) albeit with a large between-individual variability in response. Finding new biomarkers that predict UACR response to spironolactone may tailor optimal therapy. We tested an a priori defined set of metabolites to predict UACR response to spironolactone.

Methods: Samples were used from a randomized placebo controlled double blind trial of patients with T2DM and resistant hypertension assigned to spironolactone 25-50mg/day (n=50) or placebo (n=50) for 16 weeks adjunct to RAS inhibition. We used a systems medicine approach to select a priori 14 plasma metabolites (oxidative stress, biogenic amines) and 18 urine metabolites (biogenic amines, organic acids) to predict UACR response to spironolactone by matching patients to a spironolactone response model with a spironolactone mechanism of action molecular model. We performed plasma and urinary metabolomics by LC-MS at baseline. We used linear regression to develop separate baseline plasma and urine metabolite scores and tested if these scores could predict UACR response to spironolactone by analysis of covariance.

Results: Spironolactone reduced UACR relative to placebo by median -42% with large variability (5th-95th percentile -93 – 212). The urine metabolic score was inversely correlated with baseline UACR (Pearson’s r =-0.37 p<0.01). The plasma metabolite score correlated with baseline UACR (Pearson’s r =0.39 p=0.001). The urine metabolic score correlated with treatment response to spironolactone (p=0.03 urine score*treatment interaction). The plasma score*treatment interaction was not significant. Analyzed by tertiles of urine metabolic score, placebo-adjusted UACR reduction was significant only in the lowest tertile (-61% (p=0.006) vs -36% (p=0.01)).

Conclusions: An a priori defined set of 18 urine biogenic amines and organic acids predicts UACR response to spironolactone, suggesting that this urine metabolite score may be a tool to optimal therapy in T2DM.

Funding: Pharmaceutical Company Support - Novo Nordisk Foundation Grant number NNF15KSV003

FR-P0821 Changes in Health-Related Quality of Life over Time and Effect of Losartan Treatment in Patients with Type 2 Diabetes Mellitus and Nephropathy

Michelle Pena, 1 Dick de Zeeuw, Bauke Schievink, Petra Demig, 1 Hiddo Jan Lambers Heerink. 1Clinical Pharmacy and Pharmacokinetics, Univ Medical Center Groningen, Netherlands.

Background: Patients with chronic kidney disease have low health-related quality of life (HRQOL), and in general females report lower HRQOL than males. However, there is limited data about longitudinal changes in HRQOL in these patients. Additionally, the effect of angiotensin receptor blockers on HRQOL is unknown. We explored these issues in patients with type 2 diabetes mellitus (T2DM) and nephropathy who participated in the RENAAL trial.

Methods: The RENAAL trial assessed the effect of losartan versus placebo on renal outcomes in 1515 patients with T2DM and nephropathy. Analysis of HRQOL was performed for the 635 U.S. participants (42% of total cohort). HRQOL was assessed with the Short Form-36 survey and is reported as the mental health component summary (MCS) and physical health component summary (PCS). The general population reference values for both MCS and PCS are 50.0 (SD 10.0). HRQOL was measured at baseline and every 3 months until the end of follow-up. We used mixed-effects models to assess changes in MCS and PCS over time and to determine the effect of losartan on MCS and PCS.

Results: Participants (mean age 59.7 (SD 7.8) years; 64.3% males; mean eGFR 42.0 (SD 12.5) ml/min/1.73m2; median UACR 1060 [Q1–Q3 302–2259] mg/g) were followed for a median of 3.3 (Q1–Q3 2.7–3.8) years. Mean baseline MCS was 51.4 (SD 10.1) and PCS was 38.6 (SD 10.8). In the placebo arm, MCS and PCS decreased by 0.9% (95%CI -1.04, 0.46; p=0.01) and 1.1% (95%CI -1.74, 0.83; p=0.01) per year, respectively. Losartan compared to placebo did not change MCS (-0.9% (95%CI -3.00, 1.09; p=0.36) or PCS -0.80 (95%CI -2.81, 1.22; p=0.64). At baseline, males reported higher MCS and PCS compared to females, but there were no gender differences in changes in MCS and PCS over time.

Conclusions: MCS and PCS decreased over time in patients with T2DM and nephropathy. Furthermore, losartan did not appear to have an effect on MCS and PCS, although it previously showed effect on other clinical parameters in this group of patients. Both men and women reported similar declines in MCS and PCS over time.

Funding: NIDDK Support.

FR-P0823 Angiotensin Converting Enzyme Inhibitors versus Angiotensin Receptor Blockers for Control of Moderately Increased Albuminuria in Hypertensive Type 2 Diabetic Patients

Prabhukar Doddle, 1 N. Sireesha, 2 J. Rani, 2 Vivekanand Jha. 1Nephrology, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India; 2Pharmacology, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India; 3Nephrology, PGIMER, Chandigarh, India.

Background: Studies on head to head comparison of angiotensin-converting enzyme inhibition(ACEi) or angiotensin receptor blockers (ARBs) with reduction of albuminuria as a primary outcome in patients with type 2 diabetes mellitus (T2DM) and hypertension are limited.

Methods: This was a single centre, prospective, randomized, open label, active controlled study carried out in patients with well controlled type 2 DM with hypertension and urinary albumin excretion rate (UAER) of 20-200µg/min. Exclusion criteria included presence of coronary artery disease, serum creatinine>1.5 mg/dl, blood pressure more than 130/110 mm Hg, coronary artery disease, congestive heart failure, cerebrovascular accident. Thirty patients were recruited from January 2013 to December 2014 and followed for 52 weeks. Patients were randomized to receive enalapril (n=30, group A) or losartan (n =30, group B) which were titrated to the maximum of 20 mg and 100 mg respectively. Patients with blood pressure of >150/95 mm of hg at the end of 8 weeks, were started on other antihypertensive drugs. Albumin excretion rate was calculated in a 24 hr sample using EIA.
Results: The mean age (years) was 56±11.2 in group A and 54±10.8 in group B. Ratio of men to the number of women in group A and B was equal to 1:1. The mean SBP (mm of Hg), DBP (mm of Hg) and UAER (µg/min) in group A were 167.7±10.58, 99.20±4.16 and 133.33±4.79 respectively and in group B were 159.13±10.49, 100.33±6.33 and 117.80±34.0 respectively. After 52 weeks of follow up there was significant decrease in mean SBP (18.8±0.48 µg/min) and UAER in both groups (p=0.0001, <0.0001 and 0.001 respectively for group A and P=0.0001, <0.0001 and 0.0001 respectively for group B) On comparison there was no significant difference between enalapril and losartan on control of hypertension and UAER (p= 0.32, 0.28 and 0.06 for SBP and DBP and UAER respectively).

Conclusions: In patients with type 2 DM and hypertension, treatment with ACEi or ARBs is equally effective in reducing blood pressure and albuminuria.

FR-PO828

The Renoprotective Role of Paracilacton on Type 2 Diabetic Chronic Kidney Disease Filipa B. Mendes,1 Isabel Almeida,2 Luisa H. Pereira,1 Ana Paula Silva,2 Ana Marreiros,2 Pedro Neves,2 1Dept of Nephrology, Algarve Hospital Centre; 2Dept of Biomedical Science, Algarve Univ; 1Algarve Univ;

Background: Chronic kidney disease (CKD) is a public health problem and Diabetes is the number one causing it, worldwide. Albuminuria is an important sign of CKD progression, cardiovascular disease and death. Therefore, many drugs have been tested in order to decrease the albuminuria. One of those drugs have been the vitamin D analogues. In this study we analyzed the role of paracilacton in the reduction of the urinary albumin-to-creatinine ratio (UACR) in patients with type 2 diabetes and CKD. We also verified the impact of baseline vitamin D in that ratio.

Methods: In an observational prospective study, 42 patients with CKD secondary to type 2 diabetes were treated with paracilacton, 1 µl daily during at least 3 months. We analysed patients data and laboratory parameters at baseline (T0) and 12 weeks after treatment with paracilacton (T1). We also divided our population in 2 groups accordingly the vitamin D level (G 1 – vitamin D <10 ng/ml; G 2 – vitamin D ≥ 10 ng/ml). We used descriptive statistics, Wilcoxon test, Sign test, Student’s t test and the geometric average growth rate.

Results: After paracilacton treatment (T1) we found a reduction of UACR (p=0.001) and PTH (p=0.001), whereas the vitamin D level increased (p < 0.0001). G1 showed higher levels of UACR (p=0.002) at baseline. After 12 weeks (T1) of paracilacton treatment, according to the geometric average growth rate, it was found a reduction of in the UACR (1.78 %) and in the PTH (3.85%). On the other hand, Vitamin D and eGFR showed an increase of 3.38% and 10.9%, respectively.

Conclusions: In our study paracilacton showed renoprotective effects in type 2 diabetes, promoting a reduction in the urinary albumin-to-creatinine ratio. Moreover, there is an inversely proportional association between vitamin D and UACR at baseline.

FR-PO829


Background: PBI-4050 is an orally active drug candidate with anti-fibrotic efficacy in multiple preclinical models of fibrosis in kidney, liver, lung, heart and pancreas. PBI-4050 has been shown to protect against pancreatic fibrosis in db/db and db/db eNOS−/− mice by reducing macrophage and lysosomal infiltration, ER stress and increasing autophagy.

Methods: A Phase 1, open label, single center, single arm study in twenty type 2 diabetes patients with metabolic syndrome was undertaken. The objectives were to evaluate the efficacy safety and tolerability of PBI-4050 following oral administration of 800 mg doses once daily for 12 weeks; and to demonstrate pharmacological activity and translation of efficacy from preclinical studies to humans by monitoring early evidence of changes in cardiorenal disorders biomarkers.

Results: PBI-4050 was demonstrated to be safe and well tolerated without SAEs. PBI-4050 treatment reduced HbA1c (average ΔHbA1c of -0.80, p=0.003 with HbA1c baseline of >7.5%, average ΔHbA1c of -1%, p=0.003 with HbA1c baseline of >7.5%,) in twenty patients. In same patients IL-18 was reduced in the urine (p<0.05). Pentraxine-3 and resistin were reduced in blood (p<0.01).

Conclusions: PBI-4050 was well tolerated and well tolerated in type II diabetic patients with metabolic syndrome. PBI-4050 was efficacious in reducing HbA1c, waist circumference, BMI and weight, and reduced cardiac renal biomarkers II-18, Pentaxine-3 and resistin. These results demonstrated that PBI-4050 may be an efficacious therapy for chronic kidney disease patients with type II diabetes.

FR-PO830

Structured Exercise in Obese Diabetic Patients with Chronic Kidney Disease: A Randomized Controlled Trial Holly J. Leechey,1 Eileen Collins,1 Holly J. Kramer,1 Cheryl Cooper,1 Jolene Butler,1 Conor McBurney,1 Christina Jelinek,1 Domenic Reda,1 Lonni Edwards,1 Anne Arabedjian,1 Susan Oconnell.1 1Medicine and Research, Hines VA Hospital, Hines, IL; 2Medicine, Loyola Univ Medical Center, Maywood, IL.

Background: Patients with type 2 diabetes mellitus (DM), obesity, and chronic kidney disease (CKD) are generally physically inactive and may benefit from exercise. Our objective was to determine the effects of structured exercise on physical fitness, kidney function, endothelial function, inflammation, and body composition in such patients. Methods: In this single-center, randomized controlled trial, 36 obese patients (age 49-81) were randomly assigned to exercise + diet management (n=18) or diet alone (n=18). Participants were eligible if they had type 2 DM, body mass index (BMI) > 30 kg/m², CKD stage 2-4, and persistent proteinuria (> 200 mg/g creatinine for >3 months). The exercise intervention was 12 sessions 3 days per week for 12 weeks of aerobic and resistance training followed by 10 weeks of home exercise. The primary outcome measure was change from baseline in urine protein to creatinine ratio (UPCR) at 12 weeks and 52 weeks.

Results: 32 participants completed the study (14 exercise + diet, 18 diet alone group). Changes in UPCR baseline in UPCR was slightly greater in the diet alone group at 12 weeks but not at 52 weeks. Changes in both symptom-limited and constant-workrate treadmill times were significantly higher in the exercise + diet group at 12 weeks but not at 52 weeks.
weeks. There were no significant differences in urine albumin to creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), endothelial function, inflammation, or body composition between the groups.

**Conclusions:** In obese diabetic subjects with CKD, structured exercise improved exercise capacity but not body composition or renal function.

**Funding:** VA Support

**FR-PO831**

**Renal Sympathetic Activity Assessed by 123I-MIBG Scintigraphy Is Associated with Clinical Measures of Cardiac Autonomic Function**

**Time Hansen,** Bernt Johan Ilum von Scholten,1 Christian Stevens Hansen,1 Phillip Hashak,2 Andreas Kjaer,1 Peter Rossing,1,3 1Steno Diabetes Center, Denmark; 2Rigshospitalet, Copenhagen, Denmark; 3Univ of Copenhagen, Denmark.

**Background:** Scintigraphy with 123I-metaiodobenzylguanidine (MIBG) can assess functional sympathetic innervation in organs. The relation between renal 123I-MIBG uptake and measures of cardiac autonomic function has never been investigated.

**Methods:** In 25 patients with type 2 diabetes and 14 non-diabetic controls we performed three cardiac autonomic reflex tests (CARTs) and five time- and frequency domain heart rate variability (HRV) indices. We quantified functional renal sympathetic innervation by planar scintigraphy performed 15 min (early) and 4 hours (late) after administration of 123I-MIBG. Regions of interest (ROI) were drawn over left kidney (avoiding the pelvis) and the upper mediastium (avoiding the thyroid gland) in the planar posterior view, and late kidney/mediastinum-ratio was calculated from mean counts per pixel within each ROI.

**Results:** Late kidney/mediastinum ratio correlated positively with all time- and frequency domain HRV indices (p ≤ 0.02). For the CARTs, the late kidney/mediastinum ratio correlated positively with the deep breathing test (a measure of parasympathetic function) (p = 0.04), but not with response to standing or the Valsalva test (p ≥ 0.70). All significant associations persisted after adjustment for age and heart rate (p ≤ 0.02). After further adjustments, Hba1c and urinary albumin excretion rate one of the HRV indices, low frequency power, reflecting a combination of sympathetic and parasympathetic tone remained significantly correlated to late kidney/mediastinum ratio (p = 0.02). Late kidney/mediastinum ratio did not correlate with urinary albumin excretion rate, eGFR or systolic blood pressure (p ≥ 0.19).

**Conclusions:** We demonstrate a relationship between renal 123I-MIBG uptake and cardiac autonomic function. This indicates that 123I-MIBG scintigraphy of renal sympathetic tissue could be a valid measure of autonomic function in the kidneys and warrants further research in larger study populations.

**FR-PO832**

**Comparative Effectiveness of a Multifactorial Patient-Centered Intervention in Type 2 Diabetes (T2D)**

Clarissa Jonas Diamantidis,1 Hayden Bosworth,1 Uptal D. Patel,1,2 Megan M. Oakes,1 Shelby D. Reed.1 Duke Univ School of Medicine; 2Gilead Sciences, Inc.

**Background:** The STOP–DKD study is an ongoing clinical trial evaluating the impact of a multifactorial pharmacist telehealth intervention on renal complications of T2D. We sought to explore expected costs, improvements in quality-adjusted survival and cost-effectiveness of implementing such an intervention on a population level in T2D when varying program costs and age eligibility.

**Methods:** The Archimedes Model is a mathematical simulation model which represents physiologic processes using data incorporated from the National Health and Nutrition Examination Survey (NHANES) to generate population-level estimates. We used Archimedes model to simulate and compare costs and outcomes over a 20-year (yr) period among individuals with T2D receiving usual care and a multifactorial intervention consisting of statin therapy, weight reduction (5% if BMI >30 and <35; 10% if BMI ≥35) and HbA1c reduction with T2D receiving usual care and a multifactorial intervention consisting of statin therapy, weight reduction (5% if BMI >30 and <35; 10% if BMI ≥35) and HbA1c reduction with T2D receiving usual care and a multifactorial intervention consisting of statin therapy, weight reduction (5% if BMI >30 and <35; 10% if BMI ≥35) and HbA1c reduction.

**Results:** Among individuals ages 20 to 80 yrs, 9.4% are diagnosed with T2D (mean age 60.2yr). Simulated, undiscounted quality-adjusted life-years (QALYs) with usual care and QALY gains expected with the multifactorial intervention were estimated at 3.93 ± 0.02 at 5yr, 7.26 ± 0.06 at 10yr and 12.09 ± 0.22 at 20yr. At 20yr, all programs ranging from $290 to $800 per person demonstrated good value: $290/yr, cost-saving; $400/yr, $7025 per QALY; $600/yr, $18,461 per QALY; and $800/yr, $33,784 per QALY. The program was more economically-attractive when targeting older individuals with incremental cost-effectiveness ratios of $23,299 per QALY in ages 65-74 and $23,362 per QALY in ages ≥65.

**Conclusions:** Dissemination of a population-based, moderately-effective, low-cost, patient-centered intervention in T2D could increase quality-adjusted life expectancy more efficiently than standard medical therapies used to treat complications of T2D, particularly among older individuals.

**Funding:** NIDDK Support

**FR-PO833**

**Referral to a Multi-Disciplinary Diabetic Renal Clinic Is Associated with Improved Renal Functional Course in Type 2 but Not Type 1 Diabetics with Chronic Kidney Disease**

William P. Martin,1 Tomas P. Griffin,2 Damian Gerard Griffin,2 Timothy O’Brien,1,2 Matthew D. Griffin.1,2 1Regenerative Medicine Inst (REMED), National Univ of Ireland, Galway, Ireland; 2Endocrinology and Nephrology Services, Saolta Univ Health Care Group, Galway, Ireland.

**Background:** Diabetic patients with chronic kidney disease (CKD) may benefit from combined Diabetology and Nephrology care. The study aim was to examine the impact of a multi-disciplinary Diabetic Renal Clinic (DRC) on slope of MDRD eGFR and metabolic indices of type 1 (T1D) and type 2 (T2D) diabetics with CKD.

**Methods:** Patients attending a DRC at a tertiary referral center from 2008 to 2012 were identified. Serial renal and metabolic indices were recorded from 2004 to 2014, and compared pre- and post-first DRC attendance using SPSS v22.

**Results:** 200 subjects were identified (44 (22.0%) T1Ds and 156 (78.0%) T2Ds). Median [IQR] number of eGFR measurements was 31 [18, 56] per subject over 8.70 [6.34, 10.31] years. Age, n (%) female, eGFR, and urinary albumin:creatinine ratio of the two subgroups at the first time of DRC attendance were: 44.71 ± 15.71 vs. 68.94 ± 10.53 years (p < 0.001); 19 (43.2%) vs. 46 (29.5%) (p = 0.126); 57.98 ± 29.92 vs. 46.10 ± 20.57 mL/min/SA/year (p = 0.018); and 33.30 ± 4.00, 147.50 vs. 13.20 [30, 90, 11] mg/mmol (p = 0.321). An additional etiology for CKD was found in 2 (4.5%) T1D and 34 (21.8%) T2D subjects. Results for eGFR decline are shown in the Table.

**Conclusions:** Referral to a combined care DRC resulted in slower eGFR decline in T2D but not T1D subjects with CKD.

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

**FR-PO834**

**Impact of the Medical Care by Diabetologists, Non-diabetologists and Home Doctors before Nephrology Referral on Renal Prognosis in Patients with Diabetic Nephropathy**

Yukimasa Iwata, Rei lio, Terumasa Hayashi, Hiroki Okushima. Nephrology, Osaka General Medical Center, Osaka, Japan.

**Background:** Although it has been recognized that early referral to nephrologists is crucial for the protection of kidney function, it is hard to say that in the current clinical practice in Japan, nephrology referral (NR) is early enough for nephrologists to offer specialized care to patients with diabetic nephropathy (DN). Thus, we conducted single center retrospective study to compare the impact of the medical care by diabetologists, non-diabetologists and home doctors before NR on clinical status at NR and renal outcome.

**Methods:** We enrolled 469 patients with DN referred to our nephrology division from October 2010 to September 2014. Clinical status at NR were compared among the three groups and the impact of the medical care by the different specialties before NR on renal outcome was investigated. Mean age and eGFR at NR were 67.1±12.3 years and 31.2±19.6 ml/min/1.73m2, respectively and 70.5% were male. The number of patients referred from diabetologists (Group A), non-diabetologists (Group B) and home doctors (Group C) were 140, 184, and 145, respectively. A total of 105 patients started RRT: 33, 45 and 27 in Group A, B and C, respectively (P = 0.416). The cumulative incidence of renal outcome was not significantly different between the groups (P = 0.392). The median duration from NR to the renal outcome was 16.7 months (IQR : 6-25.3). Multivariate Cox proportional hazards model showed that eGFR (HR 0.90, 95% CI 0.86-0.94), proteinuria (HR 1.03, 95% CI 1.00-1.05), and systolic blood pressure (HR 1.01, 95% CI 1.00-1.03) were independently associated with renal outcome; however, pre-nephrology care by non-nephrologists including diabetologists did not have any impact on renal outcome.

**Conclusions:** In the current clinical practice in Japan, NR may be too late to offer specialized care by nephrologists to protect kidney function in patients with DN.
Additional studies are needed to determine the true effect on mortality although it appears the two groups.

Women’s Hospital, Harvard Medical School, Boston, MA. David

Implementation of a Decision Making Algorithm for Acute Kidney

Univ of Missouri

FR-PO836 Timing of Renal Replacement Therapy in Acute Kidney Injury: A Systematic Review and Meta-Analysis Rhea Bhargava,1 Saiprasad Narsingam,1 Himanshu Grewal,1 Appearance Arora,1 Remi Mustafa.2 Internal Medicine, Univ of Missouri - Kansas City School of Medicine, Kansas City, MO; 1Nephrology, Univ of Missouri - Kansas City School of Medicine, Kansas City, MO; 2Internal Medicine, Saint Vincent Hospital, Worcester, MA.

Background: Acute Kidney Injury (AKI) is common in critically ill patients and has been associated with increased mortality. The timing of initiation of renal replacement therapy (RRT) has been controversial in patients with AKI.

Methods: We searched the Cochrane Central Register, OVID MEDLINE, EMBASE and PubMed until May 15th 2016. We reviewed the reference lists of relevant reviews, registered trials, as well as relevant conference proceedings. We included all randomized controlled trials that evaluated the effect of timing of initiation of renal replacement therapy in adult patients with AKI. We followed the GRADE approach to assess confidence in the estimated effect (i.e. the quality of evidence). We conducted meta-analyses using random effects models on review Manager Version 5.3.

Results: Nine randomized control trials were included consisting of a total of xxx pts. Compared to “Late RRT”, “early RRT” had a non-significant decrease in mortality with a RR of 1.02 (95% confidence level 0.90 to 1.14, p=0.92). However, “early RRT” significantly decreased the number of patients who were dialysis dependent with a RR of 0.55 (95% CI 0.32-0.95; p=0.00). Intensive care unit length of stay (LOS) decreased with a mean difference (MD) of 1.41 days (95% CI 0.24-2.59; p=0.00) and hospital LOS also decreased with a MD of 5.15 days (95% CI 3.0-7.3; p=0.87) in the early versus late RRT group. There was no difference in the adverse events between the two groups.

Conclusions: In critically ill patients with AKI, early initiation of RRT may decrease dependence on long-term dialysis. It may also shorten the ICU and hospital LOS. Additional studies are needed to determine the true effect on mortality although it appears to be decreased.


Background: Acute kidney injury (AKI) is a common and devastating complication in hospitalized patients. AKI requiring renal replacement therapy (RRT) is associated with increased mortality ranging 46%. Clinical decision tools related to RRT initiation for AKI patients in the ICU have yet to be elucidated.

Methods: We conducted a 1-year prospective cohort study in a medical ICU of an academic medical center involving the implementation of a SCAMP Standardized Clinical Assessment and Management Program (SCAMP), a decision making algorithm. The SCAMP algorithm provided recommendations about optimal indications for initiating and discontinuing RRT based on various clinical parameters. We collected information on clinicians’ adherence or non-adherence to the SCAMP recommendations as well as clinical outcomes.

Results: Patients whose providers adhered to the SCAMP recommendation to start RRT had lower in-hospital mortality (42% vs. 63%, p<0.01) than those whose providers did not. The difference in mortality persisted after multivariable logistic regression analysis adjusting for age, albumin and severity of disease. In pre-specified subgroup analyses, adherence was associated with lower risk of death only in patients with severity of disease scores below the median (adjusted odds ratio 0.21, 95% CI 0.08 – 0.54).

Conclusions: Algorithms like the AKI SCAMP may assist in complex clinical decision making and potentially improve outcomes.

FR-PO838 Analysis of Mortality Predictors in Acute Kidney Injury Requiring Continuous Renal Replacement Therapy after Cardiac Surgery Young Lee Jung.1 Jae Young Kang,2 Soo Yoon Lee,3 Dong Jin Kim,4 ‘Dept of Internal Medicine, 1’Div of Nephrology, 2’Div of Cardiology, 3’Dept of Cardiothoracic Surgery, Sejong Hospital, Korea.

Background: Since the postoperative AKI contributes to high mortality, several risk factors have been reported to be associated with postcardiac surgery AKI. Despite the advances of CRRT and surgery techniques using cardiopulmonary bypass as the management of AKI, the mortality of postoperative AKI requiring CRRT increased. The purpose of this study was to determine the predictors of mortality in AKI requiring CRRT after cardiac surgery and to contribute to reducing mortality through correction of the determined risk factors.

Methods: The retrospective analysis included a total of 3623 patients underwent cardiac surgery; CRRT was required in 125 patients between March 2011 and March 2016. Variables predicting mortality were selected from those proven as available risk factors of postoperative AKI in the previous studies. The variables were analyzed in two groups: post-surgery survivor group who died within 30 days, and survivor group. We used a logistic regression model to assess the relationship between predictors and mortality, while adjusting for other risk factors.

Results: The mortality rate was 44.1% for 125 patients with postoperative AKI requiring CRRT. Univariate analysis identified the following as significant risk factors: Extracardiac vascular disease, eGFR, EuroSCORE, IABP before surgery, Combined operation, Operation time, Time of bypass, Aortic cross clamp time, CRP level at CRRT, the use of ECMO (P<0.05).

In multivariate analysis, mortality was significantly correlated with extracardiac vascular disease (OR=5.55, 95% CI 2.47-12.49), eGFR (OR=1.11, 95% CI 1.02-1.21), the use of ECMO (OR=3.0, 95% CI 1.7-5.3), and CRP level at CRRT (OR=0.17, 95% CI 0.07-0.50).

Conclusions: These findings demonstrated that the statistically strong predictors of the mortality following cardiac surgery were proved to be the presence of extracardiac vascular disease, preoperative renal dysfunction, concomitant surgery, the use of ECMO and high CRP level at CRRT initiation. The identification of predictors associated with mortality would help to better manage such patients with AKI requiring CRRT after cardiac surgery. Also, preventive strategy using these predictors remains the mainstay to reduce the mortality.


Background: ECMO is increasingly being used in critical care units for patients with cardiogenic shock or respiratory failure. In spite of advances, mortality associated with it is 41-49%. Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is very common and is associated with increased mortality. There is paucity of data about the predictors of AKI needing RRT and of poor outcome among these patients. Previous studies have been mostly in pediatric population and data is lacking in adults.

Methods: We performed a chart based retrospective study analyzing all the adult patients admitted to our hospital receiving ECMO.

Results: Charts on 40 patients reviewed which showed high in-hospital mortality (45% or 18.40% and the incidence of AKI was 50% (20/40). The Etiology of AKI was documented to be from a high grade of Tubular Necrosis (ATN). Out of 20 patients with AKI, 18 patients required RRT with 16 patients requiring CVVHD (Continuous Veno-venous hemodialysis) and 2 required Hemodialysis (HD) as the initial modality of renal support. Out of 18 patients who died, 10 patients had AKI requiring RRT. The data also showed that 16 patients had new onset proteinuria on dipstick and was associated with the development of AKI. We found an interesting relationship between the flow on ECMO and development of AKI. Low flow less than 2-2.5L and high flow more than 4-4.5L are associated with more AKI. This relationship has to be studied using statistical analysis at the conclusion of the data.
collection. Out of 20 patients who developed AKI, 10 patients died, another 4 went on to End Stage requiring HD at the time of discharge, with remaining 6 patients left with significant renal injury and progressed to chronic kidney disease.

**Conclusions:** What is clear from our study so far is that patients, who require ECMO, regardless of the indication, have a higher mortality and AKI requiring RRT. The flow parameters are also very low, i.e., hematocrit as very low (less than 2.5-L/min) and higher flows (more than 4-4.5-L) are associated with kidney injury which supports the hypothesis that AKI in these patients are mainly due to ischemic ATN.

**FR-PO840**

Intraoperative Hemodialysis during Liver Transplantation  
Cary H. Paine,1 Terra Pearson,2 James D. Perkins,2 Raghu V. Durvasula.1 1Dept of Medicine, Div of Nephrology, Univ of Washington, Seattle, WA; 2Dept of Surgery, Div of Transplant Surgery, Univ of Washington, Seattle, WA.

**Background:** With the introduction of the Model for End-Stage Liver Disease (MELD) in 2002 the percentage of liver transplant recipients (LTRs) with acute kidney injury (AKI) has increased. Intraoperative hemodialysis (IHD) during liver transplantation has been shown to be safe, but it is unknown whether this procedure improves perioperative outcomes.

**Methods:** We conducted a retrospective analysis of all LTRs at the University of Washington between 2003 and 2014. We compared all LTRs that received IHD with LTRs that had preoperative AKI but did not undergo IHD. AKI was defined as serum creatinine ≥1.5 mg/dL. Outcomes included postoperative serum potassium, arterial base deficit, alinine aminotransferase (ALT) (a marker of early graft function), ventilator days, ICU length of stay (LOS), and hospital LOS.

**Results:** Among 1,191 LTRs, 146 received IHD (12.3%) compared to 164 patients who received IHD but did not receive AKI (13.8%). We also had higher MELD scores (mean 34.6 vs. 24.9) and were more likely to require mechanical ventilation and vasoactive medications preoperatively. ALT and arterial base deficit were lower in the IHD group, and there was no difference in serum potassium, ventilator days, or ICU LOS. Hospital LOS was longer in the IHD group (Table 1).

**Conclusions:** Our data indicate that, despite an overall higher level of acuity among LTRs who received IHD, there was no difference in postoperative electrolyte concentrations, ventilator days or ICU LOS when compared to LTRs with AKI who did not receive IHD. However, LTRs who received IHD had lower ALT levels, which may suggest better early graft function. Clinical trials are needed to further determine the efficacy of IHD in LTRs to improve perioperative and long-term outcomes.

**FR-PO841**

Use of Novel Phosphate-Containing Replacement Solution for Treating Hypophosphatemia in Continuous Renal Replacement Therapy (CRRT): Predictions from a Mass Balance Model  
Farah N. Ali,1,2 Mary Gellens,1 Baris U. Agar,3 J. Ken Leydoldt.1 1Baxter Healthcare; 2Northwestern Univ.

**Background:** Hypophosphatemia is a common consequence of CRRT that often requires treatment with intravenous infusion of phosphate-containing solutions. Conventional replacement solutions (RS) do not contain any phosphate, but phosphate-containing replacement solutions (RS-P) now exist; however, there is limited data on optimal use of such solutions. Our objective was to predict the changes in serum phosphate concentration for hypophosphatemic patients when using RS-P in various CRRT prescriptions.

**Methods:** A mass balance model was used to predict increases in serum phosphate concentration for patients treated with CRRT when using varying ratios of conventional dialysate/replacement fluid with zero phosphate concentration and RS-P (1 mmol/L or 3.097 mg/dL phosphate). CRRT assumptions included: solution rates of 20-40 mL/min, starting serum phosphate concentrations of 1.5, 2.0, or 2.5 mg/dL, and CVVHDF modality. For each phosphate concentration level, we determined the percentage of phosphate added to the fluid and dialysate, serum phosphate concentrations in all 3 starting concentration groups; increases in serum phosphate concentrations ranged from 1.24 to 2.95 mg/dL. For starting phosphate values of 2.5 mg/dL, only use of RS-P as both replacement and dialysate resulted in values of serum phosphate higher than 5.0 mg/dL. Use of RS-P post-filter resulted in modestly higher values than pre-filter infusion.

**Conclusions:** Normalization of serum phosphate using RS-P in CRRT may be achievable using a high-volume, high-flux convection technology, high replacement phosphate levels, and the same remarking with higher baseline serum phosphate values when RS-P was used as both replacement and dialysate. Varying the proportion of RS-P as replacement fluid and dialysate during CVVHDF may allow individualization of therapy to normalize serum phosphate, while maintaining CRRT dose.

**FR-PO842**

A Comparison of Two Different Dialyse Phosphate Supplementation Approaches for Continuous Renal Replacement Therapy  
Michael Heungs,1 Alex Ryan Shaw,2 Weerachai Chaijamorn,2 Bruce A. Mueller.2 1Internal Medicine-Nephrology, Univ of Michigan, Ann Arbor, MI; 2College of Pharmacy, Univ of Michigan, Ann Arbor, MI.

**Background:** Hypophosphatemia is a common and clinically significant complication of continuous renal replacement therapy (CRRT). To decrease risk of hypophosphatemia, we routinely supplement CRRT solutions with phosphate (1.5 mmol/L). Recently, a commercially-available phosphate-containing (P-C) CRRT solution (1 mmol/L) has become available in the US.

**Methods:** We performed a time-limited substitution trial of P-C CRRT solution and compared biochemical parameters to our baseline standard approach of phosphate-added (P-A) solutions. CRRT was otherwise prescribed at discretion of treating team. Outcomes were daily serum phosphate and bicarbonate concentrations, incidence of hypophosphatemia and acidosis, and need for phosphate supplementation.

**Results:** We analyzed data from 127 patient CRRT-days using P-C solutions and compared to baseline experience with 256 CRRT-days using P-A solutions (Table). Mean daily phosphorus levels were in the normal range for both groups, but lower in the P-C compared to P-A groups; there was no difference in incidence of hypophosphatemia. The P-C group did receive more exogenous phosphate administration but at a low overall rate. No CRRT solution-related complications occurred during either period of the pilot.

**FR-PO843**

Cost Savings and Quality Improvement in an Independent Pediatric CRRT Program  
Katherine Twombly, Pediatrics, Medical Univ of South Carolina.

**Background:** CRRT is a complex method of providing dialysis to critically ill patients. Lack of education and hands on training specific to pediatric patients can lead to inadequate support for therapy initiation, sophisticated pump management, and additional staff needs. Lack of education and hands on training specific to pediatric patients can lead to inadequate support for therapy initiation, sophisticated pump management, and additional staff needs. Overall, hypophosphatemia was uncommon when using phosphate-enriched CRRT solutions, and occurred at a similar rate between the P-A and P-C groups. Commercially available P-C dialysate has the potential advantage of eliminating the risks associated with compounding errors, such as contamination or incorrect additives. Additional analyses examining clinical outcomes and cost effectiveness are needed.

**Results:** Pre education CRRT knowledge for RN and MD/DOs was 73% and post was 93%. Our average filter life before training was 8.9 hours. Our average filter life post was 55.81 hrs. Pre-education we did 7272 hours of CRRT=17.8days/pat=47hrs/pat. At 8.9hrs/filter=817 filters X $210/filter=$171,586. Assume 4 bags of fluid/day ($28.21/bag=$11,058.32

For each CRRT day:  
- $220,028.72 initiative
- $19,908.32 savings from new education
- Total=$239,967.04 savings since new education.

**Conclusions:** Overall, hypophosphatemia was uncommon when using phosphate-enriched CRRT solutions, and occurred at a similar rate between the P-A and P-C groups. Commercially available P-C dialysate has the potential advantage of eliminating the risks associated with compounding errors, such as contamination or incorrect additives. Additional analyses examining clinical outcomes and cost effectiveness are needed.
FR-PO844

Effect of Continuous Renal Replacement Therapy on Carnitine Levels and Acyl to Free Carnitine Ratio in Children  
Ki Sgambati, Asha Moudgil.  
Children’s National, Washington DC.

Background: Carnitine is essential for energy production in myocardium and removal of toxic acylcarnitines. We recently showed carnitine is rapidly depleted by continuous renal replacement therapy (CRRT), however effect of CRRT on acylcarnitine and response to therapy have not been investigated. We report effect of CRRT and carnitine therapy on carnitine homeostasis in critically ill children with acute kidney injury (AKI).

Methods: We conducted a retrospective study of children (0-26 years) who underwent CRRT at Children’s National between 2011-2015. Patients with serial total (TC) and free carnitine (FC) levels were included and acyl to free carnitine ratio (AFC) calculated. TC, FC, and AFC of patients who received intravenous carnitine during CRRT were compared with unsupplemented controls by Student’s t-test, prevalence of abnormal TC, FC, and AFC (≥0.4) by Chi-squared.

Results: The study group comprised of 49 children (9.2±0.9 years); 6 received carnitine supplementation, 43 controls did not. At initiation of CRRT, 41% were TC and FC deficient, and 64.7% had elevated AFC. Prevalence of abnormal TC, FC, and AFC increased to 100% by week 4 of CRRT in controls. In comparison, 100% of those treated with carnitine while on CRRT became TC and FC replete, and only 16.6% had abnormal AFC (p=0.003). TC and FC of treated patients (79±108 and 145.5±93.1 µmol/L) were higher vs. controls (27.1±2.3 and 18.7±1.8 µmol/L), p=0.001. Mean AFC at CRRT initiation was elevated (0.68±0.16), and increased to 0.74±0.08 within 4 weeks in controls; FC negatively correlated with AFC (r= -0.4, p=0.003). In those treated with carnitine, AFC normalized to elevated (0.68±0.16), and increased to 0.74±0.08 within 4 weeks in controls; FC negatively correlated with AFC (r= -0.4, p=0.003). TC and FC of treated patients (179±108 and 148.5±93.1 µmol/L) increased to 100% by week 4 of CRRT in controls. In comparison, 100% of those treated with carnitine supplementation, 43 controls did not.

Conclusions: CRRT is associated with disturbed carnitine homeostasis, resulting in TC and FC deficiency with concurrent elevation of AFC. This is the first study to show TC, FC, and AFC normalize in children on CRRT who receive carnitine supplementation.

FR-PO845

High Cut-Off Dialysis Is Efficient with HCO Membrane  

Background: High cut-off (HCO) membranes are indicated for enhanced removal of 20-50kDa toxins [Gondouin, Adv Chronic Kidney Dis 2011]. Applications include myeloma kidney treatment, sepsis and rhabdomyolysis. Though a classification for HCO membranes is available [Boschetti-de-Fierro, Int J Artif Organs 2013], some high-flux dialyzers are used for high cut-off dialysis. We compare the performance of two dialyzers offered for high cut-off treatment of myeloma kidney, and which, according to the mentioned classification, are categorized as high cut-off dialyzers (Theralite) and as high-flux dialyzer (APS-21EH).

Methods: High cut-off treatments were simulated with Q B=250ml/min, Q D=500ml/min and Q UF=10ml/min for Theralite (HCO, Gambro) and APS-21EH (APS, Asahi). In each experiment (HCO n=7, APS n=2), 1L of human plasma (octaplasLFG, protein conc. 60g/L) was recirculated for 60min followed by 60min treatment. Markers were spiked into the plasma at 5min of recirculation: [β2-m (5 mg), myoglobin (500 µg), L-FLC (150 mg), interleukin 6 was comprised in plasma. Samples were taken from plasma pool and dialysate at various times. Clearances were calculated from first order kinetics of pool concentration (measured by nephelometry) over time.

Results: The HCO membrane showed higher clearances than the APS high-flux membrane for the middle molecules investigated. High differences were found for myoglobin (105 vs. 60ml/min), relevant when treating rhabdomyolysis, and for L-FLC (41 vs. 7ml/min), which is relevant in the myeloma treatment.

Conclusions: Based on the plasma clearances observed, an efficient high cut-off dialysis treatment with the expected removal of middle molecules is only possible with dialyzers comprising a membrane categorized as high cut-off (HCO) membrane. Results indicate that a high-flux membrane does not offer the efficient removal required in acute cases.

FR-PO846

Use of Logarithmic Constant of Exponential Decay to Control Sodium Conductivity and Kinetics in a Patient with End Stage Renal Disease and Severe Hyponatremia  
Hoomaz Dara Dastoor,1 Chandra Mauli Jha,2 Ken J. Donaldson,3 Thalakunte Muniraju,2 Samra Abouchacra,2 Hatem Mohyeldin Ebeid,1 1Div of Nephrology, Rahba Hospital-Johns Hopkins International, United Arab Emirates; 2Div of Nephrology, Burjeel Hospital, United Arab Emirates; 3Div of Nephrology, Al Noor Hospital, United Arab Emirates; 4Div of Nephrology, Tawam Hospital, United Arab Emirates.

Background: We present a case of a patient with severe renal failure and Hyponatremia who was treated by Renal Replacement Therapy. Sodium (Na+) Kinetics and Conductivity were regulated using a complex algorithm created using a logarithmic constant “e” as measure of Exponential Decay of Na+ transfer, resulting in a controlled and predictive rise in Plasma Sodium (PNa+).

Methods: A 25-year-old male presented with renal failure and PNa+ ‘99 mmol/L, urea 58 mmol/L, Creatinine 1551 umol/L with altered mental status and seizures. The patient was initially placed on CVVHD followed by conventional HD. Over the next few days his PNa+ had a gradual and steady rise and had a complete recovery without any neurological sequelae.

Results: Using the below formulas we can predict expected post dialysis Serum Na concentration and determine Na concentration of Replacement fluid required to achieve desired post dialysis Na concentration.

Conclusions: Understanding the principles of Sodium Transfer, Conductivity and Kinetics in renal failure, allows for use of complex Logarithmic equations using Mathematical constant of Logarithmic Decay “e” as measure of exponential transfer of Sodium and Urea. By controlling the transfer of Sodium during a Hemodialysis session we can control the rate of rise in Plasma Na+ for patients with severe Hyponatremia and renal failure. This can result in a steady rise in PNa+ concentrations and avoid potentially fatal ODS.
OPTIMAL Selection for and Timing to Start Renal Replacement in Critically Ill Older Patients with Acute Kidney Injury (OPTIMAL-AKI): A Prospective Observational Cohort Study

Ron Wald, Josee Bouchard, Jean-Francois Calilhier, William Barton, Sean M. Bagshaw, St. Michael's Hospital, Canada; Univ de Montreal, Canada; Univ of Saskatchewan, Canada; Univ of Alberta, Canada.

Background: Older patients represent approximately half of those who receive renal replacement therapy (RRT) in intensive care unit (ICU) settings. We have limited information on the optimal circumstances for starting or withholding RRT in older patients with AKI.

Methods: Prospective observational cohort study performed at 16 centers from across Canada, September 2013 and July 2015. Inclusion criteria: 1) ≥ 65 y; 2) admitted to ICU, and 3) KDIGO Stage 2-3 AKI. Exclusions: 1) received urgent RRT for drug overdose and 2) receiving any RRT in preceding 4 weeks. Primary exposure was receipt of RRT. Primary outcome was 90-day mortality. Secondary outcomes included reasons for not receiving RRT and changes to goals-of-care (GOC).

Results: 499 patients were enrolled. Mean age was 75 (SD 7.2) y, 204 (41%) were female, and mean Charlson comorbidity score was 3.0 (SD 2.3). Median Clinical Frailty Score (CFS) was 4.0 (IQR 3.0-5.0), 95 (20%) had cognitive impairment and 193 (39%) has been hospitalized in the preceding 6 months. Mean APACHE II score was 28.0 (SD 8.8). Of the cohort, 361 (72%) of patients would have been offered RRT if indicated while 229 (46%) actually received RRT. Leading indications for RRT included oligo-anuria (74%), fluid overload (35%) and acidemia (33%). Reasons for not starting RRT included: kidney recovery (67%), not aligned with goals-of-care (25%) and active limitation-of- (74%), fluid overload (35%) and acidemia (33%). Reasons for not starting RRT included: kidney recovery (67%), not aligned with goals-of-care (25%) and active limitation-of-care (74%), fluid overload (35%) and acidemia (33%).

Conclusions: The majority of older adults in the ICU with AKI would be offered RRT and approximately half received RRT. Clinical need, as well as underlying frailty and severity of illness, influence decision-making regarding RRT.

Gordon: Funding Support - Non-U.S.

Temporal Trends of Dialysis Requiring Acute Kidney Injury after Orthotopic Cardiac and Liver Transplantations

Girish N. Kinsuk, Chaubhan Konjhsr, Konjhsr Konjhsr, Pranav S. Garimella, Madhav C. Menon, Charuhas V. Thakar, Icahn School of Medicine at Mount Sinai; Tufts Univ School of Medicine; Univ of Cincinnati, and Renal Section, Cincinnati VA Medical Center.

Background: We sought to assess the national epidemiology of acute kidney injury requiring dialysis (AKI-D) in stable orthotopic cardiac and liver transplant.

Methods: We used the Nationwide Inpatient Sample to evaluate the yearly trends (2002 to 2013) of AKI-D in cardiac and liver transplant. We excluded the postoperative period. We defined AKI-D by ICD-9 code 584.xx and dialysis procedure by presence of procedure code of 39.95 or diagnosis code of v45.11, v56.0 or v56.1. We used survey logistic regression to assess AKI-D impact on hospital mortality and adverse discharge and calculated adjusted odds ratios (aOR).

Results: We identified 130,143 hospitalizations with cardiac transplant of which 2776 (2.13%) had AKI-D and 266,987 hospitalizations with liver transplant of which 5689 (2.14%) had AKI-D. There was 45% increase in AKI-D in cardiac transplant, from 1.63% in 2002 to 2.33% hospitalizations in 2013; p<0.01 and a two-fold increase in AKI-D in liver transplant admissions, from 1.32% in 2002 to 2.65% hospitalizations in 2013; p<0.01.

This increase was attenuated after adjustment for temporal changes in demographics, comorbidities, and procedures. In AKI-D in cardiac transplant recipients was associated with three-fold mortality (aOR 2.85; 95% CI 2.11-3.80) and two-fold adverse discharge (aOR 1.97; 95% CI 1.53-2.55). Similarly, AKI-D in liver transplant recipients was associated with two fold mortality (aOR 1.95; 95% CI 1.53-2.55) and adverse discharge (aOR 1.91; 95% CI 1.57-2.30).

Conclusions: This study highlights the growing burden of AKI-D in non-renal solid organ transplant recipients and its impact, and emphasizes the need to develop strategies to reduce the risk of AKI.

TORCH: How a Small Charity Can Effect Significant Improvement in Kidney Care in Haiti

Robert S. Brown, Philip C. Cleophas, Brian D. Remillard, Beth Israel Deaconess Medical Center, Boston, MA; ‘Hôpital Unive de Mirebalais, Mirebalais, Haiti; Dartmouth Hitchcock Medical Center, Lebanon, NH.

Background: Though the ISN 0 by 25 initiative to avoid preventable deaths from AKI by 2025 is desirable, kidney disease care in Haiti was almost non-existent. Renal replacement therapy (RRT) was available to only a few patients in Port-au-Prince. In a World Kidney Forum (AKD Mar 2016), Haiti was not even mentioned with the 20 Latin American countries providing some RRT.

Methods: In 2014, The Organization for Renal Care in Haiti, TORCH, Inc, a 501(c) (3) tax exempt Massachusetts charity, was formed with the mission to ‘provide education, medical equipment, training and other resources to medical professionals and facilities in Haiti so that they can provide treatments to individuals with kidney disease who would otherwise not receive such treatments’. We realized that TORCH could not obtain enough monetary support to accomplish such a task by itself.

Results: TORCH served as a focus to obtain help from multiple partners. TORCH brought medical residents and nurses from the Partners in Health/Zamni Lasante hospital in Mirebalais (HUM) to Hanover and Boston for training to perform hemodialysis (HD). Then, using equipment and supplies donated by NxStage, Bridge of Life and Sustainable Kidney Care Foundation, HUM initiated HD treatments for patients with AKI. To date, 26 patients have undergone a total of 70 HD treatments with 12 complete recoveries, 2 improved, 2 ongoing treatments, 1 CKD and 9 deaths. TORCH has sent 2 advanced practice nurses from the USA to Port-au-Prince to teach peritoneal dialysis techniques to 30 professionals. With Bridge of Life, we plan a prevention program to diagnose Haitians with undetected hypertension, diabetes and proteinuria. TORCH will provide expenses to train Haitian professionals in the USA in basic nephrology care and later in kidney transplantation.

Conclusions: With dedicated volunteers, a group of charitable partners, and only limited funds, a small charity can effect large improvements in kidney care in Haiti. The success of this effort to save lives may engender future support from government and other deep pockets.
FR-PO851
A Single-Center Retrospective Study of the Effect of Residual Renal Function plus Continuous Renal Replacement Therapy (CRRT) Dose on the Prognosis of Patients with Acute Kidney Injury (AKI) Xiang-Mei Chen, Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing.

Background: Pre-CRRT residual renal function differs among patients with AKI, and "exogenous" replacement function provided by CRRT and residual renal function were considered total renal function, whose levels may affect the prognosis and renal function recovery of AKI patients.

Methods: We conducted a retrospective analysis of patients treated at our hospital between January 1, 2010 and December 31, 2014. A total of 215 AKI patients who received CRRT met the inclusion and exclusion criteria and were included in this study. Pre-CRRT residual renal function, CRRT dose, and pre-CRRT residual renal function plus CRRT dose were calculated. Moreover, the patients were divided into "high" groups and "low" groups based on the mean values of pre-CRRT residual renal function plus CRRT dose, and inpatient mortality and the 90-day renal recovery rate were compared between the two groups.

Results: Residual renal function and CRRT dose were calculated for 215 patients, and the patients were divided into a high group (55.72 ± 6.53 mL/h/kg, n = 104) and a low group (30.39 ± 7.69 mL/kg, n = 111) on the basis of their total renal function (pre-CRRT residual renal function plus CRRT dose), whereas inpatient mortality was significantly higher in the low group than in the high group (53.15% vs 39.39%, P = 0.021). Moreover, the 90-day recovery rate was higher in the high group than in the low group (67.21% vs 50.00%, P = 0.044). A multivariate regression analysis that controlled for confounding factors showed that inpatient mortality was an independent factor for inpatient mortality (HR 0.502, 95% CI 0.273–0.920, P = 0.027) and 90-day renal recovery rate (HR 0.549, 95% CI 0.383–0.796, P = 0.017).

Conclusions: "Exogenous" renal function with CRRT provided on the basis of pre-CRRT residual renal function may have improved the survival and renal recovery of AKI patients and was more effective in the high group than in the low group.

FR-PO852
Early Continuous Renal Replacement Therapy in Septic Acute Kidney Injury Could Be Defined by Its Initiation within 24 Hours of Vasopressor Infusion Seung Kyung Lee, Kyun Yong Lee, Jin Won Lee, Dept of Internal Medicine, Asan Medical Center, Seoul, Korea; ‘Dept of Internal Medicine, Dankook Univ College of Medicine, Cheonan-si, Korea.

Background: Although institution of early continuous renal replacement therapy (CRRT) reduces morbidity and improves outcomes in patients with septic acute kidney injury (AKI) by reducing inflammatory cytokines, the optimal timing for the initiation of early CRRT is uncertain and requires a practically feasible definition with acceptable evidence.

Methods: We investigated the clinical impacts of three time interval parameters on the morbidity and mortality of 177 patients with septic AKI: (1) time from vasopressor initiation to CRRT initiation (T\text{vaso-CRRT}), (2) time from ICU admission to CRRT initiation (T\text{ICU-CRRT}), and (3) time from endotracheal intubation to CRRT initiation (T\text{endotracheal-CRRT}).

Results: The proportion of the patients with T\text{vaso-CRRT} less than 24 hours (median 14 hours, interquartile range [IQR] 5–30 hours) was significantly higher in the survival group than in the non-survival group (84.3% vs. 58.5%, P < 0.001). T\text{vaso-CRRT} less than 24 hours was an independent factor for inpatient mortality associated with 28-day mortality (hazard ratio [HR], 0.449; 95% confidence interval [CI], 0.211–0.956; p = 0.038) and 90-day mortality (HR, 0.365; 95% CI, 0.165–0.825; p = 0.015; and HR, 1.566; 95% CI, 1.320–1.858; p < 0.001, respectively). T\text{ICU-CRRT} within 17 hours, T\text{endotracheal-CRRT} (median 13 hours, IQR 4–48 hours) were significantly correlated with both the length of ICU stay (p < 0.001) and mechanical ventilation duration (p < 0.001).

Conclusions: Considering the possible therapeutic measurement by physician on the basis of the results in this study, early CRRT could be defined by a T\text{vaso-CRRT} less than 24 hours. The T\text{ICU-CRRT} and T\text{endotracheal-CRRT} are associated with morbidity and mortality not.

FR-PO853
Early Mortality on Continuous Renal Replacement Therapy (CRRT): The Prairie CRRT Study Bhushan Prouad, Nephrology, Regina Qu’Appelle Health Region, Regina, SK, Canada.

Background: Patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT) have an increased short-term and long-term risk of mortality. In most north american intensive care units (ICU), these patients receive continuous renal replacement therapy (CRRT). Some patients once initiated on CRRT may not survive more than 24 hours. For these patients the rationale for the use of this invasive and costly treatment and its appropriate indication has not been established. We were interested in identification of risk factors for early mortality.

Methods: We conducted a prospective cohort study of patients undergoing CRRT for AKI in three ICUs of the Regina Qu’Appelle Health Region (RQHR) from April 2013 to September 2014. Based on demographic and clinical information, 157 patients were enrolled and followed patients from admission to 9 months post discharge. The primary outcome was <24 hour mortality after CRRT initiation. Other secondary outcomes included mortality, and renal outcomes post discharge for 90 days. A stepwise multiple variable logistic regression model was used to develop a predictive model of CRRT dependent variables, with significant variables derived from univariate analysis as covariates.

Results: 269/2634 patients admitted to the ICUs in the study period had stage III AKI. 106 (4%) were started on CRRT. 66/106 died in ICU whilst on CRRT. 17/66 (26%) died within 24 hours of initiating therapy. Patients who died within 24 hours had a higher FiO2 (0.8 ± 0.2 vs. 0.6 ± 0.2, P = 0.011), higher epinephrine (32.0 ± 29.9 vs. 6.5 ± 9.3, P = 0.005), higher norepinephrine levels (39.4 ± 23.5 vs. 19.6 ± 14.2, P < 0.005), lower pH (7.1 ± 0.2 vs. 7.3 ± 0.1, P < 0.001) when compared to those who survived the first 24 hours of initiation.

Conclusions: 26% of the patients died within the first 24 hours of starting CRRT. In stepwise multivariate logistic regression analysis, patients appear to be at high risk of early mortality if they have a high FiO2 (>0.7) and high norepinephrine > 20 µg. However, we were unfortunately unable to identify any specific clinical and biochemical indicators that suggested early mortality with a high degree of statistical confidence.

FR-PO854
Pre-Empiric CRRT Is Associated with Improved Outcome of Dialysis- Requiring Severe Acute Kidney Injury: Multicenter Prospective Study Tetsushi Yamashita,1 Eisei Noiri,1 Daisuke Sanada,2 Takayuki Tsuji,3 Hideco Yasuda,3 Masasumi Nagakura,1 Kent Doi,1 1The Univ of Tokyo, Tokyo, Japan; 2Showa Univ, Tokyo, Japan; 3Hamamatsu Univ School of Medicine, Hamamatsu, Japan.

Background: It is controversial when to start RRT for AKI patients without life-threatening complications and pre-empiric RRT is frequently considered especially in ICUs. This study was conducted to reveal the characteristics of patients with pre-empiric CRRT compared with classic CRRT.

Methods: This study enrolled 146 patients who needed CRRT as the initial method of RRT in the adult mixed ICUs of 3 university hospitals. CRRT initiation was determined by the attending physicians based on each patient condition. We considered the following factors as pre-empirical indications for RRT according to the previous study (CIASN 2014:9:1577): hyperkalemia, severe acidosis, severe azotemia, oliguria, and fluid overload with pulmonary edema. CRRT without conventional indications was defined as pre-empiric CRRT and CRRT with one or more conventional indications was defined as classic CRRT.

Results: Fifty-nine patients (40%) fulfilled at least one conventional indication before initiation of CRRT (classic CRRT). Patients with pre-empiric-CRRT had similar baseline conditions evaluated by eGFR, SOFA score on ICU admission, SOFA score at CRRT initiation. However, they had lower serum creatinine (p<0.001) and plasma NGAL (p=0.03) at CRRT initiation, less in-hospital mortality (p<0.001), and more early RRT had a 25% decrease in eGFR than patients with classic CRRT.

Conclusions: This observational study suggests pre-empiric CRRT could provide better outcomes of in-hospital mortality and renal recovery. Measures to distinguish the patients for whom RRT is beneficial is necessary to improve the performance of CRRT on AKI treatment.

Funding: Government Support - Non-U.S.

FR-PO855
Initiation Time of Renal Replacement Therapy on Patients with Acute Kidney Injury: A Systematic Review and Meta-Analysis of 7746 Participants Caixia Wang,1 Linsheng Lv,1 Xiu Liu,1 Shaomin Li,1 Yanni Wang,1 Tan-Qi Lou.1 1Div of Nephrology, The Third Affiliated Hospital of Sun Yat-sun University, Guangzhou, China; 2Operation Room, The Third Affiliated Hospital of Sun Yat-sun University, Guangzhou, China.

Background: Early initiation of renal replacement therapy (RRT) is recommended to improve clinical outcomes in patients with acute renal failure (ARF) in some studies, but its effects on mortality and renal recovery are unknown.

Methods: Randomized controlled trials (RCTs) and cohort comparative studies comparing early RRT with late RRT in patients with AKI were identified through PubMed, Embase, the Cochrane library and references of related papers. The primary outcome was all-cause mortality. Secondary outcomes were renal recovery, hospital mortality, duration of hospitalization and mechanical ventilation. Data were analyzed by Random effects model.

Results: We evaluated 52 studies (including nine RCTs) with 7746 patients with AKI. The results of the trials indicated that pre-emptive RRT could delay renal failure and improve renal function in a dose-dependent way, with a less than 50% decrease in eGFR than patients with classic CRRT.

Conclusions: This systematic review suggests pre-emptive CRRT could provide better outcomes of in-hospital mortality and renal recovery. Measures to distinguish the patients for whom RRT is beneficial is necessary to improve the performance of CRRT on AKI treatment.

Funding: Government Support - Non-U.S.
**FR-PO856**

Phase Angle Is Associated with Hospital Mortality Risk in Acute Kidney Injury Patients Irrespective of Clinical Severity

Francisco Javier Lavilla,1 María Josefina Higueras,1 Pelayo Moiron Fdez-Felechosa,2 Nuria Garcia Fernandez,3 Paloma L. Martin Moreno,2 Pedro Errasti,2 Jorge M. Nunez-Cordoba.2 1Nephrology, Clinica Univ de Navarra, Pamplona, Navarra, Spain; 2Research Support Service, Central Clinical Trials Unit, Clinica Univ de Navarra, Pamplona, Navarra, Spain.

**Background:** The phase angle (PA) is a novel marker of functional status that is determined by bioelectrical impedance analysis (BIA). A low PA has been suggested to be an adverse prognostic marker of survival, although no study has evaluated its prognostic influence on acute kidney injury (AKI) patients, independently of clinical severity. We evaluated the association between PA and hospital death in AKI patients adjusting for individual severity index (ISI), which is a validated proxy of clinical severity.

**Methods:** Clinical and analytical factors, PA, and hospital death were prospectively registered in 97 AKI patients. ISI formula includes age decade, sex, nephrotoxic, oliguria, hypotension, jaundice, coma, consciousness, and assisted ventilation. We evaluated c-reactive protein (CRP), extracellular/intracellular water ratio (ECW/ICW) and Karnofsky index (r=0.456, p<0.001). The OR (95% CI) for PA (per degree increase) was 0.33 (0.14; 0.78) after adjusting for age, sex, and clinical severity.

**Conclusions:** PA was associated with protein metabolism and chronic health status. The PA appears to be a prognosis index of hospital mortality in AKI patients irrespective of clinical severity.

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**FR-PO857**

Extracellular Hypervolemia Evaluated with Bioimpedance, as a Prognostic Marker in Acute Kidney Injury


**Background:** The bioelectrical impedance analysis (BIA) is a noninvasive and painless technique to perform, which is used for determining body composition. It can offer information about membrane cell integrity, volemia and clinical status. We evaluate use of BIA to measure extracellular water with extracellular/intracellular water ratio – ECW/ICW – as a prognostic markers in acute kidney injury (AKI).

**Methods:** We include a cohort of 159 patients (median age 66 years SD 1.8, and 72.2%; AKI etiology (Prerenal 67.6%, Renal 9.5%, Pre-renal 14.3%, Postrenal 3.8%, others 4.8%); mean ISI, 0.24 (SD: 0.12); and mean PA, 3.99 (SD: 1.35). Hospital deaths: 10 (10.31%). We evaluated association of PA with ISI (r=-0.210, p=0.031), CRP (r=-0.269 p=0.009), Albumin (r=0.298, p=0.003), ECW/ICW ratio (r=-0.374, p=0.003) and Karnofsky index (r=0.456, p<0.001). The OR (95% CI) for PA (per degree increase) was 0.33 (0.14; 0.78) after adjusting for age, sex, and clinical severity.

**Conclusions:** PA was associated with protein metabolism and chronic health status. The PA appears to be a prognosis index of hospital mortality in AKI patients irrespective of clinical severity.

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**FR-PO858**

Bioimpedance Analysis Guided Volume Expansion for the Prevention of Contrast-Induced Acute Kidney Injury

Sarassawan Kananuraks, Arkom Nongnuch. Renal Unit, Dept of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand.

**Background:** Periprocedure fluid administration is a cornerstone for prophylaxis of contrast-induced acute kidney injury (CI-AKI). Recent trials showed the benefit of personalized larger amount of fluid administration categorized by fluid status accessed by left ventricular end diastolic pressure (LVEDP) compared with conventional protocol. However, the LVEDP is invasive procedure leading to limited clinical application. Bioimpedance analysis (BIA) is non-invasive tool for determining fluid status in CKD. This study aim to prove periprocedural fluid administration categorized by BIA may lower incidence of CI-AKI comparing with conventional protocol (NCT02449317).

**Methods:** In this randomized controlled trial, we personalized isotonic bicarbonate administration categorized by total body water/extra cellular water (ECW/TBW) compared with conventional bicarbonate protocol for preventing CI-AKI in 56 CKD patients undergoing coronary angiography (CAG). For the BIA group, patients would receive fluid rate 3 ml/kg for 1 hour before CAG and 1ml/kg/h, 2 ml/kg/h and 4 ml/kg/h for 6 hours after CAG if ECW/TBW was >0.4, 0.36-0.4 and <0.36 respectively. In the conventional group, we provided fluid rate 1 ml/kg for 1 hour before CAG and 1 ml/kg/h for 6 hours after CAG. CI-AKI was defined as an increased in serum creatinine more than 0.3 mg/dl with in 48-72 hours after CAG.

**Results:** Baseline characteristics were comparable between two groups except periprocedure volume, which was significantly greater in BIA group.

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**FR-PO859**

Fluid Overload Masks AKI Diagnosis and Associated Outcomes in Critically Ill Children

David T. Selewski,1 Katja M. Gist,2 Erin K. Stenson,3 Shina Menon,4 Stuart Goldstein,5 Rajit Basu.3 1Univ of Michigan, Ann Arbor, MI; 2Univ of Colorado, Aurora, CO; 3Cincinnati Children’s Hospital, Cincinnati, OH; 4Univ of Washington, Seattle, WA.

**Background:** Acute kidney injury (AKI) occurs commonly in critically ill children and is associated with adverse outcomes. Fluid overload (FO) has been shown to mask the diagnosis of AKI in select populations (adults, congenital cardiac surgery). This study aims to evaluate the impact FO has on the diagnosis of AKI in a general pediatric intensive care unit (PICU) population.

**Methods:** Secondary analysis of The Acute Kidney Injury in Children Expected by Renal angina and Urinary Biomarkers (AKI-CHERUB) study, a single center prospective observational study conducted in a tertiary care PICU. The primary outcome was severe AKI at 48 hrs, utilizing the SCR based KDIGO definition Stage 2-3 AKI. AKI was also recalculated using ScCr corrected for FO (Cr corr = SCr x (1 + [net fluid balance/total body water])). FO was calculated daily by fluid balance from PICU admission. Secondary outcomes: length of mechanical ventilation (MV), PICU LOS, hospital LOS.

The incidence of CI-AKI was 3.7% in BIA group and 6.9% in conventional group. Relative risk for CI-AKI of conventional group was 1.86 (0.18-19.37, p=0.6).

**Conclusions:** The larger amount of isotonic bicarbonate administration guided by BIA was not show additional benefit for prevention CI-AKI when compared with conventional protocol.

**Funding:** Private Foundation Support
Results: 181 patients were in the cohort (166 with complete outcome data). Mortality was 5.7% (17 patients). There was a trend toward lower levels of biomarker concentration in the NES group compared to the Ctrl group. IL-10, IP-10, IL-6, IL-1b, IP-10, MIP-1a, INF-a, INF-g, IL-1a, IL-3 and IL-7 were associated with severe AKI in this study. There was no significant difference in the detection of PP between the NES and Ctrl groups.

Conclusions: NES has a beneficial effect on the inflammatory response during cardiac surgery, reducing the production of pro-inflammatory cytokines and chemokines. However, the results of this study should be interpreted with caution due to the small sample size and the lack of a placebo group.

FR-PO60
Nesiritide Modulates Inflammatory Response during Cardiac Surgery
Thomas M. Beaver, Jessica A. Cobb, Abhilash Koratala, A. Ahsan Ejaz. University of Florida, College of Medicine, College of Public Health, Division of Nephrology and Hypertension, University of Florida.

Background: The study was performed to investigate the effects of NES on inflammatory response during cardiac surgery. Methods: N=29 cardiac surgery patients were randomized to an infusion of NES versus placebo (Ctrl). The effect of NES on inflammatory response was investigated by measuring a panel of candidate biomarkers and clinical parameters at predetermined time points.

Results: There were no significant differences between the groups with regards to the early biomarkers of AKI: urine NGAL (N=261.3±71.5ng/mL vs. Ctrl 240±46.3ng/mL, p=0.23) and urine IL-18 (N=290.1±48.3ng/mL vs. 254.5±118.3ng/mL, p=0.090). A concerted biomarker kinetic pattern of time-differentiated peak concentrations was observed. IL-10, TNF-a, IL-6, IL-10, IP-10, MIP-1α, INF-a, INF-g, IL-1b, IL-3 and IL-7 reached peak concentration at 0hr following end of CPB; TNF-a, EGF, GM-CSF, IL-12p40, IL-17, MIP-1b and MCP-1 at 1hr; IL-18, VEGF, IL-13 and IL-1ra at 2hrs; TNF-b, G-CSF, IL-1b, IL-2, IL-4, IL-5 and IL-15 at 2hrs; and ET-1 and IL-18 at 6hrs. A generalized trend towards lower levels of biomarker concentration in the NES group compared to the Ctrl group could be observed. At 0hr, the NES group exhibited significant reduction of peak concentrations of IL-6 (p=0.009), IL-10 (p=0.009), IL-1a (p=0.020), IL-10 (p=0.001) and IFN-a (p=0.032) compared to the Ctrl group. Significant reduction in peak concentrations of TNF-a (p=0.007) and MIP-8 (p=0.027) at 1hr and ET-1 (p=0.020) at 6hrs were observed in the NES group compared to the Ctrl group.

Conclusions: Our study demonstrated a concerted inflammatory response in cardiac surgery that was modulated by nesiritide. Furthermore, nesiritide attenuated ET-1 response thus suggesting that previously observed favorable renal effect may be linked to attenuated renal vasoconstriction.

FR-PO61
Pulsatile Portal Flow and Acute Kidney Injury after Cardiac Surgery
William Beaubien-Souligny, Josee Bouchard, Yoan Lamarque, Jean-Francois Cailhier, Andre Denault. Intensive Care, Montreal Heart Inst, Montreal, QC, Canada; Nephrology, Hôpital Sacré-Cœur de Montréal, Montreal, QC, Canada; Nephrology, Cham, Montreal, QC, Canada.

Background: Acute kidney injury (AKI) is frequent following cardiac surgery and venous congestion of the kidneys may play a role in the development of AKI. We assessed whether portal flow pulsatility (PP), a sign of portal hypertension from congestive heart failure which could reflect elevated venous pressure in kidneys, may independently predict AKI, as well as risk factors for PP.

Methods: We conducted a retrospective cohort study including patients who had at least one assessment of portal flow during the week following cardiac surgery between May 2015 and February 2016 at our institution. We excluded patients with stage V CKD, AKI before surgery or liver cirrhosis. PP was defined as a pulsatility fraction ≥ 50%. We assessed AKI over the week after surgery according to the KDIGO serum creatinine criteria and performed logistic regression analyses to identify independent risk factors of AKI and PP.

Results: We screened 136 patients and included 102 patients with a mean age of 69. 37.3% of patients underwent CABG while 58.8% had valvular or complex surgeries. 21.6% had stage III CKD and 2% had stage IV CKD. PP was detected in 35% of patients. AKI developed in 68.8% of patients with 13.7% progressing to severe AKI (stage 2 or higher). The detection of PP was associated with a significant increase in the risk of AKI (OR: 6.0 CI: 2.2-16.4) and severe AKI (OR: 5.4 CI: 1.5–18.6). The association with AKI was significant in a multivariable model including baseline creatinine and the SOFA cardiovascular score during the first two days after surgery (OR: 5.7 CI: 1.9-16.8). Maximal pulmonary artery pressure (44 vs 39 mmHg p = 0.03) and percentage of cumulative fluid balance over body weight (4.9% vs 3.6% p = 0.04) were associated with PP.

Conclusions: In our study, the detection of PP during the first week after cardiac surgery was independently associated with an increased risk of AKI after adjustment for baseline serum creatinine and SOFA cardiovascular score after surgery. Further studies are required on the role of PP as a marker of venous congestion of the kidneys to predict AKI.

Funding: Private Foundation Support

FR-PO62
The Timing of Eculizumab Therapy Predicts Renal Survival in Atypical Hemolytic Uremic Syndrome
Salmaan Ahmed, Udayan Prosek, Brad H. Rovin, Samir Parikh. State University of New York, Columbus, OH.

Background: Atypical hemolytic uremic syndrome (aHUS) is a life threatening disease instigated by alternative complement pathway dysregulation and often results in acute renal failure from thrombotic microangiopathy. Treatment with eculizumab, a terminal complement blocker, is effective, but some patients are still left with significant renal impairment. This work aims to determine whether the timing of eculizumab treatment predicts renal survival in patients with aHUS.

Methods: We conducted a retrospective analysis of clinical data from 22 aHUS patients treated with eculizumab. Demographic are summarized in the table. Median follow up time was 22 months (IQR 13-43.75). The time to treatment initiation was tested as a predictor of adverse renal outcomes by univariate and multivariate analysis. Outcomes were defined as a ≥50% increase in serum creatinine (SCr), end-stage renal disease, or a composite of adverse renal outcomes after adjustment for baseline serum creatinine and SOFA cardiovascular score after surgery. Further studies are required on the role of PP as a marker of venous congestion of the kidneys to predict AKI.

Funding: Private Foundation Support

Table: Demographic information of patients treated with eculizumab

| Age at presentation (Avg ±SD) | 41.7±17.2 |
| Sex (men/women) | 5(20.8%)/ 19 (79.2%) |
| Race (White/Black/Other) | 19/79.2% / 4 (1.6%) / 1 (4.2%) |
| Patients requiring dialysis | 15 (62.5%) |
| Time on dialysis (months, Median, IQR) | 2 (0.6-12) |
| Time to Eculizumab (days, Median, IQR) | 9 (6-34) |
| Baseline Creatinine (mg/dl, Avg±SD) | 1.31±0.54 |
| Patients with identified mutation | 13 (59%) |

Results: A delay in eculizumab initiation >10 days after clinical presentation was predictive of a ≥50% increase in SCr (OR=10.5, 95% CI: 1.1 to 98.91, p=0.040), and was 100% predictive of dialysis dependence by univariate analysis. Time to treatment was a significant predictor of the composite outcome by univariate analysis (OR=22.5, 95% CI: 2.60 to 194.51, p<0.005) and multivariate analysis (OR=50.14, 95% CI: 2.67 to 942.29, p<0.005).

Conclusions: The delayed administration of eculizumab is associated with an increased risk of poor renal outcomes in aHUS. Initiation of terminal complement blockade within 10 days of clinical presentation is essential for long-term preservation of renal function in patients with aHUS.

Funding: Private Foundation Support

Poster/Friday
FR-PO863
Free Hepatic Venous Pressure as a Marker of Renal Venous Congestion: Is There a Correlation with Hemodynamic Renal Dysfunction in Patients with Cirrhosis? Neel Desai, Ladan Golestaneh. Nephrology, Albert Einstein College of Medicine - Montefiore Medical Center, Bronx, NY.

Background: Intra-abdominal hypertension (IAH, abdominal cavity pressure (>~12 mmHg) correlates with renal disease. The pathophysiology of this relationship is not clearly understood - IAH is thought to cause renal venous congestion by increasing venous pressure and impairing venous drainage. We hypothesize that in patients with cirrhosis elevated abdominal venous pressure, as represented by an elevated free hepatic venous pressure (FHVLP, routinely measured during Transjugular Intrahepatic Portosystemic Shunt or TIPS procedures), correlates with hemodynamic renal dysfunction when adjusted for other pertinent clinical factors.

Methods: We used our institution’s electronic health record based database to search for patients who underwent TIPS procedures between 2008-2015. Information collected included demographics, FHVLP, other co-morbidities and markers of parenchymal renal disease. Patients with End Stage Renal Disease (ESRD) +/- missing race information were excluded. Calculated GFR using the MDRD formula was used in all data analyses which was done using the STATA 14.0 software.

Results: A total of 122 patients were included in the study based on the criteria listed above. The mean FHVLP was 13.9mmHg and mean EF was 65%. 16.8% of the patients had evidence of parenchymal renal disease on the renal sonogram which correlated with a 19.2cc/min decrease in baseline GFR (P<0.02). 12.4% of the patients had proteinuria which correlated with a 19.4cc/min decrease in baseline GFR (P<0.04). Every 1mmHg increase in the FHVLP was associated with a 0.49cc/min decrease in baseline GFR which was not statistically significant (P=0.35).

Conclusions: Our data suggests that in patients with cirrhosis an increase in FHVLP is not associated with a statistically significant decrease in baseline GFR. It is possible that the presence of hyper-dynamic cardiac function is compensating to maintain GFR in this sample by increasing cardiac output and renal perfusion. Our study is also not adequately powered. The association of elevated venous pressure and hemodynamic renal dysfunction needs to be explored further in patients with cirrhosis.

FR-PO864
Efficacy of Eculizumab in Gemicabinate-Induced Thrombotic Microangiopathy: Analysis of a Retrospective Study Cohort Steven Grange, Maximilien Grall, Francois Provot, Coindre Jean-Philippe, Claire Pouet-Noble, Dominique Guerot, Paul Coppo.

Background: We conducted an observational, retrospective, multicenter study including all patients with gemicabinate-induced TMA treated by eculizumab in 4 French centers, between 2011 and 2014. Patients with TMA attributed to cancer and to allogenic stem cell transplant were excluded.

Results: 7 patients were included (6 women, 1 man). Gemicabinate was prescribed for pancreatic (n=3, 43%), ovarian (n=3, 43%) and pulmonary (n=1, 14%) cancer. TMA occurred after a median of 5 months (range 1.7-8.4) and a median cumulative dose of 23.7g (range 0-48.0). The main characteristics were hemolytic anemia (100%), acute renal failure (100%, including 57% stage 3 AKI and 28% renal replacement therapy), hypertension (71%) and diffuse edema (57%). Eculizumab was started after a median of 13 months after eculizumab initiation.

Conclusions: This study suggests that eculizumab is efficient on hemolysis and reduces transfusion requirement in gemicabinate-induced TMA. The benefit of eculizumab on the recovery of kidney function remains uncertain.

FR-PO865
Design of the STOP-AKI Trial: Safety, Tolerability, Efficacy and Quality of Life of Human Recombinant Alkaline Phosphatase in Patients with Sepsis-Associated Acute Kidney Injury Jacques Arend, Esther Peters, Ravindra L. Mehta, Patrick T. Murray, Jurgen Hummel, Michael Joannidis, John A. Kellum, Peter Pickkers, Afshin Azarni, EAM-Pharma, Bunnik, Netherlands; Dept of Int Care Med, Rudbøl Hospital, Næstved, Denmark; 2Div of Neph Med, Univ of California, San Diego, CA; 3School of Med, Univ Coll Dublin, Dublin, Ireland; 4PPD, Bellshill, United Kingdom; 5Div of Int Care and Emerg Med, Dept of Int Med, Medical Univ Innsbruck, Innsbruck, Austria; 6Crit for Crit Care neph, Dept of Crit Care Med, Univ of Pittsburgh, Pittsburgh, PA.

Background: Acute kidney injury (AKI) occurs in ~60% of critically ill patients, and sepsis is the most common underlying cause. No pharmacological treatment options are licensed to treat sepsis-associated AKI (SA-AKI). Administration of bovine intestinal alkaline phosphatase (AP) improved renal function in critically ill sepsis patients. To build on these observations, a human recombinant AP (recAP) was developed and is currently tested for safety and efficacy in patients with SA-AKI.

Methods: This is a randomized, double-blind, placebo-controlled, dose-finding adaptive phase I/IIb study, conducted in critically ill patients with SA-AKI (NCT02128240). A minimum of 290 patients will be enrolled at ~50 sites in the European Union and North America. The study involves 2 parts. Patients enrolled during Part 1 will be randomly assigned to receive placebo (n=30) or 1 of 3 different doses of recAP (n=30 per group) once daily for 3 days (0.4 mg/kg, 0.8 mg/kg, or 1.6 mg/kg). In Part 2, patients will be randomly assigned to receive the most efficacious dose of recAP (n=85), selected by an independent data safety monitoring board during an interim analysis, or placebo (n=85). Treatment must be administered within 24 h after SA-AKI is first diagnosed and within 96 h from first diagnosis of sepsis. The primary endpoint is the area under the time-corrected endogenous creatinine clearance curve from days 1-7. The secondary endpoint is the incidence of renal replacement therapy during day 1-28.

Results: The estimated study enrollment completion date is February 2017.

Conclusions: Results of this study will reveal the safety and efficacy of recAP to treat SA-AKI in critically ill patients.

Funding: Pharmaceutical Company Support - AM-Pharma

FR-PO866

Background: Acute kidney injury (AKI) is a prevalent condition in critically ill patients and it is associated with increased mortality in this population. Targeted analysis of this subgroup in randomized clinical trials is essential to guide an accurate conduct and lead to better outcomes. The primary goal of the present study was to quantify the representation of patients with AKI and to assess the criteria used to define it in multicenter randomized clinical trials.

Methods: A sensitive search strategy for randomized controlled trials published from 2006 to 2016 was conducted in MEDLINE using the PubMed interface selecting the keywords “sepsis”, “mechanical ventilation”, “ARDS” and “critically ill patients”. All publications of adult, randomized controlled trials carried out in the intensive care unit, with mortality as primary outcome were included and reviewed independently.

Results: A total of 379 articles were reviewed. We identified 60 eligible studies, 41 (68%) were multicenter, 51 (85%) included patients with renal dysfunction at baseline and in 14 (23%) the population with renal impairment underwent a subgroup analysis. None of studies reported the proportion of enrolled patients with acute kidney injury. In the follow up of the patients during these studies, generic scores as APACHE II, SAPS II and SOFA were used in 44 (73%) of studies to define AKI, specific AKI scores as RIFLE and the Brussels score were used in 6% and 3% respectively, and 18% of the studies did not describe any criteria to define AKI.

Conclusions: In multicenter randomized clinical trials assessing mortality as primary outcome there is an underrepresentation of AKI patients in the enrollment of the patients and no consensus in AKI definition during the follow up of the patients during studies. The consequence is that we lack evidence on interventions for this growing high-risk population.
Methods: In a multicentre cohort of MM patients presenting with biopsy-confirmed MCN between 2002-2014, we evaluated prospectively measured serum FLC levels obtained using a single nephelometric assay. We report renal outcome and overall survival (OS) relative to serum FLC level at diagnosis controlling for demographic factors.

Results: 103 patients were enrolled from 3 tertiary centres. Mean age at diagnosis was 70.6 ± 15.9 years. Males represented 56.6% (17). Admission SCr was associated with an increased risk for AKI (OR 1.27, 1.1-1.5, p=0.003) and tumor lysis syndrome (OR 1.26, 1.1-1.5, p=0.005). Prophylactic uric acid-lowering therapy and hydration resulted in lower SAU values from baseline in 88.1% of the patients. 20.4% reduction was observed on post-induction day 1. Significant linear correlations were observed between SAU and SCr (r=0.35, p<0.001) and inverse correlation was also observed between SAU and KeGFR on day 1 (r= -0.33, p<0.001) that persisted through day 4. By subgroup analysis, patients with primary AML (r= -0.49, p<0.001), baseline SAU >5.5mg/dl (r= -0.41, p=0.002) and baseline eGFR >60ml/min/1.73m2 (r= -0.51, p<0.001) demonstrated robust relationships between SAU and KeGFR. The relationship was more robust when the groups were combined (primary AML + baseline SAU>5.5mg/dl + baseline eGFR>60ml/min/1.73m2, r= -0.52, p<0.001).

FR-PO868

Renal Function Assessment in the Setting of Acute Kidney Injury Applying the Kinetic GFR Formula Jose S. Lopez Gil,1 Luis Antonio Garcia,1 Javier Zúñiga-Vargas,1 Juan Pablo Herrera Felix.1 Nephrology Dept, American British Cowdray, Mexico City, Mexico; 2Postgraduate, UNAM, Mexico, Mexico City, Mexico.

Background: There is no reliable method to estimate or assess kidney function in acute kidney injury (AKI), therefore, we applied the kinetic GFR formula proposed by Chen (JASN 24:2013) to estimate changes in GFR, evaluate renal outcomes and value the accuracy of this formula.

Methods: This is a retrospective study. 30 patients with AKI were randomly selected from 763 admissions between 2010 and 2016. Serum creatinine (SCr) values from previous years to admission were collected to establish baseline SCr. Admission SCr and MDRD formula results.

Results: Mean age was 70.6 ± 15.9 years. Males represented 56.6% (17). Admission diagnosis was infectious disease in 26.6% (8), heart disease in 13.3% (4) and neoplasms in 10% (3). Mean baseline SCr was 1.15±0.44mg/dl and the admission SCr was 2.46 ± 1.9mg/ dl. The mean SCr in the first sample was 2.32±1.8mg/dl; eGFR MDRD 40.4±25.1ml/min and kGFR 40.6±27.4ml/min. In sample 2, mean SCr was 2.56±2.1mg/dl; MDRD 38.5±24.4ml/ min and kGFR 36.8±25.5ml min. In sample 3, SCr was 2.31±1.9mg/dl; MDRD 37.8 ± 21.3ml/min and kGFR 39.6: 25.5ml/min. In sample 4, SCr was 2.22±1.9mg/dl, MDRD 42.6 ± 30.7ml/min and kGFR 40.6±27.4ml/min. Mean SCr increased 6% from sample 1 to sample 2 and MDRD GFR decreased only 4.7% while kGFR decreased by 15.6%. From sample 2 to sample 3 mean SCr decreased 3.7% and MDRD GFR declined by 1.8%, while the kGFR improved by 7.6%. Even when the SCr remains constant between samples, the kGFR formula demonstrates a recovery of GFR of 2.3 ml/min while the MDRD remains unchanged.

Conclusions: The kGFR formula seems to be more reliable than MDRD to accurately estimate kidney function in AKI. Renal function recovery is identified earlier by kGFR.

FR-PO869

Relationship of Serum Uric acid and Kinetic Estimated Glomerular Filtration Rate in Acute Myeloid Leukemia Patients Abhilash Koratara,1 Kawther Farouk Alqudadan,1 Girish Singhania,2 Michiko Shimada,3 Richard J. Johnson,1 A. Ahsan Ejaz.1 1Univ of Florida; 1Univ of Utah; 1Hiroasaki Univ, Japan; 2Univ of Colorado.

Background: We investigated the relationship between SAU and renal function using kinetic GFR (KeGFR) in a unique patient cohort wherein SAU levels fluctuate during the course of standard care.

Methods: Data from patients undergoing treatment for acute myeloid leukemia (AML) were analyzed retrospectively. Correlations between SAU and serum creatinine (SCr) and KeGFR were investigated. Statistically significant and clinically relevant determinants were studied in multivariate regression models.

Results: N=126 patients. Baseline SAU was associated with an increased risk for AKI (OR 1.27, 1.1-1.5, p=0.003) and tumor lysis syndrome (OR 1.26, 1.1-1.5, p=0.005). Prophylactic uric acid-lowering therapy and hydration resulted in lower SAU values from baseline in 88.1% of the patients, 20.4% reduction was observed on post-induction day 1. Significant linear correlations were observed between SAU and SCr (r=0.35, p<0.001) and inverse correlation was also observed between SAU and KeGFR on day 1 (r= -0.33, p<0.001) that persisted through day 4. By subgroup analysis, patients with primary AML (r= -0.49, p<0.001), baseline SAU >5.5mg/dl (r= -0.41, p=0.002) and baseline eGFR >60ml/min/1.73m2 (r= -0.51, p<0.001) demonstrated robust relationships between SAU and KeGFR. The relationship was more robust when the groups were combined (primary AML + baseline SAU>5.5mg/dl + baseline eGFR>60ml/min/1.73m2, r= -0.52, p<0.001).

FR-PO870

Subarachnoid Hemorrhage Induces Neuro-Cardio-Renal Interactions in the Acute Phase Naoki Ikegaya,1 Kiyoshi Mori,2 Takuya Yoshida,2 Hirotoshi Kumagai,3 Yasufumi Yamamura,4 Mamoru Tomida,4 George Seki,1 Akira Hishida.1 1Dept of Medicine, Yaizu City Hospital, Yaizu, Japan; 2School of Pharmaceut Sci, Univ of Shizuoka, Shizuoka, Japan; 3Dept of Nephrology, Yaizu City Hospital, Yaizu, Japan; 4Dept of Neurosurgery, Yaizu City Hospital, Yaizu, Japan; 5Dept of Clin Nutrition, School of Food and Nutritional Sci, Univ of Shizuoka, Shizuoka, Japan.

Background: Subarachnoid hemorrhage (SAH) is known to induce acute cardiovascular stress as reflected by ECG changes, and renal dysfunction is associated with poor prognosis in SAH. However, the precise mechanisms of extra-brain injury in SAH have not been fully understood.

Methods: We prospectively analyzed ECG, urinary albumin, and NGAL, and serum NT-proBNP, endothelin and inflammatory cytokines such as IL-6 and TNF-alpha in 24 consecutive SAH patients without known kidney disease on day1, 2, and 14. Results: ECG abnormalities were observed in 13 out of 24 patients with SAH at baseline. SAH patients with ECG abnormalities showed increased levels of albuminuria (Mean±SD, 627.9±1441.5 vs. 88.0±88.6 mg/g Cr), NT-proBNP (1033.8±2121.2 vs. 95.1±111.6 pg/ml) and endothelin (2.21±0.30 vs. 1.88±0.5 pg/ml), but no differences in IL-6 and TNF-alpha compared to patients without ECG abnormalities at baseline. Urinary NGAL significantly increased in patients with ECG abnormalities on day 2. Serum endothelin decreased towards normal values on day 2 and 14, and IL-6 and TNF-alpha increased on day 2 in both groups.

Conclusions: ECG abnormalities were associated with elevated levels of endothelin and albuminuria early after SAH, suggesting interactions among heart, brain and kidneys through increased endothelin in the acute phase.

FR-PO871

Inverse Interaction between Diuretics and Renin-Angiotensin Blockers in Contrast-Induced Nephropathy after Coronariography Lucero Salgado Ambrosio, Armando Vazquez-Rangel. Nephrology, Inst Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico City, Mexico.

Background: Prevention of contrast-induced nephropathy(CIN) is limited mostly to hydration, while some other interventions as diuretics and renin-angiotensin blockers seem to be counter intuitive. Nevertheless, patients with cardiovascular disease are usually under these drugs and sometimes hydration is difficult to implement if heart failure or chronic fluid overload is present.
Methods: A retrospective cohort of patients undergoing coronary angiography in our National Institute of Cardiology in Mexico City from January 2011 to December 2011. Patients with ambulatory or short-stay procedures were excluded. Clinical and biochemical characteristics were obtained through medical records. Specifically, the use of loop diuretics, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) was assessed from 24 hours before to 24 hours after coronaryangiography. CIN was defined by KDIGO criteria by serum creatinine.

Results: 515 patients were analyzed. Baseline characteristics included: male 398 (77.3%), diabetes 201 (39.0%), hypertension 273 (53.0%), cardiogenic shock 2 (4.5%), chronic renal failure 72 (14.0%), previous myocardial infarction 60 (11.6%), acute coronary syndrome 460 (89.3%), emergency procedure 178 (34.5%). Of the total, 168 (32.6%) received loop diuretics, and 420 (81.5%) required ACEI/ARB, whereas CIN was present in 61 (11.8%) patients. There was a significant difference between patients receiving loop diuretics for CIN (34 [20.2%]) vs patients without loop diuretics (27 [7.8%]) (p < 0.05). Within patients receiving loop diuretics, the incidence of CIN for those receiving ACEI/ARB was 21 (16.7%) vs 13 (30.0%) without ACEI/ARB. Multivariate analysis confirmed this observation adjusted for fluid balance.

Conclusions: For high risk cardiovascular population, mostly with acute coronary syndrome, the use of diuretics increased the incidence of CIN, nevertheless, the concomitant use of ACEI/ARB protected partially from this risk. In patients with adequate fluid status or fluid overload because of heart failure, with the need of loop diuretics, reducing local vasoconstriction with ACEI/ARB could reduce the risk of CIN.

FR-PO873
Comparing Left Ventricular Assist Device Implantation and Inotropes for Renal Function and Outcomes
Seenu Verma, 1 Emmanuel Bassili, 1 Shane Leighton, 1 Igor Sunjic, 1 Angel Iran Martin, 1 Tambi Jarmi, 1 Claude Bassili, 2 1 Internal Medicine, Univ of South Florida; 2 Nephrology, Univ of South Florida.

Background: Left Ventricular Assist Device (LVAD) implantation and inotropes serve as a bridge to heart transplantation or as destination therapy in those who aren’t heart transplant candidates. Little is known about renal function and outcomes with LVAD placement, and a study comparing LVAD recipients versus solely inotrope treatment has not been previously performed.

Methods: 169 patients with continuous flow LVAD implantations and 20 patients with solely inotrope therapy with dobutamine or milrinone were analyzed. Mann-Whitney U-Testing and chi-squared analysis compared the groups for long term renal outcomes after LVAD or continuous inotrope therapy was started. (baseline), 3, and 6 months later. We also compared incidence of AKI, defined as an increase in creatinine of 0.3 mg/dL in 48 hours or 1.5 times the baseline in the last 7 days, need for renal replacement therapy (RRT), brain natriuretic peptide (BNP), and death during 6 months following LVAD or inotrope implementation.

Results: The groups had the same age, race, gender, BMI, tobacco use, diabetes, CKD, and hypertension distribution. The median creatinine in the groups was not statistically different (p-values 0.552, 0.081 and 0.469 at baseline, 3, and 6 months respectively). The median estimated glomerular filtration rate, calculated with the modified diet renal disease equation, was not statistically different between the groups (p-values 0.822, 0.644, and 0.507 at baseline, 3 and 6 months respectively). The incidence of AKI, RRT, and mortality in the groups over 6 month follow up after treatment were not significantly different. The median BNP at 6 months in the LVAD and inotrope groups was 216 pg/dL (range 14 to 2995 pg/dL) and 497 pg/dL (range 147 to 1242 pg/dL), with p-value statistically significant at 0.005.

Conclusions: The sole use of inotropes in patients with end-stage heart failure is non inferior to outcomes in survival, incidence of AKI, need for RRT, and renal function within 6 months when compared to LVAD placement. More studies are needed to compare inotropes and LVAD implantation on renal function and outcomes over a longer period time.

FR-PO874
Optimal Blood Pressure in Acute Kidney Injury: What and When
Seon Ha Baek, Ki Young Na, Sejoong Kim. Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Republic of Korea.

Background: Blood pressure (BP) is an important target for kidney injury, but few data showed optimal BP in patients with acute kidney injury (AKI) relative to mortality. Methods: We performed a retrospective cohort study of 2304 patients who had their creatinine levels measured (≥ 1 measurement) during admission for a period of 1 year (January 1, 2013 through December 31, 2013) at tertiary hospital and were diagnosed with AKI by Kidney Disease Improving Global Outcomes (KDIGO) definition based on serum creatinine criteria. Average BP (systolic [SBP] and diastolic [DBP]) was categorized into 10-mmHg increments (at early period of admission within 48hr and at 48hr after development of AKI).

Results: The overall 90-day and 1-year mortality for patients were 17.6% (405/2304) and 29.0% (669/2304). The relationship between BP (SBP and DBP) followed a J-shaped curve association with increased 90-day and 1-year mortality at low BP value in univariable analysis (SBP <120mmHg and DBP <80mmHg at admission and after AKI).

Conclusions: Patients who sustain severe AKI requiring RRT after VAD implantation have worse outcomes. Blood transfection and positive fluid balance are predictors of severe AKI in addition to kidney function at implantation and severity of illness.

However, SBP at 48hr after AKI was only a predictor for 90-day mortality after adjustment for baseline variables (reference systolic BP ≥140mmHg, <100mmHg, Hazard ratio [HR] 4.528, P = 0.001; 100-119mmHg, HR 2.177, P = 0.005; 110-129mmHg, HR 1.764, P = 0.033; 120-150mmHg, HR 1.415, P = 0.215; 140-169mmHg, HR 1.656, P = 0.088). This trend also remained in the relationship between average SBP after AKI and 1-year mortality.

Conclusions: After AKI, a J-shaped curve association existed between SBP at 48hr after AKI and 90-day/1-year mortality, which suggests that too low of a pressure (especially <120mmHg) may be dangerous. SBP after AKI was only a predictor for mortality rather than SBP/DBP at admission or DBP after AKI.
FR-PO875
Identification of Acute Kidney Injury Using a Novel Electronic Urine Flow-Rate Device
Mort Grinstein,1 Aliza D. Goldman,2 Hagar Azran,2 Dafina Willner.2
1Massachusetts General Hospital; 2Anesthesiology and CCM, Hadassah-Hebrew Univ, Israel.

Background: Criteria for identifying acute kidney injury (AKI) include measurements of serum creatinine (SCr) and urine output (UO). Current practice for UO measurement involves manual recording of data, subject to human errors, including time errors and inaccurate urine drainage bags. A novel electronic device used in this study provided timely and accurate data for hourly urine output. We validated this device and analyzed it for the ability to identify AKI according to the AKIN (Acute Kidney Injury Network) criteria. We compared UO measured electronically to manual nursing staff records, as well as to SCr values.

Methods: Study Population: 40 hospitalized patients in the General ICU at Hadassah Hospital, Jerusalem, Israel with a urinary catheter. Materials: The RenalSense Clarity RMS™ sterile sensor kit for electronic monitoring of UO. For this study, the RenalSense drainage bag included a standard urinometer for the nursing staff to record UO as per standard practice. The drainage bag was placed on a scientific scale (gold standard) to validate the sensor measurements. Sensor data and nursing staff manual records of UO were compared to the scale data. Daily SCr, urea, and creatinine clearance were collected from patient records up to 7 days following the drainage bag removal. Relevant fluids and medication were recorded.

Results: Our observations have shown that electronically recorded data of UO is more consistent, reliable and accurate than nursing records. Moreover, our study has highlighted the weakness of SCr as an accurate measurement of kidney function. Most patients showed a steady decrease to very low levels of SCr, even below normal range, possibly due to fluid overload. We found an average length of stay in the ICU of 14 days in patients with low UO as defined by the AKIN criteria versus 10 days in patients that had normal UO.

Conclusions: Close urine monitoring during this study has provided observation of diuretic response in real-time. This study has highlighted applications of a novel electronic device for measuring UO such as identifying AKI, decisions as to timely fluid and diuretic administration, and dose response.

Funding: Pharmaceutical Company Support - RenalSense

FR-PO876
Poor Survival 12 Months after In-Hospital AKI e-Alert Regardless of Stage
Nina Gerdes, Clare Morlidge, Kate Berresford, Catherine J. Marshall, Suresh Mathavakkannan, Andrew Findlay. Dept of Nephrology, Lister Hospital, East & North Herts NHS Trust, Stevenage, Hertfordshire, United Kingdom.

Background: Acute kidney injury (AKI) is an emerging national and global health imperative. Here we review 12 month survival amongst patients following in-hospital AKI e-alert.

Methods: Data was retrospectively evaluated from secondary care hospital AKI e-alerts between 28/03-28/04/2014. Patient contact episodes (PCE) over the same period were recorded to calculate incidence. PCE were defined as adult elective and emergency attendances to a secondary care hospital. AKI e-alerts were staged by a nephrologist for accuracy according to AKIN criteria. In-hospital AKI was defined as an e-alert generated >24hrs after admission. Age adjusted co-morbidity was obtained from electronic patient record. Patients were followed up for one year.

Results: There were 412 AKI e-alerts generated from 19,530 patient contact episodes (PCE). On nephrologist review 299 (72.5%) were genuine AKI. 137 AKI e-alerts were in-hospital AKI 1,110 AKI 1, 13 AKI 2 and 14 AKI 3. This gave AKI event rates of 7.01/1000 PCE for total in-hospital AKI, 5.63/1000 PCE for AKI 1, 0.67/1000 PCE for AKI 2 and 0.72/1000 PCE for AKI 3. Patient survival 12 months after AKI e-alert for in-hospital AKI was 57.27% for AKI 1, 53.85% for AKI 2 and 50% for AKI 3. Timing of death differed between AKI stages with 37.8% of AKI 1, 67.74% of AKI 2 and 81.82% of AKI 3 in-hospital AKI dying whilst inpatients.

In-Hospital AKI, March-April 2014

Conclusions: In-hospital AKI, regardless of stage, is associated with poor survival at 12 months. High age-adjusted co-morbidity scores for AKI 1 may explain why a relatively minor AKI is associated with poor 12 month survival. Minor AKI may be a marker of underlying physiological frailty and increased risk of death.

FR-PO877
Reduction of In-Hospital AKI Incidence Using a Multidisciplinary Model and Intelligent Data Analysis
Nina Gerdes, Clare Morlidge, Kate Berresford, Catherine J. Marshall, Suresh Mathavakkannan, Andrew Findlay. Nephrology, Lister Hospital, East & North Herts NHS Trust, Stevenage, Hertfordshire, United Kingdom.

Background: In-hospital acute kidney injury (AKI) is associated with poor survival at 1 year regardless of stage. A multidisciplinary AKI service was developed to reduce in-hospital AKI incidence.

Methods: A specialist nurse interrogated daily AKI e-alerts and prioritized deteriorating AKI above severity. A daily working week ward round consisting of Nephrology consultant, Renal pharmacist and AKI specialist nurse started in February 2016 to review patients with deteriorating AKI. AKI incidence was measured retrospectively 2 months prior to the introduction of AKI team and 2 months afterwards. All AKI e-alerts from December 2015-March 2016 were staged along KDIGO guidelines. In-hospital AKI was defined as an e-alert generated >24hrs post admission. To measure incidence the number of patient contact episodes (PCE) defined as adult emergency and elective attendance to a secondary care hospital was calculated per week. The number of AKI alerts over a week was divided by the number of PCE and multiplied by 1000 to give number of AKI events per 1000 PCE per week.

Results: There was a significant reduction in total in-hospital AKI, AKI 1 and AKI 2 but not AKI 3 incidence following the introduction of the AKI team (February+March 2016) compared to the 2 months prior to introduction.

Conclusions: A model of daily AKI e-alert review, data analysis and prioritization of declining AKI over severity followed by targeted clinical multidisciplinary review of the patients with AKI has been associated with a significant reduction in in-hospital total AKI, AKI 1 and 2 incidence reduction. A preventative approach targeting early deteriorating AKI rather than severe established AKI may reduce in-hospital AKI.

FR-PO878
Telenephrology for the co-management of patients in a rural hospital
Brenda R.C. Kurnik, Jerome S. Tannenbaum. Sanderling Renal Services, Nashville, TN.

Background: Telenephrology is primarily focused on outpatients. We report a two year experience using real-time audio video technology to perform nephrology consultations, follow up visits and dialysis on in-patients in a rural hospital.

Methods: A retrospective study of inpatients requiring nephrology care between April 2014 and April 2016. Consultations were performed by reviewing the patient’s hospital EMR and performing a real-time history and physical exam with audio-video technology and Littman electronic stethoscope. Notes were typed into the hospital EMR and local physicians were contacted by phone as needed.

Results: A total of 427 consults and 1551 follow up visits were performed. Population characteristics: 213 females, 214 males; age range 25-99 yrs. old. Patient location: ICU 154, PCU 36, floor 237. Average LOS of 6.8 days. Disposition: home/rehab 360, transferred to tertiary care hospital 28, hospice 21, and deceased 18. Consults were performed by reviewing the patient’s hospital EMR and performing a real-time history and physical exam with audio-video technology and Littman electronic stethoscope. Notes were typed into the hospital EMR and local physicians were contacted by phone as needed.

Conclusions: Telenephrology for the co-management of patients in a rural hospital is both feasible and safe. Our care included pts with both ESRD and ARF requiring dialysis.
FR-PO879
A Bedside Clinical Tool Using Creatinine Kinetics to Predict Additional Renal Injury and Early Recovery 1Maurice L Khayat, 1Jonathan Deeth, 2Jonathan Sosnow. 1Internal Medicine, San Antonio Military Medical Center, Fort Sam Houston, TX; 2Anesthesiology, Evans Army Community Hospital, Fort Carson, CO; 1Nephrology, San Antonio Military Medical Center, Fort Sam Houston, TX.

Background: The characteristics of changing creatinine concentrations during acute renal failure are often confusing to clinicians and can cloud the patient’s true current state of renal injury. By modifying the formula for kinetic estimate of glomerular filtration rate, a simple bedside clinical tool can be used to identify subtle changes in renal function.

Methods: The kinetic estimate of glomerular filtration rate was rewritten to instead calculate a predicted peak creatinine after each assumed renal injury. By comparing the changes in predicted peak creatinine at two or more subsequent time intervals, the patient’s current state of renal injury can be determined: early recovery, a single ongoing renal insult, or multiple simultaneous renal injuries.

Results: Computerized algorithms are provided using the equation for predicted peak creatinine. In each case, the creatinine concentration has continued to rise at three sequentially-measured times. However, the change in predicted peak creatinine is analyzed for each case, demonstrating scenarios involving (a) multiple simultaneous renal injuries, (b) a single, ongoing renal injury, and (c) a renal process with early intervention and recovery.

Conclusions: Computerized algorithms for detection of AKI in patients visiting the ED, performed and compared to a nephrologists (gold standard). Incorporating a measure of reduction in SCr following the visit may confer benefit at the time of decreased specificity. Funding: Government Support - Non-U.S.

FR-PO881

Background: Acute kidney injury (AKI) in hospital can be alerted electronically (e-alert) to clinicians using software that tracks creatinine changes. It is unclear however if any clinical intervention at this stage has a beneficial outcome. The aim of this study was to establish whether nephrology or critical care outreach team (CCOT) review of patients identified with AKI by e-alerts resulted in improved clinical outcomes and length of hospital stay.

Methods: Patients with AKI e-alerts were reviewed by nephrologists (grade 2 and 3 AKI) and CCOT (grade 1 AKIs) on the same day. This was carried out for 30 consecutive days. Information on outcomes was prospectively collected for a follow up period of 80 days. A comparator group was formed 6 months earlier, made up of patients with an AKI e-alert generated over 60 consecutive days who were followed up with no intervention.

Results: 398 genuine AKIs were identified from all generated AKI e-alerts, 273 patients had no intervention while 125 patients were reviewed based on grade of AKI as above. There were no differences between the groups in mean age (75.0 ±14.9 vs 75.2 ±14.4 years, p = 0.909) and baseline creatinine (97.0 ±32.6 vs 99.7 ± 57.7 μmol/L, p = 0.467). The proportion of patients discharged home by 30 days post AKI was significantly higher in the intervention group (56.0% vs 44.7%, p = 0.018). The death censored median length of hospital stay was also significantly lower in the intervention group (13 vs 8 days, p = 0.034). The mortality rate trended towards being lower in the intervention group as compared to the comparator group at 80 days (32.0% vs 38.2%, p = 0.108). The rate of progression of grade 1 to grade 3 AKIs also trended towards being lower in the intervention group (10.3% vs 6.3%, p = 0.115). There were no statistically significant differences in the need for renal replacement therapy, use of ICU beds and renal recovery at 80 days.

Conclusions: Our study supports the use of intervention in patients triggered with AKI e-alert. In particular it suggests that there is significant benefit in terms of shorter length of hospital stay. Larger studies are needed to support these findings.

FR-PO882
Irisin and Inflammatory Biomarkers in End Stage Renal Disease Patients Submitted to Remote Ischemic Pre Conditioning 1Marcelo Rodrigues Bacci, Mariana Carvalho Gouveia, Fernando Luiza Affonso Fonseca. 1General Practice, ABC Medical School, Santo Andre, Sao Paulo, Brazil.

Background: Irisin is a muscle-secreted protein released into the circulation by cleavage of fibronectin type III domain containing protein 5. It has been studied as a biomarker of myocardial injury. Areas submitted to remote ischemic cardiac preconditioning in experimental models have less occurrence of necrosis. The purpose of this study is to determine the serum irisin levels associated with troponin in patients with chronic kidney disease undergoing hemodialysis submitted to RIPC.

Methods: It is a double blind randomised trial with two groups:intervention,submitted to RIPC in the right arm with sphyxomonometer with 200mm Hg of pressure with three-5 minute rounds alternating with deflation totalling 30 minutes and control group;without RIPC. Intervention group received RIPC in three consecutive hemodialysis sessions. Blood samples were taken before the first session and after the third consecutive dialysis session. BUN for calculation of single pool Kt/V, ultra sensitive I troponin and irisin were measured to evaluate blood collection of each biomarker was not affected by the RIPC. Spearman’s correlation test showed a p-value of 0.558 between irisin and troponin.

Results: A total of 14 patients were selected with 50% of men. About 64.3% had diabetes. Troponin levels were not affected by the RIPC intervention with a p<0.281. The difference between the moments of blood collection of each biomarker was not affected by the RIPC. Spearman’s correlation test showed a p-value of 0.558 between irisin and troponin.

Conclusions: In conclusion despite being a promising myocardial injury biomarker, irisin was not affected by hemodialysis in end stage renal disease. Moreover, RIPC did not affect its levels independently of the moment of the collection (before or after).

FR-PO883
Prognostic Significance of Hemodynamic Parameters in Hemodialysis Patients 1Ferruh Artunc, 2Bjoern Friedrich, 3Nils Heyne, 1Stefanie Haag. 1Internal Medicine, Div of Nephrology, Univ Hospital, Tuebingen, Germany; 2Nephrology Center, Leonberg, Germany.

Background: Hemodialysis (HD) patients have a high mortality that mainly results from cardiac impairment. Using an ultrasound dilution device various hemodynamic parameters can be measured during a HD session. So far, there is no data regarding the prognostic significance of these parameters.

Methods: We conducted a prospective cross-sectional study in 185 stable HD patients and measured cardiac index (CI), access flow (AF) and central blood volume.
index (CBVI) using the Transonic HD03 monitor at the beginning and end of a single HD session. In addition, we calculated systemic CI (SCl-Cl AF) and oxygen delivery index (DOIj SCI*hemoglobin*1.34). Survival analysis was performed after a median follow-up of 606 (interquartile range 593-621).

Results: During follow-up 33 patients (18%) died. Compared to the survivors, deceased patients tended to have a lower CI (P=0.09) and had a significantly reduced SCI and DOI (P=0.02 and 0.002, resp). Drop in CI, SCI and DOI at the end of HD (ACI, ASCI and DOI) was significantly higher in deceased patients. In contrast, AF, CBVI and hemoglobin was not different between survivors and deceased patients. Receiver-operator-characteristic (ROC) analysis revealed area-under-the-curve (AUC) values for the endpoint death of 0.68 for DOI (P=0.001) and 0.65 for SCI (P=0.013). AUC for ACI, ASCI and DOI ranged between 0.62 and 0.63 (P=0.02-0.03). The combination of two parameters such as CI with ACI or SCI with DOI or DOI with ACI and SCI increased AUC values substantially (0.71-0.75). In addition, Cox regression confirmed significant survival benefit at higher DOI and lower ACI, ASCI and DOI.

Conclusions: This study is the first to show a prognostic significance of hemodynamic parameters in HD patients. Systemic CI and oxygen delivery index at rest as well as drop of these parameters at the end of HD were associated with increased mortality. The results underscore the prognostic relevance of cardiac function for the survival of HD patients.

FR-PO884

Background: Assessment of volume status remains highly subjective and is a major challenge in managing dialysis patients. We tested a novel hand-held device that provides non-invasive assessment of left ventricular end-diastolic pressures (LVEDP), an important indicator of left ventricular volume pressure overload. We hypothesized that a low LVEDP at the start of hemodialysis (HD) will be associated with intradialytic hypotension.

Methods: We recruited HD patients from 4 Baltimore area dialysis units. Baseline data collected included demographics, medical history, KDQOL-36, NYHA dyspnea scale, intra-post dialysis symptoms, predialysis metrics [LVEDP, biopacmance, blood pressure (BP)] and echocardiogram. We assessed the association of predialysis LVEDP with change in systolic BP (SBP) during dialysis (lowest SBP predialysis SBP) and hypotension episodes requiring nursing interventions.

Results: In the first 45 participants (mean age 60 years, 58% male, 87% Black), median [25th, 75th percentiles] for predialysis LVEDP was 16 mmHg [2, 20], intradialytic weight gain (IDWG) was 1.8 kg [1.1, 2.7] and SBP was 147 mmHg [134, 162]. Significant fall in SBP (≥20 mmHg) was common and occurred in 72% (71 patients) of those who died within 7 [16%) also required nursing interventions. Predialysis LVEDP was associated with fall in SBP during dialysis (p=0.007) and intradialytic hypotension requiring nursing interventions (p=0.04). Predialysis SBP (p=0.3), IDWG (p=0.4) or biopacmance water measurement (p=0.5) were not associated with intervention requiring intradialytic hypotension.

Conclusion: Our findings suggest that non-invasive LVEDP measurement can provide an objective assessment of volume status and identify HD patients at risk of intradialytic hypotension.

Funding: NIDDK Support

FR-PO885
Measurements of Extracellular Volume and Cardiovascular Hemodynamics in Patients with Recurrent Intradialytic Hypertension Peter N. Van Buren, Javier A. Neyra, Robert D. Toto. UT Southwestern.

Background: Intradialytic hypertension (IH) is a recurrent phenomenon in some hemodialysis (HD) patients and is associated with increased mortality. Both extracellular volume overload and vascular resistance surges have been separately observed in patients with intradialytic blood pressure (BP) increases. We simultaneously compared pre-HD, post-HD, and intradialytic changes in total body water (TBW) and extracellular water (ECW), as well as cardiac index (CI) and total peripheral resistance index (TPRI) in 18 patients with recurrent IH and 18 hypertensive HD controls with intradialytic BP decreases.

Results: During screening, the mean systolic BP before and after HD was 165 (18) and 138 (21) mmHg in controls and 141 (17) and 162 (12) mmHg in patients. During the study, there were between group differences in the change in MAP, TPRI and heart rate from pre to post dialysis, but not in CI or stroke volume index.

The ECW/TBW ratio was higher in IH patients before and after dialysis.

<table>
<thead>
<tr>
<th>Controls (n=18)</th>
<th>IH (n=18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBW (L)</td>
<td>48.2 (11)</td>
<td>46.5 (10)</td>
</tr>
<tr>
<td>ECW (L)</td>
<td>21.6 (5)</td>
<td>22.0 (5)</td>
</tr>
<tr>
<td>ECW/TBW</td>
<td>0.453 (0.05)</td>
<td>0.478 (0.03)</td>
</tr>
</tbody>
</table>

There was a trend for changes in ECW and ECW/TBW from pre- to post-dialysis to be smaller in IH patients than controls (p=0.06 and 0.1, respectively).

Conclusions: Recurrent IH is associated with higher post-HD extracellular volume and TPRI. Intradialytic TPRI surges likely account for the vasoconstrictive state post-HD, but intradialytic fluid shifts may contribute to the volume expanded state post-HD.

Funding: NIDDK Support

FR-PO886
Adrenal Insufficiency (AI) Is Highly Prevalent and May Be Associated with Intradialytic Hypotension(IDH) in Hemodialysis(HD) Patients Eunjung Kim, Myung Jin Choi, Jung-Woo Noh, Dong Ho Shin, Ja-Ryong Koo, Hallym Univ, Donggun; Chuncheong; Kangnam; Gangdong.

Background: Many maintenance HD patients had been chronically exposed to pharmacologic dose of steroid and the underlying kidney disease varies from various or coexisting disease. We evaluated prevalence, risk factor and clinical impact of AI as a possible cause of IDH in HD patients.

Methods: Among 106 HD patients, 10 patients on current steroid treatment were excluded and remaining 96 patients were studied. Adrenal function was evaluated during HD by high dose ACTH stimulation test. AI was defined by baseline serum cortisol<10 µg/dL and ACTH stimulated maximal serum cortisol<18 µg/dL. Status of previous steroid exposure was identified through the evaluation of medical record and history about underlying, coexisting disease, medications and injections. IDH was defined by symptomatic decrease in systolic BP:20 mmHg and the mean IDH event during 6 consecutive HD sessions was calculated. In selected patients with IDH and AI who agreed to steroid replacement, change in the incidence of IDH before and after steroid treatment was ascertained.

Results: The prevalence of AI was 36.5% (33.5% in 34 patients with previous steroid exposure vs 16.1% in 62 patients without steroid exposure). There was no difference in the prevalence of AI according to the type of underlying kidney disease (diabetes 32.0%, glomerulonephritis 40.5%). However, the patients with coexisting disease (gout, osteoarthritis, connective tissue disease) had significantly higher prevalence of AI as compared with the patients without coexisting disease (81.3% vs 20.6%). 33 (34.4%) patients had one or more(mean 2.30±1.13) IDH event during 6 consecutive HD sessions. The proportion of patient with IDH event was significantly higher in the patients with AI as compared with the patients without AI (48.6% vs 26.2%). Moreover, in 16 HD patients with AI who treated by steroid, IDH occurred in only 3 patients after 4 weeks of steroid replacement(mean 1.90±0.74 vs 0.30±0.48).

Conclusions: In HD patients, careful evaluation of medical record and history about coexisting disease, medications, and injections is required to find out underlying AI. Steroid replacement may be a therapeutic option in IDH patient with AI.
Methods: OER (peripheral O$_2$ saturation (SO$_2$)/central venous SO$_2$) was measured by pulse oximetry and gas analysis was diminished in patients with CVC. We sampled OER before, 15’, 30’, 60’, 120’ and at the end of HD in each patient in three consecutive HD (long and short intervals) with an UF rate <10 ml/kg/h. We recorded BP, HR, UF, and symptoms.

Results: OER increased progressively during HD to 5% ±7% (p < 0.001), no values in BP or HR (table 1), no symptoms.

FR-PO890

Oxidation Extraction Ratio (OER): A Marker of Haemodynamic Stress in Haemodialysis (HD)1,2 Sandro Mazzaferrito, Silverio Rotondi, Maria Luisa Muci, Lida Tartaglione, Luciano Carbone, Marzia Pasquali. 1Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, Sapienza Univ. Rome, Italy, 2Nephrology, and Dialysis Unit, IONF Hospital, Latina, Italy.

Background: Cardiovascular stress and symptoms occur during HD sessions. Monitoring Blood Volume (BV) allows prevention but does not measure the stress entity. The OER (n=25±30%) was used to estimate tissue oxygenation, mirrors adaptation to hypoxia/ hyperperfusion. We hypothesized that, if detectable, its changes during HD could reflect haemodynamic stress.

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## Table 1: Pre and Post-dialysis SBP (mmHg), IVCD (cm), change in IVCD (cm)

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre IVCD</th>
<th>Post IVCD</th>
<th>Change in IVCD</th>
<th>UF removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euvolemic</td>
<td>131±11</td>
<td>114±9</td>
<td>1.74±0.03</td>
<td>0.90±0.01</td>
</tr>
<tr>
<td>Hypervolemia</td>
<td>148±23</td>
<td>142±16*</td>
<td>2.44±0.04</td>
<td>2.01±0.04*</td>
</tr>
</tbody>
</table>

*p < 0.05 compared when to pre-dialysis levels

Table 1 shows pre and post-dialysis SBP(mmHg), BV (cm), change in IVCD (cm) and UF removed (L). For all patients, a correlation between pre-SBP and IVCD (r=0.7801) and pre-SBP and volume removed (r=0.7179) was found. In edematous patients LR showed for every 1 cm change in pre IVCD the amount of volume removed increased by 1.43 kg controlling for edema and pre-SBP.

Conclusions: IVCD is a non-invasive, objective marker of pre-hypervolemic HD patients, is well tolerated, and correlates with UF removal. IVCD augments volume assessment and may help guide determination of UF goals in HD.

FR-PO891

Heart-Rate-Variability in Haemodialysis Joachim H. Beige. Nephrology and Dialysis, Hospital St. Georg, Leipzig, Germany.

Background: Heart rate variability (HRV) is a measure of time intervals between heartbeats and characterizes the ability to adapt to pathophysiological conditions. It can be used to hypothesically to assess the sympathetic activity during haemodialysis (HD). Because only sparse information about HRV during HD is available we investigated the course of HRV during and after HD and its correlation to anthropometrical and HD data.

Methods: Continuous measurement of five recognized HRV measures (meanRR-dist., SDNN, RMSSD, pNN50, LF/HF Ratio) in time slots of 3 hours during and immediately after HD at 2 consecutive HD sessions of 34 patients by long-term ECG including artifact flattening. During these 68 sessions, no intradialytic morbidity events (IME) appeared.
FR-PO893

Clinical Effectiveness of Intermittent Infusion Hemodiafiltration Using Backfiltration of Ultrapure Dialysis Fluid Compared with Predilution On-Line Hemodiafiltration: A Prospective, Multicenter, and Controlled Trial

Michio Minehima, Kei Eguchi. Clinical Engineering, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Intermittent Infusion Hemodiafiltration (I-HDF) has been introduced to improve the peripheral circulation of dialysis patients and to reduce the occurrence of hypotension during a hemodialysis treatment. The clinical effectiveness of I-HDF, however, has not been clarified in comparison with those in other on-line HDF therapies.

Methods: A prospective, multicenter, parallel group comparative trial was carried out to reveal the clinical effectiveness of I-HDF compared with predilution on-line HDF (Pre-HDF) that is the most popular on-line HDF therapy in Japan at present. Patients were allocated to two groups after matching for age (<5y.o.), dry weight (<5kg) and with/without diabetes. After obtained informed consent, 36 patients, namely 18 pairs, participated in this clinical trial. During the trial, we evaluated the clinical condition and quality of life (QOL) of the patients and solute removal characteristics.

Results: The results showed no difference in clinical condition and QOL scores between two groups. Reduction ratio of the systolic blood pressure originally showed no difference between two groups but it decreased slightly as the trial proceeded after changing from hemodialysis therapy. There was also no difference in the number of treatments by medical staff, but this also significantly decreased as the trial proceeded in both groups. On the other hand, the Pre-HDF group demonstrated significantly higher removal rates of β2-microglobulin and t-1-microglobulin than in the I-HDF group. As the same time, albumin leakage in a treatment was also significantly larger in Pre-HDF than that in I-HDF.

Conclusions: In conclusion, the clinical condition and QOL of the patients undergoing I-HDF was not inferior to those having Pre-HDF. Furthermore, Pre-HDF demonstrated a significantly higher removal rate in the middle and larger solutes and larger albumin leakage in comparison with I-HDF.

FR-PO894

Beta-2 Microglobulin Removal by Convective Dialysis: A Meta-Analysis

Ahmed H. Alami,1 Maria-Eleni Roumellioti,2 Gregory S. Tretiely,3 Thomas D. Nolin,2 Yue-Harn Ng,1 Zhi Xu,1 Mark L. Unruh,1 Christos Argyropoulos.1 1Internal Medicine-Nephrology, UNMHC, Albuquerque; 2Pharmacy and Therapeutics, Univ of Pittsburgh, Pittsburgh.

Background: Accumulation of Beta-2 Microglobulin (B2M) in ESRD patients is associated with cardiovascular and infectious mortality. We conducted a meta-analysis of data about the efficacy of convective dialysis therapies (CDT) i.e. (hemodiafiltration, HDF or hemofiltration, HF) in removing B2M.

Methods: We used ProQuest to search EMBASE and MEDLINE, for randomized controlled trials and observational studies in CDT between 2001-2013. Clearance measurements at blood side and/or dialysate side were included and reported via random effects meta-analysis.

Results: We identified 36 HDF and 4 HF studies. Average clearance was 90 ml/min with substantial heterogeneity among studies.

Conclusions: In conclusion, B2M clearance rates in HDF and HF are low, and further research is necessary to improve B2M removal.

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

574A

Linear regression analyses of pHN50 and RMSSD with age, gender, dialysis vintage, comorbidities, ESA index, PO4, Hbg, KtV, ultrafiltration (UF), dry weight and blood pressure yielded only one weak association between UF and pHN50 during HD (T=2,72, p=0,035).

Conclusions: All HRV markers showed high measurement precision and no interdependence with anthropometrical data. Dialysis-related HRV showed similarity to data from 695 healthy individuals (Sammitto et al.). Relationship with (not appeared) IME was not studied and no conclusion about predictibility of HRV against IME can be drawn. However, the relationship with UF points to a thinkable usefulness of HRV as HD biofeedback measure. Further investigations of time courses and patterns will be conducted.

FR-PO892

On-line Hemodiafiltration: Which Mode for Better Cost Effectiveness

Panagiotis G. Siminaris, Theodoros Papadakis, Giorgos Chatzistathis, Konstantinos Vlachos, Christos Argyropoulos, Panagiota N. Raftopoulou, Eleni Ng, Zhi Xu, Mark S. Unruh, Gregory S. Tretiely. 1Internal Medicine-Nephrology, UNMHC, Albuquerque; 2Pharmacy and Therapeutics, Univ of Pittsburgh, Pittsburgh.

Background: On-line hemodiafiltration (olHDF) in predilution (Pre-HDF) and postdilution (Post-HDF) modes is widely used in clinical practice. The combination of multi-pass pre-/postdilution HDF is the most popular mode in Japan. Meanwhile, recent studies have shown that the backfiltration mode is indicated for the removal of low-molecular weight substances. In the present study, we assessed the efficacy of removal of low and medium molecular weight substances when blood flow rates<350 ml/min are used, combining various modes of online hemodiafiltration (olHDF).

Methods: We studied 30 patients who were subjected to 4 different dialysis modes.

FR-PO893

Clinical Effectiveness of Intermittent Infusion Hemodiafiltration Using Backfiltration of Ultrapure Dialysis Fluid Compared with Predilution On-Line Hemodiafiltration: A Prospective, Multicenter, and Controlled Trial

Michio Minehima, Kei Eguchi. Clinical Engineering, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Intermittent Infusion Hemodiafiltration (I-HDF) has been introduced to improve the peripheral circulation of dialysis patients and to reduce the occurrence of hypotension during a hemodialysis treatment. The clinical effectiveness of I-HDF, however, has not been clarified in comparison with those in other on-line HDF therapies.

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Results: The results showed no difference in clinical condition and QOL scores between two groups. Reduction ratio of the systolic blood pressure originally showed no difference between two groups but it decreased slightly as the trial proceeded after changing from hemodialysis therapy. There was also no difference in the number of treatments by medical staff, but this also significantly decreased as the trial proceeded in both groups. On the other hand, the Pre-HDF group demonstrated significantly higher removal rates of β2-microglobulin and t-1-microglobulin than in the I-HDF group. As the same time, albumin leakage in a treatment was also significantly larger in Pre-HDF than that in I-HDF.

Conclusions: In conclusion, the clinical condition and QOL of the patients undergoing I-HDF was not inferior to those having Pre-HDF. Furthermore, Pre-HDF demonstrated a significantly higher removal rate in the middle and larger solutes and larger albumin leakage in comparison with I-HDF.
FR-P0895

The Standardization of Convective Volume to Body Water Predicts the Efficacy of Convective Transport in On-Line Hemodiafiltration


Background: Online hemodiafiltration (OL-HDF) with high convective volumes (CV) has been associated with improved patient survival compared to conventional hemodialysis, explained by better removal of middle-sized uremic toxins. The purpose of this study was to determine the corporal composition parameters influencing the efficacy of CV in the removal of different molecular weight (MW) molecules.

Methods: Demographic data, corporal composition with bioimpedance, dialysis features and reduction rates of different MW-molecules (urea-60Da, β2-microglobulinB2M-11.8KD, cystatin C-13KD, myoglobin-17.2KD, procladin-23KD and alpha-2-microglobulin-725KD) in a 4-hour postdilution OL-HDF session were collected in 61 patients.

Results: The mean of CV was 30.6 ± 4.7 L/session. We observed a significant negative correlation of B2M, cystatin C, myoglobin and prolactin reduction rates with body surface area, weight, total body, extracellular(ECW) and intracellular water (ICW), lean intracellular mass and body cellular mass. The multivariable regression analysis identified ECW and ICW as the only corporal composition factors independently associated to the relative reduction of B2M (Beta=-0.301, p=0.002 for ECW and Beta=-1.710, p=0.001 for ICW), cystatin C (Beta=-0.656, p=0.010 for ECW and Beta=-1.511, p=0.004 for ICW) and myoglobin (Beta=-0.745, p=0.014 for ECW and Beta=-2.103, p=0.001 for ICW), in addition to CV. Only the ratio CV/ECW was an independent predictor for higher reduction of B2M (Beta=0.866, p<0.001), cystatin C (Beta=0.745, p=0.001) and myoglobin (Beta=0.662, p=0.008).

The standardization with total body water (TBW) as the ratio CV/TBW showed similar significant results with weaker association.

Conclusions: Extracellular and intracellular water are independently associated to the reduction of medium-sized molecules. The ratio “convective volume/extracellular water” predicts higher efficacy of convective transport. Adjust the convective volume to body water features could be useful to monitor the efficacy of OL-HDF and to prescriptively individualized therapies.

FR-P0896

Impact of Different Low Molecular Weight Heparin Administration Routes in High-Flow Hemodialysis and Online Hemodiafiltration

Amir Shabaka, Jose A. Herrera, Marisol Pompa Tapia, Fernando Tornero. Nephrology, Hospital Clinico San Carlos, Madrid, Spain.

Background: Pre-filter administration of low molecular weight heparin (LMWH) in the arterial line of hemodialysis (HD) circuits during high-flow HD (HF-HD) and hemodiafiltration (OL-HDF) can lead to clearance of LMWH. The aim of this study was to evaluate whether different administration routes of enoxaparin can affect its efficacy.

Methods: 15 patients, 13 on HF-HD and 2 on HD. All sessions were done with 1.8 ml/min/kg of bodyweight, 3 hrs sessions. The mean of CV was 30.6 ± 4.7 L/session. We observed a significant negative correlation of B2M, cystatin C, myoglobin and prolactin reduction rates with body surface area, weight, total body, extracellular(ECW) and intracellular water (ICW), lean intracellular mass and body cellular mass. The multivariable regression analysis identified ECW and ICW as the only corporal composition factors independently associated to the relative reduction of B2M (Beta=-0.301, p=0.002 for ECW and Beta=-1.710, p=0.001 for ICW), cystatin C (Beta=-0.656, p=0.010 for ECW and Beta=-1.511, p=0.004 for ICW) and myoglobin (Beta=-0.745, p=0.014 for ECW and Beta=-2.103, p=0.001 for ICW), in addition to CV. Only the ratio CV/ECW was an independent predictor for higher reduction of B2M (Beta=0.866, p<0.001), cystatin C (Beta=0.745, p=0.001) and myoglobin (Beta=0.662, p=0.008).

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FR-P0897

Protein-Bound Toxin Removal with Novel High-Cut-Off Membrane Dialyzer in Limited Blood Flow Online Hemodiafiltration (OL-HDF) versus High-Efficiency OL-HDF with High-Flux Dialyzer

Waniak Ponitisskisik, Kajjohn Tiranathanagul, Maneerut Limjaruliyakul, Supeecha Wittayaalertpanya, Paweena Susantithapong, Nattachai Srirasawat, Somchai Eiam-Ong, Kearkit Praditponsirilpa.

1. Medicine-Nephrology, Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand; 2. Pharmacology, Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand.

Background: Protein-bound toxins especially p-cresol (pCS) which could not be removed by hemodialysis (HD) are obviously correlated with high mortality in HD patients. High-efficiency post-dilution online hemodiafiltration (OL-HDF) using high-flux dialyzer which requiring high blood flow rate has been reported to enhance pCS removal and improve patient survival. Unfortunately, the majority of patients could not reach that high blood flow due to the limitation of their arteriovenous access. Herein, we innovated the effective OL-HDF modality for this situation by integrating the novel high cut-off membrane dialyzer (HCM) in pre-dilution OL-HDF.

Methods: This randomized crossover control study was conducted in 9 OL-HDF patients to compare the two week periods between the new modality (limited blood flow OL-HDF with HCM) and the control (high-efficiency OL-HDF). The removals of small and middle molecular weight uremic toxins as well as protein-bound uremic toxin were determined and compared. The pCS was measured by high performance liquid chromatography. The dialysate albumin loss and patient safety were also monitored.

Results: This new modality showed significantly higher pCS removal in term of pCS reduction ratio (RR) was comparable with high efficiency OL-HDF [59.5 (IQR; 49.1, 62.6) vs. 54.7 (IQR; 48.6, 58.2) %, p<0.001]. The [2-microglobulin removal was significant higher in this new modality. Two techniques provided adequate and comparable small molecule removal. No patients developed hypoaalbuminemia despite the higher dialysate albumin loss in the new modality.

Conclusions: This new OL-HDF with HCM which could apply to every dialysis patients provided effectively protein-bound uremic toxin removal comparable with high efficiency OL-HDF and could potentially provide the comparable good long-term survival.

FR-P0898

Immersion Can Enhance Fluid Redistribution and Prevent Intradialytic Hypotension - A Prospective, Randomized, Crossover Clinical Trial

Karen Doenças-Baral, Bia Beberashvili, Nedal Garra Garra, Shai Effati. Dept of Nephrology and Hypertension, Assaf Harofeh Medical Center, Zerifin, Israel.

Background: Intradialytic hypotension (IDH) is an important cause for morbidity among hemodialysis (HD) patients. IDH occurs mainly when the ultrafiltration (UF) rate exceeds fluid redistribution from the extravascular to the vascular bed. Water immersion can be an effective method for hydrostatic pressure induced transfer of volume from the interstitium to the intravascular space. This randomized, crossover study evaluated the physiological and clinical effects of immersion on the occurrence of IDH.

Methods: Ten male HD patients, who had frequent IDH, defined as symptomatic hypotension occurring in more than 20% of the sessions were randomized to a 3 hour mid-week “wet” and “dry” HD session, in a crossover manner. The wet session was performed while immersed up to the neck in a 34°C-35°C bath, and the dry session was standard HD. UF goals were determined as the mean UF during the 10 sessions preceding the study ±10% according to body weight at admission, and the dialysis time was shortened to 3 hours instead of the usual 4. Systolic, blood pressure (BP), atrial natriuretic peptide (ANP) and aldosterone blood levels were measured during the sessions.

Results: Mean UF did not differ between the two sessions (2.990±0.64kg vs. 2.96±0.74kg in wet and dry sessions respectively). Symptomatic hypotension did not develop in any of the patients during the wet session, compared to 4 (40%) during the dry session. Systolic BP adjusted to UF was stable during the wet session, 0.22 (95% CI -0.27 to 0.70), P=0.38, but significantly decreased during the dry session, -0.68 (95%CI -1.24 to -0.11), P=0.02. Diastolic BP did not change during the sessions. Mean ANP significantly increased in the wet session, by 31.36 (95% CI 8.73 to 53.99), P=0.07, and slightly and insignificantly decreased in the dry session, by -21.66 (95% CI -52.59 to 9.25), P=0.167. Aldosterone blood levels did not change.

Conclusions: Delayed fluid redistribution during HD can be effectively reversed by immersion, with improved blood pressure stability and symptoms.
**FR-PO899**

Utility of Plasma β2-Microglobulin Levels for Estimating Residual Kidney Function without Urine Collection

*Yoshihiro Matsumoto, Kimitoshi Shiratori, Youichi Nojima, Yasushi Shimagda. Dept of Nephrology and Dialysis, Shizuoka City Hospital, Japan.*

**Background:** Residual kidney function (RKF) is associated with survival benefits in hemodialysis (HD) patients but cannot be assessed without urine collection. Plasma β2-microglobulin and cystatin C levels have been used to estimate kidney function in patients with renal insufficiency before dialysis therapy. We investigated the ability of these markers to estimate RKF in patients on HD.

**Methods:** Seventy-one patients undergoing incremental low-flux HD in a single center during 2008–2015 were enrolled. Blood was sampled before the first HD session of the week to estimate β2-microglobulin and cystatin C. Urine was collected 24 hours before the first HD session of the week. We assumed that creatinine and urea secretion per day divided by body weight before HD (Ucr and Uurea, respectively) corresponded to RKF regardless of their plasma levels, which are known to change significantly during urine collection. The relationships between plasma β2-microglobulin/cystatin C levels and Ucr/ Uurea were explored.

**Results:** The average HD duration and urine volume were 17 (1–58) months and 1280 (350–3000) mL, respectively. Ucr and Uurea were closely correlated (r = 0.84). Ucr was more closely correlated with plasma β2-microglobulin levels (r = -0.74) than with cystatin C levels (r = -0.61) and urine volume (r = 0.62). Uurea was also correlated with β2-microglobulin levels (r = -0.69), cystatin C levels (r = -0.51) and urine volume (r = 0.73).

**Conclusions:** Plasma β2-microglobulin levels before HD may provide better estimates of RKF than cystatin C. β2-microglobulin may be clinically useful for determining individual dialysis doses without the need for frequent urine collection in HD patients with RKF.

**FR-PO900**

Post-Hospital Case Management of Incident and High Risk Prevalent Hemodialysis Pts Reduces 30- and 90-Day Readmission Rates

*Rebecca L. Wingard,1 Kathryn A. McDougall,1 Billie Axley,1 Andrew D. Howard,2 Joelle Heilemann,3 Sharon Delucia,4 Sheetal Chaudhuri,3 Hao Han,1 Len A. Usvyat,1 Franklin W. Maddux.1 1Fresenius Medical Care, Waltham, MA; 2Metropolitan Nephrology Associates, Clinton, MD.*

**Background:** 30-day readmission rates for West Virginia (WV) Fresenius HD incident pts (IPs, n=384, 1 st 120 days of HD) and high risk prevalent pts (HRPPs, n=159, >6 hospitalizations/yr) were high in 2014 at 55% and 60%, respectively. 90-day readmission rates were 80% for IPs and 85% for HRPPs. The Right TracTM (RT) Program used post-hospital case management to reduce readmissions for IPs and HRPPs.

**Methods:** 26 Fresenius WV HD clinics were in RT in 2/1/15 to 2/29/16. IPs, and HRPPs with high likelihood of >6 hospitalizations/yr (identified by an internally validated predictive model) were included. A telephonic RT case manager (RTCM) attempted contact with pt or caregiver weekly during 30 days post-hospital discharge (DC) to discuss DC instructions, facilitate follow-up appointments, and review strategies to manage medications, nutrition, dry weight, access issues, and anemia. For pts alive 48 days post hospital (n=205 IPs, 369 DCs; 310 HRPPs, 605 DCs), 30- and 90-day readmission rates were compared for pts who received no RTCM calls (29% for IPs; 27% for HRPPs) vs. one call (13% for IPs; 18% for HRPPs) or >1 call (58% for IPs; 55% for HRPPs) using two sample t-test.

**Results:** 30-day readmission rates for pts with no calls vs. >1 call were 60% vs. 32% for HRPPs (p=0.001) and 62% vs 33% for IPs (p=0.001) (Figure 1A). 90-day readmission rates for pts with no calls vs. >1 call were 80% vs. 71% for HRPPs (p=0.05) and 81% vs 64% for IPs (p=0.001) (Figure 1B).

**Conclusions:** Post-hospital telephonic case management was associated with fewer readmissions for IPs and HRPPs who received >1 phone call in the 30-day post-hospital period.

**FR-PO901**

Effect of Dialysis Potassium Bath on QT Interval During Hemodialysis

*Aamir Zuberi, Hafsia Z. Zuberi, Hassaan Patel, Maggie Dickens, Fatima Zuberi. Nephrology, Wise Health System, Decatur, TX.*

**Background:** Sudden death accounts for nearly half of all cardiac deaths in dialysis patients. QT prolongation has been associated with cardiac arrhythmias that could lead to sudden cardiac death. Of interest is the question of effect of potassium concentration in dialysis solution on QT interval. This study was conducted to assess the effects of 2K and 3K dialysis baths on QT interval in stable hemodialysis patients in an outpatient dialysis facility.

**Methods:** Study was approved by the Institutional Review Board. Funding was provided by the dialysis provider, Wise Health System. EKGs were checked at the beginning and end of dialysis sessions. The following parameters were noted: age, gender, presence or absence of comorbidities including coronary artery disease and diabetes, dialysis treatment time, dialysis K concentration, pre-dialysis plasma K concentration, pre & post-dialysis corrected QT intervals (QTc), and pre- and post-dialysis change in QTc.

**Results:** We enrolled 79 patients, with a mean age of 62 years (range: 21-88 years). Male gender dominated the cohort 46/79 (58%). 50 (63%) patients had CAD. 48 (61%) had DM. Dialysis treatment time ranged from 2.75-4.5 hours with an average of 3.7 hours. Pre-dialysis QTc ranged from 408-574 milliseconds. Post- dialysis QTc ranged from 413-665 milliseconds. Pre-dialysis mean K was 4.7 mmol/L (range: 3.1 to 7.5 mmol/L). Of the 31 patients dialyzed with a 2K dialysis solution, mean QTc change was 202 milliseconds as opposed to 160 milliseconds in the 48 patients dialyzed with a 3K dialysis solution (p=NS). Subgroup analyses for duration of dialysis (>3.5 hours), pre-dialysis K (>4.5 mmol/L), CAD, DM and age>60 did not reveal any significant trends. Men were more likely to have a prolonged QTc (p=0.03). We observed an inverse relationship between pre-dialysis K and QTc (p=0.04).

**Conclusions:** Patients dialyzed with a 2K dialysis solution had longer QTc compared to patients dialyzed with a 3K dialysis solution. Men were more likely to have a longer QTc compared to women. Patients with lower pre-dialysis K were more likely to have longer QTc. Adjustments in dialysis solution K concentration could limit risk of life threatening arrhythmia in patients at risk of sudden cardiac death.

**FR-PO902**

Aiming for the Optimal Bicarbonate Prescription for Maintenance Hemodialysis Therapy in End-Stage Renal Disease

*Andreas Bozikas, Ililana Kiriakoutzik, Ioannis Petrou, Pinelopi Pisanidou, Theodoros Tourentzis, Nikolaos Georgilas, Panagiotsis Pangidis, Sofia Spaia. Nephrology, General Hospital, Thessaloniki, Greece.*

**Background:** Due to the gradual depletion of the body’s buffers and rapid repletion during hemodialysis, many problems arise as a result of current treatment routine since both acidemia and alkalinaemia can be associated with adverse consequences. We compared the effect of higher doses of [HCO3]- based dialysate to standard [HCO3]- bath plus oral bicarbonate therapy.

**Methods:** 60 HD patients were evaluated according to their predialysis acid-base status before the 1st and the 2nd session of the week with a standard [HCO3]- based dialysate of 35 mEq/L. Those with predialysis [HCO3]- < 22 mEq/l were assigned against dialysis bath with [HCO3]- levels (>2 mEq/l) for 2 weeks (period A) and subsequently to the standard dialysate bath plus oral sodium bicarbonate (5gr/1.4 for 2 more weeks (period B). Records of pre/post dialysis acid base status after each period, with evaluation of different parameters were recorded.

**Results:** Predialysis acid base didn’t present significant differences, between the 1st and 2nd dialysis session. 25 patients predialysis pH was <7.35, while 42 presented predialysis [HCO3]- <22 mEq/L. 18 patients had pH >7.45 after HD session.Comparing the 2 study periods, patients with predialysis [HCO3]- in accordance with guidelines, after 2 weeks of oral bicarbonate, while post dialysis HCO3 were increased during the 1st study period.

**Conclusions:** This study shows that conventional dialysate [HCO3]- concentrations of 35mEq/L results in a considerable degree of predialysis acidemia. Increasing [HCO3]- dialysis bath results in more prominent postdialysis alkalainsia, but it is not sufficient to maintain acid base balance in the interdialytic period. On the contrary, oral bicarbonate therapy at a dose of 5gr/d results in more balanced acid base status, avoiding post dialysis alkalainsia. Potential solutions include a multifaceted approach of oral and individualized delivery of HCO3.
FR-PO903

Growth of Cardiovascular and Infection Emergency Room and Observation Stays in the Dialysis Population Allan J. Collins,1 Peer Kidney Care Initiative Investigators.2,3 Chronic Disease Research Group, MMRF, Minneapolis, MN; 1 Peer Kidney Care Initiative.

Background: Recent efforts by CMS to incentivize hospitals to reduce readmissions have focused on acute myocardial infarction, congestive heart failure, and pneumonia. While traditional readmissions of dialysis patients have declined, little is known about changes in the use of alternative forms of acute care, namely emergency department encounters (EDE) and observational stays (OBS), following an index hospitalization.

Methods: We studied prevalent (>1 year on dialysis) and incident (<1 year on dialysis) Medicare patients dialyzing in freestanding US units for the cohort years 2004-2013. EDE and OBS (occurrence and hours) were identified from revenue codes and the place of service on Part A hospital claims. Because clinical symptoms commonly occupy the first position, we used the first 5 diagnosis codes to define disease areas by organ system.

Results: Overall, EDE or OBS increased 19.2% 2004-2013. The increase in EDE (alone) was 3.8% and in OBS (alone) 58.5%. The combination of EDE or OBS for cardiovascular disease (CVD) causes increased 43% and for infections 29.3%, 2004-2013. After stabilizing from 2010 to 2012, EDE or OBS increased 3.4% overall, 4.6% for CVD and 6.8% for infection, 2012-2013.

Conclusions: While EDEs have changed only modestly in the past 10 years, there is evidence of marked increases in the use of OBS. Data suggest that hospitals are shifting the site of care away from traditional inpatient admissions, but how this affects morbidity and mortality is unknown.

Outpatient Emergency department visit or observation stay among prevalent patients

Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by the following participating provider organizations: American Renal Associates, Atlantic Dialysis Management Services, DaVita HealthCare Partners, Dialysis Clinic, Inc., Integrated Kidney Care, Independent Dialysis Foundation, Northwest Kidney Centers, Satellite Healthcare, The Rogosin Institute, U.S. Renal Care, and Wake Forest University, Private Foundation Support

FR-PO904

Low Vitamin D as a Modifying Factor in the Relationship between Obesity and Vascular Calcification in Hemodialysis Patients Jwa-Kyung Kim,1 Sun Ryoung Choi,2 Jae-Won Lee,3 Sung Gun Kim.4 1Internal Medicine, Kidney Research Inst, Hallym Univ Sacred Heart Hospital, Anyang, Korea; 2Internal Medicine, Sahmyook Medical Center, Seoul, Korea; 3Internal Medicine, G Sam Heart Hospital, Anyang, Korea.

Background: Obesity is a risk factor for increased cardiovascular disease. Whether vitamin D deficiency modifies this association is unclear. Here, we examined the association of obesity and vitamin D deficiency with vascular calcification score (VCS) in incident end-stage renal disease (ESRD) patients.

Methods: A cross-sectional study was conducted with 213 ESRD patients who newly started hemodialysis. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D (25(OH)D) levels below 10 ng/mL, and levels below 3 ng/mL was considered very low. Obesity was defined as a percentage of body fat (PBF) higher than the sex-specific median value in the cohort (>26.8% for men, >36.2% for women). VCS was measured by plain radiographic film of the lateral abdominal in the standing position.

Results: Mean age 63.7±13.4 years and 31.9% were women. Most ESRD patients (76.6%) had 25(OH)D deficiency at the start of dialysis, and 44.7% of them had very low levels of 25(OH)D. The prevalence of 25(OH)D deficiency was much higher in obese patients than non-obese patients, and it had significant inverse association with PBF (r=-0.315, p<0.001). Abdominal aortic calcification was identified in 104 (48.9%) patients. VCS was significantly higher in obese population; 2.6 (0.23) for all patients, 4.2 (0.23) for obese and 1.0 (0.12) for non-obese patients (p<0.001). Interestingly, serum 25(OH)D affected the relationship between obesity and the risk of vascular calcification, such as vitamin D deficiency was associated with greater risk of a high VCS, especially in obese population [odds ratio (OR) 3.02, 95% confidence interval (CI) 1.09-9.38], but not with non-obese patients (OR 1.82, 95% CI 0.56-5.60).

Conclusions: The magnitude and direction of the association between obesity and the risk of vascular calcification may depend on an individual’s 25(OH)D level, a possible representative marker of cardiovascular disease in ESRD patients.

FR-PO905

Association of Vitamin K and Matrix Gla Protein with Subclinical Cardiovascular Disease in Incident Hemodialysis: Predictors of Arhythmogenic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study Esther D. Kim,1 Stephen M. Sozio,2 Michelle M. Estrella,2 Bernard G. Jaar,3 Lucy A. Meoni,2 Joao A.C. Lima,2 Rulan S. Parkh,1,2 1U of Toronto; 2Johns Hopkins U.

Background: Recent studies suggest repletion of low vitamin K levels in HD patients may have a beneficial effect in reduction of circulating inactive desphosphorylated-uncarboxylated matrix Gla protein (dp-ucMGP) and vascular calcification; however, the independent associations of vitamin K and dp-ucMGP with subclinical measurements of cardiovascular disease are unknown.

Methods: In a prospective study of 231 incident HD patients in the PACE study with available biomarker data, we examined the association of dietary vitamin K and baseline dp-ucMGP with total coronary artery calcium (CAC) score and longitudinal measures of pulse wave velocity (PWV). Vitamin K status was estimated using self-reported phylloquinone intake from 24-hour dietary recall. Baseline and longitudinal associations were examined using modified Poisson regression and mixed-effects model, respectively.

Results: The mean age of the cohort was 55±13 years, and the majority were African-American (68%), had diabetes (57%), and coronary artery disease (39%). Compared to lower vitamin K (<31mcg) intake, moderate intake was associated with lower prevalence of CAC at baseline and higher intake was associated PWV longitudinally independent of dp-ucMGP and potential confounders. Dp-ucMGP was not associated with CAC or PWV.

Conclusions: Higher vitamin K intake is not consistently associated with lower prevalence of coronary calcification but is associated longitudinally with less arterial stiffness. This suggests that dietary vitamin K supplementation may be beneficial in reducing vascular stiffness but requires further study.

Funding: NIDDK Support

FR-PO906

FGF-23 and IL-6 Are Associated with Progression of Coronary Arterial Calcification (CAC) in Patients New to Dialysis Qijun Wan,1,2 Sylvia E. Rosas.3 1Nephrology Dept, The First Affiliated Hospital of Shenzhen Univ, Shenzhen, China; 2Kidney and Hypertension, Joslin Diabetes Center, Boston, MA.

Background: Inflammation stimulates production of fibroblast growth factor 23 (FGF23). We have shown that elevated FGF23 levels are associated with CAC progression in individuals initiating dialysis. Our aim was to determine if inflammation was responsible for the association of FGF23 with CAC progression.

Methods: One hundred initial dialysis patients were enrolled. CAC were measured by multi-slice computed tomography. CAC was calculated using Agatston score (AS) and calcium volume score (VS). CAC progression was measured by the annualized difference in score AS and by the square root volume difference. Sixty-seven study participants had repeat CAC measures at one year. Linear regression was used to assess the association of IL-6 and FGF23 with CAC progression adjusting for potential confounders. The participants were also divided into 3 groups (mild, moderate and high) based on their IL-6 and FGF23 levels.

Results: The mean age of participants was 50.6 ± 12.8 years, 33 % were women, and 64.7 % were black. The baseline median IL-6 level was 3.07 mg/L [interquartile range (IQR), 1.98-5.75] and was associated with the baseline CAC [coefficient (standard error), 0.57 (0.24), p = 0.02] after adjustment for known risk factors for CAC. IL-6 was associated with CAC progression both by AS [158.1 (68.99), p = 0.03] and by the square root volume difference. When FGF23 was included in the model there was only mild change of the coefficient [135.42 (66.67), p = 0.047]. FGF remained significant in this model [171.12 (70.1), p = 0.02]. Similar results were found using the VS. Participants in the high group had increased CAC progression [AS 122.41 (49.4-447.69) and VS 3.62 (1.87-14.73) compared to mild [AS 5.64 (0-70.89) and VS 0.97 (0.258) and moderate groups [AS 18.75 (0-125.21) and VS 1.66 (0-3.11)]. This association persisted in multivariate models [AS 497.19 (168.21), p < 0.001 and VS 6.93 (1.72), p < 0.001].

Conclusions: IL-6 is strongly associated with CAC presence. Both serum IL-6 and FGF23 are independently associated with CAC progression. Individuals new to dialysis with both elevated IL-6 and FGF23 are at highest risk for CAC progression.

Funding: NIDDK Support
FR-PO907

Vascular Calcification and Left Ventricular Hypertrophy in Hemodialysis Patients: Interrelationship and Clinical Impact

Yu Ah Hong, Eun Hye Yoon, Yoon-Kyung Chang, Chul Woo Yang, Suk Young Kim, Hyeon Seok Hwang. Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Korea.

Background: Vascular calcification (VC) and left ventricular hypertrophy (LVH) is a morphological marker of vascular disorders and a significant indicator of cardiac pathology in hemodialysis (HD) patients. However, their relationship and combined effects on clinical outcomes remain undetermined.

Methods: We included 341 HD patients, who were examined with plain chest radiographs for aortic arch VC and with echocardiography for LVH. We investigated the relationship between VC and LVH, and their clinical significance for cardiovascular events (CVE) and death.

Results: VC was found in 100 HD patients (29.3%). LVH was more prevalent in patients with VC compared with those without VC (70.0% vs. 50.2%; P = 0.001). VC was independently associated with a 2.42-fold increase in the incidence of LVH (95% confidence interval [CI], 1.26–4.65). In multivariate analysis, compared with patients with neither VC nor LVH, the coexistence of VC and LVH was independently associated with VC hazard ratio [HR], 2.01; 95% CI, 1.09–3.72), whereas VC or LVH alone was not. Patients with both VC and LVH had the highest risk for a composite event of death and CVE (HR, 1.88; 95% CI, 1.15–3.06). Significant synergistic interaction was observed between VC and LVH (P for interaction = 0.039).

Conclusions: VC was independently associated with LVH. Coexistence of VC and LVH, respectively, was more often associated with death or cardiovascular events than either factor alone. There was a synergistic interaction between VC and LVH for the risk of a complete event.

FR-PO908

Factors Affecting Vascular Calcifications in Peritoneal Dialysis


Background: Vascular calcifications are associated with mortality in dialysis patients. Correlations with serum markers, therapy and dialysis modalities are not constant across the studies. We aimed to study clinical and laboratory data to determine factors influential to a higher vascular calcification index (VCI) in peritoneal dialysis (PD) patients.

Methods: 109 patients in our PD unit in December 2015 entered this retrospective analysis. VCI was determined using the Adragao score, counting the presence of vascular calcifications in a plain X-ray of the pelvis and hands (0 to 8) dating from the last 12 months. Current clinical and analytical data were collected.

Results: Mean age was 53.8 ±(14.0) and 52.3% were men. Concerning the VCI, 51 patients had 0; 20 had 1-2; 4 had 3-4 and 24 had > 4. Compared to 71 patients with score ≤2, patients with VCI >2 (n=38) were significantly older (60.2±13.0 vs. 50.3±13.4; p=0.00), more often men (73.7% vs. 42.3%; p=0.00), diabetic (60.5% vs. 14.3%; p=0.00), hypertensive (55.6% vs. 34.8%; p=0.04). They had more often a weekly Kt/V < 1.7 (29.7% vs. 10.1%; p=0.01) and were treated with Paricalcitol (12.1% vs. 0%; p=0.014). They had more often on automatic peritoneal dialysis (APD) vs. continuous ambulatory peritoneal dialysis (CAPD) (0.65±0.03 vs. 0.60±0.04; p=0.00) by bioimpedance and higher BMI (27.5±4.6 vs. 25.4±4.3; p=0.00), lower potassium (4.0±0.68 vs. 4.4±0.68 mEq/L; p=0.01) and higher ADMA levels (3.8±0.50 g/dL; p=0.00), lower calcium (9.6±0.6 vs. 10.2±1.0 mmol/L; p=0.00), lower phosphate (1.70±0.33 vs. 1.86±0.28 mmol/L; p=0.00), lower protein losses (24.5±12.7 vs.17.5±9.8 g/day; p=0.00). No differences were found in dialysis vintage, residual renal function, icodextrin use, serum calcium, phosphate, parathyroid hormone, hemoglobin or current use of phosphate-binder, vitamin D analogs, CV medication.

In conclusions: In HD patients, VCI was associated with traditional and non-traditional factors such as less efficient dialysis, APD, higher extracellular water content and serum parameters suggestive of malnutrition.

FR-PO909

Serum Fibroblast Growth Factor 21 Predicts All-Cause Mortality in End-Stage Renal Disease

Serum Fibroblast Growth Factor 21 (FGF21) is an anti-aging hormone which is secreted from liver in response to fasting. Circulating FGF21 concentration is increased in end-stage renal disease (ESRD) that may be survival response to accelerated aging. However, the impact of an increase in circulating FGF21 levels on prognosis remains unknown.

Methods: ESRD patients receiving chronic hemodialysis (HD) were included in this study. Serum FGF21 levels were measured by a sandwich ELISA. The patients were grouped into the high and low FGF21 groups by the median value. The primary outcome was cardiovascular events and all-cause death. The Kaplan–Meier method and Cox proportional hazard model were used for survival analyses.

Results: Of 107 participants (age 65.3±13.0 years, male 59.8%, HD duration 5.7±5.3 years, diabetes mellitus [DM] 41.1%, 17 (15.9%) patients died during a median follow-up of 44 months (interquartile range [IQR] 21–66 months). Median serum FGF21 levels were 1701 pg/mL (IQR 867–2957 pg/mL). Smoking rates and serum uric acid (UA) in the high FGF21 group were significantly higher than in the low FGF21 group. Kaplan–Meier analysis with log-rank test revealed that the high FGF21 group had a higher rate of all-cause mortality (P=0.040) than the low-FGF21 group, but the association between FGF21 levels and cardiovascular events was not found (P=0.795). In the multivariate Cox regression model including age, gender, DM, smoking and serum UA, high serum FGF21 remained an independent predictor for increased mortality (hazard ratio, 4.05; 95% confidence interval, 1.34 to 15.27; P=0.012).

Conclusions: These results suggest that high serum FGF21 levels are associated with increased mortality in ESRD patients. Further studies are required to evaluate a mechanistic link between FGF21 elevation and poor outcome.

FR-PO910

Asymmetric Dimethylarginine Levels Are Lower in Hemodialysis Patients Treated with Paricalcitol

Nester Oliva-Damaso,1,4 Elena Oliva-Damaso,2 Francisco Javier Rodriguez-Esparragón,1 Juan Payan Lopez,1 Alberto Maranes,1 Eduardo Baamonde,1 Yanet Parodis Lopez,1 Nicanor Vega-Diaz,1 Jose C. Rodriguez-Perez,1 Nephrology, Hospital Costa del Sol, Marbella, Malaga, Spain; Nephrology, Hospital Univ de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Las Palmas, Spain; Unidad de Investigación, Hospital Univ de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Las Palmas, Spain; Nephrology, Hospital Quirón, Marbella, Malaga, Spain.

Background: Chronic Kidney Disease (CKD) is associated with an inflammatory condition involving an increased risk of cardiovascular (CV) morbimortality. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase and may be an independent risk factor for CV disease in HD patients.

Methods: We performed a cross sectional observational study in 93 randomly selected patients on chronic HD to evaluate the association between ADMA levels and CV medication.

Results: Patients (62.4% male) had an average age of 64.7±13.1 years. 45.2% were diabetic with a median of 53.1 months (IQR 31.8-89.7) in HD. Patients treated with paricalcitol had significantly lower ADMA levels (0.2±0.19 μM/L) than the rest (0.42±0.35 μM/L) (P=0.00027).

Conclusions: Patients treated with paricalcitol were less likely to have very high ADMA levels (P=0.014) with no significant differences with other medications. Higher dose of paricalcitol was related with a median of 53.1 months (IQR 31.8-89.7) in HD. Patients treated with paricalcitol had significantly lower ADMA levels (0.2±0.19 μM/L) than the rest (0.42±0.35 μM/L) (P=0.00027).

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

Underline represents presenting author.

578A
A new risk scoring system for predicting 15-year mortality was developed. Six independent prognostic factors were retained in the final model and assigned a score proportional to its regression coefficient: 65 years or older; 3, diabetic nephropathy; 3; hypotension; 1; pre-HD cardiac ratio ≥50%; 1; pre-HD BNP ≥250 pg/ml; and 1; and pre-HD numbers of abnormal findings on electrocardiograms, 0, 1, or 2. The patients were categorized as follows with their scores: Group 1 (low risk), 0; Group 2, 1 to 3; Group 3, 4 to 5; and Group 4 (high risk), 6 and higher. In the cohort for model validation, Groups 2 to 4 showed a higher risk than Group 1: Group 2, hazard ratio 4.66 (95% confidence interval 2.25, 9.64); Group 3, 13.62 (6.48, 28.63); and Group 4, 20.86 (9.60, 45.31).

Results: Two hundred patients (64.1%) in the cohort for model development died. Six independent prognostic factors were retained in the final model and assigned a score proportional to its regression coefficient: 65 years or older; 3, diabetic nephropathy; 3; hypotension; 1; pre-HD cardiac ratio ≥50%; 1; pre-HD BNP ≥250 pg/ml; and 1; and pre-HD numbers of abnormal findings on electrocardiograms, 0, 1, or 2. The patients were categorized as follows with their scores: Group 1 (low risk), 0; Group 2, 1 to 3; Group 3, 4 to 5; and Group 4 (high risk), 6 and higher. In the cohort for model validation, Groups 2 to 4 showed a higher risk than Group 1: Group 2, hazard ratio 4.66 (95% confidence interval 2.25, 9.64); Group 3, 13.62 (6.48, 28.63); and Group 4, 20.86 (9.60, 45.31).

Conclusions: A new risk scoring system for predicting 15-year mortality was developed. This system may be useful for evaluating HD patients' prognosis.

FR-PO914
High Interleg Systolic Blood Pressure Difference and Protein-Energy Wasting (PEW) Increase Risk of Cardiovascular Events and Mortality in Incident Dialysis Patients
Sawako Kato,1 Beng Lindholm,2 Shoichi Maruyama,1 Yukio Yuyawa,2 Yoshihira Tsutura,3 Kaoru Yasuda.1 1Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan; 2Baxter Novum & Renal Medicine, Karolinska Inst, Stockholm, Sweden; 3Nephrology, Fujita Health Univ Hospital, Toyoake, Japan; 4Meyo Clinic, Toyohashi, Japan; 5Masuko Memorial Hospital, Nagoya, Japan.

Background: While high interarm blood pressure (BP) difference is a marker of arterial stiffness, PEW is linked to atheroatherosclerosis. Here we analyzed if high interleg systolic BP difference (ISBPD) used instead of interarm BP difference (as most hemodialysis patients had arm AV fistula), and concomitant PEW associates with cardiovascular (CV) events and mortality in dialysis patients.

Methods: In 125 incident Japanese dialysis pts (aged 59 ± 11 years; 84 men), ISBPD and subjective global assessment (SGA) as a marker of PEW were measured. Pts were divided into 4 groups according to median ISBPD, 6 (range, 0.98 mmHg), and if they were well-nourished (SGA A; n=28) or malnourished (SGA B, n=79, and SGA C; n=18). During follow-up for median 46.4 months (range, 1–95 months), 29 deaths and 76 CV events occurred and their corresponding relative risks (RRs) were analyzed.

Results: In Kaplan-Meier, high ISBPD and malnutrition associated with the highest mortality (Log rank 8.65, P = 0.034), while there was no difference between high ISBPD pts and low ISBPD nutrition pts. In Cox, pts with high ISBPD and malnutrition had increased RR of death (RR of high vs low ISBPD, 3.14, 95% CI; 1.21-9.15; RR of SGA category C and C vs A, 2.94, 95% CI; 0.71-20.8 and 12.3, 95% CI; 1.81-120.7, respectively) after adjustments for age and diabetes. For SGA categories A, B, and C, the cumulative number of CV events per 100 pt-years in high ISBPD pts were 4.6, 29.1, and 91.9, and in low-ISBPD pts 3.0, 5.7, and 0, respectively.

Conclusions: In incident dialysis pts, high ISBPD associated with increased risk of mortality, and with CV events which however occurred almost exclusively in pts with higher ISBPD and severe PEW, suggesting that pts with arterial stiffness have increased susceptibility to onset of CV events especially in presence of severe PEW.

Funding: Government Support - Non-U.S.

FR-PO915
Periodontitis and Early Mortality among Adults Treated with Hemodialysis: A Multinational Propensity-Matched Cohort Study
Marcella Russo,1,2 Suetonia Palmer,3 Giovanni F.M. Strippoli.3 1Diaverum Medical Scientific Office; 2Amedeo Avogadro Univ of Eastern Piedmont; 3Univ of Otago Christchurch; 4Univ of Sydney; 5Univ of Bari, on behalf of the ORAL Investigators.

Background: Periodontitis, a multifactorial disease that involves inflammation of the structures supporting teeth, is common, treatable, and may be associated with mortality in the general population and adults with chronic diseases. However, it is unclear whether periodontitis is associated with survival in the setting of kidney disease.

Methods: ORAL-D was a multinational cohort study involving 3338 demented adults with end-stage kidney disease treated in a hemodialysis network in Europe and South America. ORAL-D was designed to examine the associations between oral health and all-cause and cardiovascular-related mortality in people on long-term hemodialysis. Propensity score methods were used to assemble a matched cohort of participants with moderate to severe periodontitis with characteristics similar to patients with no or mild periodontitis. Periodontal disease was assessed using the World Health Organization Community Periodontal Index. A random-effects Cox proportional hazards model was fitted with shared frailty to account for clustering of mortality risk within countries.
Results: Among the 3338 dentate participants, 1355 (40.6%) had moderate to severe periodontitis. Moderate to severe periodontitis was associated with a lower risk of all-cause (0.91 versus 1.30 per 100 person years, hazard ratio 0.74, 95% confidence interval 0.61 to 0.90) and cardiovascular (4.3 versus 6.9 per 100 person years, hazard ratio 0.67, 0.51 to 0.88) mortality. These associations were not changed substantially in sensitivity analyses restricted to participants with 12 or more natural teeth or when analyses accounted for competing causes of cardiovascular death.

Conclusions: Periodontitis does not appear to be associated with an increased risk of all-cause and cardiovascular mortality in adults treated with hemodialysis.

FR-PO916
Accelerated Aging-Associated Immune Changes Are Associated with Cardiovascular Disease in End-Stage Renal Disease Patients
Tzu-Ying Chou,1 Hai-Siang Shiu,1,2 Fang-Yun Lay,1 Yi-Fang Chuang,1 Jean-San Chia,1 Yen-Ling Chiu,1,2 Nephrology, Far Eastern Memorial Hospital, Taiwan; 1Medicine, National Taiwan Univ Hospital, Taiwan; 2Epidemiology, National Yang Ming Univ, Taiwan; 3Graduate School of Immunology, National Taiwan Univ, Taiwan.

Background: Patients with end-stage renal disease (ESRD) exhibit accelerated aging of the immune system and increased risk for cardiovascular diseases, but the contribution of “immune system aging”, or “immunosenescence” to cardiovascular disease is not clear.

Methods: We performed comprehensive lymphocyte and monocyte immunophenotyping in 199 ESRD patients on maintenance hemodialysis and age-matched 57 healthy individuals. Peripheral blood were sampled before hemodialysis session and processed immediately for mononuclear cell isolation and staining. Using multicolor flow cytometry, lymphocytes were separated into subpopulations including naïve T cells (CCR7+CD45RA-), central memory (CCR7+CD45RA-), effector memory (CCR7-CD45RA-), and memory stem cells (naïve cells with high CD28 and CD95). Monocytes were separated into classical (CD14+CD16-), intermediate (CD14+CD16+) and non-classical monocytes (CD14-CD16+).

Results: Compared to healthy individuals, ESRD patients showed decreased numbers of naïve CD4+ and CD8+ T cells and increased numbers of intermediate monocytes (CD14+CD16+), and these changes significantly correlated with age. Lymphocyte and monocyte aging also correlated with other established cardiovascular risk factors, including hemoglobin and high-sensitivity C-reactive protein. In a multivariate-adjusted logistic regression model, a low naïve CD8+ T cell level in combination with a high intermediate monocyte level was independently associated with the existence of coronary artery disease (OR=3.58, 95% CI=1.2~10.4, p=0.019) as well as cardiovascular diseases including stroke and non-fatal myocardial infarction (OR=3.98, 95% CI=1.5~10.8, p<0.007).

Conclusions: These results indicate that cardiovascular disease burden in the ESRD population might be enhanced by the presence of accelerated immunosenescence, of aging-related immune changes.

Funding: Government Support - Non-U.S.

FR-PO917
Serum Magnesium Level Can Predict Mortality in Chinese Hemodialysis Patients: A Cohort Study and 3-Year Follow-Up
Zujin Chen,1 Zhaonong Chen,2 Xiaobo Ma,1 Haijin Yu,1 Xiaonong Chen. Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong Univ School of Medicine, Shanghai, China.

Background: To analysis serum magnesium level and its risk factors in Chinese hemodialysis, and whether serum magnesium level is associated with mortality.

Methods: MHD patients were treated in Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine in July 2012. All patients were consistently treated by 4-hour hemodialysis three times per week, with dialyzer magnesium concentration 0.5 mmol/L. All clinical data, bioethical data and medication were collected at baseline. 3 years follow up and record with the combination of death or withdrawal from dialysis therapy leading to death as the primary outcome. Reference range of magnesium in our laboratory is 0.74-1.03mmol/L.

Results: 230 MHD patients were enrolled, with 63.0% male, 11.3% diabetes. Mean age was 56.67±14.48yrs-old and median dialysis vintage 41[QIR 20.75-72.25] months. Mean magnesium was 1.12±0.16mmol/L. 34.8% patients was in normal range and 65.2% with hypermagnesemia, no one was hypomagnesemia. Pearson correlation showed that age, weight, spKt/V, BUN, Hct, Hb, pre-ALB, pre-dialysis BUN, SCR, UA, Na, K, ALB, LDL, 25(OH)D is associated with serum magnesium level(Fig 1). In multiple stepwise liner regression, BUN, Hct, Ca, spKt/V, SCR, K, Na and weight are independent factors of magnesium(Table 1). Follow 36 months, totally 54 patients died. 15 patients died of sudden death, 13 cerebral disease. Kaplan-Meier analysis showed lower magnesium is associated with higher all-cause mortality and cardiovascular mortality (Fig 2). Cox regression hazard analysis identified hypomagnesemia as a significant predictor for all-cause mortality in MHD patients(Table 2).

Conclusions: A high prevalence of hypermagnesemia is in MHD patients. Serum magnesium level can predict the mortality in Chinese dialysis patients.

FR-PO918
High suPAR Is Strongly Associated with Adverse Outcomes in Patients with End-Stage Renal Disease on Dialysis
Christiane Drechsler,1 Salim Hayek,2 David Changli Wei,3 Sanja Sever,3 Vera Krane,1 Winfried März,4,6 Christoph Wanner,4,6 Jochen Reiser,5 1Div of Nephrology, Univ Hospital Wuerzburg, Wuerzburg, Germany; 2Div of Cardiology, Emergy Univ School of Medicine, Atlanta; 3Dept of Internal Medicine, Rush Univ, Chicago; 4Div of Nephrology, Massachusetts General Hospital, Charlestown; 5Med. Clinic V, Univ of Heidelberg, Mannheim, Germany; 6Medical Univ Graz, Austria; Syndlab Academy, Germany; 7Comprehensive Heart Failure Center, Wuerzburg, Germany.

Background: Soluble urinotokinase plasminogen activator receptor (suPAR) is associated with adverse outcomes in various populations, and is implicated in the pathogenesis of kidney disease. SuPAR concentrations often increase as eGFR decreases, and it is unclear whether they remain predictive of outcomes in patients with end-stage renal disease (ESRD).

Methods: We measured serum suPAR at enrolment in 1175 hemodialysis patients with type 2 diabetes mellitus (54% male, mean age 66±8 years old), participating in the German Diabetes and Dialysis Study (4D Study). Patients were followed for 4 years for death and cardiovascular events. We examined the association between suPAR tertiles and outcomes using Cox regression analyses, adjusting for clinical characteristics.

Results: Median suPAR was 10521 pg/mL (IQR 9105–12543 pg/mL). Patients with suPAR > 11633 pg/mL (third tertile) had an almost 2-fold higher mortality compared to those with suPAR < 3599 pg/mL (first tertile) (adjusted HR 1.95; 95% CI 1.5–2.3). The risks of sudden death and stroke were strongly increased (adjusted HRstroke 2.2, 95% CI 1.4-3.5, and adjusted HRS 2.2; 95% CI 1.3-3.6, respectively, third versus first tertile), together accounting for the higher incidence of cardiovascular events combined (adjusted HR 1.7; 95% CI 1.4-2.2). In contrast, there was no association between suPAR and the risk of non-fatal myocardial infarction.

Conclusions: SuPAR is strongly associated with poor cardiovascular outcomes in patients with ESRD which may reflect pathologic processes beyond decreased renal function. Further studies are needed to determine whether suPAR is a modifiable risk factor and a potential therapeutic target.

FR-PO919
Plasma Betaine and Cardiovascular Outcomes in Hemodialysis Patients
Taria Shaf1, Neil R. Powe,2 Timothy W. Meyer,3 Tanushree Banerjee,4 Seung Young Hwang,1 Michel L. Melamed,5 Jose Coresh,1 Thomas H. Hostetter,1 Johns Hopkins Univ; 2Univ of California, San Francisco; 3Stanford Univ; 4Albert Einstein Medical College; 5Case Western Reserve Univ.

Background: Betaine (trimethylglycine) is a precursor for gut microbiome-derived trimethylamine-N-oxide (TMAO), a uremic toxin, but is also biochemically active, enhancing very-low-density lipoprotein (VLDL) activity and affecting serum homocysteine concentration.

Methods: We measured plasma betaine levels in 1276 patients of the NIDDK sponsored, Hemodialysis (HEMO) Trial and analyzed their relation over time to CV death, sudden cardiac death (SCD) and first CV event adjudicated by an outcomes committee. We used Cox proportional hazards models adjusted for potential confounders (demographics, clinical characteristics, comorbidities, residual kidney function, albumin and TMAO). We also examined interactions by race and dialysis interventions (high flux or dose).

Results: Mean age of the patients was 58 years, 63% were Black and 42% were male. Median (interquartile range) betaine concentration was 53 μM (41, 65). Median follow-up

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
was 2.3 years. In unadjusted and fully adjusted models (including adjustment for TMAO), higher betaine concentrations were associated with a higher risk of CV outcomes. Subgroup analyses did not show significant interactions with race or dialysis intervention.

**Association** of Betaine with Cardiovascular Outcomes in 1276 Patients of HEMO Study

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Mortality</td>
<td>220</td>
<td>1.52 (1.15-2.02)</td>
<td>0.003</td>
</tr>
<tr>
<td>Sudden Cardiac Death</td>
<td>126</td>
<td>1.55 (1.17-2.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>First CV Event</td>
<td>644</td>
<td>1.15 (0.98-1.35)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**Adjusted HR per 2-fold increase in solute**

**Conclusions:** Plasma betaine is a risk factor for CV outcomes in hemodialysis patients and this association appears to be statistically independent of serum TMAO concentrations. **Funding:** NIDDK Support

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**FR-PO920**

**P-Cresol Sulfate, Indoxyl Sulfate, Hippurate and Phenylacetylglutamine and Cardiovascular Outcomes in Hemodialysis Patients**

**Tariq Shaht, Tammy L. Sirich, Timothy W. Meyer, Seungyoung Hwang, Michal L. Melamed, Tanushree Banerjee, Jose Corosh, Thomas H. Hostetter, Neil R. Powe, Johns Hopkins Univ; Stanford Univ; Albert Einstein College of Medicine; Univ of California, San Francisco; Case Western Reserve Univ.

**Background:** We recently reported that a large increase in Kt/V urea in the Hemodialysis (HEMO) Study failed to achieve significant reduction in p-cresol Sulfate (PCS), indoxyl sulfate (IS), hippurate (HIPP) and phenylacetylglutamine (PAG). The goal of this study was to determine the association of these solutes with cardiovascular (CV) outcomes.

**Methods:** We measured PCS, IS, HIPP and PAG in HEMO Study samples (N=1276) and analyzed their association with CV death, sudden cardiac death (SCD) and first CV event, using Cox model adjusted for potential confounders [demographics, clinical characteristics, comorbidities, albumin, residual kidney function (RKFI)].

**Results:** Mean age of the patients was 58 years, 65% were Black and 42% were male. None of the solutes were associated with any CV outcomes (Table 1). The Cox model for SCD did not show a significant association with any of the solutes. PCS, IS, and PAG were associated with CV death only in patients with RKF (n=433; p-interaction <0.05). The goal of this study was to determine the association of these solutes with cardiovascular (CV) outcomes. In pre-specified subgroup analyses, total HIPP and PAG were associated with CV outcomes. In unadjusted and fully adjusted models (including adjustment for TMAO), higher betaine concentrations were associated with a higher risk of CV outcomes. Subgroup analyses did not show significant interactions with race or dialysis intervention.

**Associations** of Solutes with CV Outcomes in 1276 Patients of HEMO Study

<table>
<thead>
<tr>
<th>Solute</th>
<th>CV Death (n=220)</th>
<th>SCD (n=126)</th>
<th>First CV Event (n=644)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS</td>
<td>0.96 (0.96-1.07)</td>
<td>0.7</td>
<td>0.96 (0.96-1.01)</td>
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<tr>
<td>IS</td>
<td>0.96 (0.81-1.14)</td>
<td>0.6</td>
<td>0.94 (0.75-1.18)</td>
</tr>
<tr>
<td>HIPP</td>
<td>1.00 (0.98-1.21)</td>
<td>0.1</td>
<td>0.96 (0.94-1.03)</td>
</tr>
<tr>
<td>PAG</td>
<td>1.00 (0.94-1.26)</td>
<td>0.2</td>
<td>0.98 (0.90-1.30)</td>
</tr>
</tbody>
</table>

**Adjusted HR per 2-fold increase in solute**

**Conclusions:** The study showed that serum ST-2 level independently predicted mortality and non-fatal CV events in ESRD patients. High ST-2 concentration can be an additive predictor for adverse CV outcomes in incident dialysis patients. **Funding:** Private Foundation Support

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**FR-PO921**

**Adipokines, Blood Pressure and Arterial Elasticity in Dialysis Patients**

**Wenjin Liu, Meijuan Meng, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

**Background:** Previous studies have suggested that adipokines, a group of hormones and cytokines released by white adipose tissue, may exert potent and inconsistent effects on cardiovascular (CV) system. There remains a paucity of data regarding theirs associations with CV parameters in patients on maintenance hemodialysis.

**Methods:** This is a cross-sectional analysis of midterm baseline data from a cohort study. Two-hundred and twenty eight dialysis patients from dialysis centers of four tertiary dialysis centers in East China were enrolled. Blood pressure level and arterial elasticity were evaluated by ambulatory blood pressure monitoring and pulse wave velocity measurement on a nondialysis day, respectively. Adipokines (adiponectin, resistin, PAI-1, leptin, MCP-1, adipin) were detected using pre-dialysis plasma samples by multiplex assays. Associations of adipokines with ambulatory systolic blood pressure (A-SBP) and carotid-to-femoral pulse wave velocity (cPWV) were determined using generalized linear models.

**Results:** For blood pressure, in a basic age- and sex-adjusted model, adiponectin is positively associated with A-SBP (p=0.004) while resistin, PAI-1, leptin and adipin are inversely associated with A-SBP (p=0.001 for resistin, PAI-1 and leptin; p=0.021 for adipin). In more extensive adjusted models, adiponectin is still positively associated with A-SBP while resistin, PAI-1, leptin are inversely associated with A-SBP (p<0.01 for all). For arterial elasticity, only adiponectin is inversely associated with cPWV (p=0.01 for all models).

**Conclusions:** Circulating adipokines are associated with blood pressure and arterial elasticity in dialysis patients, suggesting their diverse effect on cardiovascular system in these patients. **Funding:** Government Support - Non-U.S.

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**FR-PO922**

**Additive Prognostic Utility of Serum ST2 Level as a Predictor of Cardiovascular Outcomes in Incident Hemodialysis Patients**


**Background:** ST-2 concentration is known to be a predictor for cardiovascular (CV) mortality and hospitalization due to CV disease in patients with heart failure. This study was to evaluate the prognostic value of serum ST-2 level in incident dialysis patients, in terms of mortality and CV events.

**Methods:** A total 182 ESRD patients starting maintenance dialysis were enrolled. We measured the pre-dialysis serum ST-2 level at the start of dialysis. Patients were divided into two groups according to the median ST-2 level. Factors associated with serum ST-2 level were analyzed. The associations between serum ST-2 level and mortality and CV events were investigated.

**Results:** Median follow up duration was 628 days (interquartile range 382 to 1052 days). There was no significant difference in baseline demographic characteristics and comorbidity between the two groups. The high ST-2 group showed higher levels of C-reactive protein (CRP), phosphorus, and calcium-phosphorus product, and lower albumin and calcium levels than those of the low ST-2 group. Serum ST-2 level showed significantly positive correlations with levels of phosphorus, calcium-phosphorus product, and CRP, and the ratio of peak early to late diastolic filling, while it showed significantly negative correlations with serum albumin level and ejection fraction, after age- and sex-adjustment. The patient survival rate was significantly lower in the high ST-2 group compared with that of the low ST-2 group after 3 years follow up (69.2% vs. 86.9%, P=0.023). The event rate for death and non-fatal CV event was significantly lower in the high ST-2 group compared with the low ST-2 group (59.4% vs. 80.3%, P=0.008). In multivariate Cox regression analysis, the ST-2 level was also a significant predictor for composite of end-points after adjustments for traditional CV risk factors and laboratory parameters (HR 1.011, P=0.003).

**Conclusions:** This study showed that serum ST-2 level independently predicted mortality and non-fatal CV events in ESRD patients. High ST-2 concentration can be an additive predictor for adverse CV outcomes in incident dialysis patients. **Funding:** Private Foundation Support

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**FR-PO923**

**A Lower Serum Uric Acid Is Associated Not Only with All-Cause Mortality but also Cardiovascular Mortality among Patients Receiving Hemodialysis in Japan**

**Naoki Suguno,1 Yukio Maruyama,1 Takashi Yoko,2 Atsushi Wada,2 Takashi Shigematsu,2 Ikuto Masakane,2 Division of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan; 2Department of Renal Data Registry, Japanese Society for Dialysis Therapy, Tokyo, Japan.

**Background:** High level of serum uric acid is prevalent in chronic kidney disease (CKD), however it has a controversy whether high or low serum uric acid level appears to be a risk factor of cardiovascular event and mortality in the patients of receiving renal replacement therapy.

**Methods:** We collected the baseline data of 222,434 patients receiving HD thrice weekly (males: 63.0%, 66±12 years, median HD vintage of 60 months, females: 68±13 years, median HD vintage of 72 months) extracted from a nationwide dialysis registry at the end of 2011 in Japan. Then we evaluated the patient survival and development of complication using the registry at the end of 2012.

**Results:** During one-year follow-up, 18,775 (8.4%) died of all causes including 8094 (3.6%) cardiovascular death. All-cause mortality, and cardiovascular mortality were lower in patients of serum uric acid levels lower than the median of the whole patients. Using the median of the whole patients as a cut-off point, Cox regression analysis, the ST-2 level was also a significant predictor for composite of end-points after adjustments for traditional CV risk factors and laboratory parameters (HR 1.011, P=0.003).

**Conclusions:** This study showed that serum ST-2 level independently predicted mortality and non-fatal CV events in ESRD patients. High ST-2 concentration can be an additive predictor for adverse CV outcomes in incident dialysis patients. **Funding:** NIDDK Support
Conclusions: In this large observational cohort study, lower levels of serum uric acid were independently associated not only with all-cause mortality but also cardiovascular mortality among Japanese HD patients. Close monitoring of serum uric acid is thought to be necessary for the management of HD patients.

FR-PO924
Menopause Status Is Associated with Mortality in Women on Hemodialysis Sharanaya Ramesh,1 Matthew T. James,1,2,4 Stephen B. Wilton,1,2 Jayna M. Holroyd-Leduc,1,3 Marcello Tonelli,1,2,3 Brenda Hemmelgarn,1,2,4 Sofia B. Ahmed,1,2,4 1Cumming School of Medicine, Univ of Calgary; 2Lethbridge Cardiovascular Inst of Alberta; 3Dept of Community of Health Sciences, Univ of Calgary; 4Alberta Kidney Disease Network; 5Brigham and Women’s Hospital, Harvard Univ.

Background: Young women with end-stage kidney disease (ESKD) have low survival compared to age-matched men. Women with ESKD have an abnormal hypothalamic pituitary gonadal axis, characterized by low estradiol. We hypothesized that premature menopause is associated with death in women with ESKD.

Methods: Women who initiated hemodialysis (HD) between Feb 2005 and Nov 2012 in 3 centers were classified as premenopausal, perimenopausal and postmenopausal using the Women’s Ischemia Syndrome Evaluation (WISE) criteria based on serum estradiol, follicle stimulating hormone levels and age. The associations between menopausal status and all cause, cardiovascular(CV) and non-cardiovascular(non-CV) mortality were determined by survival curves and Cox regressions.

Results: Four hundred eighty-two women (60±16years, 53% diabetic) were followed for 2.9 years (IQR=3.47 years) with 241 deaths (31% CI). Thirty percent of women had a premenopausal sex hormone profile (estradiol: 196±187 pmol/L), while 7% and 58% had a perimenopausal estradiol: 230±335 pmol/L and postmenopausal (estradiol: 55±38 pmol/L) sex hormone profile respectively. In comparison to postmenopausal women, peri- and premenopausal women had higher all-cause mortality after adjustment for covariates (hazard ratio(HR)[95% confidence interval (CI):1:87[1.72-99] and 1:8[1.32-2.46] respectively), and higher CV mortality after adjustment (HR: 2:72[1.30-5.70] and 1:8[1.32-2.46] respectively). In comparison to postmenopausal women, premenopausal women had higher non-CV mortality after adjustment (HR: 1:7[1.07-2.73]).

Conclusions: Using the WISE classification, peri- and premenopausal women with ESKD on HD have a higher risk of all-cause and CV mortality compared to postmenopausal, and premenopausal women have a higher non CV mortality compared to postmenopausal women. Further studies are required to determine the pathophysiology leading to increased mortality risk in young women with ESKD.

FR-PO925
Long-term Serial Measurements of High-Sensitivity Troponin T in Stable Hemodialysis Patients: The Effect of Angiotensin II Receptor Blockade and Associations with Clinical Variables The Safir Study Group, Depts of Renal Medicine and Cardiology, Aarhus Univ Hospital, Aarhus, Denmark.

Background: For the interpretation of high-sensitivity troponin T (hsTnT) levels in hemodialysis (HD) patients, it is important to know the expected range, variation over time, and the impact of clinical and HD specific factors.

Aim: To study the effect of angiotensin II receptor blockade (ARB), short and long-term variation in TnT, and associations with cardiac status in stable HD patients.

Methods: In 198 prevalent hemodialysis (HD) and 78 peritoneal dialysis (PD) patients 4 monthly hs-TnT and hs-cTnT measurements were obtained. Variation was assessed with reference change values and mixed models. Cox regression models were used for survival analyses, maximal follow-up 50 months.

Results: Troponin levels were similar in HD and PD patients (median [IQR] hs-cTnT; 25ng/L [14–43] vs 21ng/L [11–37], hs-cTnT; 70ng/L [44–129] vs 67ng/L [43–123]). 42% of hs-cTnT and 98% of hs-cTnT were above the decision limit of myocardial infarction (MI). Variability of troponins associated with age, male sex, protein-energy wasting and derived to be failure. The cut point for acute change values were ≥88% (hs-cTnT) and ≥29% (bs-TnT), index of individuality 0.07 for both. Constantly high hs-TnT (above 108 ng/L) predicted death [HR 2.09 95% CI 1.03-4.26] while hs-cTnT did not.

Conclusions: A large proportion of stable dialysis patients have troponins levels above the decision limit for MI. Large intra-individual differences support the use of reference change values when assessing dialysis patients with possible acute cardiac events. A constantly high level of hs-cTnT and not hs-TnT predicted a doubled risk of death.

Funding: Pharmaceutical Company Support - Aagen, Government Support - Non-U.S.

FR-PO926
High-Sensitivity Troponins in Clinically Stable Dialysis Patients: Variation and Prognostic Value Sumna Snedael,1 Peter F. Barany,2 Sigrun Helga Lund,2 Abdul Rashid Tony Qureshi,4 Olof Heimburger,1 Peter Stenvinkel,1 Christian Löweber,1 Karolina Sznurner,1 1Dept of Clinical Science, Intervention and Technology, Karolinska Inst, Stockholm, Sweden; 2Nephrology Dpt, Landskaps Univ Hospital, Reykjavik, Iceland; 3Faculty of Medicine, Univ of Iceland, Reykjavik, Iceland; 4Dept of Baxter Novum, Karolinska Inst, Stockholm, Sweden; 5Dept of Laboratory Medicine, Karolinska Inst, Stockholm, Sweden; 6Dept of Clinical Chemistry, Aleris Medilab, Täby, Sweden; 7Dept of Cardiology, Karolinska Inst, Stockholm, Sweden.

Background: Cardiac troponins are elevated in dialysis patients even without signs of cardiac ischemia. The study aim was to assess variation and prognostic value of serial high sensitivity cardiac troponin I (hs-cTnI) and T (hs-cTnT) in prevalent, stable dialysis patients.

Methods: In 198 prevalent hemodialysis (HD) and 78 peritoneal dialysis (PD) patients 4 monthly hs-cTnI and hs-cTnT measurements were obtained. Variation was assessed with reference change values and mixed models. Cox regression models were used for survival analyses, maximal follow-up 50 months.

Results: Troponin levels were similar in HD and PD patients (median [IQR] hs-cTnT; 25ng/L [14–43] vs 21ng/L [11–37], hs-cTnT; 70ng/L [44–129] vs 67ng/L [43–123]). 42% of hs-cTnT and 98% of hs-cTnT were above the decision limit of myocardial infarction (MI). Variability of troponins associated with age, male sex, protein-energy wasting and derived to be failure. The cut point for acute change values were ≥88% (hs-cTnT) and ≥29% (bs-TnT), index of individuality 0.07 for both. Constantly high hs-TnT (above 108 ng/L) predicted death [HR 2.09 95% CI 1.03-4.26] while hs-cTnT did not.

Conclusions: A large proportion of stable dialysis patients have troponins levels above the decision limit for MI. Large intra-individual differences support the use of reference change values when assessing dialysis patients with possible acute cardiac events. A constantly high level of hs-cTnT and not hs-TnT predicted a doubled risk of death.

Funding: Pharmaceutical Company Support - Aagen, Government Support - Non-U.S.

FR-PO927
High Sensitive Troponin-I Level and Hemodialysis-Induced Myocardial Injury in Chronic Hemodialysis Patients Khaiohn Tranthankala,1 Tanawat Tarapan,2 Khrongwong Musikatavorn,2 Pyarat Phairatwet,2 Pwacsia Susantitaphong,1 Kriang Tungsang,1 Somchai Eiam-Ong,1 1Medicine-Nephrology, Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand; 2Emergency Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 3Nephrology, Bhumirajankarindra Kidney Inst Hospital, Bangkok, Thailand.

Background: High sensitivity troponin I (hsTnI) is the best biomarker for myocardial injury. The current cut-off point for diagnosis of acute myocardial infarction (MI) was derived from general population. The reduction in renal clearance and the removal by hemodialysis (HD) affected the level and utility of this marker in HD ESRD patients. Unfortunately, there was unavailable well-designed study that determined the appropriated level of hsTnI in this specific population. Moreover, the HD process itself might cause undesirable myocardial injury and enhance post HD hsTn level.

Methods: This comparative study was conducted to compare the hsTnI level between 100 HD ESRD patients (age 64±5.13 years) and their 107 matched population with good renal function (age 63±8.97 years). Moreover, the pre- and post-HD hsTn levels were measured to determine the effect of HD on hsTn.

Results: The hsTnI levels in the HD ESRD group were higher than in the control group [median (IQR): 54.3(20.6-152.7) vs. 18.6(2.6-61.1) ng/L, p<.0001]. The hsTn levels reduced after HD process from 54.3 (20.6-152.7) ng/L in pre-HD to 27.1 (13.3-91.4) ng/L in post-HD (p<0.015). Of interest, 25% of HD ESRD patients had increment of hsTnI after HD and represented HD-induced myocardial injury. The significant risk factors were high HbA1C, high blood flow rate, and high dialysate flow rate.

Conclusions: In HD ESRD patients, the baseline hsTnI levels are approximately three times significantly higher than in general population. As such, the cut point for acute MI diagnosis in HD ESRD patients should be three times of reference level in general population. However, the dynamic change of hsTnI overtime was still recommended for the final acute MI diagnosis. Hemodialysis could reduce hsTn level. Certain numbers of HD ESRD patients had HD-induced silent myocardial injury and should be aggressively investigated to prevent further cardiovascular mortality.

Funding: Government Support - Non-U.S.
Native T1 Mapping Is a Highly Reproducible Measure of Myocardial Fibrosis in Hemodialysis Patients Independent of Hydration Status

Matthew P.M. Graham-Brown,1,2 Darren R. Churchward,1 Daniel Scott March,1 David J. Stensel,2 Gerry Patrick McCann,2 James Burton,2 John Walls Renal Unit, Leicester General; 3Depts of Infection, Immunology & Inflammation & Cardiovascular Sciences, Univ of Leicester, United Kingdom; 4National Centre for Sport & Exercise Medicine, Loughborough Univ, United Kingdom.

Background: Myocardial fibrosis occurs frequently in hemodialysis (HD) patients and is associated with poor prognosis. Native T1 mapping is a novel cardiac MRI (CMR) technique that measures longitudinal proton relaxation to characterize tissue with great specificity. Native T1 mapping correlates well with myocardial fibrosis in many diseases, but concerns remain about its use in HD patients due to the potential impact of changes in hydration status on T1 time. We examined the inter-study reproducibility of native T1 mapping in HD patients and the effects of hydration on native T1 time.

Methods: 3T CMR was performed twice on non-dialysis days for 10 patients (median interval 7 days) to assess reproducibility of native T1 mapping. Changes in left ventricular end-diastolic volume (ALVEDV) and changes in weight (Aweight) between scans were used as surrogates of hydration status and the effects these on change in native T1 (AT1) between scans was assessed.

Results: There was no interval difference between mean native T1 times (1267.8ms (35.4 vs 1270.7ms (30.5, P=0.6)) with an inter-study co-efficient of variation of 0.7%. Bland-Altman analysis showed narrow limits of agreement with no systematic bias. LVEDV and weight were different between scans (mean change LVEDV 11.7ml±8.7, mean change weight 0.5kg±0.5) and there was a significant correlation between LVEDV and Aweight (r=0.4, p=0.03). There were no correlations between AT1 and LVEDV or Aweight (r=0.14, P=0.7 and r=0.2, P=0.6). Linear regression confirmed AT1 was unaffected by LVEDV and Aweight (F(1,8)=0.15, adj R²=0.1, P=0.71 and F(1,8)=0.31, adj R²=0.08, P=0.59).

Conclusions: These results show for the first time that native T1 time is unaffected by hydration status. The outstanding test-retest, inter-study reproducibility demonstrated for native T1 mapping make it an attractive imaging biomarker for clinical trials to assess changes in myocardial fibrosis.

Insights from Speckle Tracking Echo in Detecting Differences in Myocardial Function in End-Stage Renal Disease

Panagioti E. Giannou,1 Vasiliki Kakiouzi,2 Athanasia Kapota,2 Aikaterini Damianaki,2 Constantina Aggelii,2 Dimitrios Petras.1 1Nephrology Dept, Hippokration General Hospital, Athens, Greece; 21st Cardiology Clinic, Univ of Athens, Hippokration General Hospital, Athens, Greece.

Background: Hemodialysis (HD) is capable of inducing subclinical myocardial dysfunction and this phenomenon is primarily related to hemodynamic instability. In contrast, peritoneal dialysis (PD) has until recently been considered to exert little, if any, significant hemodynamic effects. The aim of the current study was to assess whether speckle tracking echocardiography, by measuring global longitudinal strain (GLS), could assess differences in early myocardial dysfunction between patients with end stage renal disease (ESRD) who have undergone PD and those who are treated with HD.

Methods: Thirty-nine patients with ESRD and with no known coronary artery disease were enrolled. Patients were stratified into two groups according to the dialysis modality (i.e. 23 on HD and 16 on PD). All patients underwent comprehensive 2D echocardiographic study using standard 2D and Doppler measurements. GLS was measured using the obtained apical views. Cross-sectional comparisons of the derived parameters were made between the two groups.

Results: There was no difference in mean age (65.5 ± 9.9 vs 57.7 ± 7.9, p=0.07) and dialysis duration (mean 85 ± 106.7 vs 50.3 ± 72.2 months, p=0.4) between the two groups. Moreover, mean left atrial (40.1 ± 6.4 vs 41.6 ± 8.9mm, p=0.5), intra-ventricular septum (10.7 ± 1.8 vs 9.9 ± 1.9mm, p=0.04), EF (48.5 ± 12.3 vs 45.6 ± 8.7%, p=0.04) and E/Em (9.7 ± 4.5 vs 10.1 ± 4.8, p=0.7) measurements were not statistically different. However, GLS was less negative in the HD group (-11.6±3.8 vs -15.4±4.5, p=0.04).

Conclusions: Patients, in HD, exhibit less negative GLS values, in comparison to those in PD. It must be mentioned that less negative GLS is proven to be associated with an early myocardial dysfunction and an increased cardiovascular mortality. This could be attributed to different hemodynamic effects of each dialysis modality on myocardial function.

Impact of Left Ventricular Hypertrophy Regression after Initiation of Intensive Hemodialysis on Clinical Outcomes

Emilie Trinh, Christopher T. Chan. Nephrology, Univ Health Network, Toronto, ON, Canada.

Background: Left ventricular hypertrophy (LVH) is an independent risk factor for mortality and morbidity in chronic kidney disease (CKD). Concentric hypertrophy remains the main culprit. The aim of this study was to identify factors that could be associated with different geometric patterns of LVH on a PD population.

Methods: We evaluated 114 CKD patients who underwent both echocardiography and Peritoneal Dialysis (PD) for more than 2 months, since 1999 until 2015. LVH (mass >95 g/m² [women] and >115 g/m² [men]) and relative wall thickness (RWT) were used to define LV geometry: no LVH, LVH and RWT=0.42 (eccentric), and LVH and RWT=0.42 (concentric). Descriptive statistics and multinomial logistic regression analysis were done.

Results: Baseline demographics included age (54.6±17.6 years), gender (56.1% males), diabetes prevalence (33.3%) and clinical parameters included systolic blood pressure (143±23mmHg), residual renal function (RRF -6.0±5.6 ml/min, kT/V 2.7±1.0), normalized protein catabolic rate (nPCR - 0.99±0.32 kg/kg), hemoglobin (11.9±1.8 g/dl), phosphorous (4.9±1.6 mg/dl), PTH (650±641.8 mg/ml), high sensitivity C-reactive protein (hs-CRP - 12.7±21.9 g/l), total cholesterol (208.6±58.1mg/dl). Vintage on PD was of 33.8±24.2 months and regarding LV geometry, 38 patients presented with concentric LVH and 76 patients with non-concentric LVH.

In our population, higher phosphorus (p=0.043) and PTH (p=0.017) levels, higher systolic blood pressure (p=0.029) and lower nPCR (p=0.030) were predictive of concentric LVH, and hsCRP was predictive of eccentric LVH (p=0.048), when adjusting for gender, age, RRF, LVH diabetes, cholesterol and hemoglobin levels and using the group without LVH as reference.

Conclusions: Modifiable factors, in this population, were conditioning concentric LVH, namely higher systolic blood pressure, worse mineral metabolism and nutrition parameters. Ameliorating these variables would diminish cardiovascular mortality in CKD patients? Larger studies are needed, but worth attempting in daily practice.
Methods: Fifty two prevalent PD patients were enrolled at a single dialysis center. We measured ambulatory BP, office BP, home BP, and central BP. The ambulatory BP was recorded for 24 hours, office BP was measured at least in two visits, and home BP was measured for one week. The central BP was estimated using radial artery tonometry. Left ventricular mass index (LVMI) was measured using echocardiography and the presence of LVH was ascertained.

Results: LVH was best predicted by ambulatory systolic BP (area under the curve (AUC), 0.81; 95% CI, 0.691-0.931) and home systolic BP (AUC, 0.786; 95% CI, 0.658-0.915). The office systolic BP (AUC, 0.643; 95% CI, 0.488-0.799) and central systolic BP (AUC, 0.662; 95% CI, 0.514-0.840) were inferior to ambulatory and home BP in predicting LVH. The adjusted odds ratio (OR) for home systolic BP (OR, 1.066; 95% CI 1.001-1.17) was higher than those for ambulatory (OR, 1.052; 95% CI 1.010-1.096) and central systolic BP (OR, 1.032; 95% CI 1.021-1.173) in LVH prediction. The office systolic BP did not significantly predict LVH (OR, 1.026; 95% CI 0.986-1.068).

Conclusions: Home and ambulatory systolic BP were the strongest predictors of LVH suggesting that treatments targeting these BP measurements may prevent end organ damage in PD patients.

FR-PO934

Tallium-201 Washout Rate of Stress Myocardial Perfusion Imaging as a Predictor of Mortality in Diabetic Kidney Disease Patients Undergoing Hemodialysis: An Observational, Follow-Up Study

Toshide Hayashi, Nobuhiko Joki, Atsuku Matsukane, Masaki Iwasa, Yuri Tanaka, Hiroki Hayashi.
Div of Nephrology, Toho Univ Ohashi Medical Center, Tokyo, Japan.

Background: Tallium-201 (201Tl) washout rate of stress myocardial perfusion imaging (MPI) has been reported to correlate with coronary flow reserve which is a parameter of myocardial microcirculatory condition. It is useful to detect coronary artery disease and evaluate the severity. However, the evidence for its use in diabetic kidney disease (DKD) has been lacking, and the association between thallium-201 washout rate and adverse outcomes including death is unknown. Therefore, a hospital-based, prospective, cohort study was conducted to evaluate the predictive ability of thallium-201 washout rate for mortality in DKD patients undergoing hemodialysis.

Methods: A total of 96 DKD patients who had been started on maintenance hemodialysis undergoing pharmacologic or exercise stress MPI with thallium-201 within 1 year, 72 men and 24 women, with a median age of 67 years, were studied. The endpoint was defined as all-cause death. The Cox proportional hazards model was used to calculate hazard ratios (HR) and 95% confidence intervals (CI).

Results: During the mean follow-up period of 3.1 ± 2.4 years, 18 (18.8%) deaths occurred. Multivariable Cox-proportional hazard analysis indicated that thallium-201 washout rate levels in the lowest tertile (3.1 - 36.2%), the middle tertile (36.5 - 46.3%), and the highest tertile (46.4 - 66.2%) were 47.7%, 85.7%, and 84.2%, respectively (Figure).

Conclusions: Among DKD patients undergoing hemodialysis, thallium-201 washout rate seems to be useful for predicting death.

FR-PO935

Early Mortality and Late Outcomes for Coronary Revascularisation in End Stage Renal Disease - A Systematic Review and Meta-Analysis

Robin Ramphul, Debasish Banerjee.
Renal and Transplantation Unit, St. George’s Univ Hospitals NHS Foundation Trust, London, United Kingdom.

Background: Despite the high prevalence of coronary artery disease in patients with end-stage renal disease (ESRD), the optimal method of coronary revascularisation remains unclear. We conducted a systematic review and meta-analysis of the available literature comparing outcomes after percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) in ESRD patients.

Methods: We reviewed contemporary studies, conducted after the year 2000 as PCI was introduced in ESRD patients and PCI to CABG, using Review Manager 5.1 for statistical analysis and PRISMA guidelines for reporting. Clinical end-points compared were early (in-hospital or 30-day) and late (>1 year) mortality, repeat revascularisation, occurrence of major adverse cardiovascular events (MACE) and myocardial infarction (MI) after revascularisation.

Results: In 12 studies investigating early mortality, the analysis demonstrated less early deaths for PCI compared to CABG (4% vs 8%, p=0.001, Figure 1a). Late mortality was reported in 10 studies with late deaths similar for CABG and PCI (44% vs 50%, p=0.32). Repeat revascularisation was reported in 9 studies. CABG was less likely to require repeat revascularisation compared to PCI (12% vs 41%, p=0.001, Figure 1b). The occurrence of MACE was reported in 3 studies. CABG was associated with less events compared to PCI (16% vs 57%, p=0.001, Figure 1c). Similarly, MI alone occurred less often with CABG than PCI (5% vs 11%, p=0.003, Figure 1d). There existed a selection bias with PCI preferred to CABG in single vessel disease and CABG for multivessel or left main disease.

Conclusions: The results demonstrate better early mortality in patients with ESRD undergoing PCI, however the results favoured CABG for repeat revascularisation, MACE and MI. CABG was only marginally beneficial for late mortality.
FR-PO936
Use of Eliquis (Apixaban) in Atrial Fibrillation Patients Undergoing Hemodialysis Bobby Rajesh Malik, Anjali Om, Prabal K. Guha. Cardiology, McLeod Regional Medical Center, Florence, SC.

Background: Hemodialysis (HD) patients with multiple other cardiovascular (CV) risk factors are at high risk for development of atrial fibrillation (AFib). Most of these patients have high CHA2DS2-VASc scores requiring anticoagulation treatment. For almost fifty years, warfarin has been the gold standard treatment, but with significant limitations, especially in its interaction with antibiotics that HD patients often require. In the last few years, non vitamin K oral anticoagulation (NOAC) has emerged as a new class of drug for reducing thromboembolic complications in these patients. However, out of 4 NOACs, only apixaban is approved for use in HD patients based solely on its pharmacokinetic data.

Methods: Medical records of 65 patients on HD with history of AFib treated with apixaban were retrospectively reviewed for any thromboembolic events and any bleeding. Average follow up was 150 days with minimum follow up being 30 days.

Results: There were 65 patients (47% male) age 43 to 85 with an average age of 68. There were no clinical thromboembolic events noted. Only one patient had epistaxis that was self-limiting, not requiring hospitalization or transfusion.

Conclusions: In this small retrospective study, apixaban was found to be well tolerated and effective with no significant bleeding complications. If supported in larger studies, apixaban could be an alternative in HD patients with a history of AFib.

FR-PO937

Background: The Kidney Disease Improving Global Outcomes (KDIGO) guidelines do not recommend stopping statin medications when patients initiate dialysis. Guidelines state that statins should not be initiated for dialysis patients as large trials did not demonstrate mortality or cardiovascular benefits in dialysis population. The objective of this study was to examine current statin use and both initiation and discontinuation of statin medications in U.S. veterans receiving maintenance dialysis.

Methods: Retrospective analysis of U.S. Department of Veterans Affairs Healthcare System (VA) national databases to determine statin use in dialysis. Medications acquired with the VA system were obtained from the Managerial Cost Accounting National Data Extracts. Medications acquired outside the VA were obtained from the Corporate Data Warehouse (CDW). Statin medication use was ascertained from pharmacy dispensing records during years 2012 and 2013. The dialysis patients were identified using the CPT, ICD-9, and V A dialysis procedure codes at V A outpatient centers.

Results: A total of 17,883 veterans dialysis patients were evaluated. 97% were male, 55% aged ≥60-75 years and 32.3% aged ≥ 75 years; 38% were African-American. Diabetes and coronary artery disease were present in 59% and 32.3%, respectively. During fiscal year 2012, 63.3% of patients were using statins, and 57.7% were using statins in 2013. Of the 17,883 patients, 53.0% used statins continuously and 10.3% discontinued statin use during year 2013. Statin initiation was noted in 4.7% during 2013. Statin initiation was noted in 4.7% during 2013.

Conclusions: A large proportion of U.S. veterans on hemodialysis use statin medications. Very few discontinue statins and even fewer initiate them. Future studies should determine patient need for statin medication in dialysis patients considering large pill burden and financial costs.

Funding: VA Support

FR-PO938
Facility Use of Low Dialysate Temperature for Prevention of Intra-Dialytic Hypotension Is Associated with Lower Cardiovascular Mortality in the DOPPS Indranil Dasgupta,1 G. Neil Thomas,2 Joanne L. Clarke,2 Alice Sitch,2 Angelo Karayi,3 Brian Bieber,3 Manfred Hecking,4 Bruce M. Brunelli,3 Hugh C. Rayner,1 1Heartlands Hospital, United Kingdom; 2Univ of Birmingham, United Kingdom; 3Arbor Research; 4Medical Univ of Vienna, Austria.

Background: Intra-dialytic hypotension (IDH) occurs during 20-30% of haemodialysis (HD) sessions and is associated with cardiovascular (CV) mortality and events. Aim was to investigate associations between HD facility practices related to the management of fluid volume and hypotension and adverse events.

Methods: Data on 8807 patients from 232 HD facilities across 12 countries in DOPPS phase 4 (2009-12) were analysed. Multi-level survival models assuming a Weibull distribution (allowing for clustering of data within facilities) were used to estimate associations between facility practices reported by MDs and patient all-cause and CV mortality, CV events and hospitalizations, adjusted for country, age, gender, vintage, pre-dialysis systolic BP, CV comorbidities, diabetes (model 1) plus BMI, smoking, residual renal function, Kt/V, vascular access (model 2). We tested 10 practices: (1) protocol for fluid volume management, (2) routine orthostatic BP measurement, (3) blood volume monitor (BVM), (4) bio-impedance device (BID), (5) BVM and BID, (6) limit to fluid removal, (7) isolated ultrafiltration and use of (8) a protocol, (9) routine sodium profiling and (10) low dialysate temperature for managing IDH.

Results: Among the 10 HD facility practices studied, routine use of low temperature dialysate for patients prone to intradialytic hypotension (47% of facilities vs. infrequent or no use) was associated with lower CV deaths in both models.

Conclusions: The HD facility practice of routinely using low dialysate temperature to limit or prevent IDH is associated with lower CV mortality. This merits further investigation in a randomised trial.

FR-PO939
Standardized Dialysate Temperature of 36 Degrees Celsius: Association with Clinical Outcomes Kathryn S. Gray, Dena E. Cohen, Steven M. Brunell. Duluth Clinical Research, Minneapolis, MN.

Background: Hemodynamic insults may contribute to poor outcomes among hemodialysis (HD) patients. Individualized dialysate cooling based upon patient body temperature can improve intermediary outcomes but is difficult to operationalize. Here, we sought to test whether a standardized dialysate temperature of 36°C (dt36), which is easier to enact, might be a viable strategy to improve clinical outcomes.

Methods: Because patients with known hemodynamic instability may be selectively prescribed dt36, we minimized selection bias by considering incident adult in-center HD patients who (between Jan 2011-Dec 2013) received their first-ever HD treatment at a large dialysis organization and based exposure status on the order for this first-ever treatment (so that knowledge of intra- dialytic hemodynamics could not have factored into clinical decision-making). dt36 patients were propensity-score matched (1:5) to controls prescribed a temperature of 37°C (dt37). Outcomes (death, hospitalization, missed HD treatments) were considered from the date of first-ever HD treatment until death, loss to follow-up, crossover (month in which prescribed temperature was consistent with exposure group for ~80% of treatments), or study end (Jun 2015).

Results: 313 dt36 patients were matched to 1565 dt37 controls; groups were balanced on all matched covariates at baseline. During follow-up, rates of death, hospitalization, and missed HD treatments were not significantly different between groups; nominal risk of each outcome was greater (IRR>1) for dt36 patients.

Conclusions: The HD facility practice of routinely using low dialysate temperature to limit or prevent IDH is associated with lower CV mortality. This merits further investigation in a randomised trial.

<table>
<thead>
<tr>
<th>Low dialysate temperature for managing IDH</th>
<th>Model 1 Hazard ratio (99% CIs)</th>
<th>Model 2 Hazard ratio (99% CIs)</th>
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<tbody>
<tr>
<td>Hospitalization</td>
<td>1.02 (0.87-1.20)</td>
<td>1.02 (0.84-1.23)</td>
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<td>All cause deaths</td>
<td>0.82 (0.65-1.02)</td>
<td>0.91 (0.67-1.22)</td>
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<tr>
<td>CV events</td>
<td>0.80 (0.64-0.99)</td>
<td>0.86 (0.67-1.0)</td>
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<tr>
<td>CV deaths</td>
<td>0.56 (0.39-0.79)</td>
<td>0.55 (0.35-0.85)</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO940
Effect of Spironolactone on Heart Rate Variability in Hemodialysis - A Randomized Crossover Study
Hans Furulfjord, Erik Nilsson, Michael Eklund, Olof Hellberg.
1Renal Unit, Uppsala Univ Hospital, Sweden; 2Renal Unit, Örebro Univ Hospital, Sweden.

Background: Cardiac autonomic function is decreased and the risk of sudden cardiac death (SCD) is increased in hemodialysis (HD) patients. Spironolactone reduces the risk of SCD in congestive heart failure (CHF) and is associated with improved cardiac autonomic function as measured by heart rate variability (HRV). The effect of spironolactone on HRV in HD has rarely been studied and with varying results. This study measured HRV in HD patients treated with spironolactone.

Methods: This was a two center, open, randomized crossover study. Primary endpoint was the frequency of premature ventricular contractions (PVCs) and this sub-study represents a secondary hypothesis. Subjects on HD (n = 30) were randomly allocated into two arms with either treatment with spironolactone 50 mg daily or observation for twelve weeks, then a six week wash-out period followed by cross-over for twelve weeks. HRV (time domain and frequency domain analysis) was measured by ambulatory 24-hour Holter electrocardiogram (LTECG). Differences in change of HRV parameters during the two periods were analyzed using confidence intervals (CI).

Results: Complete LTECG data could be analyzed for 16 participants, due to drop outs. The difference of differences (dod) for SDNN (the change during treatment with spironolactone minus the change during the observation period) was 20.98 ms (CI 3.21-38.74). The dod for SDANN was 19.14 (CI 0.78-37.49). Other HRV variables did not change significantly.

Conclusions: HRV was reduced and spironolactone treatment in HD patients increased time-domain HRV variables SDNN and SDANN, indicating a possible improvement in cardiac autonomic function. This may have an impact on SCD and mortality which needs to be studied in a larger randomized study.

FR-PO941
Utilization Pattern and Clinical Outcomes of Mineralocorticoid Receptor Blockers in U.S. Dialysis Patients: A National Registry Study
Xuerong Wen,1 Rajesh Mohandas,1,2 I. David Weiner.
1Nephrology, Univ of Florida College of Medicine, Gainesville, FL; 2Nephrology and Hypertension Section, NF/SGVHS, Gainesville, FL.

Background: Mineralocorticoid receptor blockers (MRB) are important therapies for resistant hypertension and for congestive heart failure (CHF). These are common problems in ESRD patients treated with hemo- or peritoneal dialysis (HD-PD), yet MRB use is limited in HD-PD patients. The current study sought to determine the utilization pattern and clinical outcomes of MRB use in HD-PD treated patients.

Methods: We conducted a retrospective cohort study with new user design using United States Renal Data System data and Medicare Part D claims data. The study cohort was adult ESRD patients initiating HD-PD between 7/1/2006-12/31/2011. MRB use was defined as filling more than one consecutive MRB prescription following HD-PD initiation. We compared outcomes to patients either with filled prescriptions for ACE-I/ARB alone or with both MRB and ACE-I/ARB. Subjects were followed until first occurrence of each endpoint: hyperkalemia (CVD 4.276.71), mortality, composite cardiovascular disease (CVD, CVD 410, 430, 431, 433.x1, 434.x1, and 436) mortality or CVD hospitalization.

Results: 516 patients used MRB alone, 183 used MRB+ACE-I/ARB, and 26,974 used ACE-I/ARB alone. Baseline differences included race (AA: 16%, 21%, 29%; P < 0.001), female sex (57%, 46%, 51%; P < 0.001), and history of CAD (65%, 70%, 75%; P < 0.001). CHF (45%, 41%, 36%; P < 0.001), diabetes mellitus (46%, 57%, 59%; P < 0.001), hypertension (83%, 93%, and 89%; P < 0.001), and hyperkalemia prior to dialysis (20%, 21%, 29%; P < 0.001). Multivariate Cox proportional hazard analyses showed MRB use alone was associated with decreased risk of hyperkalemia (aHR (adjusted hazard ratio) 0.68; 95% CI: 0.50-0.90; P < 0.001), all-cause death (aHR: 0.79; CI: 0.70-0.90; P < 0.001), and composite CVD death and events (aHR: 0.72; CI: 0.65-0.80; P < 0.001) as compared to ACE-I/ARB use.

Conclusions: MRB use alone was associated with decreased risk of hyperkalemia, CVD composite outcome, and all-cause mortality as compared to ACE-I/ARB use alone. Funding: NIDDK Support, VA Support

FR-PO942
The Use of Beta-Blockers in Hemodialysis Patients: A Systematic Review and Meta-Analysis
Max Leitgeb,1 Areef Ishaq.2 1Div of Renal Diseases and Hypertension, Univ of Minnesota, Minneapolis, MN; 2Div of Nephrology, Minneapolis VA Medical Center, Minneapolis, MN.

Background: Beta-blockers reduce mortality in patients with heart failure and after myocardial infarction. However, dialysis patients have been excluded from all large randomized trials of beta-blockers. Limited evidence of their efficacy and safety has led to inconsistent use in this population. We conducted a systematic review and meta-analysis on the use of beta-blockers in hemodialysis patients to analyze the existing evidence and inform and encourage future research.

Methods: A medical librarian designed a search strategy. We included studies of hemodialysis patients comparing those on beta-blockers vs. placebo or active control. Randomized controlled trials of any size, prospective cohort studies with at least 100 participants were included. Subjects were randomized to beta-blockers or placebo. BNP and hs-TnI (Abbott ARCHITECT hsCRP) were measured at T0 and T4 weeks. The difference of differences (dod) for SDANN was 19.14 (CI 0.78-37.49). Other HRV variables did not change significantly.

Conclusions: Evidence supporting the use of beta-blockers in hemodialysis patients is limited and randomized control trial data is particularly sparse. Existing evidence suggests a significant mortality benefit with carvedilol in those with reduced ejection fraction and possibly a modest benefit with beta-blockers in the general population of hemodialysis patients.

FR-PO943
Effect of Carvedilol on B-Type Natriuretic Peptide and High-Sensitivity Cardiac Troponin I in Dialysis Patients
Matthew A. Roberts,1 Sunil V. Badve,2 Robert Peter Carroll, Darsey Darssan, Carmel M. Hawley, Nicole Isbel, Magid Fahim, Mark R. Marshall, Elaine M. Pascoe, Helen L. Pilmore, Paul Snelling, Ken-Soon Tan, Andrew Maxwell Tonkin, Liza A. Vergara, Francesco I. Lerino, Monash Univ, Melbourne, Australia; St. George Hospital, Sydney, Australia; Royal Adelaide Hospital, Adelaide, Australia; Australasian Kidney Trials Network, Univ of Queensland, Brisbane, Australia; Counties Manukau, Auckland, New Zealand; Auckland City Hospital, Auckland, New Zealand; Royal Prince Alfred Hospital, Sydney, Australia; Logan Hospital, Brisbane, Australia; Austin Health, Melbourne, Australia.

Background: Beta-blocker therapy may modify left ventricular (LV) stress [measured by B-type natriuretic peptide (BNP)] and myocardial damage [measured by high-sensitivity cardiac troponin I (hs-Tnl)]. We aimed to determine the effects of the beta-blocker carvedilol on BNP and hs-Tnl in adult dialysis patients.

Methods: Patients were randomized to carvedilol or placebo. BNP and hs-Tnl (Abbott assays) were measured from samples collected at baseline (T0) and 12 months (T12). Change in biomarker levels was analyzed using ANCOVA adjusted for baseline values. Associations between T0 echo measures and biomarkers were assessed by Pearson’s correlation coefficient.

Results: At T0, median (IQR) LV global strain was -14.27 (-11.93 to -22.07) and LV ejection fraction 61.0% (56.5 to 65.0). BNP was associated with LV global strain (r = 0.30, P = 0.04) and LV ejection fraction (r = -0.28, P = 0.04). 16/26 and 18/23 participants randomized to carvedilol and placebo, respectively, had serum and plasma samples at T12. Change in BNP and hs-Tnl was similar for the two groups (Table).

Conclusions:

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
586A
FR-PO945

Comparing Original and Updated Dialysis Facility Compare (DFC) Star Ratings

In this study, Nissenson et al. compared original and updated DFC Star ratings to evaluate their impact on patient outcomes.

**Background:** The Centers for Medicare & Medicaid Services (CMS) Star rating system for ESRD was introduced in January 2015 to inform patient choice by creating transparency with respect to dialysis facility performance. Facilities are assigned a Star rating on a forced bell curve (1-5) based on 9 quality metrics that include standardized mortality ratio (SMR), standardized hospitalization ratio (SHR), and standardized readmission ratio (SRR; proposed for future Star ratings), and whether change in current Star rating was associated with a change in these metrics.

**Methods:** Data for calendar years 2013 and 2014 were derived from the CMS Dialysis Facility Compare website. Facilities with Star ratings and SHR (N=4852), SMR (N=4842), and SRR (N=4852) for both years were considered. Associations of Star rating in each year and change in rating from 2013 to 2014 with SHR, SMR, and SRR were assessed using generalized linear models.

**Results:** The standardized mortality ratio (SMR) for dialysis facilities is adjusted for age, race, ethnicity, sex, DM, yrs of ESRD, nursing home status, BMI, and incident and prevalent comorbidities. 40% of facilities were classified differently in current method compared to 2.7% of facilities in the updated method.

**Conclusions:** Scoring against a baseline year lets consumers directly observe each facility’s longitudinal improvement since scoring criteria remain fixed over a period of time, while the original method rates facilities relative to each other in the same year. There are tradeoffs with each method. The original method does not permit tracking improvement over time, while the updated method uses a baseline may allow more facilities to be rated 4 and 5 stars but could obscure meaningful differences between facilities. The new methodology is responsive to the TEP recommendations.

**Funding:** Other U.S. Government Support

<table>
<thead>
<tr>
<th>Original Method</th>
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**FR-PO946**

Evaluation of Missing Data Methods for Prevalent-Comorbidity-Adjusted Standardized Mortality Ratio

Bin Nan,1,2 Jian Kang,2,3 Yang Jiao,2 Minling Zhang,2 Temple H. Shearon,2 Kevin HC,2 John Wheeler,2 J. M. Messana,2,3 1Dept of Biostatistics, Univ of Michigan, School of Public Health, Ann Arbor, MI; 2Kidney Epidemiology and Cost Center, Univ of Michigan, Ann Arbor, MI; 3Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI.

**Background:** The standardized mortality ratio (SMR) for dialysis facilities is adjusted for prevalent comorbidities from prior year Medicare claims. In year 2013, 43% dialysis pts had <12 months of claims in 2012, 16% had 0, and 27% had 1-11 months, possibly yielding missing comorbidities. The current method includes all pts, but only adjusts for comorbidities for pts with <6 months of claims in prior year. The new method imputes comorbidities for pts with missing data.

**Methods:** We use the 57% pts in 2013 with 12 months of claims in 2012 as “full data”, and randomly generate missing months to yield 100 analytic datasets mimicking the distribution of months with claims. We use logistic regression to impute the probability of comorbidity in pts with missing claims and no observed comorbidity in prior year. We calculated 3 versions of SMR using a facility-stratified Cox model adjusted for age, race, ethnicity, sex, DM, yrs of ESRD, nursing home status, BMI, and incident and prevalent comorbidities. 40% of facilities were classified differently in current method compared to 2.44% in imputation method, a 10% reduction.

**Conclusions:** The current method provides reasonably precise comorbidity-adjusted SMR. The precision can be improved slightly by imputation with a minimal increment of computing cost.

**Funding:** Pharmaceutical Company Support - DaVita Inc.
FR-PO947
Achievement of Quality Indicator Targets and Survival of Incident Hemodialysis Patients in Iceland  Thordur P. Palsson,1 Olafur S. Indridsson,2 Runolfur Palsson,1 Helga K. Mogensen,1 1Univ of Iceland; 2Landspitali - the National Univ Hospital of Iceland, Reykjavik, Iceland.

Background: The use of clinical practice guidelines and treatment targets in the care of dialysis patients has been emphasized over the past decade. The aim of this study was to investigate the quality of hemodialysis (HD) care at the University Hospital in Reykjavik with respect to common quality indicators (QI) and to assess patient survival in relation to these QI.

Methods: This was a retrospective study of all incident HD patients in Iceland during 2003-2014, who received treatment for at least 3 months. Data was obtained from medical records. The QI included hemoglobin (target range, 100-120 g/L), iron saturation (≥20%), URR (≥65%), calcium (2.2-2.6 mmol/L), phosphate (0.85-1.78 mmol/L), PTH (130-585 pg/mL), CO2 (<21 mmol/L) and albumin (>35 g/L), and the mean value of each QI for each patient was employed. Patients were assigned to 3 groups depending on how many QI targets they achieved: 1-3, 4-5 or 6-8. Kaplan-Meier plots were used to assess survival and groups were compared using the log-rank test. Cox regression was used to assess independent association of variables with survival.

Results: A total of 160 patients were included in the study, of whom 101 were males (63%). The median age at onset of HD was 68 (17-92) years. Sixteen patients (10.1%) achieved 1-3 QI targets, 56 (35.2%) achieved 4-5 targets and 87 (54.7%) achieved 6-8 targets. There was no significant difference in age or sex distribution between the three groups. Patient survival was significantly better when a greater number of QI targets was achieved (p < 0.001) and this difference remained significant in multivariate analysis even if albumin was used as covariate rather than as a QI. One- and 3-year survival of patients achieving 1-3, 4-5 and 6-8 QI targets was 58.0% (95% CI, 35.2-95.7%) and 34.8% (14.5-83.4%), 84.3% (74.8-94.9) and 47.5% (34.6-66.3%), and 96.1% (91.8-100.0%) and 78.5% (68.8-86.8), respectively.

Conclusions: A survival advantage is associated with a greater number of treatment goals achieved in HD patients. Thus, greater emphasis should be placed on achievement of treatment targets for established QI in HD care.

Funding: Government Support - Non-U.S.

FR-PO948
Attaining the Standards Proposed in Guidelines - Results from EURODOPPS  Sophie Liebeuf,1 Karlijn J. Van Stralen,2 Fergus J. Caskey,3 Francesca Tenti,3 Ronald E. Pisoni,4 Ayesha Sajjad,4 Kitty J. Jager,5 Ziad Massy.1 1INSERM U1088, CRI, Amiens Hospital Univ, Amiens, France; 2ERA EDTA Registry, Amsterdam Medical Center, Amsterdam, Netherlands; 3UK Renal Registry, Southmead Hospital, Bristol, United Kingdom; 4Arbor Research Collaborative for Health, Ann Arbor; 5INSERM U 1018 and Div of Nephrology, Univ of Versailles Saint Quentin en Yvelines, Boulogne Billancourt, France.

Background: In the field of chronic kidney disease (CKD), global clinical practice guidelines have been developed and implemented with a view to improving patient care and outcomes. We sought to measure and compare the extent to which various European countries have adopted and attained the targets set in international guidelines, with a focus on factors that can be modulated by pharmaceutical agents.

Methods: The EURODOPPS study is the European part of an international, prospective study of a cohort of adult, in-centre, haemodialyzed patients. For the current project, 6317 centers in 17 European countries were included between 2009 and 2011. The mean follow-up period was 1.5 years. Data on laboratory test results and medication prescriptions were extracted from patient records, in order to determine the overall percentage of patients treated according to the international guidelines on anaemia, dyslipidaemia, metabolic acidosis and mineral bone disease (MBD).

Results: Attainment of the targets set in international guidelines was far from complete; only 34.1% of the patients attained their target blood pressure, and 31.2% attained their target haemoglobin level. Overall, only 3% of the patients attained all the relevant targets set in the guidelines. Levels of guideline uptake and application and the use of pharmaceutical agents varied from one European country to another.

Conclusions: The results of this first ever large-scale, European study of attainment of targets and drug prescription in haemodialyzed patients highlighted the low overall levels of target attainment and emphasized the marked disparities between European countries in this respect.

FR-PO949

Background: The standardized transfusion ratio (STR) is reported by CMS on Dialysis Facility Compare and will be implemented in the ESRD Quality Incentive Program. Stakeholders raised concerns that the STR unfairly characterizes facility performance because of geographic variation, possibly related to area socioeconomic status (SES). This concern is battedress by studies reporting geographic differences in SES influence many other health outcomes. In another abstract, we describe a revised, more conservative definition for defining transfusion events in STR that results in reduced variation due to geographic-based differences. This abstract assesses the contribution of SES to the remaining geographic variation.

Methods: 2014 Medicare claims data are used to calculate STR across SES deciles. SES is measured by deciles of median zipcode-level Area Deprivation Index (ADI) scores with 2000 Census data from HIPxChange.org. We plotted mean STR by deciles of ADI indicating least to most deprived areas.

Results: As reported in the companion abstract, mean STR based on the new transfusion definition still shows some variation by geographic region. In contrast, differences in STR across deciles of area deprivation vary in a non-monotonic pattern. Interquartile range values overlap substantially between deciles of lower vs higher deprivation scores (figure). Extreme values of STR were observed in both the lowest and highest SES deciles.

FR-PO950

Background: Risk factor adjustment for hospitalization and mortality outcomes can increase model validity. Public reporting of outcomes measures has raised interest in adjusting for SDS. Studies observe black and Hispanic ESRD patients typically have lower hospitalization and mortality rates, lower SDS is predictive of higher hospitalization and mortality. Prevalent comorbidities may attenuate the impact of SDS on outcomes. We examine the relationship of SDS to hospitalization and mortality w/ and w/o comorbidity adjustment.

Methods: 2014 Medicare claims data for readmission; 2011-14 for hospitalization and mortality. Analyses are limited to the Medicare population; prevalent comorbidities are claims based. We fit Cox models stratified by facilities. One set of models adjusts for patient clinical and demographic characteristics including age, sex, race, ethnicity and dual Medicare/Medicaid status. The second adds comorbidities. Analyses include main effects only for race and ethnicity. Hazard ratios (admission, mortality) and odds ratios (readmission) are calculated.

Results: Black patients had lower admissions, readmissions and mortality. The effect of black race decreased nominally when adjusting for comorbidities. Hispanic patients had lower likelihood of hospitalization, readmission, and mortality, all effects diminished w/ comorbidities. Dual status increased likelihood of all outcomes but the effects declined w/ comorbidities. Statistical significance and direction of covariates were consistent across models.

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(all p<0.01)

Conclusions: The relationships among outcomes, SDS, and comorbidities are complex. Prevalent comorbidities may attenuate effects of SDS on outcomes. Caution is warranted in attributing outcomes directly to SDS when comorbidities may be a key driver.

Funding: Other U.S. Government Support

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

588A
FR-PO951

Low Albumin Levels prior to Transition to Dialysis and Early Dialysis Hospitalization among U.S. Veterans: A Transition of Care in CKD Study

Amanda R. Tortoriello,1 Elani Streja,1 Melissa Soofoo,1 Connie Rhee,1 Rieko Eriiguchi,1 Yoshitsugu Obi,1 Daniel L. Gillen,1 Csaba P. Koveshdy,2 Kamyar Kalantar-Zadeh.1 1UC Irvine; 2Univ of Tenn.

Background: Previous studies have shown the importance of albumin (Alb) as a predictor for a number of adverse outcomes including mortality and hospitalization in chronic kidney disease patients. However, the impact of Alb levels prior to end-stage renal disease (ESRD) on post-ESRD hospitalization is not known.

Methods: In 85,505 US veterans who transitioned to dialysis between 10/2007 and 3/2014, we identified 30,781 patients with available Alb measurements within the last 6-month prelude period (prior to ESRD transition). We examined the association of Alb (averaged over 6 months) as a categorical predictor of hospitalization within the first 6 months post transition, using Poisson models adjusted for demographics, comorbidities and 6-month prelude averaged laboratory covariates.

Results: The mean±SD age of the cohort was 68±11 years, among whom 30% were African-American, 8% were Hispanic, and 48% had diabetes listed as their primary cause of ESRD. The mean±SD Alb in the 6 months prior to transition was 3.4±0.6 g/dL. We observed a linear association between pre-ESRD Alb and 6-month post-ESRD hospitalization rate (Figure). Patients with Alb levels < 3.4 g/dL demonstrated higher rate of post-ESRD hospitalization compared to the referent group (Alb 3.4-<3.8 g/dL), whereas patients with Alb levels ≥4.2 g/dL experienced a lower rate.

Conclusions: Among veterans transitioning to dialysis, higher Alb levels are associated with lower rate of early post-ESRD hospitalization. Additional studies are needed to examine if nutritional interventions in the predialysis period can lower post-ESRD hospitalization compared to the referent group (Alb 3.4-3.8 g/dL), whereas patients with Alb levels ≥4.2 g/dL experienced a lower rate.

Funding: NIDDK Support

FR-PO952

Disparities in Age and the Association of Number of Hospitalizations Pre-ESRD and after Dialysis Transition among U.S. Veterans: A Transition of Care in CKD Study

John J. Sim,2 Connie Rhee,2 Daniel V. Nguyen,1 Csaba P. Koveshdy,2 Kamyar Kalantar-Zadeh.1 1UC Irvine; 2Kaiser Permanente SC; 3Univ of Tenn.

Background: Previous studies have shown the importance of albumin (Alb) as a predictor for a number of adverse outcomes including mortality and hospitalization in chronic kidney disease patients. However, the impact of Alb levels prior to end-stage renal disease (ESRD) on post-ESRD hospitalization is not known.

Methods: In 85,505 US veterans who transitioned to dialysis between 10/2007 and 3/2014, we identified 30,781 patients with available Alb measurements within the last 6-month prelude period (prior to ESRD transition). We examined the association of Alb (averaged over 6 months) as a categorical predictor of hospitalization within the first 6 months post transition, using Poisson models adjusted for demographics, comorbidities and 6-month prelude averaged laboratory covariates.

Results: The mean±SD age of the cohort was 68±11 years, among whom 30% were African-American, 8% were Hispanic, and 48% had diabetes listed as their primary cause of ESRD. The mean±SD Alb in the 6 months prior to transition was 3.4±0.6 g/dL. We observed a linear association between pre-ESRD Alb and 6-month post-ESRD hospitalization rate (Figure). Patients with Alb levels < 3.4 g/dL demonstrated higher rate of post-ESRD hospitalization compared to the referent group (Alb 3.4-<3.8 g/dL), whereas patients with Alb levels ≥4.2 g/dL experienced a lower rate.

Conclusions: Among veterans transitioning to dialysis, higher Alb levels are associated with lower rate of early post-ESRD hospitalization. Additional studies are needed to examine if nutritional interventions in the predialysis period can lower post-ESRD hospitalization compared to the referent group (Alb 3.4-3.8 g/dL), whereas patients with Alb levels ≥4.2 g/dL experienced a lower rate.

Funding: NIDDK Support

FR-PO953

Hemoglobin Levels prior to Transition to Dialysis and Early Dialysis Hospitalization among U.S. Veterans: A Transition of Care in CKD Study

Elani Streja,1 John J. Sim,2 Connie Rhee,2 Daniel V. Nguyen,1 Csaba P. Koveshdy,2 Kamyar Kalantar-Zadeh.1 1UC Irvine; 2Kaiser Permanente SC; 3Univ of Tenn.

Background: Patients with advanced chronic kidney disease (CKD) are often afflicted with anemia. Previous studies have found that both lower and higher hemoglobin (Hgb) levels were associated with worse outcomes in dialysis and non-dialysis dependent CKD patients. However, the association between Hgb levels in the immediate period preceding dialysis (prelude) and early post-dialysis hospitalization remains unknown.

Methods: In 85,505 US veterans who transitioned to dialysis between 10/2007 and 3/2014, we identified 31,303 patients with available Hgb measurements within the last 6 month prelude period (prior to transition). We examined the association of Hgb (averaged over 6 months) as a categorical predictor of hospitalization within the first 6 months post transition, using Poisson models adjusted for demographics, comorbidities and laboratory covariates.

Results: The mean±SD age of the cohort was 68±11 years, among whom 30% were African-American, 8% were Hispanic, and 48% had diabetes listed as their primary cause of end-stage renal disease (ESRD). The mean±SD Hgb for the cohort was 10.7±1.6 g/dL. Across all levels of adjustment, patients with Hgb ≤10 g/dL demonstrated a higher rate of hospitalization post transition to ESRD compared to the referent group (Hgb 11-<12 g/dL).

Conclusions: Patients who experience at least 1 hospitalization pre-ESRD have a higher risk of hospitalization post-transition. This association is more pronounced among younger patients who were hospitalized multiple times. Further studies are needed to understand the reasons why age and race exacerbate the impact of pre-ESRD hospitalizations on post-transition hospitalizations.

Funding: NIDDK Support

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

Underline represents presenting author.
Conclusions: Among patients transitioning to dialysis, lower pre-ESRD Hgb levels were associated with a higher rate of early post-transition to ESRD hospitalization. Clinical trials to examine the impact of anemia management during prelude post-ESRD outcomes are indicated.

Funding: NIDDK Support

FR-PO954

Association of 6-Month Pre-ESRD Potassium with Immediate Post-Dialysis Hospitalization among U.S. Veterans: A Transition of Care in CKD Study

Melissa Soochoo,1 Elani Streja,2 Connie Rhee,2 Alpesh Amin,1 Danh V. Nguyen,1 Miklos Zsolt Molnar,2 Kamyar Kalantar-Zadeh,1 1UC Irvine; 2Univ of Tenn.

Background: Recent studies have shown that both high and low potassium (K) were associated with higher rates of hospitalization in non-dialysis dependent chronic kidney disease (CKD) patients. However, the impact of potassium measured in the immediate period prior to dialysis (prelude) and hospitalization post transition remains understudied.

Methods: Among 85,505 US veterans who transitioned to dialysis between 10/2007 and 3/2014, we identified 33,499 patients with available K measurements within the last 6-month prelude period (prior to transition). We examined the association of K (averaged over 6 months) as a categorical predictor of hospitalization within the first 6 months post transition to end-stage renal disease (ESRD), using Poisson models adjusted for demographics, comorbidities and laboratory covariates.

Results: The cohort was (mean±SD) 68±11 years old, and included 29% African-Americans, 7% Hispanics, and 48% had diabetes listed as their primary cause of ESRD. The mean±SD K of the cohort prior to transition was 4.5±0.6 mEq/L. Low serum K (<3.9 mEq/L) was associated with lower rate of hospitalization compared to the reference (K 4.3–4.7 mEq/L). Furthermore, patients with higher K>4.7 mEq/L were associated with a lower rate of hospitalization post transition to ESRD.

Conclusions: Among veterans transitioning to dialysis, both low (<3.9 mEq/L) and high (>4.7 mEq/L) K levels were associated with lower rate of early post-ESRD hospitalization. These results differ from the K-hospitalization association observed in patients with non-dialysis dependent CKD. Additional studies are needed to investigate the K-hospitalization relationship in this population.

Funding: NIDDK Support

FR-PO955

Twice Weekly Hemodialysis and Mortality in the United States

Anna Mathew,1 Yoshitsugu Obi,2 Connie Rhee,2 Jolene L.T. Chen,3 Gaurang M. Shah,4 Wei Ling Lau,5 Csaba P. Kovesdy,6 Rajnish Mehrotra,3 Kamyar Kalantar-Zadeh,6 1Northwell Health; 2UC Irvine, 3VA Long Beach; 4UC Irvine; 5VA Long Beach; 6Univ of Tenn.; Univ of Wash.

Background: Most end stage renal disease patients in the United States are treated with a thrice-weekly hemodialysis(HD) regimen upon initiation of renal replacement therapy. Hemodialysis patients have the highest mortality during the first six months after HD initiation. Understanding the risk factors associated with the transition to HD is necessary to improve the outcomes of HD patients. We hypothesized that incremental transition to HD with a twice-weekly regimen does not compromise survival compared to a thrice-weekly schedule.

Methods: In a longitudinal national cohort of 1,124 incremental (twice-weekly) and 116,266 conventional (thrice-weekly) incident HD patients enrolled over five years (2007-2011), Cox regression analysis compared survival between these groups, with additional survival analyses after matching groups based on baseline and demographic parameters using coarsened exact matching methods.

Results: The matched cohort included 1,120 incremental and 54,633 conventional HD patients. In both the unmatched and cohort and matched cohorts, the incremental patients had a mean ± SD age of 70 ± 13 years, among whom 52% were male. The incremental group had lower mortality rates compared to the conventional group in both unmatched and matched cohorts, with case-mixed adjusted HRs of 0.75 [95% CI, 0.66 to 0.86], and 0.76 [95% CI, 0.67 to 0.86], respectively. Data on residual kidney function was limited, and we were thus unable to incorporate this variable into our analysis.

Conclusions: Among incident HD patients, initiation with twice-weekly HD, non-inferior survival was observed with twice-weekly compared to thrice-weekly transition to HD. Randomized controlled trials are indicated to examine the effect of residual kidney function and dialysis treatment frequency on survival and other relevant outcomes.

Funding: NIDDK Support

FR-PO956

Gender Disparities in Hospitalization among Maintenance Hemodialysis Patients in the United States

Scott V. Adams,1 Matthew B. Rivara,2 Elani Streja,2 Alfred K. Cheung,3 Onyebuchi A. Arah,4 Kamyar Kalantar-Zadeh,2 Rajnish Mehrotra,1 1Kidney Research Inst, Univ of WA, Seattle, WA; 2UC Irvine, Irvine, CA; 3Univ of Utah, Salt Lake City, UT; 4UCLA, Los Angeles, CA.

Background: Hospitalization is a major burden among maintenance hemodialysis patients; reducing hospitalizations and readmissions is a target of healthcare policy in the US. We sought to detail subgroups of patients undergoing maintenance dialysis at highest risks of hospitalization and readmission.

Methods: We analyzed data from a cohort of 111,653 adult hemodialysis patients in the US (2007-2011). Rates of hospitalization and 30-day readmission were compared by gender, age, and race, adjusting for other case-mix and laboratory/clinical variables.

Results: There were 333,756 hospitalizations over 4 years of follow-up. The overall rate of hospitalization was 1.85 per person-year (1.68 among men and 2.08 among women). Hospitalization rates were higher for women than men of the same age and race; for example, women ages 35-44 y had a 49% (95% CI: 40% to 58%) higher hospitalization rate than men of the same age and race (Figure). The gender disparity in hospitalization risk decreased with older age, and was attenuated with adjustment for serum albumin. The probability of 30-day readmission followed similar patterns to hospitalization rate. The probability of readmission was strongly associated with previous admissions, rising from 27.0% (95% CI: 26.5% to 27.4%) following a patient’s first hospitalization, to 38.6% (95% CI: 38.1% to 39.2%) following a patient’s fifth hospitalization.

Conclusions: Women undergoing maintenance hemodialysis experience excess risk of hospitalization and 30-day readmission compared to men. Additionally, patients with multiple prior hospitalizations are at particularly high risk of readmission. Interventions focused on these groups may be of benefit in reducing hospitalization and readmissions among dialysis patients.

Figure:
FR-PO957

Geographic Variation in Hospital Readmissions

Allan J. Collins,1 Peer Kidney Care Initiative Investigators,2 Chronic Disease Research Group, MMRF, Mpls, MN; 3Peer Kidney Care Initiative.

Background: Reducing 30-day hospital readmissions is a major CMS policy objective. Readmissions have fallen for both targeted and non-targeted diseases. USRDS reports show readmissions for the dialysis population almost twice those of the general Medicare population (35% versus 17%). We studied geographic trends over time in 30-day hospital readmissions, comparing the US census divisions.

Methods: The 2004-2013 prevalent dialysis population was assessed yearly from January 1 to November 30 to determine 30-day hospital readmission patterns. We categorized the hospitalization, used to define a primary cause of hospitalization, was categorized by organ system and included causes targeted by CMS (MI/acute coronary syndrome, CHF/fluid overload, pneumonia), and causes not targeted (GI bleeding, hyperkalemia, vascular access complications, bacteremia/sepsis, Clostridium difficile infections). We assessed how readmission rates changed over time by US census division, a marker of geography.

Results: Overall, the relative decrease in readmission rates, 2011-2013, was 8%, greater than reported in the general Medicare population. The greatest decline was in the Mid-Atlantic division, 9.1%, and the least in the Pacific division, 7.2%. Overall, divisions with the greatest declines also had the highest admission rates. Index hospitalization causes leading to the highest percentage of 30-day readmissions were C, d infections followed by MI/acute coronary syndrome, CHF/fluid overload, and bacteremia/sepsis.

Conclusions: The dialysis population, although not specifically targeted by CMS, has experienced a greater reduction in readmissions than the general Medicare population across broad geographic regions and index causes of hospitalization.

Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by the following participating provider organizations: American Renal Associates, Atlantic Dialysis Management Services, DaVita HealthCare Partners, Dialysis Clinic, Inc., Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Satellite Healthcare, The Rogosin Institute, U.S. Renal Care, and Wake Forest University, Private Foundation Support

FR-PO958

Mortality by Hospital Readmission Window among U.S. Hemodialysis Patients

Laura Plantinga,1 Janice P. Lea,1 Rachel E. Patzer,1 Bernard G. Jaar,2 Emory Univ, Atlanta, GA; 2Johns Hopkins Univ, Baltimore, MA.

Background: U.S. dialysis facilities will be accountable for hospital readmissions in 2017, but whether the 30-day window defined by pay-for-performance predicts poor outcomes as well as earlier windows is unknown. We examined the prevalence of hospital readmissions within 7 or 14 days of discharge and compared 1-year mortality by readmission window.

Methods: We identified 153,349 U.S. hemodialysis (HD) patients from a national registry (United States Renal Data System) who had at least one hospitalization in 2010 (first-index) and survived on HD for at least 30 days. Readmissions were defined by admissions within windows of 0-7, 8-14, or 15-30 days after discharge from the index admission. Kaplan-Meier analyses and multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and incidence rate ratios (IRRs).

Results: Overall, 13.1%, 5.9%, and 9.6% of patients had readmissions within 0-7, 8-14, and 15-30 days of discharge from index admission; 45.8% of readmissions were within 7 days. Regardless of readmission window, patients with readmissions had about two times the risk of death within 1 year, compared to those with no readmissions; this effect was attenuated after 6 months.

Adjustment for age, sex, race/ethnicity, dialysis vintage and comorbid conditions made little difference: 15-30 days, HR=2.05 (95% CI, 1.98-2.12); 8-14 days, HR=2.06 (95% CI, 1.97-2.15); and 0-7 days, HR=1.80 (95% CI, 1.74-1.86).

Conclusions: Nearly half of 30-day readmissions occurred within the first 7 days after discharge, suggesting that opportunities for dialysis providers to prevent readmission may be limited. These results also suggest that readmission, regardless of timing, is associated with about 2-fold increased risk of mortality in the following year among U.S. HD patients.

Funding: Other NIH Support - NIMHD

FR-PO959

Long-Term Outcomes among Hemodialysis Patients Readmitted in the First Year of Dialysis

Bernard G. Jaar,1 Rachel E. Patzer,2 Janice P. Lea,2 Laura Plantinga,1 Medicine - Nephrology, Johns Hopkins Univ, Baltimore, MD; Medicine - Nephrology, Emory Univ, Atlanta, GA.

Background: Readmissions are common among hemodialysis (HD) patients and may predict poor outcomes. We examined long-term outcomes among incident-in-center HD patients readmitted in their first year of treatment.

Methods: We categorized 275,475 U.S. incident patients from a national registry (USRDS) who started HD between 9/2005 and 9/2009 and remained on HD alive for at least 1 year as having no admissions, admissions but no readmission (within 30 days), and 30-day readmissions in the 90-365 days after HD start. Outcomes (mortality, transplantation, and hospital admissions) were examined between 366 and 730 days. Multivariable Cox proportional hazards and Poisson models were used to estimate hazard ratios (HRs) and incidence rate ratios (IRRs).

Results: Overall, 15.8%, 25.0%, and 59.1% of patients had readmissions, hospital admissions but no readmission, and no admissions, respectively, in the first 90-365 days of HD. Patients with readmissions in year 1 were more likely to die and be hospitalized, and less likely to be transplanted in their year 2 of HD, compared to their counterparts with no readmission or no admission.

Outcomes in second year of hemodialysis

With adjustment for age, sex, race/ethnicity and comorbid conditions, those with readmissions and those with admissions but no readmission remained far more likely than those without admission in year 1, to have poor outcomes in their year 2: mortality, HR=2.84 (95% CI, 2.77-2.90) and 1.61 (95% CI, 1.51-1.65); and hospital admissions, IRR=5.02 (95% CI, 4.97-5.06) and 2.66 (95% CI, 2.64-2.68), respectively.

Conclusions: Having hospital readmissions (within 30 days) early in the course of HD, even beyond having hospital admissions alone, is highly predictive of poor long-term subsequent outcomes, including death, not being transplanted, and further hospital admissions.

Funding: Other NIH Support - National Institute on Minority Health and Health Disparities

FR-PO960

Potentially Avoidable Readmissions in United States Hemodialysis Patients

Anna Mathew,1 Lisa M. Rosen,1 Renee Pekmezaris,1 Andrzej Kozikowski,1 Daniel W. Ross,1 Thomas Megini,2 Kannay Kalantar-Zadeh,1 Steven Fishbane,1 Hofstra Northwell School of Medicine, Northwell Health, Great Neck, NY; 2Harold Simmons Center for Kidney Disease Research, Div of Nephrology, Orange, CA; 3Fielding School of Public Health, UCLA, Los Angeles, CA.

Background: Patients with end stage kidney disease have a high risk of 30-day readmission after hospital discharge, associated with excessive financial cost and poor quality of life. Whereas all-cause readmissions have been described, potential avoidability of readmissions has not been previously analyzed. We aimed to analyze the frequency, causes and predictors associated with 30-day potentially avoidable readmission to hospital in maintenance hemodialysis patients.

Methods: In this historical cohort study using the United States Renal Data System, 107,940 prevalent HD patients with 248,680 index hospital discharges were assessed for the main outcome of 30-day potentially avoidable readmission after an index hospital discharge, as identified by a computerized algorithm.
Results: Of 83,209 thirty-day readmissions, 59,045 (70% of all readmissions and 24% of all hospital discharges) resulted in a 30-day potentially avoidable readmission. Figure 1: Index hospital discharge outcomes and frequencies

Characteristics associated with 30-day potentially avoidable readmission included younger age, shorter time on dialysis, greater number of hospitalizations in preceding 12 months, black race, unemployed status, treatment at a for-profit facility, longer length of index hospital stay, and index hospitalizations which involved a surgical procedure.

Conclusions: Maintenance hemodialysis patients are at high risk for 30-day readmission to hospital, with over two-thirds (71%) of all 30-day readmissions potentially avoidable. Research is warranted to develop cost-effective and transferrable interventions to improve care transitions from hospital to outpatient dialysis facility and reduce readmission risk for this vulnerable population.

FR-PO961
Effect of a Medication Intervention on Acute Care Utilization after Hospitalization in Patients with ESRD

Methods: The End Stage Renal Disease-Medication Intervention Trial (ESRD-MIT) (www.clinicaltrials.gov NCT01459770) was a randomized, controlled clinical trial conducted between 2013 and 2015. Participants were patients with ESRD (treated by hemodialysis or peritoneal dialysis) acutely hospitalized at Providence Health Care. They were randomized to usual care or the intervention, a single home visit for medication management by a study pharmacist within 7 days of discharge. Acute care utilization (hospital readmission, emergency department or urgent care visits) for 90 days after hospital discharge was the primary outcome.

Results: Study participants (n=39) were 61±16, mean±SD, years of age and 41% (16/39) women. Hypertension and diabetes were present in 51% (20/39) and 59% (23/39), respectively. Duration of dialysis was 22 (3–71), median (IQ range), months. The most common primary diagnoses for index hospital admission included: infections 23% (9/39), cardiovascular diseases 15% (6/39), and vascular access procedures 18% (7/39). Length of stay was 3 (1.5–7) days. The primary outcome, analyzed as time-to-first event, occurred in 40% (8/20) of participants in the intervention group and in 47% (9/19) of those in usual care (p=0.64). Rates for each type of acute care event were similar between groups. For total hospital readmissions, the most common primary diagnoses included: infections 24% (5/21), respiratory diseases 19% (4/21), vascular access procedures 14% (3/21) and cardiovascular diseases 14% (3/21).

Conclusions: Acute care utilization after hospital discharge in patients with ESRD was not reduced by a medication management intervention. Comprehensive strategies to enhance care pre- and post-discharge may be needed to improve health outcomes.

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

FR-PO962
Hospitalization Rates before and after the Initiation of a Fluid Management Quality Improvement Project Using Crit-Line Monitors during Inpatient Hemodialysis

Background: Patients on hemodialysis (HD) are at high risk for hospital admissions, especially fluid-related admissions. A fluid management quality improvement (QI) project utilizing Crit-Line monitors® (CLM) was conducted by the Renal Research Institute. CLM non-invasively assess intra-dialytic relative blood volume and provide real-time data that allow for ongoing fluid monitoring by clinical staff. The aim of this analysis was to determine whether fluid-related admission rates decreased during the year-long QI project. All-cause hospital admissions and mortality rates were also assessed.

Methods: Data were de-identified and extracted from routinely collected electronic data. Crude rates and rate ratios (RR) were calculated to compare baseline (BL, 12 months before the QI project) to follow-up (12 months during the QI project, after 1 month of CLM transition). To ensure complete outcome ascertainment, all outcomes occurring within 7 days of the last HD treatment were captured for each period. Patients treated in 2 or more centers during baseline and/or follow-up were excluded.

Results: Overall, 2,673 adult patients at 16 HD centers were eligible for analysis. Demographic characteristics varied minimally between study periods (p=0.05); although, a difference in reported congestive heart failure was noted (BL: 19.1% vs. 15.5%, p=0.02). Fluid-related hospitalization rate declined by 19% from 0.21 to 0.17 per patient-year (PY); RR: 0.81 (95% confidence interval: 0.67-0.97), and all-cause hospitalization rate declined by 10% from 1.88 to 1.70 per PY; RR: 0.90 (0.85-0.96). A non-significant decline in mortality rate was observed (16% decrease from 0.19 to 0.16 per PY; RR: 0.84 (0.69-1.01)).

Conclusions: Fluid-related and all-cause hospitalization rates decreased by 19% and 10%, respectively, during a year-long QI project utilizing CLM in 16 HD centers.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America.

FR-PO963
Compression Stockings Improve Sleep Apnea in Hemodialysis Patients

Background: Sleep apnea (SA) is prevalent in edematous states, such as in hemodialysis (HD) patients. As nocturnal rostral fluid shift from the legs is implicated in its physiopathology, we hypothesized that avoiding fluid retention in the legs during the day, by wearing compression stockings (CS), would improve SA in HD patients.

Methods: We included 14 HD patients with SA (AHI)>5 events/hour) by polysomnography exam (PSG). Pts were submitted to another two PSGs: one for continuous positive airway pressure (CPAP) titration and another 1-week after daytime use of medium (20-30 mmHg) CS. Neck circumference (NC) and bioimpedance analysis (BIA) were performed before and after PSG.

Results: Mean age was 53±9 years (75% men), body mass index was 30.7±6.0 Kg/m², and dialysis vintage was 6.0±6.2 months. Dry weight gain during a week of fluid restriction was similar in the three exams. AH1 decreased from 20.8 (14.2±9.2) at baseline to 16.7 (3.5±2.8) after CS use (p<0.001) and to 7.9 (2.8±2.5) events/hour with CPAP (p=0.004).

Conclusions: Wearing compression stockings in HD pts during the day avoided fluid retention in the legs, leading to lower nocturnal rostral fluid shift and, consequently, attenuated SA. Even though CPAP remains the mainstream treatment for SA, this study highlights an alternative treatment to such syndrome in HD patients.

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

FR-PO964
Asymptomatic Sleep Apnea Syndrome in End-Stage Renal Disease: Implications of Volume Overload for Obstructive Sleep Apnea Syndrome

Background: Sleep apnea syndrome (SAS) has been reported in up to 50% to 70% of patients with end-stage renal disease (ESRD). It is hypothesized that SAS in patients with ESRD is caused by narrow upper airway due to volume overload. SAS is considered an independent risk factor for hypertension, congestive heart failure, acute coronary syndromes, pulmonary hypertension, arrhythmias and cerebrovascular events. To improve the prognosis of patients with ESRD, management of appropriate body fluid in reference to degree of obstructive sleep apnea syndrome (OSAS) is essential. The aim of present study is to evaluate the association between severity of OSAS and volume overload in patients with ESRD.

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

Underline represents presenting author.

592A
Methods: The apnea-hypopnea index (AHI) and its severity were measured in fourteen patients with ESRD (CKD stage 5) using a portable sleep monitoring device. Body weight (BW), cardio thoracic ratio (CTR), serum levels of BNP, AHI were measured during the therapeutic course of hemodialysis. The association of AHI with age, gender, body mass index (BMI), history of smoking and complication of ESRD were analyzed.

Results: In our study, 8.8% were diagnosed as asymptomatic SAS. Those patients were divided according to AHI scores into mild (AHI 5-14.9, 21.4%), moderate (AHI 15-29.9, 21.4%), and severe OSAS (AHI≥30, 50.0%) groups. Age, gender, BMI, smoking and complication of ESRD were not associated with AHI. Improvement of AHI due to modification of fluid overload was associated with decreased BW and BNP (P=0.032, P=0.062, respectively).

Conclusions: Present study suggested that the OSAS is a major complication in patients with ESRD. The OSAS is caused by narrow upper airway due to volume overload. Assessment of AHI using a portable sleep monitoring device is useful tool to evaluate the appropriate body fluid in patients with ESRD.

FR-PO965
Visual Changes in Response to Haemodialysis
Huda Mahmoud,1,2 Philip Wright,1 Lawrence Hodder,1 Andrew B. Newsham,1 Simon E. De Sousa,1 Patrick Richardson,1 Nicholas M. Selby,1 Oliver R. Smith.1,2 1Dept of Renal Medicine, Royal Derby Hospital, United Kingdom; 2Centre for Kidney Research and Innovation, Univ of Nottingham, United Kingdom

Background: Haemodialysis (HD) patients report visual disturbances associated with dialysis sessions although causes for these symptoms are poorly documented and understood. We performed an observational study to describe and assess the change in visual acuity (VA) in response to HD therapy.

Methods: All patients receiving chronic HD at our centre were invited to participate. VA of each eye was assessed before and after a single HD session. The Snellen result was converted to Logarithm for Minimal angle of resolution (LogMar) score for comparative analyses and categorized according to the World Health Organisation (WHO) classification of visual loss into normal, mild, moderate and severe. Patients’ subjective perceptions of visual disturbances and HD treatment details were recorded.

Results: 148 (281 eyes) patients participated. The WHO classification of visual impairment based on best eye pre-dialysis results; 34% of patients had normal vision, 40% mild, 21% moderate and 5% severe visual impairment. This incidence of moderate and severe visual impairment based on best eye pre-dialysis results; 34% of patients had normal vision, 40% mild, 21% moderate and 5% severe visual impairment. This incidence of moderate and severe visual impairment was higher than would be expected from general population (MOCA <17). Cognitive function declined significantly over a dialysis session (p<0.001, 95% CI 1.05-2.16; p=0.01) and IL-6 (OR: 1.54, 95% CI 1.10-2.16; p=0.01) were associated with an increased odds of sleep disturbance. In contrast, the highest tertile of 25(OH)D was associated with a decreased odds of sleep disturbance (OR: 0.65, 95% CI 0.47-0.90; p=0.04) when compared to the lowest tertile.

Conclusions: Decreased serum levels of vitamin D and increased circulating levels of PTH are associated with poor sleep quality in chronic hemodialysis patients. Future work should examine the link between sleep quality with abnormalities of mineral metabolism and inflammation.

Funding: NIDDK Support

FR-PO967
Parathyroid Hormone as a Novel Risk Factor of Hemodialyzer Clotting
Kyoei Ogawa,1 Keita Hirano,1 Izumi Yamamoto,2 Yukio Maruyama,2 Ichiro Ohkido,2 Nobuo Tsuibo,2 Takashi Yokoy.2 1Nephrology, Ashikaga Red Cross Hospital, Ashikaga, Tochigi, Japan; 2Kiyose, Tokyo, Japan

Background: Hyperparathyroidism gives rise to low levels of HDL-cholesterol (HDL-C), and hence imposes a cardiovascular risk (Clin Endocrinol 2002;56:253).

However, it is unknown whether parathyroid hormone (PTH) level also represents a risk factor for dialyzer clotting.

Methods: All outpatient dialysis sessions performed at Ashikaga Red Cross Hospital in 2015 were examined as a historical cohort. Blood remaining in more than 10 hollow fibers at the end of each session was taken as significant dialyzer clotting.

Results: Out of 4,207 dialysis sessions derived from 36 patients, significant dialyzer clotting was observed in 144 sessions (3.4%). Sessions were then stratified by the median of alkaline phosphatase (ALP) to 2,094 sessions as low ALP group and 2,113 sessions as high ALP group, because there was a significant interaction for the risk of cloting between PTH and ALP. On multivariate analysis adjusted with hemoglobin, albumin and APPT, PTH was associated with the risk of clotting especially in low ALP group (OR 2.10, 95%CI 1.43-3.06, per 100mg/ml of intact PTH), but the association was not observed in high ALP group (OR 1.17, 95%CI 0.87-1.58, P=0.2). Of note, although PTH was proportional to HDL-C in high ALP group (B 3.592, SE 0.279, P<0.001), it was inversely proportional to HDL-C in low ALP group (B -2.108, SE 0.441, P<0.001).

Conclusions: PTH is associated with dialyzer clotting especially in hemodialysis session with low ALP level, which may imply decreased fibrin formation when working towards more biocompatible dialysis with reduced dialyzer clotting.

Funding: Private Foundation Support
Polymorphisms of Vitamin D Signaling Pathway Genes and Calcium Sensing Receptor Gene in Respect to Survival of Hemodialysis Patients – A Prospective Observational Study (Part I) Alicia E. Grzegorzaewska, Monika K. Sviderska, Adrianna Mostowska, Wojciech J. Warchoł, Paweł P. Jagodzinski. Poznan Univ of Medical Sciences, Poland.

Background: Studies on associations of single nucleotide polymorphisms (SNPs) of vitamin D signaling pathway genes and calcium-sensing receptor gene (CASSR) with survival of hemodialysis (HD) patients are scarce. We evaluated whether SNPs of abovementioned genes are determinants of mortality in HD patients.

Methods: Prevalence HD patients without history of renal transplantation (n = 532, men 56%, RRT vintage prior to the study 2.2, 0.0–24.7 years, age at the start of the study 61.2±14.6 years, diabetic nephropathy 25.8%, dyslipidemia 41.0%) were enrolled in the 7-year prospective observational study at January 30, 2009. HRM analysis was used for GCrs2298849, GC rs1155563, RRAr rs10776990, RRAr rs10811578, and CASSR rs17552859 genotyping. GC rs7041, RRAr rs749759, VDR rs2228570, and VDR rs1544410 were genotyped using PCR-RFLP analysis. Survival analyses were conducted using the Kaplan-Meier method and the Cox proportional hazard model.

Results: GC rs2298849 was associated with all-cause mortality in dominant model of inheritance (log rank test P = 0.02), and VDR rs2228570 - with cardiovascular mortality in additive model of inheritance (log rank test P = 0.04). Subjects bearing the minor allele in rs2298849 demonstrated the higher risk of death during 7 years on HD than the major allele homozygotes (OR 1.81, 95%CI 1.13 - 2.92, P = 0.02). Cardiovascular mortality was associated with major homozygosity (CC) in rs2282570 (HR 1.90, 95%CI 1.16 – 3.09, P = 0.03). The CC genotype patients were more often dyslipidemic compared to the TT genotype subjects (46 vs 31%, P = 0.03). Dyslipidemic HD patients showed higher frequency of the rs1544410-rs2282570 haplotype AC than non-dyslipidemic subjects (26 vs 18%, Pcorr = 0.005), whereas the TT genotype patients were at lower risk of dyslipidemia compared to patients with CC/CT genotypes (OR 0.59, 95%CI 0.37 – 0.96, P = 0.04).

Conclusions: GCrs2298849 and VDRrs2228570 SNPs are associated with survival of HD patients. VDR-related cardiovascular mortality may occur due to connections of rs2228570 with dyslipidemia.

Polymorphisms of T Helper Cell Cytokine-Associated Genes in Respect to Survival of Hemodialysis Patients – A Prospective Observational Study (Part II) Alicia E. Grzegorzaewska, Monika K. Sviderska, Adrianna Mostowska, Wojciech J. Warchoł, Paweł P. Jagodzinski. Poznan Univ of Medical Sciences, Poland.

Background: We evaluated in the 7-year prospective study whether variants in T helper cell cytokine-associated genes are determinants of mortality in hemodialysis (HD) patients (n=532).

Methods: HRM analysis was used for IFNL3, IL12A, IL1L3 and IL12R genotyping. CCL2, IL12B, and IL18 were genotyped using PCR-RFLP analysis. Survival analyses were conducted using the Kaplan-Meier method and the Cox proportional hazard model.

Results: IFNL3 rs8099917 was associated with all-cause mortality in recessive model of inheritance (log rank test P = 0.044), IL12A rs658408 - in dominant model (log-rank test P =0.029). Minor homozygotes (GG) in rs8099917 showed shorter survival than major allele (TT) patients (3.6, 1.0–7.8 years vs 4.7, 0.1–7.0 years, P = 0.009), although their RRT vintage prior to the onset of the study was also shorter (1.4, 0.0–6.6 years vs 2.3, 0.0–22.2 years, P=0.010). The rs8099917 GG patients demonstrated higher risk of death than the remaining patients (GT+TT) (OR 1.94, 95%CI 1.11-3.40, P = 0.020). Major homozygosity (GG) in rs568408 was associated with higher mortality than that shown in bearers of the minor allele (AA+AG) (HR 1.31, 95%CI 1.02–1.69, P = 0.035). There were less responders (GG) in rs568408 with cardiovascular mortality in dominant model (26 vs 18%, Pcorr = 0.005), whereas the TT genotype patients were at lower risk of dyslipidemia compared to patients with CC/CT genotypes (OR 0.59, 95%CI 0.37 – 0.96, P = 0.04).

Conclusions: GCrs2298849 and VDRrs2228570 SNPs are associated with survival of HD patients. VDR-related cardiovascular mortality may occur due to connections of rs2228570 with dyslipidemia.

Residual Urine Output and Mortality in a Prospective Hemodialysis Cohort Amy Seung You, Kamyar Kalantar-Zadeh, Danh V. Nguyen, Alpesh Amin, Elani Streja, Yoshitsugu Obi, Tracy Nakata, Lidia Lou, Mary Veliz, Daniel L. Gillen, Csaba P. Kovesdy, Connie Rhee. UC Irvine; ‘Univ of Tenn.; ‘Univ of Wash.

Background: Assessment of residual urine output (UOP) is an important aspect of native kidney function evaluation in hemodialysis (HD) patients given its associations with better survival and quality of life. As frequent measurement by 24-hour urine collection may be cumbersome, self-reported UOP may be used as an adjunctive method of routine assessment in the clinical setting. We examined the association of patient-reported UOP with all-cause mortality in a prospective HD cohort.

Methods: Among 670 HD patients from the prospective Multinutrition, Diet, and Racial Disparities in Kidney Disease study, we examined the association of patient-reported UOP with all-cause mortality. Patients underwent protocolized surveys querying about presence and frequency of UOP (absent, every 1-3 days, >1 time/day) every 6 months over 2011-16. We hypothesized that patient-reported UOP would be associated with survival.

Results: UOP was reported by 28% patients. There were 1,076 deaths during follow-up. In unadjusted models, UOP was associated with lower mortality (HR 0.88, 95%CI 0.78–0.99, P = 0.001). Adjustment for case-mix characteristics and 9 laboratory variables associated with nutritional and inflammatory status did not alter the primary analysis.

Conclusions: patient-reported UOP is a valid marker of native kidney function and is associated with survival in a prospective HD cohort.
1.78 (1.16-2.72) and 2.01 (1.35-2.99), respectively. In baseline and time-varying analyses of UOP frequency, point estimates suggested a graded association between lower UOP frequency and higher mortality, although estimates for UOP every 1-3 days did not reach statistical significance: HR (95%(CI) 1.29 (0.82-2.05) and 1.97 (1.24-3.12) for absence of UOP and UOP every 1-3 days, respectively (ref: UOP >1 time/day).

Conclusions: In HD patients there is a graded association between higher frequency of self-reported UOP and lower mortality. Further studies are needed to validate self-reported UOP as an alternative metric of residual kidney function, and to determine optimal approaches for preserving UOP.

Funding: NIDDK Support

FR-PO974

Serum Potassium and Clinical Outcomes among Hemodialysis Patients: Impact of the Long Interdialytic Interval
Steven M. Brunelli,1 Charles Du Mond,2 Nina Oestreichter,3 Viatechslav Rakov,4 David M. Spiegel,1 DaVita Clinical Research, Minneapolis, MN; 5Relypa Inc, Redwood City, CA; 6Univ of California San Francisco, San Francisco, CA; 7Vjfor Pharma, Glattbrugg, Switzerland.

Background: Hyperkalemia among hemodialysis (HD) patients is associated with morbidity and mortality. Among those who dialyze twice weekly, adverse outcomes peak after the 2-day interdialytic interval. Here, we estimated the independent association between serum potassium (K) concentration and outcomes among HD patients, and estimated how these associations were impacted by day of week.

Methods: This retrospective (2010-2011) study considered patient-interval data, defined as a routine K measurement made among adult Medicare Parts A & B enrollees receiving in-center HD on Monday/Wednesday/Friday (Mon/Wed/Fri) at a large US dialysis organization. Outcomes considered over the day of K measurement and the next 3 days were: hospital admission, death, and emergency department (ED) visits.

Results: The association between high serum K and hospitalization risk was present on all days but most potently on Fri (Pinteraction=0.008). Adjusted odds ratios (OR) for K 5.5–6, 6–6.5, 6.5–7, ≥7 (ref: 4–4.5) were respectively: 1.68, 1.63, 2.19 and 3.51 on Fri; 1.04 (P=0.43), 1.37, 1.91 and 2.09 on Wed and 1.12, 1.22, 1.70, 2.78 on Mon. Associations of high serum K with death and ED visit were significant but did not differ by day of week. Adjusted ORs for K 6–6.5, 6.5–7, ≥7 were 1.52, 2.42, 3.37 for death, and 1.19, 1.48, 2.62 for ED visit (for all, P<0.05 except as noted).

Conclusions: Higher serum K is associated with greater risk of hospitalization, death, and ED visit. The effect on hospitalization is modified by day of week, suggesting an enhanced burden of high K over the long interdialytic interval. Further work is needed to determine whether directed intervention ameliorates this risk.

Funding: Pharmaceutical Company Support - Relypa Inc

FR-PO975

Oral Sodium Bicarbonate Reduces Inter-Dialytic Potassium Gain - The BiHD Trial
Stella Kourtellidou, Damien Ashby, Lina Johansson. Imperial College Healthcare NHS Trust, United Kingdom.

Background: The intermittent nature of haemodialysis (HD) has adverse effects on clinical outcomes, with excess mortality associated with long intervals. High potassium contributes to this, but low levels post-HD can cause arrhythmias: a treatment reducing inter-HD potassium gain, would therefore be useful. Acidosis develops during each interval causing extracellular potassium shift - oral bicarbonate replacement may therefore limit potassium gains.

Methods: Prevalent in-centre HD patients with pre-HD bicarbonate <22mmol/l were randomly assigned to oral sodium bicarbonate or no treatment for 12 weeks. Starting dose was 2g/day with titration up to 4g/day. Electrolyte and blood pressure data are presented by paired testing in the intervention group. ECG and nutritional outcome analysis is in process.

Results: Forty-two patients were recruited, of which 16 (aged 27–74, 75% male) were randomised to and started the intervention. Average sodiumbicarbonate dose after intervention was 2.49g/day. Baseline and final serum bicarbonate was 21.60±2.98mmol/l and 22.10±3.61mmol/l respectively (P=0.4). Pre-HD potassium was 4.26±0.41mmol/l and 4.20±0.43mmol/l respectively (P=0.45). The HD interval was 4.93±0.46days and 5.99±1.14days respectively (P=0.001). Despite adjusting for missing data, 11 patients died during the intervention. Cox regression models adjusted for age, sex, diabetes, autoimmune disease, and smoking status found no difference in power or mortality between the two groups.

Conclusions: Oral sodium bicarbonate is a well-tolerated treatment that reduces inter-HD potassium gain, hence lowering pre-HD levels. The effect size is modest, with achievable reductions in pre-HD potassium around 0.3mmol/l, but the impact on relevant hyperkalaemia and clinical events may be more substantial.

Funding: Government Support - Non-U.S.

FR-PO976

Persistent and Episodic Hyponatremia Are Prevalent in Hemodialysis Patients and Associated with Increased Mortality
Ryan A. Brenness,1,2 Darcy R. Visscher,3 Branko Braam.1 Univ of Alberta, Edmonton, AB; 2The King’s Univ, Edmonton, AB, Canada.

Background: Hyponatremia is common in many patient populations and has been linked to increased mortality and undesirable outcomes. Limited information about hyponatremia in hemodialysis (HD) patients indicates a high prevalence, yet, information is lacking regarding outcome. The hypothesis of the current study was that both persistent and episodic hyponatremia in HD patients is prevalent and associated with increased mortality.

Methods: Hyponatremia (Na <135 mmol/l) of 2473 patients on in-center HD was evaluated using monthly plasma Na over a median of 4.6 years. Prevalence of 10 patterns was studied: persistent hyponatremia, and combining episodic low (1-3 episodes), medium (4-7 episodes) or high (>8 episodes) frequency with short (1-2 months), medium (2-<4 months) and long duration (>4 months). Mortality was assessed for persistent and episodic hyponatremia compared to normonatremia.

Results: Of the patients 34% had normal sodium (no hyponatremia), 1% had stable hyponatremia and 65% had an episodic sodium pattern. Frequencies of episodic hyponatremia and mortality are displayed in the table.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Short 1-2 months/episode</th>
<th>Average 2-&lt;4 months/episode</th>
<th>Long &gt;4 months/episode</th>
<th>% % mortality % % mortality % % mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>High(-8 episodes</td>
<td>9</td>
<td>20</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Medium(3-7</td>
<td>13</td>
<td>26</td>
<td>5</td>
<td>42</td>
</tr>
<tr>
<td>Low(&lt;3</td>
<td>18</td>
<td>33</td>
<td>2</td>
<td>51</td>
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</table>

Both persistent hyponatremia and average and long duration, low and medium frequency were associated with decreased survival compared to patients without hyponatremia. High frequency hyponatremia episodes did not predict mortality compared to normonatremia. Persistent high sodium (episodic) In this HD cohort, episodic hyponatremia was found that a cross-sectional analysis of hyponatremia underestimated prevalence. Moreover, average and long duration with low and medium frequency hyponatremia is associated with increased mortality. Factors that are associated to episodic hyponatremia need further study.

Funding: Relypsa Inc

FR-PO977

Predicting Clinical Outcomes Using Phase Angle in Maintenance Hemodialysis Patients
Chae Rim Kim, Jung-Ho Shin, Jin Ho Hwang, Su Hyun Kim. Dept of Internal Medicine, Chung-Ang Univ Hospital, Seoul, Korea.

Background: Protein-energy wasting is common in hemodialysis patients, and it is an independent risk factor for major adverse events. Recently, bioelectrical impedance analysis (BIA) has been widely used as a non-invasive method to estimate nutritional status. We retrospectively investigated whether nutritional markers measured by BIA can predict clinical outcomes in end-stage renal disease (ESRD) patients receiving hemodialysis.

Methods: ESRD patients who had been treated with outpatient hemodialysis were recruited. Using BIA, phase angle (PA), a nutritional marker, was obtained every 6 months, and patients were divided into two groups, based on PA: group A included those with PA <-4.5°; and group B included those with PA <-4.5°.

Results: A total of 142 patients (77 [54.2%] in group A and 65 [45.8%] in group B) were included and were followed for 29 (12, 42) months. The baseline PA was 4.6 ± 1.0°. We found that the decrease in the PA was associated with an increased risk for death, but it was disappeared after the adjustment for age, sex and comorbidity (HR 0.58, 95%CI=0.34-1.00; P = 0.051). Cardiovascular event was not associated with PA (P = 0.685). However, we found that PA predicted the occurrence of infection, independent of age, sex and comorbidity (HR 0.65, 95%CI=0.45-0.94; P = 0.20). Although the levels of hemoglobin were different between two groups during the study period, patients in group B received higher doses of erythropoiesis-stimulating agents and intravenous iron, compared with those in group

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

595A
NR-PO978
Obestatin Predicts Clinical Outcomes in Hemodialysis Patients: A Prospective Cohort Study

Methods: A prospective cohort study on 261 MHD outpatients (39% women, mean age 68 ± 13.6 years) with median follow-up - 28 months (interquartile range - 19-34 months). We measured obestatin, acyl-glycine (AG) levels, appetite, nutritional and inflammatory markers, prospective all-cause and cardiovascular (CV) mortality.

Results: Obestatin positively correlated with AG (r=0.25, P=0.001) and negatively correlated with BMI (r=-0.14, P=0.03) and lean body mass (r=-0.15, P=0.01). During follow-up, 109 patients died, 51 due to CV causes. For each 1 ng/ml increase in baseline obestatin levels, multivariable adjusted all-cause death HR was 0.85 (95% CI 0.75 to 0.96, P=0.01) and CV death HR was 0.82 (95% CI, 0.69 to 0.97, P=0.02). Adjusted models included age, sex, vintage, diabetes, smoking, co-morbidity index, vascular access type, Kt/V, residual renal function, malnutrition-inflammation score and IL-6. Associations between obestatin and mortality risk continued to be significant in analyses that additionally accounted for AG levels. CUBic spline survival models confirmed linear trends.

Conclusions: Higher obestatin level is associated with lower death risk in MHD patients independent of nutritional status and inflammation. Future studies are needed to elucidate underlying mechanisms associated with improved outcomes in MHD population.

NR-PO979
Metabolically Abnormal Non-Obese Phenotype Is Significantly Associated with Increased Mortality in Incident Dialysis Patients

Methods: During 2009 and 2015, Total 1,141 Patients who started dialysis were recruited from the Clinical Research Center for End Stage Renal Disease data set. Metabolic abnormality was determined by the presence of 2 or more of the following: 1) HbA1c ≥6.5% or history of diabetes, 2) Triglyceride ≥150 mg/dL, 3) HDL-C ≤40 mg/dL in men, 4) Hs-CRP ≥3 mg/L. Obesity was defined by BMI ≥25.0 kg/m². Metabolically abnormality was determined by the presence of 2 or more of the following: 1) HbA1c ≥6.5% or history of diabetes, 2) Triglyceride ≥150 mg/dL, 3) HDL-C ≤40 mg/dL in men, 4) Hs-CRP ≥3 mg/L. Obesity was defined by BMI ≥25.0 kg/m². Patients were divided into four groups [metabolically healthy obesity (MHO), metabolically abnormal obesity (MAO), and metabolically abnormal non-obesity (MANO)].

Results: A 63 (5.5%), 316 (27.7%), 240 (21.0%), and 522 (45.7%) patients were classified into MHO, MAO, MANO, and MANO group, respectively. All-cause mortality was observed with 5 (7.9%), 43 (13.6%), 35 (14.5%), and 148 (28.3%) patients in each groups, respectively. In Cox proportional hazard analysis, MANO group showed significantly higher all-cause mortality events (hazard ratio, 2.700; 95% confidence interval, 1.096-6.4; P=0.031) even after adjustment for age, sex, smoking status, systolic blood pressure, diastolic blood pressure, serum albumin, calcium, phosphate, uric acid, and total cholesterol and intact-PTH.

Conclusions: MANO group was significantly associated with higher mortality compared to other groups in dialysis patients. Obese phenotype stratified metabolic abnormality is substantially different from that in general population.

NR-PO980
Natural Course of Muscle Mass Change and Related Factors in Patients Undergoing Hemodialysis

Methods: We studied 67,752 HD pts, 26,057 cases (mean age 68%, 58% males; 28% Blacks) and 41,695 controls (mean age 61%; 56% males; 38% Blacks). Across vintage groups, the number of Pts were distributed as follows: yr1, 13,300 cases & 41,308 controls; yr2, 6,546 cases & 23,216 controls; yr3, 3,872 cases & 11,798 controls; yr4, 2,339 cases & 4,446 controls. In both cases and controls scores increased with longer vintage; we observed distinct differences between cases and controls.

Conclusions: The rate of SMI change over time differs among patients. Chronic inflammation and nutritional status may affect SMI change while the amount of protein intake or dialysis adequacy may not.

FR-PO978
Dynamics of Nutritional Status in Chronic Hemodialysis Patients before Death

Methods: The goal of this study was to assess nutritional competency in vintage-matched cohorts of HD Pts. We included all Pts who started HD in FMCNA clinics between 01/2006 and 12/2011. Nutritional competency was quantified monthly using a nutritional score that comprised of mean serum albumin, creatinine, phosphate, enPCR, and IDWG. In Pts who died (cases), the score was calculated in the 12 months (mo) before death. Vintage-matched survivors served as controls.

Results: We studied 67,752 HD pts, 26,057 cases (mean age 68%, 58% males; 28% Blacks) and 41,695 controls (mean age 61%; 56% males; 38% Blacks). Across vintage groups, the number of Pts were distributed as follows: yr1, 13,300 cases & 41,308 controls; yr2, 6,546 cases & 23,216 controls; yr3, 3,872 cases & 11,798 controls; yr4, 2,339 cases & 4,446 controls. In both cases and controls scores increased with longer vintage; we observed distinct differences between cases and controls.

Conclusions: Our study shows that nutritional competency is stable in survivors but declines in cases before death. This may indicate a deteriorating nutritional status and may alert health care workers.

Funding: Pharmaceutical Company Support - Renal Research Institute
FR-PO982

Low Body Mass Index and All-Cause Mortality in Patient with Hemodialysis

Ha Yoon Kim, Eun Hui Bae, Seong Kwon Ma, Soo Wan Kim. Dept of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea.

Background: Malnutrition is common in patients with hemodialysis and is a major risk factor of mortality. The Korean Society of Nephrology (KSN) collected data of end-stage renal disease registry since 1985. We evaluated whether body mass index (BMI) can affect the mortality in patient with hemodialysis.

Methods: From 2004 to 2015, a total of 32,163 patients starting hemodialysis were included. The patients were divided into four groups according to quartiles of BMI measurement.

Results: At baseline, mean age was 59.0 ± 14.3 years old, and 60.0% were men. The 5-year mortality of hemodialysis patients was 16.9% (N=5,435) and ratio of unknown state was 24.9% (N=7,996). The mean of BMI in each quartiles were 18.2 ± 1.2, 20.8 ± 2.2, 22.8 ± 0.6, 26.4 ± 2.6 kg/m² respectively. The mean of BMI between survivor and non-survivor were not different (18.3 vs. 21.5 ± 3.2 kg/m²). Cox-proportional regression multivariate analysis revealed that the 5-year all-cause mortality was associated with age (HR 1.04, CI 1.03–1.05), diabetes (HR 1.34, CI 1.07–1.74), coronary heart disease or heart failure (HR 1.5, CI 0.9–1.7), 2° BMI quartile (HR 0.7, CI 0.5–0.9), 3° BMI quartile (HR 0.6, CI 0.46–0.88), 4° BMI quartile (HR 0.59, CI 0.43–0.82), hypoalbuminemia (HR 2.9, CI 2.3–3.7) and anemia (HR 1.6, CI 1.2–2.0).

Conclusions: Higher quartiles of BMI was significantly associated with better survival rate in hemodialysis patients in Korea. Traditional risk factors of malnutrition, such as hypoalbuminemia, anemia were also independent risk factors for mortality. This result suggests that hemodialysis patients require nutritional support.

FR-PO983

Body Mass Index and Causes of Death in Incident Hemodialysis Patients in Korea

Seoogin Kim,1 Shin-Young Ahn,2 Jong Cheol Jeong,3 Ki Young Na,3 Su-Jae Kim,3,4,5 Junichiro Kawaguchi,6 Sejoong Kim.1,7,8,9 1Korea Kidney Center, Seoul, Korea; 2Division of Nephrology and Hypertension, Seoul National University Bundang Hospital, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea; 3Department of Internal Medicine, Chonnam National University Guro Hospital, Republic of Korea; 4Aju University School of Medicine, Republic of Korea; 5The Catholic University of Korea, Republic of Korea.

Background: In dialysis patients, higher body mass index (BMI) leads to better survival, so called “reverse epidemiology”. However, distribution of BMI in Korea is different from western countries, and cause-specific death is still unknown. We examined 10,299 incident hemodialysis patients from Korean Society of Nephrology registry.

Methods: We performed a multicenter nonrandomized single-arm prospective clinical trial. 15 Japanese patients receiving hemodialysis were administered L-carnitine tablets (Kawaguchi, Japan; 3Apheresis and Dialysis Center, Keio Univ, School of Medicine, Tokyo, Japan; 2Div of Endocrinology, Metabolism and Nephrology Dept of Internal Medicine, Keio Univ, School of Medicine, Tokyo, Japan; 4The Catholic Univ of Korea, Republic of Korea; 5Department of Medical Microbiology and Laboratory Medicine, Kidney Center, Tokyo Women’s Medical Univ, Tokyo, Japan; 2Division of Nephrology and Hypertension, Seoul National University Bundang Hospital, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea; 6Department of Laboratory Medicine, St. Luke’s International Hospital, Tokyo, Japan; 7Department of Laboratory Medicine, Saiseikai Koganei Hospital, Tokyo, Japan; 3Apheresis and Dialysis Center, Keio Univ, School of Medicine, Tokyo, Japan; 5Department of Medical Microbiology and Laboratory Medicine, Kidney Center, Tokyo Women’s Medical Univ, Tokyo, Japan; 6Division of Laboratory Medicine, Department of Internal Medicine, Kyungpook National Univ Hospital, Daegu, Republic of Korea.

Results: Oral supplementation of L-carnitine to the patients receiving hemodialysis improved not only their muscle discomfort but also their gastrointestinal disorders and microbiota, although its effect on the prognosis of hemodialysis patients should be further investigated.

FR-PO985

Albumin Values with C-Reactive Protein Taken into Account Can Be a Good Predictor of Dialysis Patient Survival

Norio Hanafusa,1 Hiroshi Kawaguchi,2 Ken Tsuchiya,3 Kosaku Nitta.1 1Dept of Blood Purification, Kidney Center, Tokyo Women’s Medical Univ, Tokyo, Japan; 2Jyoban Hospital, Iwaki, Fukushima, Japan; 3Medicine, Kidney Center, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Albumin is often used for the markers of wasting or malnutrition. However, albumin can also be affected by inflammation. We speculated that albumin values with the inflammatory status taken into account would be a better index in assessing albumin index, namely “C-reactive protein considered albumin”. We investigated the association of this index with mortality, and compared the power of prediction of this index with other albumin indices.

Methods: In total, 397 patients were included into this study. Baseline data were obtained in July 2012. The survival until the end of August 2014 (follow up period of 25 months at most) was investigated. Firstly, the regression line was obtained from the entire population between albumin and CRP. Thereafter, the CRP-considered albumin levels were determined as a dichotomous variable; the patients with the albumin values above the regression line were considered high, vice versa. We investigated the association of three albumin indices (the actual values, the dichotomous index by median, and CRP-considered values) and mortality by Cox proportional hazard models.

Results: Among total population, albumin and CRP were correlated reciprocally and weakly significantly; albumin (g/dl) = 3.438 – 0.215 logCRP (log mg/dl), R2=0.126. During the observational period, 73 patients deceased. In univariate Cox analysis demonstrated that all three indices were associated with survival; HR 0.40 (95%CI0.25 – 0.68), 0.41 (95%CI 0.25 – 0.68), and 0.46 (95%CI0.28 – 0.74) for each increase of actual albumin, the higher CRP-considered albumin, and the higher dichotomous albumin, respectively. On the other hand, only the higher CRP-considered albumin related to the better survival (HR 0.51, 95%CI: 0.30 – 0.85). The degree to which the deviation of albumin was attributable to that of CRP was 12.9%.

Conclusions: CRP-considered albumin was shown to be a better predictor of mortality among dialysis population. In assessing albumin values, inflammatory status should be taken into account.

Funding: Private Foundation Support

FR-PO986

Individualized Prediction of Mortality Using Multiple Inflammatory Markers in Patients on Dialysis: A Prospective Multicenter Cohort Study

Sun-Hee Park, Hee-Yeon Jung, Kyu Yeun Kim, Min Jung Kim, Wonseok Do, Younagae Yang, Taehoon Yun, Inryang Hwang, Sukyung Lee, Ji-Young Choi, Sang-Hye Cho, Chan-Duck Kim, Yong-Jun Kim. Internal Medicine, Kyungpook National Univ Hospital, Daegu, Republic of Korea.

Background: This study was aimed to evaluate whether the incremental combination of inflammatory markers captured on routine clinical practice could improve predictive powers for mortalities in patients on dialysis and to develop a predictive model for mortality according to dialysis modality.

Methods: Inflammatory markers obtained at the time of enrollment from 3,309 patients on dialysis from a prospective multicenter cohort were used. Cox proportional hazards regression methods and time dependent ROC curves were constructed and net reclassification index and integrated discrimination improvement were calculated. Cox proportional hazards regression analysis was used to derive a prediction model of mortality.

Results: Addition of the three predictors (WBC, hsCRP, and albumin) one by one to the conventional risk factors had more predictive powers than conventional risk factors alone for all-cause and infection-related mortality in entire population. hsCRP and albumin had additional predictability for cardiovascular mortality in entire population and for infection-related mortality in HD patients. The incremental combination of WBC, hsCRP, and albumin improved predictive powers for all-cause mortality in entire population. hsCRP and albumin gradually increased predictive powers for all-cause and infection-related mortalities in HD patients. Cox multivariate analysis showed age, sex, presence of diabetes, history of coronary artery disease and dialysis vintage were statistically significant predictors of all-cause mortality. The prediction model using multiple inflammatory markers stratified mortality according to dialysis modality.

Conclusions: Multi-marker approaches using multiple inflammatory markers practically available in clinic provided higher predictive power for all-cause mortality in dialysis patients. The predictive model for mortality based on different combinations of inflammatory markers according to dialysis modality enables a stratified risk assessment in this population.

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

Underline represents presenting author.
FR-PO987
Infection Hospitalization Trend among Hemodialysis and Peritoneal Dialysis Patients

Jianrong Liu,1 Peer Kidney Care Initiative Investigators.2
1CDRG, MMRF Mps, MN; 2Peer Kidney Care Initiative.

Background: Infections are a major cause of morbidity and mortality in maintenance dialysis patients (pts). Previous work has shown that peritoneal dialysis (PD) pts are at higher risk for dialysis access (DA)-related infections and hemodialysis (HD) pts for most other infections. However, whether and how infectious hospitalization (IH) rates have changed over time, especially in recent years, is unknown.

Methods: Using the 2000-2013 CMS ESRD database, we identified pts and mortalities on January 1 of each year. Pts were followed from January 1 to the earliest of death, transplant, loss of Medicare coverage, or year end. I Bs were identified from medical claims and classified as circulatory, pulmonary, DA-related, or other based on the primary diagnosis code. A Poisson regression model was used to test the trend in IH rates and the trend differences between HD and PD pts, 2008-2015.

Results: Before 2008, the overall IH rate was stable among PD pts at approximately 46 per 100 patient-years, but increased among HD pts from 30.1 in 2000 to 36.0 in 2008. Rates then decreased by an average of 5.4% per year for PD and 4.6% per year for HD pts (P<0.001, PD-HD decrease rate comparison).

PD pts had much higher rates of DA-related IH than HD pts; rates decreased since 2008, on average 12.4% per year for HD and 9.1% per year for PD pts (P<0.001). Pulmonary, circulatory, and other IH rates were higher for HD pts. Since 2008, pulmonary IH rates decreased by 3.7% and 0.7% per year for HD and PD pts, respectively (P<0.001); circulatory IH rates increased by 0.2% and 3.3% per year for HD and PD pts, respectively (P<0.001); IH rates for other infections decreased 3.4% per year for HD and remained unchanged for PD pts (P<0.001).

Conclusions: Overall, IH rates decreased for both HD and PD pts in recent years, but more improvement is needed, especially for PD pts and for DA-related infections.

Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by the following participating provider organizations: American Renal Associates, Atlantic Dialysis Management Services, DaVita HealthCare Partners, Dialysis Clinic, Inc., Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Satellite Healthcare, The Rogosin Institute, U.S. Renal Care, and Wake Forest University

FR-PO988
Associations between Apolipoproteins and Infection, Cardiovascular Events and Mortality in Patients Receiving Dialysis

George A. Kayser,1 Loren S. Dalrymple,1 Glenn Matthew Chertow,2 Barbara A. Grimes,3 Kirsten L. Johansen.4 *Nephrology, UC Davis, Sacramento, CA; #Nephrology, Stanford Univ, Palo Alto, CA; $Dept of Epidemiology and Biostatistics, UCSF, San Francisco, CA; "Nephrology, Section, SFVAMC, San Francisco, CA

Background: Lipid lowering therapy may not be beneficial in the dialysis population. Lipoproteins play a role in the innate immune system, providing a potential link to infection that may counterbalance cardiovascular (CV) effects.

Methods: We examined the associations between serum concentrations of apolipoproteins A1, B, C2, and C3 and all-cause mortality, CV- and infection-related hospitalization or death in 442 participants in the ACTIVE/ADPSSI study of prevalent HD patients recruited 2009-2011, followed through March 2014. We examined associations between each lipoprotein and outcomes using Cox models with time-varying apolipoprotein concentrations (q 6 mos).

In univariate models, higher levels of each of the apolipoproteins were associated with statistically significantly lower risk of infectious events and, except for apo A1, with lower all-cause mortality. Apolipoproteins were not associated with CV events. In multivariable models, higher Apo A1 concentration was associated with lower risk of infection and higher Apo B was associated with lower risk of all-cause mortality.

FR-PO989
Association between Plasma Macrophage Stimulating Protein Levels and Risk of All-Cause Mortality in Hemodialysis Patients

Tetsuo Miyamoto,1 Mika Matsumoto,2 Yumi Furuno,1 Kenichiro Bando,1 Junichi Nakamata,1 Yoko Fujimoto,1 Ken Otsuji,1 Ikutaro Furuno,1 Yutaka Otsuji,1 Masahito Tamura.2
12nd Dept of Internal Medicine, Univ of Occupational and Environmental Health School of Medicine, Kitakyushu, Japan; 2Yukushahi Clinic, Yabushahi, Japan; 3Kidney Center, Univ of Occupational and Environmental Health School of Medicine, Kitakyushu, Japan.

Background: Persistent low-grade inflammation, a condition observed in a majority of hemodialysis patients, is a major driving force of the uremic phenotype which leads to increased morbidity and mortality. Macrophage stimulating protein (MSP), also known as Hepatocyte Growth Factor-like protein (HGF), has been demonstrated to play a key role in reducing inflammation in the peripheral tissues of multiple disease models.

Methods: In this multicenter prospective cohort study comprising 236 maintenance hemodialysis patients (37% female; median age 66 years; age range 21-92 years), we investigated the effect of MSP levels, measured by enzyme-linked immunosorbent assay, on all-cause mortality, with a particular focus on inflamed patients. We used Kaplan-Meier analyses and multivariate Cox regression analyses to estimate mortality risk.

Results: During the observation time (median observation time 25 months), a total of 31 patients died during the observation period. Patients were categorized into two groups according to serum C-reactive protein (CRP) levels. In the inflamed patient group (CRP > 0.5 mg/dL, n=49), Kaplan-Meier analysis comparing the survival rate between lower and higher plasma MSP levels, showed that patients with lower MSP levels, defined as the lowest tertile of plasma MSP (< 223 mg/mL), had an significantly higher mortality risk (Log rank X2=8.0, P=0.005). When adjusting for age, sex, dialysis vintage, diabetes mellitus and cardiovascular disease, lower MSP levels was independently related to increased mortality (Hazard ratio [HR]=3.8, 95%CI:1.3-11.1, P<0.01). Conversely, no association was observed in patients in the non-inflamed patient group (CRP < 0.5 mg/dL).

Conclusions: Plasma Macrophage Stimulating Protein levels provide a useful biomarker for assessing 2-year mortality risk in maintenance hemodialysis patients with high CRP levels.

FR-PO990
B-Lymphocytes Depletion, a New Mortality Risk Factor in Hemodialysis


Background: Acquired quantitative disturbances in immune system are known in hemodialysis patients (HDP). It could explain the deaths for infection events, and a effect on the atherosclerosis process is discussed. The aim of this study was to analyze the effect of immune cell subsets (ICS) in the mortality of HDP.

Methods: Prospective observational single centre study in HDP from 2011-12. Total and ICS (CD4, CD8, CD56, CD19) were measured. We used a new score of mortality with this variables: Charlson’s index ≥7 points (p), Kt/V <1.2>3 points (p), previous failed transplantation=2p, low CD19 with normal serum albumin (SA)=3p, low SA with previous failed transplantation (OR=0.4 (0.2-0.8), p<0.01), low CD19 (OR=2.2 (1.1-4.3), p<0.01), high serum albumin (OR=0.8 (0.7-0.9), p<0.01). Forty-eight (46%) patients died. The causes of death were 40% for cardiovascular disease, 31% infection disease and 13% oncology disease. The death risk factors showed in the univariable analysis were Charlson’s index ≥7 (OR=2.5 (1.3-4.6), p<0.01), Kt/V <1.2 (OR=3.8 (1.6-9.4), p<0.01), previous previous renal transplantation (OR=0.4 (0.2-0.8), p<0.01), low CD19 (OR=2.2 (1.1- 4.3), p<0.01) and SA <3.5 g/dL (OR=2.5 (1.3-4.8), p<0.01). We classified HDP according their punctuation in score: Group 1 with 0-2 points, Group 2 with 3-5 points and Group 3 with > 6 points. Survival is shown on the graphic.
Conclusions: Lower CD19 lymphocyte is a new independent mortality risk factor in HDP. Our score could be a new tool to predict the risk of death in HD patients. Our score needs to be validated in other populations for be generalized.

FR-PO991
Cardiac, Musculoskeletal, and C. diff Infections in Hemodialysis Patients
David T. Gilbertson, Peer Kidney Care Initiative Investigators. Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN; Peer Kidney Care Initiative.

Background: Dialysis patients are at significantly increased risk of hospitalization due to infection. Trends in overall infection rates have been well described, but less is known about cause-specific infections. We assessed trends in cardiac (e.g., endocarditis), musculoskeletal (e.g., osteomyelitis, septic arthritis), and C. diff (e.g., colitis) infections in dialysis patients, 2004-2013.

Methods: We used the Centers for Medicare & Medicaid Services End-Stage Renal Disease database to examine rates of hospitalization with a primary cause of cardiac, musculoskeletal, or C. diff infection among dialysis patients. Analyses were performed separately for prevalent patients (> 1 year on dialysis) and incident patients (≤ 1 year on dialysis).

Results: For all three infection types, rates were higher in incident than in prevalent patients, particularly for C. diff infections. While rates of cardiac and musculoskeletal infections declined from 2004-2013, C. diff infections increased ~40% among incident and prevalent patients.

Conclusions: While overall hospitalized infection rates were relatively constant from 2004-2013 despite decreasing all-cause hospitalization rates, trends varied by infection type. These infections comprise only a modest percentage of all-cause infections, but the decrease in hospitalizations for cardiac and musculoskeletal infections is encouraging. However, dialysis patients with C. diff infections are at increased risk for morbidity and mortality, and interventions to reduce risk are needed.

Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by the following participating provider organizations: American Renal Associates, Atlantic Dialysis Management Services, DaVita HealthCare Partners, Dialysis Clinic, Inc., Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Satellite Healthcare, The Rogosin Institute, U.S. Renal Care, and Wake Forest University

FR-PO992
Infective Endocarditis in Dialysis-Dependent Chronic Kidney Disease: One Centre’s Experience
Andrew Nixon, Naem Desai, Ajay Prabhakar Dhaygude. Renal Medicine Dept, Royal Preston Hospital, Preston, Lancashire, United Kingdom.

Background: Infective Endocarditis (IE) is a devastating complication of dialysis-dependent chronic kidney disease (CKD).1,2 One-year survival rates were reported to be as low as 38.4% over a decade ago.3 We wished to establish if there had been any improvement in outcomes in recent years.

Methods: The local echocardiogram database was reviewed to identify all reports suggesting a valve vegetation between August 2002 and March 2016. Clinical records were then reviewed to identify all those with dialysis-dependent CKD diagnosed with IE.

Results: Fourteen patients were identified (15 episodes). The median age was 65 years (range 32-84 years). The male:female was 1:1. The median dialysis vintage was 9 months (range 1-46 months). Table 1 demonstrates patient clinical characteristics.

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Number of Episodes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemodialysis</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Central Venous Catheter</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Pre-existing Valve Lesion</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Previous Valve Surgery</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Valve Affected</td>
<td></td>
</tr>
<tr>
<td>-Mitrail</td>
<td>10 (67)</td>
</tr>
<tr>
<td>-Aortic</td>
<td>4 (27)</td>
</tr>
<tr>
<td>-Tricuspid</td>
<td>4 (27)</td>
</tr>
<tr>
<td>-L1 Valve</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Causative Organism(s)</td>
<td></td>
</tr>
<tr>
<td>-Staphylococcus Aureus</td>
<td>8 (53)</td>
</tr>
<tr>
<td>-Enterococcus sp.</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>

Valve surgery was performed for 3 patients (21%). Survival rates were as follows: 30-day: 71% (n=10); 90-day: 50% (n=7); 1-year: 36% (n=5). Figure 1 demonstrates Kaplan-Meier survival analysis (months).


FR-PO993
Urinalysis in the Diagnostic Workup of Dialysis Patients with Possible Infection
Katerina Oikonomou, Adib Alhaddad. Internal Medicine, NYU Lutheran Medical Center; Brooklyn, NY.

Background: Data on the role of urinalysis (UA) in the diagnostic workup of dialysis patients with possible infection are limited, and there is also variability in the coexistence of urinary tract infection (UTI).

Methods: A retrospective study was conducted to assess the sensitivity, specificity, and positive and negative predictive values of urinalysis parameters in dialysis patients who were hospitalized between 9/2008 and 8/2015 with an admitting diagnosis of fever, sepsis or urinary tract infection. Characteristics of patients were recorded, and their associations with urinalysis parameters were assessed with Fisher’s exact test. Receiver operating characteristic (ROC) analysis of urinalysis parameters was also performed.

Results: 275 dialysis patients (141 males, mean age 73±14.9 years) were assessed. Pyuria of different cut-offs (>10, >50 WBC/HPF) was associated with urine culture positivity (P < 0.001), and growth ≥10^5 CFU/ml (P=0.039), but not with presence of fever or sepsis. There was also association with urinary catheter use (P=0.001). Pyuria >10 WBC/...
HPF had a sensitivity of 86%, and a specificity of 35% for identification of a positive urine culture with growth ≥10⁵ CFU/ml (P=0.025). Pyuria > 50 WBC/HPF had a sensitivity of 66% and a specificity of 58% (P=0.032). Bacteriuria, and leukocyte esterase (LE) positivity were associated with positive urine culture but not with growth ≥10⁶ CFU/ml. LE was also associated with presence of urinary catheter (P=0.031). No difference was found in patients with or without fever or sepsis in terms of bacteriuria, LE or nitrite positivity.

**Conclusions:** In the absence of adequate specificity and positive predictive value of urinalysis in dialysis patients with fever, sepsis or suspected UTI, a urine culture should be obtained to guide further treatment. Physicians should be vigilant for sources of infection other than the genitourinary tract.

**FR-PO994**

**Association between Low Serum Testosterone and All-Cause Mortality and Infection-Related Hospitalization in Male Hemodialysis Patients: Prospective Cohort Study**

**Background:** Infectious diseases are the second-highest cause of death in patients on dialysis. In addition, testosterone deficiency is prevalent in dialysis. However, no studies have investigated the association between testosterone levels and infection-related hospitalization (IRH). We aimed to evaluate whether serum testosterone levels are associated with IRH and mortality in male hemodialysis patients.

**Methods:** We divided the study population into three groups based on serum testosterone levels. Associations between testosterone levels and the clinical outcomes of IRH, and all-cause mortality were analyzed using the Cox proportional hazard model after controlling for important clinical covariates.

**Results:** 902 male patients were enrolled and followed up for a median of 24.7 months. Their mean age (±SD) was 63.4 (± 11.8) years. 123 participants died during follow-up. IRH occurred in 116 patients. IRH rates were significantly more frequent in the lower testosterone tertile (hazard ratio [HR], 2.12; 95% confidence interval [CI], 1.18-3.79) in different years hospital-based dialysis centers had a higher positive MRSA rate compared to 2015 and with 1.4% significantly lower in 2016 (p=0.002). The MRSA rates of single local health authority. MRSA-positive patients were decolonized according to a standardized hospitalization and temporary dialysis access are known risk factors for MRSA colonization. Werner

**FR-PO996**

Efficacy and Safety of Sofosbuvir-Based Treatment in Patients with Chronic Hepatitis C Infection and End Stage Renal Disease

**Background:** Treatment for hepatitis C infection for patients of end stage renal disease on regular haemodialysis is difficult, treatment option are limited. We have treated hepatitis C-infected patients on regular haemodialysis, genotype 1-positive patients treated with fix dose combination of sofosbuvir and ledipasvir on alternate day, and genotype 3-positive patients with sofosbuvir and daclatasvir [alternate day].

**Methods:** In haemodialysis unit total 14 patients were infected with hepatitis C, 11 patients of genotype-1, and 3 patients of genotype-3, genotype-1 infected patients were treated with fix dose combination tablet containing ledipasvir 90 mg and sofosbuvir 400 mg administered orally alternateday for 12 weeks, genotype-3 infected patients treated with tablet of sofosbuvir 400 mg and tablet of daclatasvir 60 mg given orally alternate day for 12 weeks routine clinical and laboratory data were collected at base line and during treatment. Routine primary outcome was sustained virological response at week 12 (SVR12).

**Results:** total 14 patients, 10 male ane 4 female, of various age group between 34 to 71 years were included in this study. therapy was well tolerated. no patient discontinued treatment because of side effects. comparison of lab at baseline and nadir level during treatment revealed no significant change in haemoglobin, plateletcount, ALT and bilirubin, all 14 patients had undetectable HCV RNA at the end of treatment, no cardiac or hepatobiliary toxicity observed during treatment, one patient had nausea, one patient had drop in haemoglobin by 1 gm/dl, other wise no side effects at all.

**Conclusions:** Alternate day fix dose sofosbuvir and ledipasvir for HCV genotype-1 infection, and also alternate day sofosbuvir and daclatasvir for HCV genotype-3 infection was highly effective in previously untreated hepatitis C infection in patients of end stage renal disease, on regular dialysis. treatment was safe, no significant adverse events were observed during the period of treatment.

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

**Underline represents author.**

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**FR-PO997**

Sofosbuvir and Ribavirin Is Safe and Effective Therapy in Chronic Hepatitis C Patients with End-Stage Renal Disease and GFR (30 ml/min)

**Background:** Direct acting antiviral (DAAs) have been very effective in chronic hepatitis C. However, treatment of HCV in patients with advanced CKD on HD and low GFR (30ml) remains a major challenge due to the lack of reported efficacy and safety data of DAAs in this population. We investigated the efficacy and safety of Sofosbuvir (SOF) and Ribavirin (RBV) in chronic HCV infected CKD patients on HD and CKD stage 3 and 4 Patients and methods: Patients with CKD on HD and GFR (30 ml/min) having chronic HCV infection, were prospectively enrolled between September 2015 – June 2016 to receive SOF with RBV for 24 weeks. Patients were started on SOF 400 mg daily and RBV at 200 mg once to thrice weekly (as per tolerability of patients and serial Hb values). Safety and efficacy data were collected; including SVR12 and SVR24 data for all patients after completing therapy. Results: 48 patients have been enrolled, with mean age of 44.99±11.99 yrs. 39(81.3%) patients were on dialysis and 7(14.6%) in stage 4, 2(4.1%) with stage 5.44 of 48 patients were having Chronic liver disease and one patient was post liver Cleft surgery. The mean value of log at baseline was 5.786 and median value varies from 1.0–7.8 copies). HCV genotype 1 was present in 28(58.3%) and genotype 3 in 20 (41.7%) patients. 39 % (19) patients have completed 24 weeks of therapy. The virological cure was achieved in 19 (100%) of patients who have completed 24 weeks. Those who have reached 12 weeks & 24 weeks post-treatment had 100 % SVR at 12 & 24 Wk. 34% patients required adjustment in ribavirin dosage and increase in erythropoietin dose. Conclusions: Sofosbuvir plus ribavirin therapy, given for 24 weeks appears to be well tolerated in patients with advanced renal failure and carries good efficacy results with 100% SVR at 12 weeks.

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

**FR-PO998**

Effects of End-Stage Renal Disease (ESRD) and Dialysis Modalities on Blood Ammonia Level

**Background:** Effects of End-Stage Renal Disease (ESRD) and Dialysis Modalities on Blood Ammonia Level

**Methods:** We investigated the efficacy and safety of Sofosbuvir (SOF) and Ribavirin (RBV) in chronic HCV infected CKD patients on HD and CKD stage 3 and 4 Patients and methods: Patients with CKD on HD and GFR (30 ml/min) having chronic HCV infection, were prospectively enrolled between September 2015 – June 2016 to receive SOF with RBV for 24 weeks. Patients were started on SOF 400 mg daily and RBV at 200 mg once to thrice weekly (as per tolerability of patients and serial Hb values). Safety and efficacy data were collected; including SVR12 and SVR24 data for all patients after completing therapy. Results: 48 patients have been enrolled, with mean age of 44.99±11.99 yrs. 39(81.3%) patients were on dialysis and 7(14.6%) in stage 4, 2(4.1%) with stage 5.44 of 48 patients were having Chronic liver disease and one patient was post liver Cleft surgery. The mean value of log at baseline was 5.786 and median value varies from 1.0–7.8 copies). HCV genotype 1 was present in 28(58.3%) and genotype 3 in 20 (41.7%) patients. 39 % (19) patients have completed 24 weeks of therapy. The virological cure was achieved in 19 (100%) of patients who have completed 24 weeks. Those who have reached 12 weeks & 24 weeks post-treatment had 100 % SVR at 12 & 24 Wk. 34% patients required adjustment in ribavirin dosage and increase in erythropoietin dose. Conclusions: Sofosbuvir plus ribavirin therapy, given for 24 weeks appears to be well tolerated in patients with advanced renal failure and carries good efficacy results with 100% SVR at 12 weeks.

**Funding:** Government Support - Non-U.S.
Conclusions: The post-HD fall in blood area levels is paradoxically accompanied by a rise in breath ammonia. This rise is directly related to the extent of ultrafiltration and inversely related to the rise in bicarbonate concentration. Ultrafiltration can result in an acute reduction of hepatic perfusion limiting the liver’s ability to convert gut-derived ammonia to urea. Additionally, the acute correction of mild acidosis in which ammonia is held as a nonvolatile ammonium, to a normal or alkalotic state can result in increased levels of volatile ammonia.

Funding: Other NIH Support - Univ. Calif., Irvine Institute Clinical Translational Science: Grant UL1 TR001414

FR-PO1000
Residual Renal Function Is Associated With Vascular Calcification and Valvular Calcification in Hemodialysis Patients 

Dong Ho Shin, Eunjung Kim, Jung-Woo Noh, Ja-Ryong Koo. Hallym Univ College of Medicine.

Background: Vascular calcification (VC) and cardiac valvular calcification (CVC) are common and may contribute to cardiovascular mortality in hemodialysis patients. Although there are multiple risk factors associated with VC and CVC in hemodialysis patients, little is known about the potential influence of RRF on VC and CVC in hemodialysis patients. Thus, we investigated VC and CVC according the degree of RRF in hemodialysis patients.

Methods: A total of 144 patients with RRF on maintenance hemodialysis for ≥ 3 months were recruited between January 2014 and February 2016 at Kangdong Sacred Heart Hospital, Kangnam Sacred Heart Hospital, and Dantun Sacred Heart Hospital. Abdominal aortic calcification (AAC) score was calculated on lateral lumbar radiographs and arterial stiffness was assessed by brachial-ankle pulse wave velocity (baPWV). Additionally, CVC was assessed by echocardiography. Univariate and multivariate logistic regression were conducted to ascertain the potential influence of RRF on VC and CVC.

Results: The median age and dialysis duration were 56.4 ± 10.8 years and 36.3 ± 11.2 months, respectively. The median RRF was 1.2 ml/min/1.73 m² (interquartile range 0.4-2.1 ml/min/1.73 m²). Aortic calcification (AAC) score [9 (3-22) vs. 5 (0-17), p = 0.04] and baPWV [1895.0 (1707.0-2155.5) cm/s vs. 1785.0 (1558.0-1983.0) cm/s, p = 0.003] were significantly higher in patients with RRF ≤ 1.2 ml/min/1.73 m². CVC was common in patients with RRF ≤ 1.2 ml/min/1.73 m² (45.1% vs. 23.1%, p = 0.04). In multivariate analysis, RRF significantly to the VC and CVC. Therefore, continuous monitoring of RRF may be useful to predict the risk of cardiovascular event in hemodialysis patients.

FR-PO1001
The KUMC Calciphylaxis Registry—Clinical Characteristics and Factors Associated with Mortality 

Peter W. Santos, Jianghua He, Ahmad M. Tufvála, James B. Wetmore. 1AKDHC, Phoenix, AZ; 2Univ of Kansas Medical Center, Kansas City, KS; 3Hennepin County Medical Center, Minneapolis, MN.

Background: We sought to describe clinical characteristics, methods of diagnosis, treatments prescribed, and mortality in CUA patients using cases reported in the University of Kansas Medical Center Calciphylaxis Registry (KUMC CR), a voluntary web-accessible registry.

Methods: Descriptive was reported as percents or means. Univariate analysis using the Cox survival model was conducted to estimate the hazard ratios (HRs) for factors associated with mortality. Kaplan-Meier survival curves of subgroups with different risk burdens were compared with log-rank tests.

Results: Of 117 patients, mean age was 58.5 years, females comprised 63.8%, and 63.8% were white. Mean BMI was 31.9 kg/m². DM was present in 66.7% and cardiovascular disease (CVD) in 62.2%. Warfarin was used in 40.2%. The mean iPTH level was 459 pg/ml, Pwas 6.3 mg/dl, uncorrected Ca was 9.0mg/dl, and Alb was 3.1 g/dl. Clinical suspicion (56.7%) was the most common diagnostic approach, while 32.5% had a histological diagnosis; only 9.4% underwent a bone scan. While nonspecific wound care was initiated in 70.9% of patients, debridement was undertaken in only 42.6% of cases. Sodium thiosulfate (STS) was initiated in 54.7% of patients, with the majority (74.1%) receiving ≥ 12.5 mg of STS, most often for <3 months (79.7%). In univariate analysis higher mortality was observed in patients with CVD (HR=10.47; 95% CI, 1.40 to 78.38), and those taking warfarin (HR=2.74; 95% CI, 1.16 to 6.51).

Conclusions: In real-world clinical practice, there is substantial heterogeneity in the diagnosis and treatment of CUA. Bone and mineral parameters were not often strikingly abnormal. The presence of CVD and use of warfarin appear to be mortality risk factors.

FR-PO1002
UK Calciphylaxis Study: Interim Analysis 


Background: Calcific uremic arteriopathy (CUA or calciphylaxis) is a rare condition associated with a high mortality. It predominantly affects dialysis patients and is characterised by debilitating skin ulceration and calcification of cutaneous arterioles.

Methods: The UK Calciphylaxis Study is a UK-wide prospective observational internet-based study of CKD associated calciphylaxis. Data including demographics, laboratory results, medication use and therapeutic interventions are collected from enrolled patients on a 4 monthly basis.

Results: Data was available for 63 patients enrolled between 2012 and 2016. 76.2% were on renal replacement therapy (peritoneal or haemodialysis). 52.4% were female, median age was 57.5 years (IQR 52-66). 58.2% had a BMI >30 and 80.8% a BMI of >25. Prior to lesion development 66.7% (n=42) were prescribed a phosphate binder, 36.5% (n=23) vitamin K antagonist. Baseline measured corrected calcium was 2.41 (SD0.290) mmol/l, phosphate 1.68 mmol/l (SD0.58) and iPTH median was 91.1 (IQR29.6-189.8) mmol/l. The majority of lesions were on the lower extremities (57.1%), followed by the thighs (28.6%) and abdomen (15.9%). The treatment used varied considerably between patients.

Conclusions: 80.8% of patients in this study were overweight in comparison to the average dialysis population. Vitamin K antagonist use was highly prevalent in keeping with the literature; both may be important risk factors for the development of CUA. Therapeutic strategies varied greatly identifying a need for more research and consensus on the management of this condition.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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601A
Direct Links between Coronary Artery Calcification, Abnormal Cardiac Function, and Mortality in CKD-5D

Paul Anaya, Gustav A. Blomquist, Daniel Davenport, Marie-Claude M. Faugere, Vincent L. Sorrell, Hartmut H. Malik. 1 Div of Cardiovascular Medicine; 2 Dept of Internal Medicine; 3 Dept of Radiology; 4 Dept of Surgery; 5 Div of Nephrology, Bone & Mineral Metabolism, Univ of Kentucky, Lexington, KY.

Background: Coronary artery calcification (CAC) is common in patients with chronic kidney disease on hemodialysis (CKD-5D) and is an important predictor of mortality, but cardiac functional links between CAC and mortality have not been well-established. This study tested the hypothesis that CAC increases mortality by adversely affecting cardiac function.

Methods: Patients were recruited from 37 regional dialysis centers. 2-D and Doppler echocardiographic (Echo) analyses were performed and CAC was measured using 64-slice computed tomography. Relationships between CAC and Echo measures of left ventricular (LV) function were analyzed. Survival was assessed with median follow-up of 37 months.

Results: There were 157 patients: 59% men, 46% Caucasian, 48% diabetic. Median age was 55 years and median duration of CKD-5D was 45 months. Agatston CAC scores >100 were found in 69% of patients with 51% having a score >400. CAC was associated with measures of LV systolic and diastolic function (global longitudinal strain [GLS]; r=0.270, p=0.004), mean LV systolic velocity (r=0.259, p=0.004), and GLS of LV filling pressure (E/E'; r=0.286, p=0.001). Multivariable regression confirmed these relationships after adjustment for age, gender, ejection fraction and coronary artery disease. Valvular calcification varied linearly with CAC (p<0.05). Both LV systolic and diastolic functional measures were significant predictors of mortality; the strongest of which was LV diastolic dysfunction.

Conclusions: These findings show a link between CAC, cardiac function, and mortality in CKD-5D. LV diastolic function (E/E'), peak LV systolic velocity, and GLS are independent predictors of mortality. Valvular calcification may be an important marker of CAC in CKD-5D. These effects on cardiac function likely explain the high mortality seen with CKD-5D and describe a potentially valuable role for Echo in the routine management of these patients.

Funding: NIDDK Support

Vascular Calcification

Conferences for Friday

FR-PO1003

Clinical Significance of Vascular Calcification Volume Assessed by 3D Imaging Software

Koari Takao, Hirotsugu Iwata, Yuta Asahina, Shintaro Koizumi, Yoko Tomiyama, Iku Nagayama, Takahito Ito, Masayama Yamato, Nephrology, Osaka National Hospital, Osaka, Japan; 2 Nephrology, Kataguchi Medical Center, Shibata, Niigata, Japan.

Background: Vascular calcification (VC) is closely associated with cardiovascular events and mortality. Quantification methods of VC vary among studies. We studied clinical significance of vascular calcification volume (VCV) assessed by 3D imaging software.

Methods: This is a retrospective cross-sectional observational study. Out of 69 patients undergoing thoracoabdominal computed tomography from May 2014 to December 2015 in our department of Osaka National Hospital, 65 patients were subjected to the analysis. The patient characteristics were as follows; 71 ± 11 y.o., 36 males, eGFR 20.4 (8.9-40.0) ml/min/1.73m², P3.8±1.1 mg/dl, hypertension 27 (42%), diabetes 16 (25%), macroangiopathy 19 (29%), use of ACE-IARB 28 (43%), use of phosphate-binder 6 (9%), and Brinkman Index (BI) 130 (0-750). Four patients were excluded because of the treatment history of aortic aneurysm. Using the Hounsfield Unit more than 130 as the cut-off level, VCV of the entire aorta was measured with 3D imaging software. Statistical analysis was performed by JMP and p-value less than 0.05 was considered significant.

Results: VCV was 6.6 (2.7-18.1) ml. Univariate analysis showed that log(VCV) was significantly associated with age, sex, log(eGFR), log(BI), use of phosphate-binder, use of ACE-I/ARB, hypertension, and macroangiopathy. Use of warfarin was marginally significant. Multivariate analysis with log(VCV) by these 9 parameters indicated that age (beta=0.43, p=0.026), log(BI) (beta=0.5, p=0.035) and use of ACE-I/ARB (beta=0.5, p=0.002) were independent positive predictors and log(eGFR) (-0.69, p=0.015) was an independent negative predictor of high aortic VCV.

Conclusions: The quantification method of VC using 3D imaging software is visible and reportedly useful. Our results are consistent with the already known risk factors of VC. Unexpectedly, ACE-I/ARBs seemed to promote VC. Our results are, however, compatible with a recent report that angiotensin II prevents phosphate-induced calcification in human aortic smooth muscle cells.

FR-PO1005

Abdominal Aortic Calcifications as a Prognostic Factor of All Cause Mortality in Hemodialysis Patients

Kyriaki Stamatelekou, Dimitra Bacharaki, Ioannis Griveas, John Kyriazis, Dimitrios V. Vlahakos. 1 Nephrology, Galinoi Hospital, Athens, Greece; 2 Nephrology, Aktoion Hospital, Chaidari, Greece; 3 Dialysis, NEOFRONTIKI, Athens, Greece; 4 Nephrology, General Hospital, Chios, Greece.

Background: Vascular calcification has been associated with adverse clinical outcomes in hemodialysis patients. In this prospective study we examined the role of abdominal aortic calcification (AAC) in predicting all cause mortality in HD patients.

Methods: We studied 53 HD patients, 26 men, 27 women. After assessing the degree of AAC in the abdominal aortic region on X-rays, patients were prospectively followed for two years, while recording fatal events. Kaplan-Meier survival analysis and univariate and multivariate Cox model were used.

Results: Median follow-up was 19.8 months, 13 deaths recorded, of which 11 (72.7%) due to cardiovascular causes. Kaplan Meier survival analysis showed that patients with AAC score higher than the median score of 4, had worse survival compared to patients with AAC score ≤ 4 (17.6 versus 23.6 months; p < 0.05).

Conclusions: The degree of AAC is a reliable indicator for estimating the risk of death in hemodialysis patients.

FR-PO1006

Aortic Calcification Area Index Predicts Increased Mortality in Peritoneal Dialysis Patients

Fumiko Kuwahara, Saeko Miura, Kenji Harada, Hidetoshi Kanai. Nephrology, Kokura Memorial Hospital, Kitakyushu, Japan.

Background: Patients with end-stage renal disease have a high prevalence of vascular calcification, and cardiovascular diseases are an important cause of deaths. Here, we investigated the relationship of aortic calcification area index (ACAI) and mortality using the aortic calcification rate as an indicator of arteriosclerosis.

Methods: 76 patients (50 men and 26 women) who initially started peritoneal dialysis (PD) therapy and who took an abdominal computed tomography (CT) scan between February 2010 and November 2013 were included. We calculated the calcification area index (ACAI) for abdominal aortic vascular volume by using the abdominal CT. Patients were divided into two groups; low ACAI<11.7% (low ACAI group) n=43, and high ACAI≥11.7% (high ACAI group) n=33. We analyzed the abdominal aortic calcification and mortality in PD patients using the Kaplan-Meier method.

Results: Median follow up period was 47.7±13.1 months. Median patient age was 63.6±11.7. Median value of ACAI was 11.7±10.5. High ACAI group were significantly older, higher ALP value and higher calcification rate of change than low ACAI group. Calcium, phosphorus, whole parathyroid hormone, uric acid, albumin, hemoglobin A1c, blood pressure, residual renal Kt/V and urine volume were not significantly differences in the two groups. In the Kaplan-meier method, high ACAI group was increased mortality (log-rank test: p=0.0348). In the univariate Cox proportional hazards model, ACAI was a significant predictor of survival (hazard ratio 1.056 per 1.0% increment ACAI, 95% CI 1.007-1.108, P=0.05). However, in the multivariate Cox proportional hazards model, we could not show that ACAI was prognostic factor for survival.

Conclusions: In this study, we found that high ACAI group was associated with increased mortality by Kaplan-meier method. However, non cardiovascular death such as infection and cancer death is in the majority, therefore we could not show ACAI was prognostic factor for survival. We suggest that ACAI might be associated with mortality in PD patients.

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602A
Phosphorus and Panthotenic Acid Intake Are Related to Vascular Calcification in Class III and IV CKD: The PROGRESDIR Study

Alicson Kalani,1 Michael B. Chen,1 Joachim Ferrer,2 Carmen Marchioni,3 Mark Jürgen Canals,4 Michael Raphael,5 and Dirk Joachim Zeralda1

Background: Vascular calcification (VC) is a widespread condition in CKD. Diet may be a determinant, but its role is not clear. We analysed the association between nutrient intake and VC in class III and IV CKD.

Methods: Data from 454 participants (Progresdir Study) was used. A validated food frequency questionnaire was applied and nutrient intake was estimated using the USDA Database, adjusted for energy. Agatston Score (CAC) was obtained and those with coronary stent were excluded (artifact), leaving 372 people, which were classified by CAC (>100). Results: Median CAC was 165, with 50% of values >100. Age, male sex, race, diabetes, hypertension and smoking were related to CAC. While macronutrient intake was not different, a higher intake of phosphorus, calcium, vitamin D, vitamin B6, panthothenic acid (vitB5), potassium and magnesium was observed in the CAC>100 group. In logistic regression, all micronutrients except vitamin B2 remained related to CAC, even after adjustment for age, sex, diabetes, smoking, and protein intake. Lastly, we added micronutrient intake to the adjusted model and phosphorus intake remained significantly related to CAC [OR=1.002, 95%CI 1.001-1.003, p=0.001], whereas vitB6 showed a nearly significant relation [OR=1.286, 95%CI 0.98-1.70, p=0.067].

Conclusions: Our results show that (1) phosphorus intake is independently associated to VC in CKD, responsible for the major effect among nutrients related to CAC; (2) panthothenic acid intake may be related to VC. This last finding raises questions about vitB5 in VC, considering its role in coenzyme A, fatty acids and cholesterol synthesis, metabolic pathways which have been related to the osteogenic differentiation of the vascular smooth muscle cell. Funding: Government Support - Non-U.S.

Sodium Thiosulfate Intervenes Coronary Artery Calcification in Maintenance Hemodialysis Patients Yi Yu,1,2 Dept of Blood Purification, Dept of Medical Imaging, Dongfang Hospital of Fuyun Province, Fuzhou, Fujian, China.

Background: The purpose is to investigate the factors correlated to coronary artery calcification in maintenance hemodialysis (MHD) patients, further to observe the effect of sodium thiosulfate (STS) on the progression of vascular calcification and its safety.

Methods: All subjects underwent coronary artery CT scan using the 64-slice CT and the calcification degree was evaluated by calcification scores. First, the MHD patients were divided into coronary artery calcification group (CAC scores >10) and non-coronary artery calcification group (CAC scores <10). The differences of age, duration of dialysis and some demographical information between the two groups were analyzed. Then, those with coronary artery calcification (CAC scores >50) received intravenous 0.18g/kg STS (dissolved in 100ml saline) in 30 minutes after each dialysis for 3 months (n=15) or received conventional treatment (n=10). The changes of vascular calcification imaging, CAC scores, biochemical and bone mineral density were compared between two groups before and after the treatment. Besides, adverse reactions were observed during the treatment of STS.

Results: 27 in 38 patients (71.05%) had coronary artery calcification, The patients with coronary artery calcification had significantly higher age, duration of dialysis, phosphate, the product of calcium and phosphate, PTH and hsCRP and lower serum albumin (P<0.05) than patients without coronary artery calcification. There was no significant difference in the baseline characteristics between STS treatment group and the conventional treatment group. CAC score was unchanged in the STS treatment group (P=0.053), but increased significantly in the conventional treatment group (P=0.021). Difference of calcification score parameters before and after treatment showed statistically significant difference between the two groups (P=0.004). After STS treatment, hsCRP and HCO3 levels decreased, and serum calcium levels increased (P<0.05).

Conclusions: Coronary artery calcification is commonly present in MHD patients. STS treatment seems to be feasible, safe and may decrease the rate of progression of vascular calcification, reduce inflammation in MHD patients. Funding: Government Support - Non-U.S.

Aki/mTOR Signalling Is Involved in VSMC Calcification Induced by High Phosphate Yi Yu,1,2 Dept. of Blood Purification, Dongfang Hospital of Fuyun Province, Fuzhou, Fujian, China.

Background: The aim is to characterize the possible role of Aki/mTOR signalling in the vascular smooth muscle cells (VSMC) calcification induced by high phosphate.

Methods: Passage 3 to 5 of VSMC were used for experiments. VSMC were divided into two groups: normal phosphate group (P 1.3 mmol/L) and high phosphate group (P 2.6 mmol/L). Cbfα1 and OPN mRNA levels were determined by real-time PCR. p-Akt (ser473), p-mTOR (S2448), Cbfα1 and OPN protein expressions were quantified by Western Blot. When p-Akt and p-mTOR expression of VSMC were enhanced by high phosphate, Aki/mTOR inhibitors were respectively added in high phosphate group. VSMC then were divided into seven groups: high phosphate group (P 2.6 mmol/L); high phosphate+Wortmannin(10, 50, 100 mmol/L); high phosphate+rapamycin (1, 10, 100ng/mL). After 24-48h, Cbfα1 and OPN mRNA levels were determined, and p-Aki, p-mTOR, Cbfα1 and OPN protein expressions were quantified. All experiments were repeated 3 times. Calcium deposition was visualized by Alizarin stain method at day 7-14.

Results: After 7 days, compared with normal phosphate group, calcium deposition was obvious in high phosphate group. Cbfα1 and OPN mRNA expressions were significantly increased, and p-Akt and p-mTOR expression of VSMC were enhanced by high phosphate, Aki/mTOR inhibitors were respectively added in high phosphate group. VSMC then were divided into seven groups: high phosphate group (P 2.6 mmol/L); high phosphate+ Wortmannin(10, 50, 100 mmol/L); high phosphate+rapamycin (1, 10, 100ng/mL). After 24-48h, Cbfα1 and OPN mRNA expressions were significantly decreased; p-Aki, p-mTOR, Cbfα1 and OPN protein expressions were quantified. All experiments were repeated 3 times. Calcium deposition was visualized by Alizarin stain method at day 7-14.

Results: After 7 days, compared with normal phosphate group, calcium deposition was obvious in high phosphate group. Cbfα1 and OPN mRNA expressions were significantly increased, and p-Akt and p-mTOR expression of VSMC were enhanced by high phosphate, Aki/mTOR inhibitors were respectively added in high phosphate group. VSMC then were divided into seven groups: high phosphate group (P 2.6 mmol/L); high phosphate+ Wortmannin(10, 50, 100 mmol/L); high phosphate+rapamycin (1, 10, 100ng/mL). After 24-48h, Cbfα1 and OPN mRNA expressions were significantly decreased; p-Aki, p-mTOR, Cbfα1 and OPN protein expressions were quantified. All experiments were repeated 3 times. Calcium deposition was visualized by Alizarin stain method at day 7-14.

Conclusions: Aki/mTOR inhibitors may suppress VSMC calcification and expressions of p-Aki/p-mTOR, Cbfα1 and OPN. Aki/mTOR is involved in VSMC calcification induced by high phosphate. Funding: Government Support - Non-U.S.

SNAF472 - A Potential Novel Calcification Inhibitor in CKD-MBD

Nadine Kaesler,1 Ayse Hyusein,1 Miquel D. Ferrer,2 Ana-Zeraldina Canals,2 Carolina Salcedo,2 Joan Perelló,2 Jurgen Floge,3 Vincent Brandenburg,4 Nephrology, Univ Hospital of the RWTH Aachen, Germany; 5Laboratories Sanitof SL, Palma, Spain; 6Cardiology, Unio Hospital of the RWTH Aachen, Germany.

Background: Chronic kidney disease (CKD) is associated with cardiovascular calcification (CVC) in response to mineral and bone disorder, SNF472 (an intravenous formulation of the hexaammonium salt of myo-inositol hexaphosphate) directly inhibits calcium binding by seed growth sites of the hydroxyapatite crystal. We investigated the effects of SNF472 upon vascular smooth muscle cell (VSMC)-mediated calcification triggered by high calcium (Ca++) concentration.

Methods: The anti-calcific effects of SNF472 or sodium thiosulfate (STS) were analyzed on primary VSMC from rat aorta treated with 3 mM calcium phosphate (CaPO4).

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Ca content, apoptosis rate and gene expression were measured. Dose Finding: Calculating VSSP was performed with 30, 50 and 100 µM SNF472 and 25, 50, and 100 µM of STS for 5 days. Apoptosis was measured by TUNEL assay, gene expression by Taqman real-time PCR. Time dependency: Using the most efficient anti-calcification dosage, treatment with SNF472 was started 3, 5, and 7 days after the beginning of the calcification experiment.

Results: SNF472 significantly reduced Ca concentrations compared to untreated VSMCs (maximum inhibition of 97%). CaPO treatment increased apoptosis rate compared to the control group after 7 days (control group: 0.69% vs. CaPO group: 1.5%). SNF472 treatment increased apoptosis rate by 0.8% at 30 µM. STS was most effective at 100 µM in reducing calcification (96% inhibition) but increased apoptosis rate by 77%. SNF472 (30 µM) is also effective in lowering the Ca content in later calcification stages. SNF472 treatment prevented CaPO-induced downregulation of SMA and also prevented upregulation of ALK Phos and c-fos.

Conclusions: SNF472 decreases the calcium deposition in the ECM of rodent VSMC in a high CaPO microenvironment without inducing apoptosis. Moreover, it prevented upregulation of genes indicating switch form contractile VSMC to osteoblast-like cells. SNF472 qualifies as a promising research target to inhibit vascular calcification in CKD patients undergoing dialysis.

Funding: Pharmaceutical Company Support - Sanifit

FR-PO1012

Safety, Pharmacokinetics and Pharmacodynamics of SNF472 in Hemodialysis Patients: New Data from a Phase 1b/2a Randomised Placebo-Controlled Clinical Trial Carolina Salem,1,2 Joan Perelló,1,2 Raquel Ojeda,3 Pieter H. Joubert,1,4 Marta Arias,5 Ana-Zeraldia Canals,1 Miquel D. Ferrer,3 Maria del Mar Perez,1 Jose-Vicente Torregrosa,1 Francisco Maduell.1 Laboratori Sanifit, Palma, Spain; Univ de les Illes Balears, Palma, Spain;1 Dept Nephrology, Hospital Clinic, Barcelona, Spain; Inst of Pharmaceutical Science, King's College, London, United Kingdom.

Background: SNF472 (an intravenous formulation of inositol hexaphosphate) inhibits calcification by binding to the growing sites of hydroxyapatite (HAP). SNF472 is being developed for the prevention of vascular calcification in patients with end-stage renal failure on hemodialysis (HD). Non-clinical investigations and a single dose study in healthy volunteers and HD patients supported proceeding to a repeated dose trial in HD patients. Methods: A double-blind, randomized, repeat dose study was performed in two cohorts of eight HD patients on three HD sessions per week. SNF472 was administered by a 4-hour infusion during the HD sessions. Doses of 1, 3, 5, 12.5, and 20 mg/kg were administered in cohorts of eight HD patients on three HD sessions per week. SNF472 was administered by a 4-hour infusion during the HD sessions. Doses of 1, 3, 5, 12.5, and 20 mg/kg were given during three consecutive HD sessions, with a 3-week washout period between doses. A second cohort received 10 mg/kg during 12 consecutive HD sessions. Standard safety parameters, serum bio element concentrations, pharmacokinetics, and calcification pharmacodynamics (PD) were determined.

Results: No adverse events, systemic side effects or local irritation related to SNF472 administration were reported. Dose linearity was observed in terms of Cmax and AUC between 3 and 20 mg/kg. No SNF472 accumulation was observed after 1 month of administration at 10 mg/kg. Serum P, Mg2+, and K+ were decreased as a consequence of HD, but SNF472 did not affect these changes. Ionized calcium was unaffected by SNF472 administration. The doses of 5, 12.5, and 20 mg/kg were on a P D plateau and reduced the HAP formation propensity by 80%. The Emax using this assay was 2.18 mg/kg.

Conclusions: The findings support continuation of the clinical development program, namely a 2 phase 3-month study in calciphylaxis assessing wound healing and a phase 2 one-year dose-finding study in HD patients evaluating coronary artery calcification progression. Supported by RETOS COLABORACIÓN: RTC-2014-2460-1 ISCIII grant.

Funding: Government Support - Non-U.S.

FR-PO1013


Background: Vascular calcification (VC) is considered to be an important risk factor for cardiovascular morbidity and mortality in CKD patients. Loss of calcification inhibitors is one of the mechanisms responsible for the development of VC in the media of the vessel wall. Matrix gla protein (MGP) is a strong inhibitor of VC and its activity depends on vitamin K–mediated γ-carboxylation. As warfarin interferes with vitamin K recycling, active (carboxylated) MGP is depleted and VC consequently develop. Here, we investigated cellular mechanisms underlying warfarin-induced VC as well as its effects on the bone.

Methods: Calcifications were induced in rats by daily administration of a warfarin-supplemented diet (3mg warfarin/g diet + 1.5mg vitK1/g diet). Rats receiving a standard diet, served as controls (CTR). At sacrifice at 4, 6, 8 and 10 wk, VC, aortic mRNA expression and bone status were assessed by bulk calcium (Ca) analysis, q-RT PCR and bone histomorphometry.

Results: Aortic Ca concentration gradually increased and significantly differed from CTR in 4-wk treated rats (p=0.0286), reaching a 50-fold increase in 10-wk treated rats, 0.0061 vs CTR). mRNAs of osteochondrogenic transdifferentiation markers were upregulated, among which the transcription factor Sox9 and β-catenin, an important protein in the vascular and cardiac components of the CKD-MBD. ActRIIA signaling may be a therapeutic target in Alport’s syndrome.
FR-PO1016

Reducing Dietary Phosphate in Experimental CKD Is Sufficient to Attenuate Vascular Stiffness and the Associated Left Ventricular Hypertrophy

Bruno Svajger,1 Kimberley J. Laverty,1 Cynthia M. Pruss,1 Emilie C. Ward,1 Paul S. Jeronimo,1 Mandy E. Turner,1 Martin P. Petkovich,1 Rachel M. Holden,1 Michael A. Adams,1 Biomedical and Molecular Sciences, Queen’s Univ, Kingston, ON, Canada; 2Medicine, Queen’s Univ, Kingston, ON, Canada.

Background: Impaired renal function in CKD causes hyperphosphatemia and alters hormonal regulators (calcitriol, FGF-23). One hypothesis is that the increased phosphate (Pi) pool combined with elevated FGF-23 and the generation of vascular calcification (VC) cause cardiovascular disease (CVD). Understanding this mechanism is important as CVD-related outcomes in CKD patients account for over half of all CKD mortality. To determine the importance of dietary Pi on CKD-based CVD we sought to determine the effects of low versus high dietary Pi in a rat model of CKD.

Methods: 16 wk male SD rats were fed a CKD-inducing diet (0.25% adenine, 0.5% Pi, n=35) for 4 wks, were taken off adenine and separated into 3 diet groups: 0.5% Pi (n=14), 1% Pi (n=11), and 1.5% Pi (n=10). Non-CKD-control groups on 0.5% Pi (n=8) or 1.5% Pi (n=5) were compared. After 4 wks, hemodynamic changes were measured and the rats sacrificed.

Results: Low Pi (0.5% diet) in CKD rats did not change serum Pi, or aortic VC vs controls; while high PO4 (1% and 1.5% diets) led to increased serum Pi (6.2±2.1 vs 1.5% Pi, p<0.05) and VC compared to controls (413±525.6 vs 4.1±0.76 & 6.1±2.8 mmol/mg). PWV was elevated in high Pi group compared to controls and low Pi (0.13±0.1 vs 0.06±0.02 ms²/mmHg, p<0.05). CKD induction increased serum FGF-23 (p<0.05) with significant elevations in high Pi groups compared to low Pi (30±28.4 vs 2±1.6 mg/mL, p<0.05). High Pi groups have significant LVH compared to low Pi groups (p=0.05).

Conclusions: Increasing dietary Pi in CKD leadsto greater propensity for VC and this appears to directly contribute to the development of CVD. Our findings show that maintaining low dietary Pi protects vessels against VC and vascular stiffening, ultimately reducing the extent of LVH in CKD. These findings support the value of dietary Pi regulation for CKD patients and the use of dietary Pi binders to help improve CVD complications in CKD patients.

Funding: Pharmaceutical Company Support - OPOK, Government Support - Non-U.S.

FR-PO1019

Indoxyl Sulfate Promotes Aortic Calcification through Notch Signaling Pathway Activation in Vascular Smooth Muscle Cells

Maimaiti Yisirevil,1 Kyoysuke Takeshita,1 Toshimitsu Niwa,2 1Dept of Cardiology, Nagoya Univ Graduate School of Medicine, Nagoya, Aichi, Japan; 2Faculty of Health and Nutrition, Facultad de Health and Nutrition, Shabun Univ, Ichinomiya, Aichi, Japan.

Background: Vascular calcification is common in chronic kidney disease (CKD), and recognized as surrogate marker for cardiovascular disease (CVD). Indoxyl sulfate (IS) is a protein bound uremic toxin to exacerbate vascular calcification in CKD patients, and its therapeutic target has been searched for. We hypothesized that Notch signal pathway alterations caused by IS is involved in vascular calcification because Notch signal activation increase cell survival of vascular cells in developmental and pathological status.

Methods: IS (200 mg/kg/day in drinking water) administered Dahl rat and vehicle rat were used to evaluate vascular calcification. Human arterial smooth muscle cells (HASMCs) was culture under various concentration of IS, and the expression of Notch 1 and 3, and apoptosis were assessed with RT-PCR, caspase activity assay, and TUNEL staining.

Results: Aortic calcification was observed solely in IS-administered rats. The expression of Notch1 and 3 was slightly increased in aortic SMCs from IS-administered rats compared to vehicle rat. Notably the expression of Notch1 and 3 was fainted in vascular calcification in IS-treated rats. In cultured HASMCs, the expression of Notch1 and 3 was peaked at 24h after administration of IS (1000 μM), and fainted within 72h. Exposure to IS increased TUNEL positive cells and caspase3/7 activity in a dose- and time-dependent manner. IS and Notch signal inhibition accelerated inorganic phosphate-induced calcification in HASMCs, and the effect was canceled by pharmacological inhibition of apoptotic signaling.

Conclusions: IS transiently activates Notch signal in vascular smooth muscle cells, but the effect was fainted getting along with higher concentration and longer duration of exposure to IS. The decreased Notch activity induced formation of apoptotic body and calcified lesions. Thus Notch signal would be a novel therapeutic target for vascular calcification in CKD patients.

Funding: Pharmaceutical Company Support - Merck KGaA, Darmstadt, Germany

FR-PO107

In Vivo Effect of Indoxyl Sulfate (IS) and p-Cresyl Sulfate (PCS) on the Development of Vascular Calcification in Rats with Adenine-Induced Uremia

Brett Opdebeeck,1 Annelies De Mare,2 Bjorn Meijers,2 Pieter Evenepoel,2 Anja Verhulst,1 Patrick C. D’Haese,1 Ellen Neven.1 1Pathophysiology, Univ of Antwerp, Belgium; 2Nephrology, Univ Hospitals Leuven, Belgium.

Background: Vascular calcification (VC) is frequently seen in patients with chronic kidney disease (CKD). Recently uremic toxins, IS and PCS, have been postulated as novel promoters for VC development. To provide further evidence for this, a rat model with adenine-induced uremia was used to define whether IS and PCS are major contributors to VC development during CKD.

Methods: To induce CKD, rats were treated with adenine sulfate during 10-days via daily oral gavage (600 mg/kg/day). Simultaneously, rats were continuously exposed to either (i)IS or (ii)PCS via the drinking water until wk2 followed by oral gavage at a dose of 150 mg/kg/day until sacrifice at wk7. Control animals received vehicle. Calcium(Ca), phosphorus(P), and creatinine were determined in serum and urine samples. Serum and PCS levels were analyzed by LC MS/MS. As uremic toxins may interfere with glucose(Glu) metabolism serum Glu was measured at the start and end of the study. At sacrifice, VC was evaluated by bulk calcium(Ca) and Von Kossa staining.

Results: IS was present in all groups as indicated by a significant reduction of the creatinine clearance and increasing serum P levels. CKD rats exposed to IS showed a significantly higher creatinine clearance and lower serum P levels as compared to vehicle treated CKD rats. Induction of CKD resulted in significantly increased serum IS and PCS levels which were comparable to levels in CKD patients. Glu levels were significantly elevated at the end of the study in both IS and PCS treated rats. No calcification had developed in the aorta, femoral or carotid arteries in CKD rats exposed to vehicle. Development of moderate to severe VC as indicated by a distinct Von Kossa positivity was recognized as surrogate marker for cardiovascular disease (CVD). Indoxyl sulfate (IS) is a protein bound uremic toxin to exacerbate vascular calcification in CKD patients, and its therapeutic target has been searched for. We hypothesized that Notch signal pathway alterations caused by IS is involved in vascular calcification because Notch signal activation increase cell survival of vascular cells in developmental and pathological status.

Methods: IS (200 mg/kg/day in drinking water) administered Dahl rat and vehicle rat were used to evaluate vascular calcification. Human arterial smooth muscle cells (HASMCs) was culture under various concentration of IS, and the expression of Notch 1 and 3, and apoptosis were assessed with RT-PCR, caspase activity assay, and TUNEL staining.

Results: Aortic calcification was observed solely in IS-administered rats. The expression of Notch1 and 3 was slightly increased in aortic SMCs from IS-administered rats compared to vehicle rat. Notably the expression of Notch1 and 3 was fainted in vascular calcification in IS-treated rats. In cultured HASMCs, the expression of Notch1 and 3 was peaked at 24h after administration of IS (1000 μM), and fainted within 72h. Exposure to IS increased TUNEL positive cells and caspase3/7 activity in a dose- and time-dependent manner. IS and Notch signal inhibition accelerated inorganic phosphate-induced calcification in HASMCs, and the effect was canceled by pharmacological inhibition of apoptotic signaling.

Conclusions: IS transiently activates Notch signal in vascular smooth muscle cells, but the effect was fainted getting along with higher concentration and longer duration of exposure to IS. The decreased Notch activity induced formation of apoptotic body and calcified lesions. Thus Notch signal would be a novel therapeutic target for vascular calcification in CKD patients.

Funding: Pharmaceutical Company Support - Merck KGaA, Darmstadt, Germany

FR-PO1019

Metformin Prevents from Severe Kidney Failure, Vascular Calcification and High Bone Turnover Disease

Patrick C. D’Haese,1 Benjamin Arthur Vervaet,1 Kerstin Brand,2 Ulrike Gottwald-Hostalek,2 Geert Dams,1 Anja Verhulst,1 Jean-Daniel Lalau,1 Said Kamel,1 Marc E. De Bros,1 Ellen Neven.1 1Laboratory of Pathophysiology, Univ of Antwerp, Wilrijk, Antwerp, Belgium; 2Global Medical Affairs, Merck KGaA, 64293 Darmstadt, Germany; 3Research and Development, Merck KGaA, 64293 Darmstadt, Germany; 4Unité INSERM U-989, Univ de Picardie Jules Verne, Amiens, France.

Background: Chronic renal impairment causes systemic dysregulation of the mineral metabolism and coincides with vascular calcification and bone disorders which is called ‘Chronic Kidney Disease-Mineral and Bone Disorder’ (CKD-MBD). Metformin, an oral anti-hyperglycemic agent used for type II diabetes mellitus as a standard treatment, has been shown to have beneficial effects on kidney fibrosis and atherosclerosis. This study aims to investigate the effect of metformin on renal function and structure, arteries and the bone in CKD-MBD.

Methods: To induce CKD, rats received a 0.25% adenine/low vitamin K diet for 8 weeks. Animals were daily treated with 200 mg/kg metformin or vehicle by oral gavage from 1 week after CKD induction onwards until week 8. Renal function, histology, fibrosis and inflammation were assessed. The calcium content in the arteries was determined and static and dynamic bone parameters were measured.

Results: Severe, stable CKD along with serious hyperphosphatemia and hypocalcemia had developed in vehicle treated rats which led to calcification in the arteries and high bone turnover disease. Metformin treatment protected adenine dosed rats from the evolution towards severe CKD and serum phosphorus and calcium concentrations remained within the normal range. The kidney of the metformin group showed significant less cellular infiltration, fibrosis and inflammation. Metformin also prevented the development of vascular calcification and inhibited the progression towards high bone turnover disease.

Conclusions: In conclusion, metformin treatment protected against the development of severe renal failure and preserved the calcium phosphorus homeostasis which presumably prevented the onset of vascular calcification and development of high bone turnover disease.

Funding: Pharmaceutical - Pharmaceutical Company Support - Merck KGaA, Darmstadt, Germany

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

605A
FR-PO1020

High Dose Vitamin D-Induced Vascular Calcification Is Abated in TLR4 Deficient Mice Jianheng Zhou, 1 Yuan Min Wang, 1 David C. Harris, 2 Heather J. Medbury, 1 Helen Williams, 3 Anne M. Durkan, 1 Grahame J. Elder, 1 Steven J. Chadban, 1 Huling Wu, 1 Stephen I. Alexander, 1 Vincent W.S. Lee, 1 1Centre for Kidney Research, Children’s Hospital at Westmead, Westmead, NSW, Australia; 2Centre for Transplantation and Renal Research, Westmead Inst of Medical Research, Westmead, NSW, Australia; 3Vascular Biology Research Centre, Westmead Hospital, Westmead, NSW, Australia; 4Renal Medicine, Royal Prince Alfred Hospital, Kidney Node Laboratory, Charles Perkins Centre, Univ of Sydney, NSW, Australia.

Background: Vascular calcification is strongly associated with cardiovascular morbidity and mortality. Several studies have suggested that monocytes/macrophages are involved in arterial vascular calcification, while the involvement of the TLR4 pathway in vascular calcification has also been proposed.

Methods: WT C57BL/6 and TLR4-/ mice aged 8 weeks were injected with a high dose of vitamin D (50000IU/kg/day) subcutaneously at 0, 24 and 48 hours. All mice were sacrificed 4 days after the final injection. Kidneys were collected for examination of injury by histochernistry. Whole aortas were dissected. Macrophage infiltration, TLR4 expression and vascular calcification were examined by immunohistochemistry and histology.

Results: High dose vitamin D treated WT mice demonstrated significantly higher calcium deposition in their aortas (15.5% of area) than did WT and TLR4-/ mice without injection (0.5% < 0.001, 0.2% < 0.001). Aortic calcium deposition was significantly attenuated in TLR4-/ mice with vitamin D injection (1% < 0.001) as compared to vitamin D treated WT mice. This was accompanied by a lower level of macrophage infiltration and TLR4 expression in aortas of high dose vitamin D treated TLR4-/ mice compared to high dose vitamin D treated WT mice, whilst untreated mice had more aortic macrophage infiltration. High dose vitamin D treatment did not induce kidney fibrosis or tubular injury in WT and TLR4-/ mice, as assessed by GT fibrosis score and PAS tubal damage score.

Conclusions: Accelerated vascular calcification and macrophage infiltration with high dose vitamin D treatment was reduced in TLR4-/ mice compared to WT mice. These data suggest a potential role for macrophages and the TLR4 pathway in vascular calcification.

FR-PO1021

Effect of Pioglitazone on Calcification of Rat Vascular Smooth Muscle Cells through the Down-Regulation of Wnt/β-Catenin Signaling Pathway Huijuan Ma, 1 Nephrology, First Affiliated Hospital of Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: To investigate the effect and possible mechanism of Pioglitazone (PIO) on calcification of rat vascular smooth muscle cells (VSMCs) in vitro.

Methods: 1) β-glycerophosphate (10 mM) was used to induce calcification of VSMCs, with different concentrations (5, 10, 15, 20 μM) of PIO to intervene for 12 d. Calcium deposits were tested by Alizarin red staining. Extracellular calcium content was detected by Calcium Assay Kit. Western Blot was used to measure the expressions of α-smooth muscle actin (α-SMA), runt-related transcription factor 2 (Runx2), bone morphogenetic protein 2 (Bmp2), p-β-catenin, β-catenin (β-Cat), and cyclin-D1. On the basis of 10 μM β-glycerophosphate and 20 μM PIO, 20 μM L-PPARγ antagonist GW9662 was added to the cell culture media. The changes of the above indexes were observed.

Results: 1) The calcium content in calcification group increased significantly compared with control group. With the increase of different concentrations of PIO reduced extracellular calcium content (*p<0.05). Alizarin red staining was strong positive in calcified VSMCs, and PIO (20 μM/L) intervention group was almost negative. 2) The expressions of Runx2, β-catenin, p-β-catenin, Bmp2, and cyclin-D1 increased significantly in calcification group, and 20 μM L-PIO obviously down-regulated the expressions of all the above proteins, while up-regulated the expression of α-SMA. 3) PPARγ antagonist GW9662 could partly block the effect of PIO on calcified VSMCs. 4) PIO aginst PPARγ agonist PIO can alleviate rat aortic VSMCs calcification induced by β-glycerophosphate via inhibiting the activity of Wnt/β-catenin signaling pathway.

Funding: Government Support - Non-U.S.

FR-PO1022

Vascular Calcification Induced by High Extracellular Phosphate Imply Activation of Aldosterone Receptor and Transactivation of Epithelial Growth Factor Receptor Victor Manuel Barrientos, 1 Rodrigo Alzamora, 2 Luis F. Michea, 1, 2 Facultad de Medicina, ICBM, Univ of Chile, Chile; 2Millennium Inst on Immunology and Immunotherapy, Univ of Chile, Chile.

Background: Vascular calcification (VC) is a major mortality risk factor in CKD patients. During VC the vascular smooth muscle cells (VSMC) of the tunica media differentiate into osteoblast-like cells. High extracellular phosphate (HP) promotes VC through the induction of the sodium-dependent phosphate cotransporter (P1b). Recent studies indicate that spironolactone (mineralocorticoid receptor antagonist) ameliorated VC in Klotho-deficient mice. However, the potential activation of mineralocorticoid receptor (MR) and the potential mechanisms that could mediate the activation of the MR are unknown. MR activation produces transactivation of epidermal growth factor receptor (EGFR), a mechanism that can facilitate VC. We analyzed if HP, via sodium-dependent phosphate transport, activates MR leading to EGFR transactivation and VC.

Methods: At 75 VSMC cells were switched from normal to HP medium. We analyzed the transactivation of receptor activity and the dependence on sodium-dependent phosphate cotransport by using buffers with/without sodium (sodium replaced by choline and potassium). We determined the role of MR and EGFR with pharmacological antagonists (spironolactone and AG1478 respectively) and the intracellular signaling pathways: ERK1/2 and MR genomic effect on an early response gene, the Neutrophil Gelatinase-Associated Lipocalin (NGAL).

Results: HP (2.5mM, sodium buffer) induced a time-dependent activation of ERK (2.7 times, 10 min vs. 0 min; P<0.05; n=4). The incubation of VSMC with no-sodium HP buffer did not cause ERK activation. Spironolactone (10μM) or AG1478 (10μM) in the culture medium suppressed HP-induced activation of ERK (P<0.05 vs. 0 min; n=4). Finally, HP induced NGAL mRNA expression (1.67 times vs. NT; P<0.05; n=4). Spironolactone prevented the induction of NGAL. In contrast, AG1478 did not prevent NGAL induction by HP (n=4).

Conclusions: We conclude that HP activates the MR via sodium-dependent phosphate transport, leading to EGFR transactivation in VSMC. Funding: FONDECYT 1130550-1151423, IMH P99-016-F.

FR-PO1023

Inhibiting Post-Translational Core Fucosylation Prevents Vascular Calcification in Chronic Kidney Disease Wen Xin Yu, 1 Nephrology, The First Affiliated Hospital of Dalian Medical Univ, Dalian, Liaoning, China.

Background: Vascular calcification (VC) is an independent risk factor for cardiovascular disease and mortality in chronic kidney disease. Post-translational core fucosylation is implicated in a number of pathological processes.

Methods: We investigated the role of core fucosylation on calcification of rat vascular smooth muscle cells (VSMCs) to assess the role of core fucosylation in VC.

Results: Core fucoside could be detected at markedly higher levels in calcified VSMCs than control. Fuc (α-1,6 fucosyltransferase), the only enzyme responsible for core fucosylation in humans, was significantly upregulated by high phosphate. Exposed to high phosphate condition, blocking core fucosylation in VSMCs by knocking down Fuc (α-1,6 fucosyltransferase) using a siRNA reduced calcium deposits and reduced phosphorylated-β-catenin to total-β-catenin ratio, suggesting that core fucosylation affects the calcification process of vascular SMCs.

Conclusions: We conclude that core fucosylation plays a major role in the process of VSMCs calcification and appropriate blockade of core fucosylation may represent a potential therapeutic strategy for treating VC in end-stage renal disease.

Funding: Government Support - Non-U.S.

FR-PO1024

The Anti-Calcific and Anti-Apoptotic Effects of GSK-3 Inhibitors in Cultured Human Aortic Smooth Muscle Cells Narhito Tatsuno, 1, 2 Masaki Arioka, 2 Shunsuke Yamada, 3 Masanori Tokumoto, 1 Kazuhiko Tsumiya, 3 Takanari Kitazono, 1 Toshiyuki Sasaguri, 2 1Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 2Dept of Clinical Pharmacology, Faculty of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 3Dept of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; 4Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: Vascular calcification is an active, cell-mediated, and complex pathology that includes apoptosis of vascular smooth muscle cells (SMCs). Recent experimental studies showed that Wnt/β-catenin signaling pathway is involved in the pathogenesis of vascular calcification. However, it still remains unclear whether or not inhibition of glycogen synthase kinase (GSK)-3, a critical downstream component of Wnt/β-catenin signaling, affects the calcification process of vascular SMCs.

Methods: Human aortic SMCs were incubated in the calcification medium containing 3 mM phosphate and 10% fetal bovine serum. Calcification media were supplemented with either vehicle, lithium chloride (15 mM), or SB216763 (10 μM); the latter two are known as GSK-3 inhibitors. After 14 days of incubation, calcification of human aortic SMCs was assessed by von Kossa staining and calorimetric quantification of calcium (Ca) content after elution with 0.6N hydrochloric. The expressions of Wnt/β-catenin signaling pathway and apoptosis-related proteins were analyzed by western blotting.

Results: Calcification medium increased the Ca content of human aortic SMCs in parallel with an increased expression of cleaved caspase-3. Both GSK-3 inhibitors decreased Ca deposition and reduced phosphorylated-β-catenin to total-β-catenin ratio, suggesting the activation of Wnt/β-catenin signaling pathway. The increased expression of cleaved caspase-3 was suppressed by a co-treatment with both GSK-3 inhibitors.

Conclusions: GSK-3 inhibitors attenuated Pi-induced calcification via suppression of apoptosis in human aortic SMCs.
**Results:** Regardless of P load amount, the degree of both calcification and CPP formation was similar. The expression of bone-saturation factor 2 (BMP2), an osteoblastic differentiation marker, at Day 14 were the lowest in human VSMCs with the alternation of DMEM from high to low glucose (caloric restriction). At Day 8, the expression of SIRT1 and osteoprotegerin (OPG), a calcification inhibitor, was up-regulated by caloric restriction. The content of calcification at Day 14 correlated with CPP content and BMP2 expression at Day 14, and inversely with SIRT1 and OPG expression at Day 8. The OPG expression at Day 8 correlated with SIRT1 expression at Day 8, and inversely with BMP2 expression at Day 14.

**Conclusions:** In conclusion, caloric restriction maintained the phenotype of VSMCs and inhibited P-induced calcification via the up-regulation of SIRT1 expression in human VSMCs.

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

**FR-PO1028**

**Heparin Induces Sclerostin Release in Humans**

Jacek Borawski, Justyna Zolftko, Barbara Labij-Reduta, Beata Naumnik. 1Dept of Nephrology, Medical Univ, Biaylskost, Poland.

**Background:** Sclerostin (Scl) - an inhibitor of bone formation is also involved in cardiovascular calcification that is highly prevalent in maintenance HD patients. Recently, intriguing heparin-binding features of Scl molecule were discovered. We conducted a pilot study to challenge for the first time the hypothesis that intravenous (ENX) releases Scl into the blood.

**Methods:** In 16 males (46.7±11.3 yrs, 85.5±8.62 kg, BMI 26.7±3.11 kg/m²) fasted venous blood samples (T0) were obtained and an iv bolus of ENX was injected (82.5±6.83 mg, 0.97±0.06 mg/kg, 3.12±0.32 mg per kg/m²). The consecutive samples were drawn after 10 min (T10), 2 h (T2h), 6 h (T6h) and 24 h (T24).

**Results:** Plasma immunoreactive Scl levels changing following iv ENX administration (r² ANOVA=50.7, P<0.0001). They increased consistently by a mean of 184% (min 51% - max 461%) from 0.56±0.17 ng/mL at T10 to a median of 1.36 (1.08–1.97) ng/mL at T24 (Wilcoxon P=0.0004). At T2h Scl levels were 0.71±0.19 ng/mL, lower than those at T10 (P=0.004) and elevated by a median of 21% vs baseline (P=0.0005). At T6h Scl levels were 0.61±0.16 ng/mL and still higher by a median of 8.7% vs baseline (P=0.017). At T24 they normalized (0.56±0.16 ng/mL).The percent decrease in plasma Scl (ΔScl) at T10 tended to be directly associated with the dose of ENX per kg (Spearman r=0.430, P=0.096) and was significantly and directly correlated with ENX dose per kg/m² of BMI (r=0.587, P=0.017).

**Conclusions:** The rapid, extensive and dose-dependent increase in plasma Scl constitutes a novel pharmacological effect of iv ENX. Plausible hypotheses to prove and of importance to nephrologists are: 1) the rise in Scl results from its liberation from vascular stores; 2) the effect leads to depletion of the inhibitor; 3) the use of ENX for HD anticoagulation (<75.000 mg a year!) promotes/propagates vascular calcification in HD patients.

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

**FR-PO1029**

**Microrna-34b/c Inhibits Uremia Related Vascular Smooth Muscle Cells Calcification via a Satb2/Runx2 Pathway**

Jianbing Hao, Linrong Hao. 1Second Nephrology and Hemodialysis Center, The First Affiliated Hospital of Harbin Medical Univ, Harbin, Heilongjiang, China.

**Background:** Vascular (vascular smooth muscle cell, VSMC) calcification is a common complication of end stage renal disease (ESRD). Increasing evidence shows that aldosterone and specific microRNAs play an important role in VSMC calcification. In this study, we aimed to explore the mechanistic links between miR-34b/c and aldosterone in VSMC calcification in vitro and in vivo.

**Methods:** First, the levels of aldosterone, miR-34b/c, and specific AT-rich sequence-binding protein 2 (SATB2) were measured. Then, miR-34b/c mimics or inhibitors were transfected into VSMCs to evaluate the function of miR-34b/c. Luciferase reporter assays were used to demonstrate whether SATB2 was a direct target of miR-34b/c.

**Results:** Aldosterone and SATB2 were found to be markedly upregulated during VSMC calcification, whereas miR-34b/c expression was downregulated. Treatment with the angiotensin receptor blocker (ATR blocker) enalapril inhibited VSMC calcification. In aldosterone-induced VSMC calcification, miR-34b/c levels were downregulated and SATB2 protein was upregulated. Furthermore, miR-34b/c overexpression alleviated aldosterone-induced VSMC calcification as well as inhibiting the expression of SATB2 protein, whereas miR-34b/c inhibition markedly enhanced VSMC calcification and upregulated SATB2 protein. In addition, luciferase reporter assays showed that SATB2 is a direct target of miR-34b/c in VSMCs. Overexpression of SATB2 induced Runx2 overproduction and VSMC calcification.

**Funding:** Government Support - Non-U.S.
FR-PO1031

Matrix Vesicles Induce Cell-Cell Communication That Facilitates Vascular Calcification  Neal X. Chen,1 Kalisha O’Neill,1 Sharon M. Moe,1,2 Medicine, Indiana Univ School of Medicine; 1Roduebush VAMC, Indianapolis.

Background: In patients with CKD and ESRD, the major risk factor for progression of arterial calcification is the presence of existing (baseline) calcification. We have shown that VSMC from CKD rats produce matrix vesicles (MV) that are similar to exosomes. We hypothesized that calcification of arteries is propagated/extended by MV induced cell-cell communication from calcifying VSMC to normal VSMC.

Methods: We isolated MV from VSMC from Cy+/rats with advanced CKD incubated with high phosphorus media. MVs were co-cultured with VSMC from normal littermates and endocytosed examined by confocal microscopy. MV mediated alteration of intracellular calcium ([Ca++]i), MAP kinase signaling, and gene expression in recipient VSMC were assessed using calcium Rhod-3 Calcium Imaging, Western blot, and qPCR, respectively.

Results: The addition of MV from VSMC from CKD rats enhanced the calcification of recipient VSMC. Confocal imaging confirmed that MV can be endocytosed by recipient VSMC. The addition of MV to normal VSMC increased [Ca++]i. In contrast, the addition of MV similarly isolated from NIH-3T3 fibroblasts to VSMC had no effect on [Ca++]i, despite evidence that both MV can be endocytosed. MV-induced increased in [Ca++]i in recipient VSMC is partially mediated by 1,4,5-trisphosphate (IP3)-induced [Ca++]i release as treatment with an IP3 inhibitor reduced MV-induced increase in [Ca++]i. In contrast, blocking L-type calcium channel with verapamil had no effect. The addition of MV also increased the activity of phospho-p44-42 MAPK and phospho-MEK1 in recipient VSMC. The inhibitor of MAP kinase, U0126, also decreased MV-induced increase in [Ca++]i. Finally, the addition of MV altered gene expression involved in VSMC phenotype (SM22α), osteoblastic differentiation (BMP-2) and oxidative stress [NOX1 and angiotensin II type I receptor (AT1R)] in recipient VSMC.

Conclusions: MV isolated from VSMC from rats with CKD are endocytosed by recipient VSMC from normal rats, increase [Ca++]i, and MAPK cell signaling, modify gene expression and increase calcification of the normal recipient VSMC. This cell-cell communication may lead to propagation of arterial calcification in CKD.

Funding: Other NIH Support - NIH/Niams, VA Support

FR-PO1032

Vitamin K2 Supplementation and Arterial Stiffness in the Renal Transplant Population—A Single-Arm, Single-Center Clinical Trial  Sola Aoun Bahbou,1,2 Essa Hariri,1 Anthony G. Mansour,1 Yazen Daaboul,1 Serge Korjian,1 Andrew El Alam,1 Hala Kilany,1,2 Albert Karan,1,2 Antoine Stephan,1,2 School of Medicine, Lebanese American Univ, Byblos-Ball, Lebanon; 1Division of Nephrology, Lebanese American Univ Medical Center - Rizk Hospital, Ashrafieh, Lebanon.

Background: Functional vitamin K2 deficiency is highly prevalent among renal transplant recipients and is associated with an increased risk of cardiovascular (CV) disease. The association between vitamin K2 supplementation and improvement in arterial stiffness, a surrogate of early CV disease, has not been investigated.

Methods: The KING trial is a single-arm pilot study that evaluated the association between the change in measures of functional vitamin K2 status and arterial stiffness following 8 weeks of vitamin K2 supplementation (360 µg qd) among 60 renal transplant recipients with stable graft function. Functional vitamin K2 deficiency was defined as serum 25(OH)D <30 nmol/L, serum 1,25(OH)2D <80 pmol/L, and a ratio of serum 25(OH)D and 1,25(OH)2D <0.5. Arterial stiffness was evaluated by carotid-femoral pulse wave velocity (CFPWV).

Results: At baseline, the prevalence of functional vitamin K2 deficiency was 53.3%. After supplementation, mean dp-ucMGP concentration was significantly reduced by 55.1%, and the prevalence of functional vitamin K2 deficiency decreased to 13.3% (p=0.001). Vitamin K2 supplementation was associated with a 14.2% reduction in mean CFPWV at 8 weeks (mean pre-CFPWV=10.0±2.4 m/s vs. mean post-CFPWV=8.4±1.5 m/s; p<0.001). When controlled for age, duration of hemodialysis and transplant, and change in mean arterial pressure from baseline to 8 weeks, the improvement in arterial stiffness remained independently associated with the improvement in dp-ucMGP (p=0.02).

Conclusions: Among renal transplant recipients, vitamin K2 supplementation for 8 weeks is associated with improvement in functional vitamin K2 status and arterial stiffness.

Funding: Other NIH Support - NIH/Niams, VA Support

FR-PO1030

β-glucans Counteract Phosphate-Induced Vascular Calcification by Reducing miR-145-Driven Osteogenic Differentiation of Vascular Smooth Muscle Cells  Sara Panizo,1 Natalia Carrillo-Lopez,1 M. Vittoria Arcidiacono,2 Anabel Castro,1 Petya Valcheva,1 Laura Martinez-Arias,1 Emerenziana Ottaviano,1 Isabel Rodriguez,1 Jorge B. Cannata-Andia,1 Adriana S. Dusso,1 Bone and Mineral Research Unit, HUCA. RedinRen del ISCIII. Univ de Oviedo, Oviedo, Spain; 1Experimental Nephrology, IRB/Lleida, Lleida, Catalonia, Spain.

Background: In CKD, high phosphorus (P)-induced inflammatory signals and osteogenic vascular smooth muscle cell (VSMC) differentiation contribute to vascular calcification. Because anti-inflammatory dietary barley β-glucans reduce arterial calcification in uremic rats fed high P, this study characterized β-glucans anti-calcifying properties.

Methods: Aortic calcification, miR-145 content, mRNA levels of inflammatory (TNFa, ADAM17) and/or osteogenic differentiation (a-actin, Runx2, Osterix) markers were measured in: a) Aortas from 5/6 nephrectomized rats fed high P, with or without 40mg of barley β-glucans daily, for 4 weeks; b) Aortic rings from normal rats or c) A7r5 cells (rat VSMC) exposed to calcifying media (2mM Ca; 3mM P), with or without synthetic barley ß-glucans (100 ug/ml) for 4 days.

Results: In uremic rats, dietary β-glucans reduced aortic calcium content by 50%, which paralleled 80% decreases in TNFa and ADAM17 mRNA expression, an inflammatory loop that down-regulates miR-145, critical to maintain VSMC phenotype. Importantly, in these uremic rats, miR-145 reductions correlated with increased calcification (r=0.83; p<0.05). Overexpression and silencing of miR-145 in A7r5 cells corroborated this novel role for miR-145 reductions in the osteogenic differentiation and calcium deposition induced by a calcifying medium. Significantly, in aortic rings and A7r5 cells exposed to calcifying media, β-glucans reduced calcium deposition by 68% and attenuated both miR-145 reductions (35%) and osteoblastic VSMC differentiation (a-actin reductions (53%); Runx2 (54%) and osterix (57%) increments).

Conclusions: β-glucans protect against high P-induced calcification, at least in part, by an unprecedented action. The maintenance of miR-145 levels and the phenotype of VSMC.

Funding: Pharmaceutical Company Support - Unrestricted grants from Shire, Amgen and VIFOR/Fresenius, Government Support - Non-U.S.

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

Underline represents presenting author.

608A
Introduction: It is well known that the incidence of ESRD becomes increasingly higher all over the world. Given that it is difficult to randomize ESRD patients to either HD or PD, differences between these two renal replacement therapies are of major interest and still controversial.

Methods: All data of maintenance dialysis patients including HD and PD during 2009 to 2013 in Ren Ji Hospital, China and San Bortolo Hospital, Italy were selected by Network, Patients who changed the therapy from HD to PD or PD to HD during this study were excluded.

Results: 919 maintenance dialysis patients were included in this study (HD = 509, PD = 410). Baseline laboratory test data were comparable. After five years follow-up, to compare with PD, MAP and weight were higher in HD patients. The level of HCO₃⁻ was significantly better in PD patients than in HD patients. Regarding the infection markers such as WBC and CRP were significantly higher in PD patients than HD patients. Hemoglobin was significantly higher in PD patients than HD patients. Total albumin and phosphate were higher in HD patients than PD patients. The top three causes of death in HD patients ranged as cerebral vascular disease, infection and cardio vascular disease. In PD, infection was the main cause of death, followed as cerebral vascular disease and cardio vascular disease. The Kaplan-Meier patient survival was similar between HD and PD patients.

Conclusions: Based on 5 years data of two international dialysis centers, we demonstrated that lipid metabolism and nutrition were better in HD patients. However, BP control, acid-base balance, P control and the concentration of Hb and iron were better in PD patients. PD patients might have more choice of infection. The main cause of death in HD and PD is cerebral vascular disease and infection respectively. Considering to dialysis vintage, the 5-year survival rate for HD and PD patients was similar.

FR-PO1035

Outcomes of Pediatric Peritoneal Dialysis Patients: Experiences from a Single Center in Khartoum, Sudan

Aisha. 1,3 Alice. 1 Virginia. 1 Jochen G. Raimann, 1 Peter Kotanko, 1,2 Hasan Abu-Aisha. 1 Renal Research Inst, New York, NY; 2Soba Univ Hospital, Khartoum, Sudan; 3Icahn School of Medicine at Mount Sinai, New York, NY; 4Sudan PD Program.

Background: Pediatric peritoneal dialysis (PD) is the most common modality for pediatric patients (pts) with end stage renal disease (ESRD) (Warady, et al 2012) and is particularly advantageous in developing countries due to less resource requirements. The Sudan University Hospital (SUIH) in Khartoum, Sudan, began its PD program in 2005. It aims to encourage PD use, particularly in children, and train health professionals on PD. This descriptive analysis aims to characterize the population and their outcomes at the hospital.

Methods: Retrospective study of all pediatric PD pts treated at SUIH from 06/2005 to 06/2015. Descriptive statistics of pt demographics, causes of ESRD and clinical outcomes including episodes of peritonitis. Factors associated with mortality are analyzed by development of a Cox Proportional Hazards (PH) model.

Results: One hundred twenty pts who received treatment during the study period were included in this analysis (44% male, median age 10 yrs [1-17 yrs], median length of PD 350 days). Forty pts traveled >200km to the center for treatment. The most common causes of ESRD were glomerulopathy (38%) and congenital urogenital malformation (24%). Fifty-two cases of peritonitis were recorded, 46 first episodes (eps) and 6 secondary eps. The rate of first peritonitis ep was 1 episode/2.85 years of follow-up. The rate of second peritonitis ep was one episode/39 years of follow up. During the study period, 24% of pts died, 32.5% switched to HD and 17.5% received transplants. The mortality rate was 16.6 deaths/100 patient years at risk. The Cox PH model shows 3 times higher hazard of death in winter compared to summer [HR 3.0 (95% CI 1.67-5.39)] and a 2.5 higher hazard in autumn (95% CI 1.43-4.54). Age was also associated with risk of death [HR 1.07 [95% CI 1.01-1.13]].

Conclusions: PD is a common and appropriate method of renal replacement therapy for pediatric ESRD pts. These results provide a view into the potential of PD in pediatric pts in developing countries. Funding for PD programs such as at SUIH can help provide essential services to children with ESRD.

Funding: Pharmaceutical Company Support - Fresenius Medical Care
In adjusted analysis, the mean percentage of regional facilities offering PD increased 2.8% [95% CI 1.6%, 4.1%] before and after the bundled payment (2011-13). Regional PD prevalence, while ESRD patients, concentrated dialysis markets (versus more competitive markets), and per capita income were associated with increases PD supply; employed ESRD patients was associated with diminished PD supply (all p < 0.0001).

Conclusions: Results suggest the success of bundled payment to align patient preferences as demonstrated by increasing availability of PD. Future research should explore the extent to which modality choice is available and accessible to various subgroups of patients with ESRD.

Funding: NIDDK Support

FR-PO1037

Effect of Distance and Time to a Home Dialysis Unit on Home Dialysis Utilization
Rajat Maheshwari,
Sangeetha Lakshmi,
Amit Choudhary,
E ric L. Wallace,
1 Nephrology, Univ of Alabama at Birmingham, Birmingham, AL.
2 Dept of Epidemiology, Univ of Alabama at Birmingham, Birmingham, AL.

Background: Distance to a home dialysis unit (HDU) may pose a barrier to home dialysis uptake and impact outcomes. Studies have shown that with increasing distance to an HDU, home dialysis utilization increases, however its impact on outcomes has received less attention.

Methods: This is a retrospective cohort analysis of incident dialysis patients in 2010 using USRDS data. Patients and dialysis units were geocoded to the population center of each zip code using from which the travel distance and time to their closest HDU was calculated. Driving distance was further categorized as: 0-10 miles, 10-30 miles, >30 miles, and the travel time was categorized as: 0-30, 30-60, >60 mins. We assessed the first six dialysis modalities in-center hemodialysis (ICHD), and home dialysis which included PD and home hemodialysis (HDH). Bivariate associations were reported using one-way ANOVA and chi-square testing to determine if this association was statistically significant. The association of demographics, and medical conditions were used to determine the effect of distance and time to the closest HDU on utilization of home dialysis compared to ICHD.

Results: We analysed 8420 incident dialysis patients. Overall, 91% utilized ICHD, 8.3% PD, and 0.7% HDH. Dialysis patients living <30 miles from a HDU were more likely to utilize PD (OR=1.40; 95% CI 1.28-1.53) but less likely to use IHD (OR=0.66; 95% CI 0.47-0.93) than those living <10 miles. Patients living <30 miles from their closest HDU on home dialysis trended towards higher technique failure rates than those <10 miles (OR=1.17 95% CI 0.77-1.77) but this did not reach statistical significance. Patients >30 miles from an HDU whose primary modality was ICHD trended towards an increased likelihood of switching to home dialysis (OR=1.13, 95% CI 0.96-1.32). Significant similar effects were observed when stratifying by time to a HDU.

Conclusions: Patients living remotely from their closest HDU are more likely to use PD but less likely to use IHD. Larger studies are needed to determine if the effect of distance from a HDU truly impacts outcomes such as technique failure rates.

Funding: Pharmaceutical Company Support - Baxter Healthcare

FR-PO1038

Does Dialysis Modality Impact Employment? A Cross Sectional Study
R Ram,
Boju Sangeetha Lakshmi,
Anil Kumar Cheni Venkata,
Harsha Krishna Reddy Mogili,
V Siva Kumar,
Abhijith Koratula.
1 Sri Venkateswara Inst of Medical Sciences, India; 2 Univ of Florida.

Background: Long-term dialysis therapy for End stage renal disease (ESRD) takes a heavy toll on quality of life the patient. Dialysis creates a whole range of obstacles to employment which includes, health related barriers, economic barriers and attitudinal barriers. This study was designed to gain insights into the employment rates in maintenance dialysis patients which no Indian study has reported so far to the best of our knowledge.

Methods: A cross-sectional study of employment of patients on hemodialysis (HD) and peritoneal dialysis (PD) in a state government run tertiary institute in south India was performed between June 2015 and December 2015. Only patients who completed 3 months of regular dialysis were included. The data was collected using a de-identified, self-administered patient survey after obtaining a formal written consent.

Results: The number of patients on HD was 157 and on PD was 69. The employment status before initiation of dialysis was: working (43% of 155) and 63.7% (44 out of 69) in HD and PD groups respectively. After initiation, loss of employment was observed in 44% (41 out of 93) in HD and 51.2% (26 out of 44) in PD group (p = 0.2604). Even though there was fall in absolute number of job holders in both the blue and white collar jobs, the proportion of job holders in the white collar jobs improved. On univariate analysis, the factors that are associated with the loss of employment were male sex, age between 50 and 60 years, number of comorbidities > 2, illiteracy and blue collar versus white collar job before the initiation of dialysis. The majority of patients had the scores above 80 on Karnofsky Performance Scale and the majority belonged upper and middle strata than lower strata on Modified Kuppuswamy’s socioeconomic status scale.

Conclusions: Our study shows that there was no difference between HD and PD in the loss of employment of our patients which is in contrast to the impression that the PD offers freedom from treatment schedules and possibility for out-of-work-hours dialysis, making it a suitable option for employed patients.

FR-PO1039

Factors Associated with Routine Decision Making Tools Increases Peritoneal Dialysis Choice and Take on in an International Setting
Belen Marron,
Janusz Ostrowski,
Delia Timofte,
Marietta Török,
Michael Roesch,
Claudia Martin,
Pawel Kochman,
Orosz Attilla,
Jose C. Divino-Filho,
Jörgen B.A. Hegbrant,
1 Diaverum Home Therapies, Medical Office, Munich, Germany; 2 Wloclawe Diaverum Clinic, Wloclawek, Poland; 3 Soma Diaverum Clinic, Bucharest, Romania; 4 Rokus Diaverum Clinic, Stettin, Poland; 5 Schlankreye Diaverum Clinic, Hamburg, Germany; 6 Barracas Diaverum Clinic, Buenos Aires, Argentina; 7 Bajczy Diaverum Clinic, Budapest, Hungary; 8 Karolinska Inst., Stockholm, Sweden; 9 Diaverum Medical Office, Lund, Sweden.

Background: Lack of patient choice or inability to offer high quality modality information programs remain as causes for low PD use.

Objectives: To analyze the impact of a structured modality information program with the use of decision making tools (DMTs) on type of modality choice and take on.

Methods: Observational, prospective and international registry. All patients under ESRD 4-5 and/or after an unplanned dialysis start (if non-informed before) were recruited to undergo a DMTs process for RRT choice. Process included: personal values evaluation, RRT information with different tools, deliberation support and patient’s modality election. Results: 1141 patient-aimed modality information between Aug. 2014-Dec. 2015 in 252 patients (mean age 63.2±14.1 years, 52% female, 75.8% Chinese and 24.2% diabetics) were enrolled during PD. Older patients (PALL:79.5±7.6 yrs vs PD:62.4±14.3 yrs vs HD:61.1±12.0 yrs) with a higher Charlson Comorbidity Index (PALL:9.35±1.80 vs PD:7.02±2.72 vs HD:7.07±2.46; p=0.0022), requiring ADL (PALL:47.1% vs PD&HD:11.5%; p=0.002) and mobility assistance (PALL:82.4% vs PD&HD:43.8%; p=0.006) were likely to accept PD&HD after PDA. For patients who eventually started dialysis, those who continued with the decision for PD were more likely not to have received interim HD (68.4% vs 42.2%; p=0.001), and had higher serum albumin (30.7±5.5 vs 28.6±6.0; p=0.0096). Factors which were traditionally thought to have a poorer choice of PD were not significantly different between the dialysis groups, including BMI, DM, DBA1c, prior abdominal surgery, APDKD, respiratory diseases, small housing size or having pets.

Conclusions: Engagement on the option of palliative treatment could be considered for older patients with poorer functional status. Exposure to prior hemodialysis is likely to waive the initial decision for PD. With improved PD technology and effective mitigation of social factors, traditional issues that were previously unattactive are no longer obstacles to PD.

FR-PO1040

Routine Use of Decision Making Tools Increases Peritoneal Dialysis Choice and Take on in an International Setting
Belen Marron,
Janusz Ostrowski,
Delia Timofte,
Marietta Török,
Michael Roesch,
Claudia Martin,
Pawel Kochman,
Orosz Attilla,
Jose C. Divino-Filho,
Jörgen B.A. Hegbrant,
1 Diaverum Home Therapies, Medical Office, Munich, Germany; 2 Wloclawe Diaverum Clinic, Wloclawek, Poland; 3 Soma Diaverum Clinic, Bucharest, Romania; 4 Rokus Diaverum Clinic, Stettin, Poland; 5 Schlankreye Diaverum Clinic, Hamburg, Germany; 6 Barracas Diaverum Clinic, Buenos Aires, Argentina; 7 Bajczy Diaverum Clinic, Budapest, Hungary; 8 Karolinska Inst., Stockholm, Sweden; 9 Diaverum Medical Office, Lund, Sweden.

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Conclusions: Use of DMTs at the time of RRT modality choice complies with patient empowerment. A remarkable increase in PD take-on occurred in our clinic network after DMTs process introduction. Therefore, modality information should always be delivered through a structured information process based on decision sharing.
Peritoneal Dialysis Annual Dropout in a Large International Setting
Belen Maranon,1 Gustavo Lorenzo Moretta,2 Michael Roesch,3 Janusz Ostrowski,4 Marietta Török,5 Daniel Eduardo Perez,6 Delia Timofte,7 Carlos Zuniga,8 Paul Strozuma,9 Elisabeth Fabriches,10 Jorgen B.A. Hegbrit,11 1Diaverum Home Therapies. Medical Office, Munich, Germany; 2Diaverum LA Medical Office, Buenos Aires, Argentina; 3Schlankrey Clinic, Hamburg, Germany; 4Wlokawlek Clinic, Wloclawek, Poland; 5Rokos Diaverum Clinic, Budapest, Hungary; 6SEINE Clinic, Montevideo, Uruguay; 7Sema Clinic, Bucharest, Romania; 8Colina Clinic, Concepción, Chile; 9Marseille Clinic, Marseille, France; 10Visby Medical Clinic, Visby, Sweden; 11Diaverum Medical Office, Lund, Sweden.

Background: Peritoneal dialysis (PD) growth is limited by a high annual drop out (DO) (40-75%) which is often not routinely measured.

Objectives: To analyze the introduction of a new tool based on the monitoring of accumulated annual PD DO and the underlying DO causes.

Methods: Observational, prospective registry in 6 European (EU) countries (FR, GE, HU, PL, RO, SWE) and 3 Latin American (LA) countries (AR, CH, UR). LA provided results as a one single region. During Jan 1-Dec 31 2015, all prevalent and incident PD patients were included in a monthly basis for DO due to: transplantation (TX), residual renal function (RRF) recovery, transfer to HD (due to peritonitis, exit site issues, catheter problems, ultrafiltration failure, low adequacy, burnout or others), transferred to other centers or death. Total DO, controllable DO (transfer to HD and to other centers) and uncontrollable DO (death, catheter withdrawal: 312 pt. Total DO, controllable DO varied among regions: 49% and 19% in EU vs. 42 and 18% in LA. TX accounted for 8% (higher in PL and lower in LA, GE and RO). RRF recovery 0.3%, transfer to other centers 4%, death 18% (lower in LA and higher in EU vs. 42 and 18% in LA). TX accounted for 8% (higher in PL and lower in LA, GE and RO).

Results: Among 270 pts, 214 received and 203 completed UPS-EP while 56 pts did not have access to the internet. Seven patients were excluded as they refused to give informed consent. About 190 patients receiving urgent start PD (30.4%). The survival rate at 3 months, 1 year for urgent and non-urgent start PD group were 95.2%, 83.3% vs. 97.4% and 90.7% respectively (P=0.025). And there is no significant difference of the technical survival rate and peritonitis frequency between urgent and non-urgent start PD patients. For urgent start PD patients, 25 patients (13.2%) received APD (30.4% women, 62.1±19.1 years old), and 48.0% of them were diabetic nephropathy. Both APD group and non-APD group had no significant difference of age, gender, Ki/V, CCr and nPCR at baseline. The median survival time of APD and non-APD group was similar (42m vs 49m, P=0.227). The survival rate and the technical survival rate at 3 months and 1 year of were also similar. The peritonitis frequency of APD and non-APD was 1 episode/82.71 months and 1 episode/81.18 months. After adjusted by gender and PD modality, age (1 year, HR=1.051, 95%CI 1.029-1.074, P=0.000) and diabetic nephropathy (P=0.002) independently predicted the mortality in urgent start PD patients. Our study showed a lower 1-year survival rate than non urgent start PD patients. However, there is no difference of the 3-month and 1-year survival and technical survival rate between APD and non-APD urgent start PD.

FR-PO1042
Offering Therapy Options in Unplanned Start (OPTIONS) for Patients Receiving Urgent Start Peritoneal Dialysis
Anna Machowska,1 Mark Dominik Alischer,2 Satyanarayana Reddy Vanga,3 Michael Koch,4 Michael Aarup,5 Abdul Rashid Tony Qureshi,6 Bengt Lindholm,7 Peter Rutherford.8 1Renal Medicine & Baxter Novum and Renal Medicine, CLINTEC, Karolinska Inst, Huddinge, Sweden; 2Robert-Bosch-Krankenhaus, Stuttgart, Germany; 3Univ Hospital of North Staffs, Stoke, United Kingdom; 4Nephrological Zentrum, Mettmann, Germany; 5Odense Univ Hospital, Odense, Denmark; 6Quintiles, Reading, United Kingdom.

Background: Patients (pts) with unplanned dialysis start (UPS) have worse clinical outcomes than non-UPS pts, and receive peritoneal dialysis (PD) less frequently. In the OPTIONS study an educational programme (UPS-EP) aiming at improving care of UPS patients and enabling informed choice of dialysis modality was implemented. We report impact of UPS-EP on modality choice and clinical outcomes in UPS pts.

Methods: This non-interventional, prospective, multi-centre, observational study included 270 UPS pts from 26 centres in 6 European countries (Austria, Germany, Denmark, France, United Kingdom and Sweden) presented acutely, or followed by nephrologist but required urgent start dialysis. Effects of UPS-EP on choice and final decision of dialysis and outcomes in 12 months follow up were analyzed.

Results: Among 270 pts, 214 received and 203 completed UPS-EP while 56 pts were older (p<0.01) and had higher Charlson comorbidity index (CCI; p=0.01) - did not receive UPS-EP. Among 177 pts who chose dialysis modality, 103 (58%) chose PD (but only 81% of them received PD) and 74 (42%) chose HD (95% received HD). Logistic regression analysis showed that diabetes, OR=2.62 (CI, 1.38 - 4.97) and receiving UPS-EP, OR=8.30 (CI, 1.63 – 8.89) predicted receipt of PD. Patients choosing PD had higher CCI (p=0.01), higher prevalence of congestive heart failure (p<0.01) and myocardial infarction (p=0.02), and were more likely in-patients (p<0.02) or referred from primary care (p=0.02). One year survival did not differ significantly between PD and HD pts. Peritonitis and septicaemia rates were better than international guideline standards.

Conclusions: UPS-EP predicted patient use of PD but 19% of those choosing PD after UPS-EP did not receive the modality they preferred. Patient survival in patients choosing and/or receiving PD was similar to HD despite age and comorbidity disadvantages of the PD groups.

Shared Medical Appointment for Peritoneal Dialysis Patients

Shared Medical Appointment for Peritoneal Dialysis Patients

Results: The SMA comprised of 4-5 patients, a dietitian, a social worker, patient’s primary nurse and a nephrologist. We spend an hour discussing their laboratory data, dietary changes and social issues. We collected laboratory data on patients who take part in the SMAs (n=9) and compared the quality metrics of patients to the ones who do not (n=32).

Results: Majority of patients in both groups were Caucasian males. There were no significant differences in terms of outcomes between the two groups.

Results:

Results: Our results emphasize that despite requiring less provider time, patients attending SMAs have similar medical outcomes as patients who are seen individually. In our program, SMAs for PD patients were started in an effort to expand our home dialysis population despite provider time constraints. Since giving patients the option of attending SMAs, our program census has increased from 35 to 50, which accounts for 19% of our total dialysis population—a number much higher than the national average. Moreover, these meetings provide a support system for home dialysis patients as they can discuss their struggles with others who are undergoing similar experiences. In conclusion, SMAs provide our total dialysis population—a number much higher than the national average. Moreover, our home program census has increased from 35 to 50, which accounts for 19% of our total dialysis population—a number much higher than the national average. Moreover, these meetings provide a support system for home dialysis patients as they can discuss their struggles with others who are undergoing similar experiences. In conclusion, SMAs provide an efficient system for expanding care to PD patients and are an attractive alternative to the conventional clinic visits for PD patients.

Pilot Use of Assisted Peritoneal Dialysis for Temporary Interruptions in Self-Care Peritoneal Dialysis

Pilot Use of Assisted Peritoneal Dialysis for Temporary Interruptions in Self-Care Peritoneal Dialysis

Results: The 53 PDA patients had an 88% (95% CI: 78-97%) 1-year death and transplant centered technique survival on PD, which was similar to the general CCPD cohort (84% [95% CI: 81-87%]) and PDA eligible cohort (86% [95% CI: 77-96%]). PDA cohort had lower peritonitis rates (0.18 episodes per patient-year vs 0.22 and 0.36), but higher hospitalization (55% vs. 34% and 35%). Qualitative feedback from patients and PD clinicians were overwhelmingly positive for PDA. The cost of PDA was approx. $15,000/year in addition to existing PD costs. PD with PDA costs $29,000/year less than HD or $23,500 less than long term care.

Conclusions: PDA was an effective way to support independent CCPD patients who were not eligible at risk of PD (PD eligible) in addition to the general CCPD population comparator.

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Peritoneal Dialysis Dropout - Experience from an Integrated Healthcare System with High PD Prevalence

Leonid Pravcovich, Chitra R. Reddy, Neelam M. Bhalla, Joanna Mroz, Maribeth Ann Alcaraz, Sijie Zheng

Nephrology, The Permanente Medical Group, CA.

**Background**: Peritoneal Dialysis (PD) is an excellent option for renal replacement therapy (RRT). Kaiser Permanente Northern California (KPNC) is an integrated health care system with approximately 4 million members and 4700 patients on dialysis. KPNC has a higher PD prevalence (24%) compared with the national average (10%). We retrospectively analyzed the reasons patients discontinue PD.

**Methods**: Retrospective analysis of all patients on PD from 10/1/2013 to 12/31/2014 was conducted. Patients were followed through 3/31/2015. Patients who stopped PD for at least 60 days were identified and analyzed further. We excluded patients who lost KP membership while active on PD and included patients who stopped PD due to a kidney / SPK transplant.

**Results**: 562 PD patients were identified in the study period. Death (29%) and Transplantation (23%) were the two main reasons for discontinuing PD. Other reasons included: 1. Psychosocial (12%); 2. Peritonitis (11%); 3. Non-PD related medical issues (8%); 4. Peritoneal membrane failure (7%); 5. Mechanical complications (5%); 6. Medical – Dialysis related (3%); 7. Peritoneal Catheter Leaks (2%); 8. Other (<1%). The average time on PD was 2.01 years (Median 1.36 years, with a range from 0.02 to 17.59 years).

**Conclusions**: Besides death and transplantation, psychosocial issues and peritonitis were the top potentially preventable reasons for patients to discontinue PD in our study. Further analysis is required to identify primary cause of death; strategies to prevent peritonitis, and steps to provide psychosocial support for patients to remain on PD.

Peritoneal Dialysis Dropout - Experience from an Integrated Healthcare System with High PD Prevalence

Leonid Pravcovich, Chitra R. Reddy, Neelam M. Bhalla, Joanna Mroz, Maribeth Ann Alcaraz, Sijie Zheng

Nephrology, The Permanente Medical Group, CA.

**Background**: Peritoneal Dialysis (PD) is an excellent option for renal replacement therapy (RRT). Kaiser Permanente Northern California (KPNC) is an integrated health care system with approximately 4 million members and 4700 patients on dialysis. KPNC has a higher PD prevalence (24%) compared with the national average (10%). We retrospectively analyzed the reasons patients discontinue PD.

**Methods**: Retrospective analysis of all patients on PD from 10/1/2013 to 12/31/2014 was conducted. Patients were followed through 3/31/2015. Patients who stopped PD for at least 60 days were identified and analyzed further. We excluded patients who lost KP membership while active on PD and included patients who stopped PD due to a kidney / SPK transplant.

**Results**: 562 PD patients were identified in the study period. Death (29%) and Transplantation (23%) were the two main reasons for discontinuing PD. Other reasons included: 1. Psychosocial (12%); 2. Peritonitis (11%); 3. Non-PD related medical issues (8%); 4. Peritoneal membrane failure (7%); 5. Mechanical complications (5%); 6. Medical – Dialysis related (3%); 7. Peritoneal Catheter Leaks (2%); 8. Other (<1%). The average time on PD was 2.01 years (Median 1.36 years, with a range from 0.02 to 17.59 years).

**Conclusions**: Besides death and transplantation, psychosocial issues and peritonitis were the top potentially preventable reasons for patients to discontinue PD in our study. Further analysis is required to identify primary cause of death; strategies to prevent peritonitis, and steps to provide psychosocial support for patients to remain on PD.
FR-PO1054

Dialysis Modality Change and Complications in Patients following CABG or Laparoscopic Surgery

Lu Y. Huber, 1 Matt Day, 1 Sandra Tadrós, 1 Jennifer L. Waller, 1 Mufaddal F. Kheda, 2 Jake Everett Turrentine, 1 Rhonda E. Colombo, 1, 2 Stanley N. Nahman, 1, 2 Medicine, Augusta Univ, Augusta, GA; 1, 2 Medicine, Charlie Norwood VA Medical Center, Augusta, GA; 1 Biostatistics and Epidemiology, Augusta Univ, Augusta, GA; 2 Dermatology, Augusta Univ, Augusta, GA.

Background: There is an increasing effort to avoid interruption of PD when PD patients undergo surgery. We queried the USRDS to investigate patterns of dialysis modality change and post-op complications in PD patients undergoing CABG and laparoscopic surgeries.

Methods: Incident PD patients in 2004-2011 who underwent CABG or laparoscopic surgeries were queried. Groups with no interruption of PD (group P), planned temporary (PHP) or permanent switch to HD (PHH), urgent temporary (UHP) or permanent switch (UHH) were identified. Demographics and comorbidities were assessed. The relative risk (RR) for complications within 3 months post-op was estimated.

Results: 8743 incident PD patients with CABG (1445), laparoscopic (7298) or both (332) were evaluated. 57% female, 19% black. Age 55.18 years. Average time on PD 185.19mos. Post-op outcomes Table 1. Risk factors for complications in Table 2.

Conclusions: Continuing PD during CABG or laparoscopic surgery appears safe. Need for urgent HD (UHH) is uncommon but associated with a higher risk of post-op complications. Future studies may focus on risk stratification to identify these patients prior to surgery.

FR-PO1055

Longer Peritoneal Dialysis Is Associated with Better Survival in Peritoneal Dialysis Patients

Hironori Nakamura, Yasushi Makino, Anayama Mariko, Masaki Nagasawa. Dept of Nephrology, Shiono in General Hospital, Nagano, Japan.

Background: The Japanese Society for Dialysis Therapy reported 5- and 10-year survival rates of 60.5% and 36.2% for hemodialysis (HD) patients. However, the survival rate of peritoneal dialysis (PD) patients after the therapy is switched to HD remains unknown in Japan and worldwide.

Methods: One hundred and thirty-five patients who underwent PD were retrospectively analyzed. We investigated the long-term survival rate of patients, including those who switched from PD to HD, and evaluated the correlation between survival time and clinical factors at PD initiation. Death was considered a final event, and patients who were transferred to another hospital, who underwent transplantation, or the end of the study period (April 2016) were censored. Age, gender, body mass index (BMI), diabetes, serum albumin (Alb), creatinine (Cr), PD duration, diabetes to plasma creatinine ratio (D/PCR), peritoneal protein excretion (PPE) amount, and urine volume were included and analyzed by the Cox proportional hazard model and Kaplan–Meier tests.

Results: 1) The following patient characteristics were observed: mean age, 63.8 ± 15.1 years; BMI, 23.8 ± 4.6 kg/m²; diabetes, 35.2%; Alb, 3.3 ± 0.5 g/dL; Cr, 8.6 ± 4.1 mg/dL; D/PCR, 0.67 ± 0.16; urine volume, 716 ± 522 mL; and PPE, 5644 ± 2723 mg. Mean PD duration was 44.8 ± 35.8 months, and survival was 66.5 ± 57.8 months. 2) Univariate analysis revealed significant effects of age, PD duration, Alb, PPE, and urine volume on survival. Cox proportional hazard analysis revealed that survival was significantly affected by age [hazard ratio (HR), 1.07; 95% confidence interval (95% CI), 1.03–1.11; p < 0.001] and PD duration (HR, 0.96; 95% CI, 0.94–0.98; p < 0.001). 3) Survival analysis between the two groups revealed an estimated survival of 47.2 ± 7.0 months in the short-duration PD group and 141.7 ± 10.3 months in the long-duration PD group (log rank, p < 0.001). Cumulative patient survival rates were: 58.3% (5 years) and 39.3% (10 years).

Conclusions: Longer PD duration was significantly associated with better survival of PD patients. The long-term survival of PD patients was similar to that of HD patients, although these were non-comparable situations.

FR-PO1056

Incidence, Hospital Charges, Length of Stay, and Mortality for Peritonitis in Children Undergoing Chronic Peritoneal Dialysis in the U.S.A.

Neha Dhingra, Brian Becknell, Rose M. Ayoub. Pediatric Nephrology, Nationwide Childrens Hospital, Columbus, OH.

Background: Peritoneal dialysis (PD) is the most common modality utilized for children with End Stage Renal Disease (ESRD) worldwide. Peritoneal dialysis catheter-related infections cause significant morbidity and mortality in children. The frequency of peritonitis in children is increased compared to adults. The Pediatric Health Information System (PHIS) is a comprehensive pediatric database which includes clinical, administrative, and financial details for more than six million patients in participating US children's hospitals.

Methods: Data was collected for patients hospitalized with the principal diagnosis of PD catheter-related infection and ESRD (ICD-9 codes 996.68 and 585.6) from 2007 to 2015 using the PHIS database.

Results: From 2007 to 2015, the total number of hospitalizations with the diagnosis of PD catheter-related infections was 944, of which 62% were male. The total number of patients age 0-18 years was 881, with 30% of patients in the 1-4 year age group. Individuals <1 year of age accounted for 10% of total hospitalizations, but had the longest mean length of stay (60.9 days), highest mean charges ($317,093), and the highest aggregate charges (over $28 million dollars). Furthermore, in the patients in the < 1 year of age group, there were more reported deaths. More than 50% of patient hospitalizations occurred in the southern region of the United States.

Conclusions: PD catheter-related infections remain a significant cause of morbidity and mortality in children with ESRD. Patients <1 year of age account for only 10% of total discharges but have longer LOS, mean charges and aggregate charges as well as higher number of deaths. The PHIS database can be a useful tool to follow trends specifically related to mortality and hospital charges in pediatric-related disease, in which there are often smaller number of patients.

FR-PO1057

Death Risks over Time from 2001 to 2015 in Incident Peritoneal Dialysis Patients: A Retrospective Cohort Study with 15-Year Follow-Up

Byeongwoo Yeon, Sungwook Kim, 1 Yeong Hoon Kim, 1 Miyeon Kim, 1 Hyun Woo Kim, 1 Tae Hee Kim. 1 Internal Medicine, Inje Univ, Busan, Republic of Korea; 2 Internal Medicine, Jeju National Univ, Jeju, Republic of Korea.

Background: Even though previous study has shown that there was no difference for survival between hemodialysis and peritoneal dialysis (PD) since 2002, the incident rate to initiate PD in patients with end-stage renal disease has decreased in developed countries. Hence, we investigated the change in trends and death risk in incident PD patients followed over up to 15 years.

Methods: In a 15-year (1/2001-12/2015) cohort of 592 incident peritoneal dialysis patients in our dialysis center, we examined death risk across the year of PD initiation from 2001 to 2014 using Cox proportional hazard models. To account for the competing
risk of transplantation across the year of PD initiation, we conducted the competing risk regression to estimate sub-hazard ratios of death risk. Models were adjusted for age, female, and diabetes.

Results: Patients were 50±13 years old, 45% female, and 50% diabetic. A total of 178 (30%) all-deaths were reported. 133 (23%) among 592 patients received kidney transplantation. Median follow up period was 2.8 years (IQR 1.4, 4.8 years) Compared with the patients who started PD in 2001, death risk tends to decrease with each subsequent year of PD initiation since 2010, but there was no significant difference across the year of PD initiation.

These trends were very similar in competing risk regression as well.

Conclusions: The survival rates in PD patients did not change until 2009 and then tended to improve since 2010. However, it has not shown significant association with the year of PD initiation over up to 15-year follow-up period. Further studies to understand the conditions influencing these death risks are needed.

FR-PO1058
Body Mass Index Trends in Patients Undergoing Peritoneal Dialysis for Decades and Their Effect on Patient Survival: Analysis of Data from an End-Stage Renal Disease Registry (1985-2014) in Korea
Seon Deok Hwang,1 Moon Jae Kim,2 Seoung Woo Lee.3 Inha Univ College of Medicine; 3Inha Univ College of Medicine.

Background: Significant increases in the prevalence of obesity have been observed among patients with incident end-stage renal disease (ESRD). However, the changes in body mass index (BMI) status in prevalent Korean patients undergoing peritoneal dialysis (PD) over the recent decades and their impact on patient survival remain unknown.

Methods: Among 80,674 patients from the ESRD registry of the Korean Society of Nephrology since 1985, 6075 patients who were undergoing PD were included in the study. According to BMI, registered year, and serum albumin (SA) concentration the patients were classified as follows: underweight (UW; <18 kg/m²), normal weight (NW; 18-22.9), overweight (OW; 23-24.9), and obese (OB; ≥25), low (<2.5 g/dL) and high (>2.5), respectively. The patients’ BMIs were compared with those of 4986 subjects in the general population who participated in the sixth Korea National Health and Nutrition Examination Survey (KNHANES), 2014.

Results: The mortality risks of the OW and OB groups were respectively 1.149 and 1.188 times higher than that of the NL group after adjustments. When the patients in the NL and high SA groups were considered as reference groups, the mortality risks of the patients in the UW + low SA group and UW + high SA groups were respectively 2.73 and 1.72 times higher than that of the reference groups, even after adjustment for age, sex, diabetes, hemoglobin level, and blood pressure. We found that the mortality risk of the patients with OB and high albumin levels was 1.165 times higher than that of the reference patients. When the analysis was restricted to patients who were undergoing PD for 1 year, the mortality risks were similar to those of all the patient groups.

Conclusions: In the Korean PD patients, no significant increase in the number of UW patients was observed over the recent decades, but the proportion of OB patients tended to increase, similar to that of the general population. Both the UW and OB patients showed increased mortality risk.

FR-PO1059
Relationship between Future BMI and Baseline Nutritional Markers in Incident Peritoneal Dialysis Patients
Emma H. Elphick, Mark Lambic, Simon J. Davies. Keele Univ.

Background: A higher body mass index (BMI) is known to relate to better survival in haemodialysis, but this remains uncertain in peritoneal dialysis (PD). BMI is frequently used as an epidemiological marker of nutritional status in the PD population however it is not known what biological determinants are involved in this assessment.

Methods: We used incident PD patients from the Global Fluid Study to test for associations between nutritional markers with baseline BMI and change in BMI after 2 years on PD. These included plasma and dialysate interleukin 6 (IL6), serum albumin, creatinine generation rate, urine volume, urine urea, ultrafiltration, dialysate glucose exposure, icodextrin use, age, gender, ethnicity and comorbidity score. A multivariate linear regression analysis was used.

Results: 297 patients had BMI measurements taken before 6 months and after 2 years on PD. Of these 214 were used. At baseline there was a significant positive association between BMI and creatinine generation rate (coefficient 0.17% CI 0.6 1.3 p = 0.006), glucose exposure (coefficient 0.02% CI 0.007> -0.030>0.011), urine urea (Wald 3.5 p = 0.03) and urine volume (coefficient 0.01% CI 0.0002-0.002 >0.015). There was a negative association with male gender (coefficient -1.2% CI -2.5 to -0.02>0.045) and Korean ethnicity (vs Caucasian) (coefficient -2.5% CI -4.0 to -1.0 >0.001). Change in BMI over 2 years had a significant positive association with age (coefficient 0.03% CI 0.006 - 0.05 p = 0.012), comorbidity score (Wald 2.49 p = 0.044), Korean ethnicity (coefficient 1.0% CI 0.3 - 1.8 p = 0.009) and a negative association with creatinine generation rate (coefficient -9.8% CI 17 to -2.4 p = 0.009).

Conclusions: An increase in muscle mass is associated with an increase in BMI at baseline but a larger reduction in BMI over time. Korean centres had a lower initial BMI but less of a reduction in BMI over time. Fluid balance is positively associated with BMI at baseline but did not influence change in BMI. Albumin and inflammation did not have a significant effect.

FR-PO1060
The Association between Body Mass Index and Mortality in Peritoneal Dialysis Patients
Jin Ho Hwang,1 Chee Rim Kim,2 Geun Joo Choi,2 Hyun Kang.2 Internal Medicine, Chung-Ang Univ Hospital, Seoul, Republic of Korea; 1Anesthesiology and Pain Medicine, Chung-Ang Univ Hospital, Seoul, Republic of Korea.

Background: Unlike the general population, a higher body mass index (BMI) was consistently found to be a strong predictor of decreased mortality in patients with end-stage renal disease who receive maintenance hemodialysis (HD). This phenomenon has been referred to as the “Obesity paradox” or “reverse epidemiology”. Similar tendency has been observed in several studies with peritoneal dialysis (PD) patients, but the studies have reported conflicting results. We conducted this study to evaluate the association between BMI and all-cause mortality in PD patients.

Methods: A systematic search was conducted for published studies in Medline, EMBASE, and the Cochrane library databases from 1970 to April 2015. We identified the studies evaluating the impact of BMI on mortality among PD patients. Data of hazard ratios and 95% confidence intervals (CIs) were obtained for respective BMI groups provided by each study. We performed meta-regression analysis using unrestricted maximum likelihood model.

Results: The Medline, EMBASE, and the Cochrane library search provided a total of 3,047 articles. After screening of all titles, 513 abstracts were selected. Finally, 9 cohort studies with 33,090 patients were included in the final analysis. Log hazard ratio for all-cause mortality showed a trend negatively associated with increasing four square root of BMI (slope coefficient: -0.1976, 95% CI -0.4110 to 0.0158, p = 0.0695).

Conclusions: In PD patients, BMI was inversely associated with mortality as in HD patients. Other outcomes such as cardiovascular death, peritonitis incidence, and technical failure will be additionally evaluated.

FR-PO1061
Impact of Metabolic Syndrome in Incipient Peritoneal Dialysis Patients
Silvia Ros. Nephrology, Regional Malaga Hospital, Malaga, Spain.

Background: Metabolic syndrome (MS) is a clustering of risk factors among which are included diabetes mellitus (DM) and cardiovascular disease (CVD). It is associated with a high morbidity and mortality in general population. Its prognostic implication among patients undergoing peritoneal dialysis (PD) is not clearly defined. We studied MS and its individual components effect on both patient and technique survival.

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

615A

Background: A single dosage of ferric carboxymaltose (FCM) has proven effective to control iron-deficiency anemia in hemodialysis patients as well as in situations of end-stage renal disease. Its application in patients on peritoneal dialysis (PD) is less known. We show the observation of FCM administration in PD patients.

Methods: Patients on PD treatment were included in this study. The criteria for the administration of the iv iron therapy were: hemoglobin <12 g/dL, serum ferritin levels<200, TSI<30, oral iron therapy and/or the erythropoietic stimulating factors (ESF) treatment of patients with a previous reaction to other iv iron formulations were excluded. The dosage was 1,000 mg FCM, and not to exceed 15 mg of iron per Kg. of body weight.

Results: Sixteen PD patients were administered the iv FCM. At the time of the study, two had received a kidney transplant only 6 months prior and three still have not followed up since the 6 month check-up. Finally eighteen patients have completed at least 6 months of the treatment after the administration of FCM. The average age was 53±16 years. The etiology of kidney disease was glomerulonephritides in 6 cases, 5 diabetes cases, 2 interstitial nephritis, unknown in 2 cases and 1 patient, polycystosis. The results are reflected in the table. Five patients received oral iron therapy at the beginning, and all but one received ESF.

Conclusions: The FCM is an easy alternative to manage and has few side effects. It also maintains recommended levels of ferritin up to at least six months after administration. The requirements of ESF and oral dosage of iron could be reduced.

FR-PO1064

Serum Phosphorus and Phosphate Binder Pills per Day in Peritoneal Dialysis Patients Switched to Sucroferric Oxycitrate (SO) as Part of Routine Care Vidhya Parameswaran, Linda H. FicocIELLO, Carey R. VanZandt, Norma J. Olshun, Claudia Munnion, Franklin W. Maddox, Robert J. Kossman. Fresenius Medical Care North America, Waltham, MA.

Background: The majority of dialysis patients require phosphate binders (PB) to control serum phosphorus (sP) levels. However, poor adherence to PB prescription is common and may be related to high pill burden. This retrospective analysis assesses changes in sP control and PB pills/day in peritoneal dialysis (PD) patients who switched to sucralferric oxycitrate (SO) as part of routine clinical care.

Methods: PD patients (n=92) prescribed SO through a renal pharmacy service for 6 months were analyzed. Patients were required to be on PB monotherapy. Changes in percent of patients achieving sP ≤ 5.5 mg/dl and PB pills/day were compared during baseline (BL; 3 months prior to SO switch), F1 (1-3 months of SO) and F2 (4-6 months of SO).

Results: At BL, 84.8% of patients had hyperphosphatemia (sP > 5.5 mg/dl), and were being prescribed, on average, 9.9 PB pills/day. After SO prescription, a 58% and 54% reduction (p<0.0001) in pill burden was observed at F1 (4.2 pills/day) and F2 (4.6 pills/day), respectively. Significant improvement (all comparisons, p<0.001) in percent of patients achieving sP ≤ 5.5 mg/dl was observed comparing BL to F1 (153% increase) and BL to F2 (149% increase). Additionally, percent of patients with sP between 5.6 – 7 mg/dl decreased by 33% and 40% between BL and F1 (60% to 40.7%, p<0.002) and BL and F2 (60.9% to 36.5%, p<0.0001).

Conclusions: In a cohort of PD patients prescribed SO for 4-6 months, >50% fewer PB pills/day (mean decrease of >5 pills/day) were prescribed and patients with sP ≤ 5.5 mg/dl more than doubled.

FR-PO1065

Impact of Anemia on Loss of Residual Kidney Function in Patients on Peritoneal Dialysis Kazuhiro Tsuruya, Hiakso Yoshida, Takanari Kitazono. 1Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ; 2Fukuoka, Japan.

Background: Anemia has been considered to be important for the reduction of mortality in end-stage kidney disease patients on peritoneal dialysis (PD) as well as those on hemodialysis. Recent studies have demonstrated the importance of RKF in the survival of chronic dialysis patients, and also stressed the importance of RKF in anemia management. However, it remains elucidated whether anemia impacts on RKF.

Methods: In the present study, we investigated the effect of anemia on loss of RKF in 106 PD patients treated at our hospital. The primary outcome was loss of RKF defined as urine output <500 ml/dL. The subjects were divided into four groups based on their hemoglobin (Hb) levels: <9, 9-9.9, 10-10.9, and ≥11 g/dL. The time-dependent Cox hazard model was used to determine the impact of Hb levels on loss of RKF.

Results: The analysis of the time between 42 (±10) months, 31 subjects developed RKF loss. The univariable and multivariable-adjusted incidence rate of RKF loss increased significantly with lower Hb levels (P for trend = 0.03). Compared with those with Hb of ≥11.0 g/dL, the multivariable-adjusted hazard ratios for the development of RKF loss were 9.55 (95% confidence intervals, 1.05–9.40), 1.71 (1.03–5.55), and 4.65 (1.47–15.63) for subjects with Hb of 10-11 g/dL, 9–10 g/dL, and <9 g/dL, respectively, adjusted for age, gender, prior dialysis therapy, duration of diabetic nephropathy, and renal potassium-vitamin B12, serum albumin, logarithmic serum brain natriuretic peptide, PAD, and use of icodextrin solution, 2.5% glucose solution, dual mode PD, iron supplements, and receptor antagonists.

Conclusions: This result suggests that severe anemia as indicated by an Hb level <9 g/dL is a significant risk factor for loss of RKF, thus indicating the importance of anemia management. To the best of our knowledge, no reports have described the effect of anemia on RKF, which makes the findings of the present study particularly noteworthy.
Peritoneal Dialysis in Orthotopic Liver Transplantation Recipients: Chronic Cardiorenal Syndrome Predictors of Outcome in Patients Commenced on Peritoneal Dialysis for FR-PO1067

Pedro Peso, 2

Canada; 2Div of Nephrology, Univ de Sao Paulo, Sao Paulo, Brazil.

with placebo are needed to confirm the effect of paricalcitol on PPL.

p=0.021) was related with PPL, adjusted for diabetes, PD modality, RCP, D/P creatinine (6.35±2.28 vs. 5.30±1.85 g/24h, p=0.026) and lower transport status (6.43±2.11 g/24h with higher transport status (D/P creatinine>0.68) had higher PPL than patients in APD found higher PPL in G2 (6.34±2.07 vs. 5.01±1.87 g/24h, p=0.003). Patients in CAPD and

Vitamin D Receptor on the peritoneal membrane. is known about the effect of paricalcitol on PPL in PD, namely after the identification of
dysfunction and an independent predictor for mortality in Peritoneal Dialysis (PD). Little

patients undertaking PD. Peritonitis and mortality rates were no different from other solid organ transplant recipients or even from the general PD population. The hepatic graft was never threatened, even during peritonitis. Therefore, these patients should not be denied the option for peritoneal dialysis.

Conclusions: There appears to be no specific concern related to liver transplant patients undertaking PD. Peritonitis and mortality rates were no different from other solid organ transplant recipients or even from the general PD population. The hepatic graft was never threatened, even during peritonitis. Therefore, these patients should not be denied the option for peritoneal dialysis.

Peritoneal Dialysis for Patients with Refractory Heart Failure and Chronic Kidney Disease Naegeswara Pamidi, 1 Aruna Mangipudi, 1 Hari Krishna Reddy Mogili, 1 Anil Kumar Cheni Venkata, 1 Boju Sangeetha Lakshmi, 1 R. Ram, 1 V. Siva Kumar, 1 Abhilash Koratala. 2 'Sri Venkateswara Inst of Medical Sciences, India; 'Univ of Florida; 'Care Hospitals, Hyderabad, India.

Background: Heart failure (HF) is a major public health problem in India and the proportion of patients presenting with both HF and chronic kidney disease (CKD) is large and steadily increasing. Currently available therapies for decongestion mainly rely on diuretics which have their shortcomings. Peritoneal dialysis (PD) is a relatively simple choice for chronic, gentle fluid removal, and appears to be an useful option for the management of patients with HF with difficult to manage volume status. Our objective is to study the impact of PD on CKD patients with refractory HF for which, there is limited data in Indian patients.

Methods: In this 3-year prospective study conducted at a tertiary health center in South India, we initiated PD in patients with refractory HF (NYHA class IV) with varying degrees of CKD. We excluded patients with end stage renal disease. We recorded the pertinent data before and after initiation of PD.

Results: During the study period, we treated 7 patients with HF & CKD with PD. Mean age of the patients was 56.8 years and 6 out of 7 were males. The mean duration of follow up was 11.4 ± 9.8 months. Results are as follows:

- The asterisk (*) symbol indicates significant P value. 2 episodes of non-refractory peritonitis were observed.

Conclusions: We conclude that PD is a beneficial treatment strategy for optimizing fluid status in patients with refractory HF with CKD. It improves laboratory parameters including ejection fraction, diuretic resistance and decreases the hospital stay of patients. Larger controlled trials are needed to explore the potential impact of PD on the mortality of patients with HF.

Peritoneal Dialysis in Adult Polycystic Kidney Disease Ying Ma, Haiyun Wang, Zijuan Zhou, Bingyan Liu, Xuemei Li, Limeng Chen. Nephrology Dept, Peking Union Medical College Hospital, Beijing, China.

Background: Adult Polycystic kidney disease (APKD) is the most common hereditary cause of renal failure. PKD renal failure has been traditionally considered a relative contraindication for peritoneal dialysis (PD) because of overexposing to technique failure and peritonitis. This study was to compare the outcomes and dialysis efficacy in PKD renal failure patients treated with PD, in comparison with hemodialysis (HD) and non-PKD subjects.

Methods: From1993 to 2015, total 47 ESRD patients with PKD in Peking Union Medical College Hospital were recruited. Dialysis adequacy, PD-related complications, PD-technique failure, clinical outcomes and survival rate were compared among patients with PKD-HD group (n=33), PKD-PD group (n=14) and non-PKD-PD group (n=43), random sampling from 622 cases PD patients).

Results: The average age of PKD-PD patients was 56.1±14.9 years old, of which 57.1% were women. One patients received APD treatment and others were CAPD. When compared with PKD-HD group, PKD-PD group and non-PKD-PD group, the proportion of patients with both HF and chronic kidney disease (CKD) was significantly different (p<0.05). There were no significant difference of the peritonitis rate and technical survival rate between the PKD-PD group and non-PKD-PD group. The survival rate at 1 year, 3 years, and 5 years for PKD-PD group was similar to non-PKD-PD group and PKD-HD group respectively. Three PKD-PD patients convert to HD because of peritonitis and 3 received kidney transplantation. Multivariate Cox regression analysis showed that neither PKD nor PD independently predicted the mortality.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: PD could be an option for ESRD patients with APKD.
Funding: Government Support - Non-U.S.

FR-PO1071
A Multicenter, Randomized, Controlled Trial Comparing Cefepime Monotherapy versus Combination of Cefazolin plus Ceftazidime for Empirical Treatment of CAPD-Associated Peritonitis
Thidarat Kitrunghaphirom,1 Piyarat Chueungsaman,2 Guttiga Halue,3 Monchai Siribamrungwong,4 Sarapon Matayat,5 Kamronat Chongthanhakorn,6 Ussance Poonvivathachat,7 Chanchana Boonyakrai,8 Wanida Somboonsilp,9 Piset Katavetin,1 Talergsak Kanjanabuch,1,7 Chalalongkorn Univ, Bangkok, Thailand; 2Banphao Hospital, Bangkok, Thailand; 3Phayao Hospital, Phayao, Thailand; 4Lerdsin Hospital, Bangkok, Thailand; 5Buddhasathorn Hospital, Chachoengsao, Thailand; 6Charoenkrung Pracharut Hospital, Bangkok, Thailand; 7Nakhonpathom Hospital, Nakhonpathom, Thailand; 8ChaoPhraya Yommarat Hospital, Suphanburi, Thailand.

Background: To avoid laboring and contamination risk of combination empiric antibiotics for empirical treatment of continuous ambulatory peritoneal dialysis (CAPD)-associated peritonitis, single broad-spectrum antibiotic should be proposed instead.

Methods: In a multicenter, open-label, noninferiority trial, we randomly assigned patients who diagnosed CAPD-associated peritonitis to receive intraperitoneal cefazolin 1 g loading then 250 mg all exchanges (dose increased by 25% in patients with residual renal function) or combination of cefazolin and ceftazidime with the same regimen for 14 to 21 days. Patients were followed for 28 days after treatment completion. A primary outcome was primary response (at day 10) rate, with a noninferiority limit of 10 percentage points.

Results: 146 patients were randomized (72 in the monotherapy group and 74 in combination group). Patient characteristics of both groups were comparable. Cefepime monotherapy was noninferior to cefazolin plus ceftazidime as the primary response rate was 81.9% in monotherapy group and 81.1% in combination group (difference points = 0.8, 95% confidence interval (CI) -9.7 – 21.4). Initial response (at day 5) and end treatment response rates were 66.67% and 87.5% in monotherapy group versus 60.81% and 89.2% in combination groups ([difference points = 5.86, 95% CI: -9.7 – 21.4], [difference points = -1.7, 95% CI: -12.1 – 8.7]), respectively. No serious adverse event of cefepime were reported. Cefepime monotherapy was primary response (at day 10) rate, with a noninferiority limit of 10 percentage points. Further research is needed to delineate its role in the success/failure of long term PD.


FR-PO1072
Identifying Peritoneal Fluid Microbiome in Patients Receiving Maintenance Peritoneal Dialysis
Escho Georges, Holly J. Kramer, Vinod K. Bansal, Julia Schneider, Michael Zilliox, Kathiva Vellangi, Dept of Nephrology and Hypertension, Loyola Univ Medical Center, Maywood, IL.

Background: Peritoneal fluid is considered to be sterile in patients receiving peritoneal dialysis (PD) in the absence of peritonitis. No data exists on the microbiome of peritoneal fluid in stable PD patients. The aim of this single site pilot study is to identify peritoneal fluid microbiome characteristics in PD patients without clinical peritonitis.

Methods: Patients who are 18 years and older, receiving maintenance PD with no symptoms of peritonitis were included. We collected 10 cc of PD output from each patient participant using routine sterile techniques and 16S rRNA gene sequencing was used to identify bacteria not routinely cultivated by clinical microbiology laboratories. The bacterial types for each specimen were identified.

Results: Of the 25 patients receiving PD at our site, 20 were included in the study. Baseline characteristics are shown in table 1.

Table 1: Baseline Characteristics of Study Population (n=20)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years</td>
<td>57.5 years</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>1:1.2 (9:11)</td>
</tr>
<tr>
<td>Race</td>
<td>AA: 35% (7) Hispanic: 25% (5) Others: 40% (8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45% (9)</td>
</tr>
<tr>
<td>History of peritonitis (over last year)</td>
<td>15% (3)</td>
</tr>
<tr>
<td>History of abdominal surgery</td>
<td>85% (17)</td>
</tr>
<tr>
<td>Type of transporter</td>
<td>High Average: 55% (11) Low Average: 20% (4) High: 15% (3) Low: 0% (0) Undefined: 10% (2)</td>
</tr>
<tr>
<td>Native urine output</td>
<td>45% (9)</td>
</tr>
<tr>
<td>Mean dialysis vintage time in years</td>
<td>2.65 years</td>
</tr>
</tbody>
</table>

Two patients tested positive for bacteria above the cut off threshold (~ 2000 reads).

Both patients with positive reads are females with no history of peritonitis and are high average transporters.

Conclusions: Peritoneal microbiome may not be sterile in some PD patients without clinical peritonitis. Further research is needed to delineate its role in the success/failure of long term PD.

FR-PO1073
Impact of Hypokalemia on Peritonitis in Peritoneal Dialysis Patients: A Systematic Review
Kentarou Nakai,1,2 Kei Saitou,1,3 Shinich Nishi,1,3 ‘Div of Nephrology and Kidney Center, Kobe Univ Graduate School of Medicine, Kobe, Japan; 2Dept of Nephrology and Kidney Center, Kakogawa East City Hospital, Kakogawa, Japan.

Background: Hypokalemia is a common electrolyte disorders in peritoneal dialysis patients. Some studies showed the association of serum potassium levels with all-cause and cardiovascular mortality and infection, and hypokalemia can cause muscle weakness, paralytic ileus and peritonitis. This review aims to clarify the relationship of hypokalemia and peritonitis in peritoneal dialysis.

Methods: The MEDLINE and Cochrane Library databases were searched for articles published from 1990 to May 2016. The following search terms were used: hypokalemia, potassium, peritoneal dialysis, peritonitis, infection. Additional studies were identified by hand searching through references and using the MEDLINE related articles option.

Results: A total of 159 abstracts were identified, and 6 trials were included in the systematic review (n=3613). One prospective study and three retrospective studies indicated that hypokalemia increases the risk of peritonitis, whether a prospective observational study and a case-control study indicated otherwise.

Conclusions: Convincing clinical trial data are unavailable to show the association of hypokalemia with peritonitis in peritoneal dialysis patients, and we need to clarify whether the therapeutic intervention to normalize serum potassium levels, such as KCl, spironolactone, adjustment of food or dialysate, decreases the risk of peritonitis and infection-related mortality in peritoneal dialysis patients.

FR-PO1074
Risk Factors and Outcomes of Vancomycin-Resistant Enterococcus Colonization in Patients on Peritoneal Dialysis
Jason Yeung, John Yu, Han Chan, Wai-Leung Chak. Medicine, Queen Elizabeth Hospital, Hong Kong.

Background: Vancomycin-resistant Enterococcus (VRE) colonization is common among patients with chronic renal diseases, including those undergoing peritoneal dialysis (PD). The aim of this study is to evaluate the risk factors and various clinical outcomes for VRE colonization among PD patients within a tertiary dialysis centre in Hong Kong.

Methods: This is a single-centered retrospective cohort study of 166 hospitalized patients who used PD as mode of renal replacement therapy from 1 August 2013 to 31 July 2014. All patients were screened for VRE colonization status via rectal swab or stool specimen during hospitalization. They were categorized into two groups: VRE-positive group and VRE-negative group. Baseline characteristics and other potential risk factors were analyzed in both groups. Clinical outcomes including all-cause mortality, infection with VRE, peritonitis-free survival, length of hospitalization, VRE spontaneous clearance rate and VRE relapse rate were also analyzed.

Results: Among the 166 PD patients, 28 (16.9%) were VRE-positive. Multivariate analysis showed that previous contact history with VRE-positive patients (OR: 4.17; 95% CI: 1.27-14.04; p<0.01), previous use of vancomycin in 3 months (OR: 1.30; 95% CI: 5.35-3176.30, p<0.01) and age (OR: 1.13; 95% CI: 1.02-1.24, p=0.02) were the key risk factors. The VRE positivity rate was highest in patients with a history of peritonitis. Patients with a history of peritonitis had a significantly higher risk of VRE colonization (41.4% vs. 8.6%, OR: 6.26; 95% CI: 1.56-25.16, p<0.01). Patients with VRE colonization had a significantly higher risk of mortality (32.1% vs. 11.1%, OR: 3.02; 95% CI: 1.21-7.47, p<0.01) and peritonitis (41.4% vs. 12.5%, OR: 3.02; 95% CI: 1.21-7.47, p<0.01). Patients with VRE colonization had a significantly longer length of hospitalization (mean: 27.8 days vs. 14.5 days, p<0.01).

Conclusions: Previous contact history with VRE-positive patients, previous use of vancomycin and a history of peritonitis are key risk factors for VRE colonization in PD patients. Further research is needed to investigate the role of VRE colonization in the outcomes of PD patients.
FR-PO1075

Electron Microscopy in the Evaluation of Renal Transplant Biopsies: Global Practices and Trends Indicate the Need for Standardization

Harsharan Kaur Singh, Volker Nickelet, Candice A. Roufousse. 1Dept of Pathology, The Univ of North Carolina, Chapel Hill, NC; 2Dept of Cellular Pathology, Hammersmith Hospital, Imperial College, London, United Kingdom.

Background: Electron microscopy (EM) is universally accepted in workup of native renal biopsies with established criteria in use worldwide. However, use of EM in the transplant setting outside of the workup for recurrent / de novo glomerular diseases is not well standardized. Glomerular basement membrane (GBM) duplications / remodeling, including changes seen by EM only, presence of peritubular capillary basement membrane (PTC) multi-laminations (PTCL) and endothelial cell activation are considered adjunct EM features of rejection induced injury. In 2015, a Banff-EM Working Group was created to define and validate EM criteria for diagnosing rejection related changes. A survey was conducted to evaluate current EM practices and results are reported here.

Methods: Members of the European Society for Pathology-Nephropathology Working Group and The Banff Society were surveyed (SurveyMonkey).

Results: 135 members responded (79% United States–Europe; 10% Asia; 5% Latin America; 2% Middle East; 1% each-Russia, Africa, Australia). 75% were specialized renal pathologists with >10 year experience, access to EM facilities, and evaluation of >100 transplant biopsy annually. EM was performed in only 38% of indication biopsies worldwide after 3 months post-transplantation. Presence of proteinuria (69%) or suspicion of recurrent disease (80%) were the most common triggers for EM evaluation. The approach to find and study lesions varied greatly (<50% agreement) including: #glomeruli/glomerular loops examined, scope magnification and #PTC optimal for PTCL assessment, criteria to record results and to approach diagnostic decision-making [geographic location showed no significant differences].

Conclusions: The current survey shows that ultrastructural changes in rejecting renal allografts are incompletely defined and diagnostic criteria lack standardization. The Banff-EM Working Group will next develop criteria to standardize detection and recording of EM changes followed by evaluation of diagnostic cut-off levels for GBM and PTCL lesions.

FR-PO1076

Association of Donor CYP3A5 Genotype and Tacrolimus Nephrotoxicity in Kidney Transplantation

Natavudh Kroongpiboon, 1Nephrology, Chulalongkorn Univ, Thailand; 2Pharmacology, Chulalongkorn Univ, Thailand; 3Pharmacology, Chulalongkorn Univ.

Background: The CYP3A5, which is mainly expressed in liver, is also expressed in kidney tissue and might contribute to local drug clearance. This study aims to evaluate the association between the kidney allograft CYP3A5 (donor genotype) and transplant outcomes in Asian population which has variety of CYP3A5 expression.

Methods: Genotyping for donor CYP3A5 expression were carried out by RT-PCR of the available specimens, blood samples from living donor and extraction from kidney biopsy paraffin tissue in deceased donor. CNI nephrotoxicity was documented by renal pathologist from surveillance biopsy, blindly to CYP3A5 genotype. The primary outcome is time-to-CNI nephrotoxicity in the expressor genotype compared to the non-expressor genotype.

Results: The total of 51 patients were enrolled. 21 donors were the expressor genotype (*1/*1 and *1/*3) and 30 donors were the non-expressor genotype (*3/*3). Baseline characteristic showed no difference in donor age, follow-up time, and tacrolimus dosage(C0/mg) between groups. The incidence of CNI nephrotoxicity was significantly higher in non-expressor compared to expressor (73% vs 33%, p<0.05). Median time to event was 11 months in non-expressor group and 165 months in expressor group (p=0.05).

Conclusions: Donor CYP3A5 non-expressor genotype (*3/*3) is an independent risk for CNI nephrotoxicity, probably due to poor local allograft tissue drug clearance.

FR-PO1077

Impact of Tacrolimus Formulation Switching on Trough Variability


Background: For a narrow therapeutic index drug like tacrolimus (TAC), variations in exposure could result in reduced immunosuppression or toxicity.

Methods: This retrospective cohort study examined differences in trough variability between fixed regimen (FR) and variable regimen (VR) patients (pts). US National Drug Codes (NDC) for TAC, 3–15 months post-transplant (tx), were used to allocate pts to FR or VR groups. VR was defined as a change in NDC within a specific strength or a dose adjustment that resulted in an NDC change for any continuing dose strength. Adult adult tx pts, between 09/2009 through 12/2012, with stable renal function (SCr<1.5mg/dL), and no acute rejection at 3 mos post-tx, were eligible. A total sample size of 816 pts was expected.

Results: Data on 305 of the proposed 816 pts were collected from 4 sites: 261 pts (86%) in the FR group and 44 (14%) in the VR group. Thirty-five (80%) VR pts came from a single site. VR pts tended to be non-white (70% v 36%), on dialysis longer (57 vs 44 mos), and had received an ECD kidney (30% vs 4%). Key results were summarized:

Conclusions: Preliminary findings show that VR pts in this study were more vulnerable and were associated with greater TAC trough level excursions and a difference in T/D ratio, and may explain why more TAC trough measurements were observed in VR pts. This may be relevant given recent evidence linking several outcome measures with increases in TAC variability. However, small sample size and potential for selection bias in VR pts needs to be considered when interpreting results.

Funding: Pharmaceutical Company Support - Astellas pharma
FR-PO1078

Variation in Tacrolimus Level Is Associated with Pediatric De Novo DSA and Renal Allograft Rejection
Hilda E. Fernandez,1 Sandra Amaral,1 Susan L. Furth.1
1Columbia Univ Medical Center; 2Children’s Hospital of Philadelphia.

Background: De novo donor specific anti-HLA antibodies (dnDSA) following kidney transplant (txplt) have been demonstrated to increase risk of rejection (rjxn) in renal allografts. Variation in tacrolimus (CV TAC) immunosuppression has been associated with non-adherence to medical therapy and increased risk of rjxn. This study assessed CV TAC in relation to appearance of dnDSA and allograft rejection in pediatric (ped) kidney transplant.

Methods: Retrospective study of pre and post txplt patients (pts) at CHOP from 2008 to 2011 with routine monitoring of DSA post txplt.

Results: From 9/2008 - 12/2011, 47 pts were transplanted and had serially monitored DSA post-transplant. Induction was primarily antithymocyte globulin (85%), 57% were male, 21% had living kidney txplt, 62% were Caucasian, with 43% having CAKUT as cause of ESRD. 25% had a prior allograft txplt, and 83% had >2 HLA mismatches. During a median follow-up time of 4.3 yrs, 23 pts developed dnDSA in a median 0.77 yrs following txplt. No sig diff in sex, ethnicity, living donor, HLA MM seen between pts w/ and w/o dnDSA. Pts w/ dnDSA had higher allograft rejection (15 v 1) and allograft loss (7 v 1) than pts w/o dnDSA (p < 0.01). Pts w/ dnDSA had significantly higher CV TAC following KT than pts w/o dnDSA up to 18 months post-txplt (p = 0.04). Also, pts w/ dnDSA had a faster rate of decline of creatinine over the period of follow-up than pts w/o dnDSA (p = 0.03).

Conclusions: Pts with dnDSA had higher CV TAC, more allograft rejection and loss, and greater decline in creatinine than pts without dnDSA. As CV TAC has been associated with allograft rejection, this suggests that higher variation in tacrolimus levels are reflected in the development of dnDSA.

Funding: NIDDK Support

FR-PO1079

Antibiotics and Tacrolimus Trough Variability in Kidney Transplant Recipients
Nephrology and Transplantation Medicine, Weill Cornell Medical Center; New York, NY.

Background: Based on our recent finding suggesting that the gut microbial community structure is associated with tacrolimus dose requirements, we tested the hypothesis that antibiotics, documented to alter the gut microbiota, increase tacrolimus trough variability.

Methods: We conducted a retrospective study of 229 kidney recipients transplanted 2012 to 2013 at New York Presbyterian Hospital - Weill Cornell. Patients receiving antibiotic therapy during post-operative day (POD) 0-30 were assigned to the Antibiotic group (ABX, n=60) and those who did not receive antibiotics were assigned to the No Antibiotic group (No ABX, n=169). We analyzed anti- biotic post-to-pre-tacrolimus trough and dose changes in the ABX group. We also compared tacrolimus trough variability using intra-patient Standard Deviation (SD) and Coefficient of Variation (CV) between both groups.

Results: In the ABX Group, the mean tacrolimus dose did not change from pre- to post-antibiotic day 7 and 15 (p=0.30 and p=0.99, Panel A), but tacrolimus trough levels increased (p=0.06 and p=0.055, Panel B) and the ratio of tacrolimus trough to dose increased (p=0.008 and p=0.01, Panel C) from pre- to post-antibiotic day 7 and 15. The ABX subgroup that received penicillin class antibiotics had an increased percentage of trough to dose (p=0.03) after antibiotics.

Tacrolimus Trough and Concentration-to-Dose Ratio Increase After Antibiotic Administration

Conclusions: Intra-patient SD and CV of tacrolimus troughs taken during POD 31-45 were significantly higher in the ABX group than the No ABX group (SD: median 2.6 ng/mL vs. 1.4 ng/mL, p<0.008, Wilcoxon; CV: median 0.29 vs. 0.17, p=0.004, Wilcoxon).

Conclusions: We have identified that antibiotic use impacts tacrolimus trough level variability and recommend closer monitoring of tacrolimus trough concentrations after antibiotic treatment.

Funding: Other NIH Support; KL-2 TR000458 (John Lee) and by the award K23 AI 124464 (John Lee)

FR-PO1080

Pharmacokinetics of Once-Daily Envarsus XR in Diabetic versus Non-Diabetic Kidney Transplant Recipients: A Pooled Subgroup Analysis
Daniel C. Brennan,1 Patricia West-Thielke,2 Daniel R. Stevens.3
1Washington Univ, St. Louis; 2Univ of Illinois, Chicago; 3Veloxis Pharmaceuticals.

Background: Tacrolimus (tac) has a narrow therapeutic range. In transplant recipients, too low exposure risks graft rejection while too high risks toxicity. The pharmacokinetics (PK) of tac may be unfavorably affected by diabetes. In particular, gastroparesis is common in individuals with diabetes and may impact drug absorption and ultimately, drug exposure. In clinical studies, the MeltDose® formulation of once-daily extended release tac (Envarsus XR; LCPT) showed improved bioavailability with quicker attainment of therapeutic trough levels, lower peak-to-trough fluctuation, and a lower dose requirement vs. twice-daily immediate release tac (Prograf®; IR-Tac). With LCPT the release of tac occurs over a larger portion of the GI tract and over an extended period of time vs. IR-Tac. We sought to assess LCPT PK in patients with diabetes, a high proportion of whom may have gastroparesis.

Methods: This pooled analysis of data from two phase III and one phase II randomized trials examined tac PK in 123 stable kidney transplant patients with (n=50; 72% male; mean age: 52.9±9.9) and without diabetes (n=73; 58% male; mean age: 45.5±11.3) who were converted from IR-Tac to LCPT at doses 67-80% of the pre-conversion total daily tac dose. C24 and C27 were compared with LCPT (lower C24 and lower peak-to- trough fluctuation while maintaining a therapeutic trough) were evident regardless of diabetes status [Table1]. All PK comparisons for LCPT were not statistically significant.

Conclusions: Results show that the improved PK previously documented with LCPT is maintained in kidney transplant patients with diabetes.

Funding: Veloxis Pharmaceuticals

FR-PO1081

Evaluation of Flexible Tacrolimus Drug Level Monitoring Approach in Patients Receiving Extended-Release Envarsus XR®
Benjamin Philosoph,1 Nicola Leca,2 Patricia West-Thielke,2 Timothy A. Horweld,4 Daniel R. Stevens.2
1Johns Hopkins Univ; 2Univ of Washington Medical Center; 3Univ of Illinois; 4Barnes Jewish Hospital; 5Veloxis Pharmaceuticals.

Background: Tacrolimus is a drug with a narrow therapeutic range. To ensure adequate exposure in transplant patients, 12-hour post-dose monitoring is required for twice-daily tacrolimus capsules. Due to timing of every 12-hour administration of twice daily tacrolimus, most patients will need phlebotomies at similar times which creates clinic backlogs and logistical challenges. Once daily tacrolimus tablets (Envarsus XR®) are made with proprietary MeltDose technology which results in a tacrolimus formulation with 50% increased bioavailability vs. twice-daily immediate-release tacrolimus capsules (Prograf®) and similar efficacy and safety, at a 30% reduced dose.

Methods: This analysis examined whether the trough measurement window could be extended for Envarsus XR due to its flatter kinetic curve. Extending the window for trough measurement level would allow greater flexibility in timing of blood draws for tacrolimus levels, potentially reducing early morning patient overload in clinics. PK data from 30 Envarsus XR-treated kidney transplant patients participating in an open label clinical study were used. Primary results were previously reported; here, the 21-27 slow-tail analysis is reported.

Results: For Envarsus XR showed that AUC24 and C24, C28, C30 are highly correlated (Pearson’s correlation coefficient 0.9168; p<0.0001) with corresponding levels of (mean(SE)) 7.204 (0.538; 8.011 (0.521; 2.696 (0.506 respectively. The elimination rate was -1.90% per hour between C21 and C24 and -2.61% per hour between C24 and C27. The results show that therapeutic drug monitoring window of 1/3 hours for LCPT tacrolimus levels in clinics can be performed with confidence and without any/minimal adjustment for the differences in time points. This offers an alternate solution with greater flexibility for clinicians and patients.

Conclusions: Extending “trough measurement window” provides the opportunity for potentially improving the provider and out-patient experience.

Funding: Veloxis Pharmaceuticals
FR-PO1082
Long-Term Results of a Prospective Randomized Study of Efficacy and Safety of Early Tacrolimus Conversion to Sirolimus after Kidney Transplantation
Amgad E. El Agroudy. Medicine, Arabian Gulf Univ, Manama, Bahrain.

Background: We report a prospective, open-label, randomized study to evaluate the safety and efficacy of converting patients with stable renal function from Tacrolimus (Tac)-based regimen to a Sirolimus (SRL)-based regimen after kidney transplantation.

Methods: Fifty eight renal allograft recipients who were eligible to the study, had been discharged from our Tacrolimus-based regimen 6 months posttransplant and receiving Tac, were randomly assigned to continue Tac (n=29) or convert to SRL (n=29). We evaluated the 3-year outcomes including patient and graft survival, graft function and safety profile.

Results: 3-year patient and graft survival in SRL and Tac groups was 93.1% vs 100% (P=0.32), and 89.7% vs 100% (P=0.11), respectively. However, the SRL group had significantly better renal function, from the second year post-transplant until the last follow-up. Four (13.8%) patients in the SRL group and 3 (10.3%) in the Tac group (P=0.5) developed biopsy proven acute rejection. Mean proteinuria and protein excretion increased significantly after SRL conversion. Diastolic blood pressure was significantly lower at the end of the study in patients who eliminated tacrolimus (80.4 vs. 75.6 mmHg in Tac and SRL group, respectively) (P=0.03). Mean hemoglobin concentrations decreased after SRL conversion and remained significantly lower from 12 months to 36 months (P=0.01). The mean serum cholesterol (6.1±0.5 mmol/l) and triglyceride (2.0±0.3 mmol/l) levels increased significantly in the SRL group, compared to Tac group (5.5±0.7 mmol/l (P=0.03) and 1.6±0.3 mmol/l (P=0.04).

Conclusion: Our experience demonstrates that conversion to sirolimus from calcineurin inhibitors (CNI)-based therapy may result in better renal function and blood pressure control.

FR-PO1083
Inadequate Mycophenolate Mofetil Exposure Is Associated with More Ejection and Graft Loss in Kidney Transplant Patients
Amgad E. El Agroudy, Medicine, Arabian Gulf Univ, Manama, Bahrain.

Background: Although MMF is generally well tolerated, optimal therapy may be limited by adverse effects, in particular gastrointestinal toxicity. MMF dose changes resulting from these adverse events may lead to sub-therapeutic dosing and impaired clinical outcomes. Aim of our study is to investigate the impact MMF dose reduction on the incidence of acute rejection and graft survival.

Methods: In this study, a cohort of 150 kidney transplant recipients who received immunosuppression using MMF in conjunction with cyclosporine and prednisone was evaluated. We classified patients into 3 groups according to MMF dose per day in gm; group I with 2 gm/day, group II 1.5 gm/day and group III 1 gm or less per day. Clinical outcomes were compared and contrasted between patients with and without MMF dose changes post-transplantation. The study followed the Declaration of Istanbul (DOI) ethics statement. The study was undertaken in accordance with the Declaration of Helsinki, and all amendments, and was approved by the local ethics committee.

Results: The majority of patients (52.7%) had at least one dose change within the first post-transplant year. Compared with the 79 patients who did not have a dose change, these patients had a significantly higher incidence of acute rejection within the first post-transplant year (30% vs. 10%, p<0.01). This resulted in a significantly decreased 5-year death-censored graft survival (77% vs. 68% and 57% in the groups I, II and III, respectively, p = 0.04). The incidence of acute rejection for patients who had a dose change was highest if the dose change occurred within the first post-transplant 6 months (38%). The duration to the first acute rejection was dose related (2.3±1.1 and 4.6±1.4 months in group II and III, respectively, p<0.05). In addition, renal function losses, related to these dose changes, varied significantly in terms of incidence of infections and malignancy within five year of follow-up.

Conclusion: Altering the dose of MMF within the first post-transplant year correlated with a significantly worse clinical outcome in renal transplant recipients. These data suggest that avoidance of MMF dose changes would result in improved graft survival.

FR-PO1084
Outcome of Conversion from Calcineurin Inhibitors or mTOR Inhibitors to Belatacept in Renal Transplant Patients
Manat Abdullin, Medicine, Arabian Gulf Univ, Manama, Bahrain.

Background: Belatacept (BELA) is a novel immunosuppressive agent that is being studied in a variety of transplant populations.

Methods: This is a single center retrospective analysis of 32 kidney transplant recipients who were treated with CNI or mTOR inhibitors before transplantation and were switched to BELA postoperatively. Information regarding the indication for switch, age, sex, time since transplant, blood pressure control, creatinine and other parameters were collected.

Results: BELA was reported.Blood Pressure is still being evaluated and be reported later.14 Pts reported feeling better after conversion,none of them felt worse.10 out of 14 Pts felt that side effects they had with conventional immunosuppression either resolved or improved. None of the Pts we asked wanted to go back to the old immunosuppressive regimen.

FR-PO1085
Effectiveness and Safety Profile Comparison of Sirolimus and Everolimus in Renal Transplantation
Priscilla P. How,1 Li Fang Goh,2 Puay Hoon Lee,2 Petrina Fan,2 Terence Kee Yi Shern.1 1Dept of Pharmacy, National University of Singapore; 2Dept of Pharmacy, Singapore General Hospital; 3Dept of Medicine (Nephrology), National Univ Hospital.

Background: Mammalian target of rapamycin inhibitors (MTOR-I), such as sirolimus (SRL) and everolimus (ERL) are used as alternative immunosuppressive agents in renal transplant patients who develop calcineurin-inhibitor intolerance. However, no head-to-head trials comparing ERL and SRL have been reported. This study aimed to compare the effectiveness and safety outcomes between receiving ERL and SRL over a 12-month period.

Methods: A retrospective cohort study was conducted on kidney transplant patients in the Singapore General Hospital who were started on ERL or SRL as part of their immunosuppressive regimen. Patients who converted from CNI to mTOR-I or vice versa were included.

Results: The patients were followed for 12 months or until MTOR-I was discontinued. The primary endpoint was the incidence of biopsy-proven acute rejection (BPAR) and calculated creatinine clearance (CCT). Secondary endpoints included patient’s protein-to-creatinine ratio (Tg), serum glucose (SG), urinary protein/creatinine ratio (PCR) and incidence of infections and malignancy within five year of follow-up.

Conclusion: The incidence of acute rejection was similar in the two groups. No significant difference in the effectiveness and safety endpoints between ERL and SRL were noted. However, SRL may be preferred in patients with severe proteinuria and uncontrolled lipid profile at baseline.

FR-PO1086
Long-Term Outcomes with Everolimus (EVR) and Other Regimens in Kidney Transplantation in the United States
Diane Cibrik,1 William Irish,2 Kevin M. Mccague,1 Dharmesh Patel,1 Helio Tedesco Silva.3 1Univ of Michigan, MI; 2CTI Consulting, NC; 3Novartis, NJ; 4Hospital do Rio UNIFESP, Brazil.

Background: Using the United Network for Organ Sharing database, we compared long-term clinical outcomes of regimens used in kidney transplant (KTx) recipients.

Methods: First time kidney only transplant recipients ≥18 years old, transplanted between January 1, 1998 and December 31, 2014, receiving EVR or sirolimus (SIR) or mycophenolic acid (MPA) + calcineurin inhibitor (CNI) ± steroids at time of discharge were included in the analysis. KTx recipients were excluded if their allograft failed prior to hospital discharge, they had received a donor organ with cold ischemia time >40 hours or transplantation occurred in 2001 or 2008-2009 (when EVR was not used). Treatment selection bias was addressed using risk-adjusted methods in the design and analysis. Cohorts were matched based on the propensity score for EVR using a greedy matching algorithm within donor type (living vs. deceased). Two mutually exclusive transplant periods were defined (ERAT 1998-2007 and ERAR 2010-2014; EVR was approved in the US in 2010). Kaplan-Meier and stratified Cox hazard models were used to estimate and compare outcomes between cohorts.

Results: Median follow-up was 8 years. Propensity score matching created clinically well balanced cohorts. Results (rate ± standard error) are below. Risk of graft failure was comparable between the ERV vs SIR and EVR vs MPA cohorts. The relative effect of EVR vs SIR and EVR vs MPA was comparable when the analysis was restricted to tacrolimus-based regimens.

Conclusion: Long term graft survival outcomes were similar for EVR vs SIR and EVR vs MPA regimens in KTxs regardless of donor status and CNI.

Funding: Pharmaceutical Company Support - Novartis Pharmaceuticals Corporation
FR-PO1087
Everolimus-Facilitated Cyclosporine A Sparring Immunosuppression Might Improve Glycemic Control in Kidney Transplant Recipients – A Retrospective Analysis
Florian Kälble,1 Jörg Seckinger,2 Matthias Schraier,1 Christian Morath,1 Martin G. Zeier,1 Claudia Sommerer,1 1Nephrology, Medical Univ, Shinjuku Central Hospital, Tomishiro, Tokyo, Japan; 2Urology, Tokyo Women's Medical Univ, Shinjuku-ku, Tokyo, Japan.

Background: Mammalian target of rapamycin inhibitors (mTORI) allow calcineurin inhibitor (CNI)-sparring therapy and can reduce tacrolimus exposure. However, the effects of CNI on glucose metabolism have been documented, the influence of mTORI is still under discussion.

Methods: In a retrospective analysis, allograft recipients switched from a cyclosporine A (CsA) to an everolimus (EV) based immunosuppression in the first year after transplantation were compared with patients on continued CsA treatment. Clinical and biochemical data were collected at 6-month intervals. The prevalence of impaired fasting glucose (IFG), diabetes, hyperlipidemia after transplantation (pDAT) and diabetes (pDAT) was documented.

Results: A total of 146 renal transplant recipients were included in the present study. The cumulative prevalence of IFG and pDAT 30 months post transplantation was significantly lower in patients switched to a primary immunosuppression with EVR compared to patients on continued CsA treatment (10% versus 22%, p=0.049). Patients switched to EVR revealed a mean HOMA-IR (homeostasis model assessment insulin resistance) -2 while the index in patients on continued full-dose CsA was 4 (1.7±1.3 versus 3.9±1.1, p=0.05), suggestive of insulin resistance. Patients switched to a CsA-sparing regimen showed a higher incidence of acute cellular rejection episodes in the first 12 months (23% versus 12%, p=0.048).

Conclusions: The switch to an EVR-based immunosuppression was associated with an improvement in glycemic control. However, due to higher rates of acute cellular rejections, patients switched to EVR should be carefully selected and closely monitored.

FR-PO1088
Effect of Everolimus on the Cardiac Function in Kidney Transplant Recipients
Kazuma Tsujimura, Surgery, Tomishiro Central Hospital, Tomishiro-shi, Okinawa, Japan.

Background: In this study, we evaluated the effect of everolimus (EVR), one of the mammalian targets of rapamycin on cardiac function in kidney transplant recipients.

Methods: We retrospectively studied 76 participants who underwent kidney transplantation (KTx) between March 2009 and May 2017. All participants received tacrolimus or cyclosporine, mycophenolate mofetil, and myeloid/prodiginine for maintenance immunosuppression after KTx. To standardize EVR administration at our institution, the following criteria were used: (1) The recipient did not have donor-specific antibodies (DSA) at the time of transplantation. (2) In a retrospective analysis, renal allograft recipients switched from a CsA-sparing regimen showed a higher incidence of acute cellular rejection episodes in the first 12 months (23% versus 12%, p=0.048).

Results: The characteristics of the 2 groups did not differ significantly (Table 1). The mean observation period of the treatment and non-treatment group was 41.3 ± 12.6 and 43.9 ± 12.6 years post-transplant. The eGFR (mL/min/1.73m²) at conversion and post-conversion is shown in Table 1.

Table 1 Patient Characteristics (Mean±SD)

<table>
<thead>
<tr>
<th>Treatment group (n=30)</th>
<th>Non-treatment group (n=46)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Male, n (%)</td>
<td>22 (73.3%)</td>
<td>29 (63.0%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.7 ± 14.2</td>
<td>49.2 ± 12.9</td>
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<tr>
<td>SCr before KTx (mg/dL)</td>
<td>0.8 ± 1.3</td>
<td>1.1 ± 1.3</td>
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<tr>
<td>EF before KTx (%)</td>
<td>56.5 ± 8.9</td>
<td>56.4 ± 8.9</td>
</tr>
<tr>
<td>FS before KTx (%)</td>
<td>36.4 ± 5.8</td>
<td>36.3 ± 6.4</td>
</tr>
<tr>
<td>E/A ratio before KTx</td>
<td>1.00 ± 0.38</td>
<td>0.95 ± 0.33</td>
</tr>
<tr>
<td>SCr, serum creatinine</td>
<td>EF, fractional shortening</td>
<td>E/A ratio, E-wave/A-wave</td>
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</table>

In a retrospective analysis, renal allograft recipients switched from a CsA-sparing regimen showed a higher incidence of acute cellular rejection episodes in the first 12 months (23% versus 12%, p=0.048). Patients switched to a CsA-sparing regimen showed a higher incidence of acute cellular rejection episodes in the first 12 months (23% versus 12%, p=0.048).

Conclusions: We evaluated a cohort of 7 patients biopsyed for a rising creatinine. These patients were found to have chronic tacrolimus toxicity with at least 1+ IF/TA and 1+ arteriolar hyalinosis on biopsy. Once toxicity develops, a tacrolimus minimization strategy is often used but ongoing allograft injury can still occur even with reduced tacrolimus exposure. Conversion from tacrolimus to belatacept may be a potential strategy to preserve renal function.

Methods: We evaluated a cohort of 7 patients biopsyed for a rising creatinine. These patients were found to have chronic tacrolimus toxicity with at least 1+ IF/TA and 1+ arteriolar hyalinosis on biopsy. Once toxicity develops, a tacrolimus minimization strategy is often used but ongoing allograft injury can still occur even with reduced tacrolimus exposure. Conversion from tacrolimus to belatacept may be a potential strategy to preserve renal function.

Results: The mean age at conversion was 52.3. Four of 7 patients were male. Causes of ESRD were IgA nephropathy, lithium toxicity, obstructive uropathy, FSGS, dysplastic kidney disease, and nephrocalcinosis. Patients were converted to belatacept 7.7 ± 18.3 years post-transplant. The eGFR (mL/min/1.73m²) at conversion and post-conversion is shown in Table 1.

Table 1 Patient Characteristics (Mean±SD)

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<th>Patient</th>
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Three of 7 patients had no infections post-transplant, while 1 patient had a citrobacter urinary tract infection, 1 had gastroenteritis, and 2 patients had bacteremia. All grafts survived except for patient 1, whose graft dysfunction led to retransplantation 13 months after conversion.

Conclusions: In patients with late allograft dysfunction due to chronic tacrolimus toxicity, conversion to belatacept stabilized the eGFR in 4 out of 7 patients, and resulted in increased eGFR in 2 of 7 patients. This strategy should be evaluated in a larger cohort of patients to better assess the efficacy of this approach.

Funding: Clinical Revenue Support

FR-PO1091
One Year Outcome of Preemptive Low Dose Rituximab in Flow Cytometry Crossmatch Positive Kidney Transplant Recipients
Sagar Gupta, Thul Thaw Maw, Daniel Wojciechowski. Nephrology, Massachusetts General Hospital.

Background: The calcineurin inhibitor tacrolimus is excellent at preventing acute rejection in renal transplantation. However, it is associated with chronic nephrotoxicity, manifested as interstitial fibrosis/tubular atrophy (IF/TA) and arteriolar hyalinosis on biopsy. Once toxicity develops, a tacrolimus minimization strategy is often used but ongoing allograft injury can still occur even with reduced tacrolimus exposure. Conversion from tacrolimus to belatacept may be a potential strategy to preserve renal function.

Methods: We evaluated a cohort of 7 patients biopsyed for a rising creatinine. These patients were found to have chronic tacrolimus toxicity with at least 1+ IF/TA and 1+ arteriolar hyalinosis on biopsy. Once toxicity develops, a tacrolimus minimization strategy is often used but ongoing allograft injury can still occur even with reduced tacrolimus exposure. Conversion from tacrolimus to belatacept may be a potential strategy to preserve renal function.

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Funding: Clinical Revenue Support
tend to be younger with a mean age of 43 years. The mean serum creatinine (Scr Cr) tended to be lower in rituximab group at all points during the 12-month follow up period, though this was not statistically significant. Acute cellular rejection (ACR), antibody mediated rejection (AMR) and graft loss at 1 year were lower in rituximab group, not reaching statistical significance given low sample size and incidence numbers.

<table>
<thead>
<tr>
<th>Rituximon(n=28)</th>
<th>No Rituximab(n=127)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs)</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>Prior transplant</td>
<td>14(50%)</td>
<td>32(25%)</td>
</tr>
<tr>
<td>T cell flow (MCS)</td>
<td>79</td>
<td>49</td>
</tr>
<tr>
<td>B cell flow (MCS)</td>
<td>125</td>
<td>127</td>
</tr>
<tr>
<td>Performed DSA</td>
<td>8(28.6%)</td>
<td>2(1.6%)</td>
</tr>
<tr>
<td>Denovo DSA</td>
<td>19(35.7%)</td>
<td>21(16.5%)</td>
</tr>
</tbody>
</table>

**Conclusions:** Although there is no statistically significant difference in Sr Cr, acute rejection rate and graft loss at 1 year between rituximab group and no rituximab group, there was a trend towards lower acute rejection rate and graft loss in rituximab group.

**FR-PO1092**

Effects of Basiliximab on Lymphocyte Subsets in Living-Related Kidney Transplantation. Xianping Yu, Jianhua Chen. The Kidney Disease Center; The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang Province, China.

**Background:** To observe the effects of basiliximab on peripheral lymphocyte subsets in early time of living-related kidney transplantation (LRKT).

**Methods:** 28 LRKT recipients were enrolled in the study. 12 accepted the induction therapy of basiliximab (induction group), and 16 were not given induction therapy (control group). The maintenance immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil and steroids. The peripheral lymphocyte subsets were monitored before and one week after the operation by using flow cytometry. The renal allograft function, infection and acute rejection were observed by month six after transplantation.

**Results:** One week after the operation, the percentages of Th lymphocyte, Ts lymphocyte and B lymphocyte in the induction group were 44.1±6.4%, 28.1±7.0% and 23.8±5.6%, whereas the percentages in the control group were 39.9±8.6%, 28.2±10.0% and 21.9±6.4% respectively. (p<0.1, p=0.1, p=0.6, respectively).

**Conclusions:** Basiliximab would not influence the lymphocyte subsets of LRKT recipients in the early time after transplantation, and would not influence the renal allograft function, occurrence of infection and acute rejection either.

**FR-PO1093**


**Background:** Percutaneous biopsies of Tx) are guided with ultrasound (US) guided percutaneous bxs in both enteric and bladder drained pancreas transplants (Tx). Since then, pancreas Tx surgical techniques have evolved, including mostly enteric rather than bladder drained Tx. We hereby review the series of (S) and computed tomography (CT) guided percutaneous pancreas allograft bxs in 109 consecutive bxs of enteric drained pancreas allografts.

**Methods:** We reviewed 271 cases of pancreas Tx performed at our institution between 2001 and 2014. 68 bxs (30 simultaneous pancreas kidney, 19 kidney after pancreas, and 19 pancreas Tx alone) underwent one or more percutaneous allograft bxs. Biopsies were performed with an 18-gauge needle, under direct US or CT guidance.

**Results:** A total of 109 bxs were performed. 30 bxs were in patients with enteric everted venous pouch drainage (PD) and 79 in patients with systemic drainage (S). All bxs were performed under CT guidance and 84 under US guidance. 84% of the bxs in the CT group and 86.6% of the bxs in the US group were adequate (p=0.74). There were a total of 4 bxs related complications (3.6%), all occurring in the US guided group. Those included 2 inadvertent small bowel punctures that were clinically silent and 2 intra abdominal bleeds that were managed conservatively. The small bowel punctures occurred in patients with PD as opposed to the bleeds that occurred in those with SD. No complications occurred in the CT guided group. There were no graft losses and no complications requiring surgical intervention.

**Conclusions:** Percutaneous pancreas allograft bx has a low incidence of complications in the most recent era of enteric drained pancreas Tx, and appears to be as safe as renal allograft bx. The more recent widespread use of CT guided bx, rather than US guided bx, seems to be promising in decreasing the incidence of bx related complications, but larger studies are needed to corroborate this hypothesis.

**FR-PO1104**

Antiproteinuric Effect of Spironolactone in Kidney Transplant Recipients: A Brazilian Reference Center Experience. Vinicius Sousa,1 Jose Paulo Siqueira Guida,2 Marilda Mazzatti,1 *Nephrology, State Univ of Campinas, Campinas, SP, Brazil; 1Obstetrics, State Univ of Campinas, Campinas, SP, Brazil.

**Background:** Proteinuria is a marker of kidney damage and increases cardiovascular risk. Onset of proteinuria in transplantation is associated with impaired allograft function and mortality. Aldosterone is involved in progression of chronic transplant dysfunction. Spironolactone appears to be protective in kidney allograft, reducing proteinuria.

**Methods:** Retrospective cohort in kidney transplant recipients with persistent proteinuria treated with spironolactone. Exclusion criteria: hyperkalemia, medication hypersensitivity, graft dysfunction (serum creatinine >3 mg/dl) and hard-to-control hypertension (MAP>120 mmHg). Discontinuity criteria: refractory hyperkalemia, drug intolerance. Demographic, clinical and laboratory data were obtained at beginning and at 1st, 3rd, 6th, 9th and 12th months. Data were analyzed using EpiInfo7; categorical data were compared with Bartlett test and numerical data with T-student test.

**Results:** 144 individuals, mean age: 49±13.2 years, 75% male. Average time post transplant: 90±136.5 months. Most cases (78%) were from deceased donor, 18.7% expanded donor, with cold ischaemia time of 20.4±6 hours. 96.1% of recipients were previously hypertensive and 15.7% diabetic. None of the subjects were discontinued of the study due to hyperkalemia or drug intolerance. Individuals were divided into 3 groups according to initial proteinuria and results are shown in Table 1, *indicates p<0.05.

<table>
<thead>
<tr>
<th>Artery (mg/g creatinine)</th>
<th>Time post transplantation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>58±4.6±0.5</td>
</tr>
<tr>
<td>Skin</td>
<td>85±6.9±0.3</td>
</tr>
<tr>
<td>Liver</td>
<td>74±5.9±0.3</td>
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**Initial proteinuria**

<table>
<thead>
<tr>
<th>Artery (mg/g creatinine)</th>
<th>Initial proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>0.6±0.2</td>
</tr>
<tr>
<td>Skin</td>
<td>1.6±0.5</td>
</tr>
<tr>
<td>Liver</td>
<td>5.9±2.2</td>
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</table>

**Initial GFR**

<table>
<thead>
<tr>
<th>Artery (mg/g creatinine)</th>
<th>Proteinuria 6m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>43±5.2±2</td>
</tr>
<tr>
<td>Skin</td>
<td>44±6.1±2</td>
</tr>
<tr>
<td>Liver</td>
<td>36±4.1±1</td>
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</tbody>
</table>

**Proteinuria 6m**

<table>
<thead>
<tr>
<th>Artery (mg/g creatinine)</th>
<th>Proteinuria 12m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>0.6±0.6</td>
</tr>
<tr>
<td>Skin</td>
<td>1.1±1</td>
</tr>
<tr>
<td>Liver</td>
<td>3.3±2.8</td>
</tr>
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</table>

**Proteinuria 12m**

In B and C groups, a significant reduction in proteinuria was observed at 6th month and 1 year follow-up. Half of group B and a third of group C decreased their proteinuria to less than 1g after one year.

**Conclusions:** Spironolactone seems to be an alternative to control and reduce proteinuria in this population, particularly in proteinuria over 1g, and it is a safe drug for this population.

**FR-PO1095**

Double-Negative T Cells Are Reduced in Transplanted Patients Treated with mTOR-Inhibitor. Marehretja Gigante,1 Giuseppe Castellano,2 Nada Chourli,2 Rossana Francesini,2 Marco Fiorentino,2 Giuseppe Grandalino,2 G. Stallone,2 Loreto Gesualdo,1 Elena Ranieri,2 *D.E.T.O., Univ of Bari, Italy; Medical and Surgical Sciences, Univ of Foggia, Italy.

**Background:** CD4-CD8-double-negative T cells (DNTs) are CD3+ T lymphocytes which lack CD4, CD8 and CD56. They are specifically involved in immune regulation and tolerance and constitute about the 1-5% of lymphocytes in healthy human donors. DNTs express either αβ or γδ T-cell receptors (TCR) and can act both as regulatory T cells (Tregs) or as cytotoxic T cells. The aim of this study was to assess the frequency and the phenotype of circulating DNTs in transplanted patients (pts) treated with mTOR-inhibitor compared with pts treated with CNI (without mTOR-inhibitor) and healthy donors as controls.

**Methods:** Peripheral blood (PB) samples of 15 transplanted pts (6/24 months from Tx) treated with mTOR inhibitors (Everolimus or Rapamycin) and 15 pts with CNI (Cyclosporine or Tacrolimus) were selected. As control PB samples of 10 healthy donors were collected. Circulating DNT subsets (TCRαβ and TCRγδ) were characterized for their ontogeny, tolerogenic or cytotoxic phenotype by staining with the following antibodies:
Consequences of Using Estimated GFR in Living Kidney Donors: The Nephrologist in the Mist

FR-PO1096
Inconsistency between KDIGO Draft and Japanese Living Kidney Donors Guidelines in Kidney Function Evaluation

Yoshinari Yasuda, Takeyuki Katsuno, Shoichi Maruyama. CKD Initiatives/Nephrology, Nagoya Univ, Nagoya, Japan.

Background: KDIGO Living Kidney Donors draft guideline (GL) recommends that estimated GFR (eGFR) be calculated by Japanese and CKD-Epi equations based on Cr, Cys and combination, and inconsistent rate was analyzed.

Methods: The study subjects were 69 (42 female) kidney transplant donor candidates whose GFR were measured by inulin clearance in Nagoya University Hospital. IDMS-traceable Cr values were measured by enzymatic method and standardized Cys values were measured by colloidal gold immunooassay. Estimated GFR was calculated by Japanese and CKD-Epi equations based on Cr, Cys and combination, and inconsistency rate was analyzed.

Conclusions: Japanese GFR equations were superior to EPI equations, and eGFR-Cys was the most accurate among Japanese kidney transplant donor candidates, however GFR should be measured because of considerable under- and overestimation rate, especially in female.

Funding: Government Support - Non-U.S.

FR-PO1097
Consequences of Using Estimated GFR in Living Kidney Donors: The Nephrologist in the Mist


Background: An accurate assessment of GFR before donation is crucial to reduce the risk of renal impairment after donation and to provide acceptable renal mass to the donor. Formulas that estimate GFR (eGFR) have a wide error in reflecting real GFR. This may have consequences in the evaluation of living kidney donors.

Methods: 54 consecutive donors with eGFR <80 ml/min (cut-off level for donation) based on MDRD and/or two 24-h creatinine clearances (CCL) underwent the plasma clearance of iohexol to measure GFR (mGFR). Subjects with mGFR <80 ml/min who had eGFR >80 ml/min were analyzed. The agreement between mGFR and eGFR assessed by 52 Brody School of Med; 6Western Univ; 7Cleveland Clinic; 8Washington Univ; 9Johns Hopkins.

Background: Implications of narcotic use in living kidney donors for key outcomes, including readmission rates after nephrectomy, are unknown.

Methods: We integrated 1) national Scientific Registry of Transplant Recipients data with 2) pharmacy fill records from a nationwide pharmacy claims clearinghouse, and 3) administrative records from an academic hospital consortium (98 centers, 2008-2012). Narcotic fills in the yr before donation were assessed and normalized to morphine equivalents. Associations of predonation narcotic use (adjusted odds ratio, aOR) and other baseline clinical, procedural, and center factors with readmission within 1 yr postdonation were examined using multivariate logistic regression.

Results: Among 14,959 living donors, 11.3% filled ≥1 narcotic prescription in the year before donation. Pre-donation narcotic use level bore graded associations with 1-yr readmission; donors with the highest pre-donation narcotic use were twice as likely to be readmitted as non-users (6.7% vs. 3.2%; aOR 1.95, 95% CI 1.38-2.77). Adjusted readmission risk was also significantly (p<0.05) higher for women (aOR=2.23), African Americans (aOR=1.43), exchange participants (aOR=1.44), uninsured donors (aOR=1.36), donors with pre-donation estimated glomerular filtration rate <60 ml/min/1.73 m² (aOR=2.42), and after robotic nephrectomy (aOR=1.90). Donors at high-volume centers (>50 per yr) had lower readmission rates (aOR=0.83).

Results: In 5 subjects of 54 (9.6%) GFRF was <80 ml/min (~70 ml/min) while MDRD and/or CCR were >90 ml/min. All were women, with reduced weight, height, BMI and Body Surface Area (BSA) compared with those in whom MDRD, CCR and mGFR were >80 ml/min.

Results: Formulas and CCL are not appropriate to evaluate living donors since they may overestimate real renal function, particularly in women with reduced BSA. Measured GFR is an important tool in the evaluation of living donors.

Funding: Government Support - Non-U.S.

FR-PO1098
Pre-Donation Prescription Narcotic Use: A Novel Risk Factor for Readmission after Living Kidney Donation

Krista L. Lentinent,1 Ngan Lam,2 Mark Schnitzer,3 Gregory P. Hess,4 Bertram L. Kasikis,5 David A. Axelrod,6 Amit X. Garg,7 Jesse D. Schold,8 Daniel C. Brennan,9 Dorry L. Segov,10 Saint Louis Univ;1 Univ Alberta;2 Symphony Health;3 Hennepin County Med Center;4 Brody School of Med;5 Western Univ;6 Cleveland Clinic;7 Washington Univ;8 Johns Hopkins.

Background: Consequences of using estimated GFR in living kidney donors for key outcomes, including readmission rates after nephrectomy, are unknown.
Conclusions: Pre-donation narcotic use is independently associated with readmission after discharge, yet research should further examine underlying mechanisms and approaches to reducing risks of post-donation complications.

Funding: NIDDK Support

FR-PO1099

Identifying Donors at Risk for Developing Chronic Kidney Disease Using Non-Invasive Ultrasound-Based Measurement of Glomerular Diameter

Asnaf El-Meanawy, Liliana Osadchuk. Medicine, Medical College of Wisconsin, Milwaukee, WI.

Background: There is a non-significant risk for developing chronic kidney disease (CKD) or end stage renal disease (ESRD) in the donor. The lifelong risk of ESRD in living kidney donors is as high as 11 folds that of control group. One important risk factor which is neglected, mainly due to technical, way to access, is nephron endowment in the donor. Donors how have low nephron endowment are at risk for developing hyperfiltration injury. The persistent hyperfiltration injury leads to chronic kidney disease and ultimately ESRD.

Methods: Technique was validated using pig kidney. Cohort: Single center prospective study. All living donors at Froedtert transplant program who are willing to participate were included in the study. Clinical Data and Biochemical analysis: Standard of care data. Sonographic data collection: Raw radiofrequency data were collected of renal anatomy and vasculature. Recent data suggest that renal morphology (kidney volume) is produced per milliliter (ml) kidney tissue.

Results: The technique is valid and provide accurate measurement of glomerular diameter. Moreover, we encountered donors with glomerular diameters which are significantly larger than the median. Donors who expected low nephron endowment (prematurity and/or low birth weight) have larger glomeruli predonation or have significant glomerular enlargement over time. Those donors failed to recover renal function 6 month after donation.

Conclusions: Pre-donation Glomerulomegaly or significant increase in glomerular diameter after donation could indicate low nephron endowment. These subjects are at higher risk for post-donation CKD. Measuring glomerular diameter using ultrasound could prove to be very useful tool in assessing live donor risk for CKD post donation. Failure to identify kidney donors who have reduced nephron endowment will put them at risk for developing CKD and possibly ESRD in their life time. The renal disease progression in these subjects is usually driven by hyperfiltration injury from surgical reduction in nephron number below a threshold that meets the metabolic demand.

FR-PO1100

Utilizing Renal Efficiency to Determine Graft Quality in Live Kidney Donors

Alejandro Diez, Garrett P. Dultz, Rima Kang. Div of Nephrology, The Ohio State Univ, Columbus, OH.

Background: Donor age and renal function along with mass and volume donated kidney graft are factors that have been associated with subsequent living donor kidney transplant outcomes. Measurements of renal volume (size) and function (measured or estimated GFR and Creatinine Clearances) are routinely performed prior to donation. Currently, there is no term which describes the quality of the donated tissue. We coined the term: “Renal efficiency”.

Methods: Under IRB approval, we designed a single center retrospective study of all consecutive living kidney donors who donated between January 1, 2008 and December 31, 2013; abstracting demographic and clinical data. Renal function was determined using the CKD-EPI equation and 24 hour timed creatinine clearance measurements (mCrCl). 24 hour urine collections were included when the observed urine creatinine excretion rate was ≥80mg/dl. We found a strong correlation between renal efficiency as defined by 24 hr timed creatinine clearance measurements (mCrCl) and renal volume as determined by 3D reconstructions of CT angiograms (CT-V). We set forth to determine if a strong correlation exists in a large cohort utilizing strict data validation and enhanced imaging techniques.

Methods: Under IRB approval, we designed a single center retrospective study of all consecutive living kidney donors who donated between January 1, 2008 and December 31, 2013; abstracting demographic and clinical data, pre-donation mCrCl and CT-V. 24 hour urine collections were included when the observed urine creatinine excretion rate was within 25% of the expected production (derived from Cockroft-Gault). All CT-V were calculated using semi-automated region of interest [ROI] volumetry. Results: 322 cases met inclusion criteria: (Male vs Female 102:220 (32%:68%); White vs Non-White ~ 284:38 (88%:12%); Ave Age: 43y/o (sd 11.64). The average total CT-V (combined right and left kidneys) was 349.91 ml (sd 65.96). The average mCrCl was 123.21 ml/min (sd 27.34) Univariable linear regression modeling showed male sex, weight, height, and BSA to be associated with both increasing renal volume and function (all p<0.001). Increased age was inversely associated with mCrCl (p<0.001). Multivariable linear regression modeling (adjusted) showed that BSA remained associated with both increasing renal volume and function (p<0.001). Increased age remained inversely associated with mCrCl (p<0.001). Pearson correlation between CT-V and mCrCl was 0.65 (P = 0.001).

Conclusions: Our analysis of a large cohort using strict data validation methodology and improved imaging reconstruction shows the strong linear relationship that exists between renal size and function.

FR-PO1102

Living Renal Donation – Gender Effects on Quality of Life

Claudia Sommerer, Sarah Estelmann, Matthias Schaier, Christian Morath, Martin G. Zeier. Nephrology, Medical Univ Hospital, Heidelberg, Germany.

Background: A careful donor selection is important as well as a consistent donor follow-up. Gender specific effects might be detected concerning quality of life.

Methods: Living renal donors at the Transplant Center Heidelberg, University Hospital were evaluated using the standardized 36-item short form health survey [SF-36] questionnaire.

Results: Altogether 211 living renal donors were evaluated (131 female, 62.1%). The SF-36 physical component summary score was comparable in female and male donors (51.8±10.1 versus 53.9±7.9; ns). The SF-36 mental component summary score was significantly lower in female donors compared to male donors (47.6±13.0 vs. 51.7±11.0, p =0.012). In all sub-scale male donors presented higher scores compared to female donors. Male donors had the highest scores in social functioning, female donors in physical functioning. In most of the SF-36 scales, female donors showed comparable or even better results compared to a German general population. However, in the scales social functioning, emotional role functioning and mental health female donors had lower scores compared to an age- and gender-matched general population. Male donors presented higher scores in all SF-36 sub-scales compared to an age- and gender-matched general population (significant scales: vitality, physical component summary score).

Conclusions: Quality of life assessed by the SF-36 questionnaires shows several gender specific differences in living renal donors. Especially, female donors are on increased risk concerning mental and emotional health after donation. Careful evaluation of these female donors is mandatory.

FR-PO1103

5 Year Follow-Up Results of the HERAKLES Study: Superior Renal Function after Early Conversion to an Everolimus-Based Calcineurin Inhibitor Free Regimen

Claudia Sommerer, 1 Wolfgang Arns, 1 Ingeborg A. Hausser, 1 Volker Kliem, 1 Petra Reineke, 1 Rolf A. Stahl, 1 Bruno Vogl, 2 Martina Porstner, 3 Thomas Rath, 3 Frank Lehner, 1 Oliver Witzke, 1 Klemens Budde. 1 Herakles Study Group, Germany; 2Herakles Study Group, Switzerland; 3Novartis Pharma GmbH, Germany.

Background: To follow up on renal function (GFR) 5 years after kidney transplantation (KTx) in patients (pts) on immunosuppressive regimen with different everolimus (EVR) and calcineurin inhibitor (CNI) exposures.

Methods: 1 year, prospective, open-label, randomized, controlled multi-center study with observational follow-up (FU) to Mo 60 post Tx. After induction therapy all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3 Mo post Tx, 116 pts were randomized 1:1:1 to either a) continue standard CsA (100-180mg/ml) + EC-MPS (n=166) (STD) or b) calcineurin blocker free regimen with EVR (5-10mg/ml) + EC-MPS (n=171) or c) to a CNI-reduced regimen with EVR (3-8mg/ml) + reduced CsA (50-75mg/ml; n=162). All pts continued on steroids according to centers practice. In total 81% of pts completed the FU period.

Results: GFR (Nankivell, ITT) was similar at randomization 3 Mo post Tx and had significantly improved at Mo12 by +5.6ml/min (p<0.001) in all subgroups. Patients on EVR-CNI regimen showed a statistically meaningful correlation between renal function as defined by 24 hr timed creatinine clearance measurements (mCrCl) and renal volume as determined by 3D reconstructions of CT angiograms (CT-V). We set forth to determine if a strong correlation exists in a large cohort utilizing strict data validation and enhanced imaging techniques.

Methods: Under IRB approval, we designed a single center retrospective study of all consecutive living kidney donors who donated between January 1, 2008 and December 31, 2013; abstracting demographic and clinical data, pre-donation mCrCl and CT-V. 24 hour urine collections were included when the observed urine creatinine excretion rate was within 25% of the expected production (derived from Cockroft-Gault). All CT-V were calculated using semi-automated region of interest [ROI] volumetry. Results: 322 cases met inclusion criteria: (Male vs Female 102:220 (32%:68%); White vs Non-White ~ 284:38 (88%:12%); Ave Age: 43y/o (sd 11.64). The average total CT-V (combined right and left kidneys) was 349.91 ml (sd 65.96). The average mCrCl was 123.21 ml/min (sd 27.34) Univariable linear regression modeling showed male sex, weight, height, and BSA to be associated with both increasing renal volume and function (all p<0.001). Increased age was inversely associated with mCrCl (p<0.001). Multivariable linear regression modeling (adjusted) showed that BSA remained associated with both increasing renal volume and function (p<0.001). Increased age remained inversely associated with mCrCl (p<0.001). Pearson correlation between CT-V and mCrCl was 0.65 (P = 0.001).

Conclusions: Our analysis of a large cohort using strict data validation methodology and improved imaging reconstruction shows the strong linear relationship that exists between renal size and function.
FR-PO1104
Living Renal Donation – Association between Gender and Mental Stress after Living Donation
Claudia Cohen, Sarah Estellmann, Matthias Schauer, Christian Morath, Martin G. Zeier
Nephrology, Medical Univ Hospital, Heidelberg, Germany.

Background: In living renal donation, careful donor selection is as important as consequent donor follow-up. This includes both, physical and mental health. There might be some gender specific differences. The question to be answered by this evaluation was: Are there any associations between gender and signs of mental stress or impairment?

Methods: Living renal donors at the Renal Transplant Center Heidelberg were evaluated using standardized questionnaires (Hamilton Anxiety Depression Scale, HADS-D; Perceived Stress Scale (PSS)).

Results: Altogether, 211 of 261 (80.8%) questionnaires could be analyzed. Mean age at time of donation was 51.7±9.9 years (131 female), and mean time after donation was 9.7±5.2 years. Results on the HADS-D depression scale (4.0±3.65 vs. 3.68±3.58) and the anxiety scale (5.09±3.54 vs. 4.4±3.56) were comparable in female and male donors. Female and male living donors aged >60 years had better results compared to a German general population. Female mental stress was evaluated using the PSS. Female donors presented significantly increased mental stress compared to male donors (p<0.003).

Conclusions: Generally, there is no increased mental stress after living donation compared to a general population. However, there are distinct gender- and age-specific differences. Female donors should be evaluated carefully concerning mental health.

FR-PO1105
Using the Baseline Creatinine Instead of the Terminal Creatinine to Calculate the Kidney Donor Risk Index
Mariana C. Chiles,1 Dustin Carpenter,1 Rachel E. Patzer,1 Stephen O. Pastan,1 Bekir Tanriover,2 Jae Hyung Chang,1 David J. Cohen,2 Sumit Mohan,2 1Columbia Univ Medical Center, New York, NY; 2Emory Univ School of Medicine, Atlanta, GA.

Background: The Kidney Donor Risk Index (KDRI) is a numerical expression of decreased donor organ quality and is currently used as part of the New Kidney Allocation System in the US. The KDRI includes the terminal creatinine (Crter) even though the baseline creatinine (Crbase) may be a more appropriate, particularly for kidneys with AKI that are already at increased risk of discard.

Methods: Our analysis included 112,809 deceased donor kidneys from 62,370 donors with data provided by the Organ Procurement Transplant Network (OPTN) procured for the United Network for Organ Sharing (UNOS) from 2002-2015 with Crbase over Crter is limited, using the lower KDRIbase in individual instances is more reflective of the true quality of the kidney and may help to lower the discard of kidneys with AKI.

Conclusions: CNI-free EVR regimen was associated with significant higher eGFR maintained for 5 years after Tx. The results of this large trial confirm previous reports of improved GFR after CsA withdrawal with EVR-based regimen.
**FR-PO1107**

Overweight Young Female Donors Have a Lower Post-Donation Reserve Capacity - Implications for Preeclampsia

Marco van Londen,1 Anouk Wma Schaefiers,1 Gerjan Navis,1 Martin H. De Borst,1 Titia Lely.1 1Univ Medical Center Groningen, Groningen, Netherlands; 2Univ Medical Center Utrecht, Utrecht, Netherlands.

**Background:** Young female kidney donors are at increased risk of gestational hypertension or preeclampsia. Absence of pregnancy-induced renal vasodilatation is a hallmark of preeclampsia and might reflect lower renal reserve capacity (RC). We previously observed that higher donor BMI is associated with a lower RC after donation. Therefore, we now studied the relationship between BMI and renal RC before and after donation in female donors of childbearing age.

**Methods:** RC, defined as rise in glomerular filtration rate (GFR, 125I-Iothalamate clearance) during dopamine, was measured in female donors of childbearing age (<45 years) at 4 months prior and 2 months after kidney donation. Difference between overweight (BMI>25) and non-overweight donors was tested by t-test; the association between BMI and renal hemodynamics was tested with linear regression analysis.

**Results:** We included 105 female donors who were 41 [36-43] (median[IQR]) years old at donation with a BMI of 25 [22-27] kg/m2. Pre-donation GFR was 118 [17] ml/min (mean[SD]) rising to 128 [19] ml/min during dopamine; mean RC was 10 [10] ml/min. BMI was positively associated with GFR (st. beta 0.31, p=0.001) but not with pre-donation RC (st. beta -0.04, p=0.70). Post-donation GFR was 76 [13] ml/min, rising to 80 [12] during stimulation; RC was 3 [6] ml/min (p=0.001 vs. predonation). Loss of RC was more prominent in overweight donors (-7 vs. -4 ml/min, p=0.05), and higher BMI was associated with lower RC after donation, independent of GFR, age, and use of antihypertensives or contraceptives (st. beta -0.37, p=0.002).

**Conclusions:** BMI is inversely associated with post-donation RC in female donors of childbearing age. Reduced renal RC might be involved in the increased risk of preeclampsia and gestational hypertension in overweight female kidney donors. Overweight female kidney donors with the desire to have children should be counselled to reach a normal BMI.

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**FR-PO1108**

Clearance and Delays in the Live Kidney Donor Evaluation Process

Joseph Leana, Dorry L. Segev. Surgery, Johns Hopkins Univ, Baltimore, MD.

**Background:** The live kidney donor evaluation process is a poorly understood barrier to live donation. We quantified clearance time for each evaluation phase and identified factors associated with spending excessive time in each phase, i.e. getting “delayed.”

**Methods:** Eligible potential donors (PDs), who initiated evaluation at Johns Hopkins between 1/1/2011 and 12/31/2014, were followed through five evaluation phases: 1. questionnaire; 2. blood and tissue typing; 3. routine screening and physical exam; 4. evaluation and clearance; 5. recipient clearance, scheduling and donation. Delay was defined for each phase as ≥ 90th percentile of time spent by PDs who cleared that phase for a kidney than those >25.

**Results:** Of 2,738 PDs, 90.3% completed phase 1, 27.4% phase 2, 18.8% phase 3, 9.6% phase 4, and 9.6% phase 5. Donors were 41, 159, 149, 106, and 328 days.

**Conclusions:** Nearly 50% of PDs were delayed at some point, particularly those of African American race. Efforts to improve LKD rates in this subgroup may benefit from nephrologist involvement at early phases or optimizing the evaluation process.

**Funding:** NIDDK Support, Private Foundation Support

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**FR-PO1109**

Clinical Outcome of Elderly Living Kidney Donors

Kohei Unagami, Masayoshi Okumi, Kazunari Tanabe, Hideki Ishida. Urology, Tokyo Women’s Medical Univ, Tokyo, Japan.

**Background:** Previous studies and current guidelines have suggested that elderly persons can be living kidney donors; however, reports on elderly donors >70 years old are limited. In order to clarify the donor safety and feasibility, we investigate the clinical outcomes of living kidney donors > 70 years old after nephrectomy.

**Methods:** We conducted a case-series study of living kidney donations involving 48 donors aged >70 years at the time of transplantation. The kidney donations occurred between 2001 and 2014 at our institution. The primary outcomes were survival or end-stage renal disease (ESRD)-free rate and all cause event-free rates, including cardiovascular-, infection-, ESRD-, or death-free rate. The secondary outcome was serum creatinine level at the end of the follow-up period.

**Results:** The 48 cases were followed up for a median of 4 years. The survival rate among the donors was 100% until the fifth year, and only two donors died during follow-up. The ESRD-free rate was 100% during the follow-up period. The overall event-free rate was 100% at 1 year, 85.7% at 3 years, and 75.0% at 5 years. The mean serum creatinine level was 1.18 ± 0.24 mg/dL at the time of hospital discharge and did not increase (1.18 mg/dL) at the end of follow-up.

**Conclusions:** Living kidney donation from elderly donors >70 years old appears to be a safe and acceptable option for patients requiring renal-replacement therapy.

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**FR-PO1110**

Opinions of the Medical Community at the University of Iowa Regarding Disincentives and Incentives in Living Kidney Donation Based on Age

Maria T. Story;1 Sarat C. Kuppachi.1,2 1Internal Medicine, Univ of Iowa Hospitals and Clinics, Iowa City, IA; 2Organ Transplant Center, Univ of Iowa Hospitals and Clinics, Iowa City, IA.

**Background:** As the kidney transplant waiting list continues to increase annually, transplant societies have been debating options of incentives to increase organ donation. We surveyed healthcare employees at our institution regarding removal of disincentives and providing incentives to living kidney donors to determine if differences in opinions exist based on age.

**Methods:** The opinions of employees in Internal Medicine, General Surgery, Nursing, and medical students were collected via a web-based survey of 18 questions. IRB approval was obtained. Responses were analyzed using the chi-square test for independence.

**Results:** Of 624 who completed the survey, 120 were <25 years old. 58.7% thought it acceptable to reimburse expenses, while 25.7% advocated for additional incentives. 38.3% believed it was unethical to offer financial incentives for exchange of an organ, but 22.8% believed it was ethical. 82.5% were concerned about exploitation if financial incentives were offered. There were no differences in these opinions based on age < or >25. Respondents aged <25 were significantly more likely (p=0.0002) to accept money for a kidney than those >25.

On multivariate logistic regression, African American donors had lower odds of ultimately donating (p=0.01) and of clearing phases 1 (p=0.01), 3 (p=0.03), and 5 (p=0.001). African Americans had higher odds of delay in phase 3 (p=0.03) and phase 5 (p=0.03).

**Conclusions:** Individuals < 25 were more likely to accept financial incentives for kidney donation than those >25. As transplant societies contemplate incentives in organ donation, we believe awareness of the increased interest from the younger community is important given that long-term outcomes of living kidney donation at a young age are not well understood. Further studies will be necessary to better understand factors for the differences in opinion.

**Funding:** NIDDK Support, Private Foundation Support

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**FR-PO1111**

Abstract Withdrawn
FR-PO1112
Nationwide Strategy for Kidney Transplantation with Controlled Cardiac Death Donor (cDCD) Has Improved Global Results. Spanish Multicentre SENTRA-GEODAS Group
José M. Portoles,1,2 María Jose Perez Saez,1,2 Anna Manonelles,1,2 María Marques Vidas,1,2 Nora Maruri,1 Antonio Fernandez Garcia,1 Auxiliadora Mazuecos,1 Rosalía Valero,1 Alberto Rodriguez-Benot,1 Julio Pascual,1,2 María Jose Perez Saez.1 Nephrology, Hospital Puerta de Hierro SENTRA / GEODAS, Majadahonda, Spain; 2Public Health Research NetRedin16/009/009 RETYC ISCIII.

Background: Controlled donation after cardiac death (cDCD) programs are running in US for years and some European countries has recently started on it. National transplant organization (ONT) has developed a nationwide program in Spain from jan-2012 and 45 Centers had joined by Dec2015 (370 cDCD donors on 2012-15). Eighteen centres have entered our study group. We present here the main clinical outcomes.

Methods: Observational prospective multicentre study. Systematic inclusion of every kidney transplant-KTx from cDCD at joined units. Local center surgical procedures and IS protocols.

Results: We included 215 cDCD, donors aged 56.9 year who have died mainly due to CV events (74%). Effective harvest rate was 93% higher than reported for uncontrolled DCD by ONT (66%) 13 kidneys were discharged for several reasons; his pairs were successfully implanted. 28 transferred and implanted in centers out of our group. We include 389 ESRD recipients: 56.3% 161 males, for 75.6% of them were the first KTxs. Immunosuppression regimen included 98.8% induction (Thymoglobulin 67.3%, Basiliximab 31.5%) plus prednisone-MMF-Tacrolimus (83.1%) or mTOR (6.9%). Median Cold ischemia time (CIT) was 12.5h and warm IT 24min. Median HLA-mismatch was 4 [0-5]. Clinical outcomes: Primary graft failure (PGF) rate was 3% mainly associated to vascular problems no single hyperacute rejection case. Delayed graft function (DGF) was defined as dialysis use on 1st week after KTxs. In spite of DGF rate of 49.7% the death censored graft survival was 97.9% at 1 yr and 92.7% at 2 yr.13 patient died with functional graft and patient survival was 95.3% (Kaplan-Meier).

Conclusions: Harvested graft rate for cDCD are higher than reported for uncontrolled DCD. KTxs with cDCD present higher DGF than historic reference for brain death donor but similar PGF rate and patient or graft survival rates. Our results aim us to promote this cDCD all over the country.

FR-PO1113

Background: Little is known about the association of neighborhood poverty with gender differences in live donor kidney transplant (LDKT) outcomes in the United States.

Methods: Using data from the Scientific Registry of Transplant Recipients and the US Census, we tested whether neighborhood poverty modifies gender disparities in death-censored graft loss and patient death after LDKT. We performed Cox regression models to compare 5-year outcomes among 27,978 men and 17,263 women who received a first LDKT in 2005-2013. We adjusted all models for recipient, donor, and center factors, and to compare 5-year outcomes among 27,978 men and 17,263 women who received a first LDKT. Targeted efforts to address barriers among women living in poor areas may help to mitigate gender disparities in LDKT outcomes.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO1114
Diabetes Mellitus in Living Pancreas Donors: Use of Integrated National Registry and Pharmacy Claims Data to Characterize Donation-Related Health Outcomes Negan L.,1,2 Mark Schnitzler,2 Dorry L. Segev,1 Catherine P. Hess,2 Bertram L. Kasiske,2 David A. Axelrod,3 Amit X. Garg,1 Daniel C. Brennan,1 Krista L. Lenting.1 1Univ of Alberta, Edmonton, AB; 2Saint Louis Univ, St. Louis, MO; 3Johns Hopkins School of Medicine, Baltimore, MD; 4Univ of Pennsylvania, Philadelphia, PA; 5Univ of Minnesota, Minneapolis, MN; 6Dartmouth Hitchcock Medical Center; Hanover, NH; 7Western Univ, London, ON; 8Washington Univ School of Medicine, St. Louis, MO.

Background: Most transplant centers now accept kidney grafts from victims who have acute drug intoxications. Despite the widely acceptance of many of these donors the effect of the acute intoxication on graft outcome is poorly understood.

Methods: We integrated national Scientific Registry of Transplant Recipients data (1987-2015) with results from a nationwide pharmacy claims warehouse (2005-2015) to examine prescriptions for diabetic medications and supplies as a measure of post-donation diabetes mellitus. To compare outcomes in controls with baseline good health, we matched living pancreas donors to living kidney donors (1:3) by demographic traits and year of donation.

Results: Among 73 pancreas donors in the study period, 45 were identified in the pharmacy database: 62% women, 84% white, and 80% relatives of the recipient. Over a mean post-donation follow-up period of 16.3 years, 26.7% of pancreas donors filled prescriptions for diabetes treatments, compared with 5.9% of kidney donors (odds ratio [OR] 4.13, 95% confidence interval [CI] 1.91-9.83; P = 0.0003). Use of insulin (11.1% vs. 0%) and oral agents (20.0% vs. 5.9%; OR 4.50, 95% CI 2.09-9.68; P = 0.0001) was also higher in pancreas donors.

Conclusions: Diabetes is more common after living pancreas donation than after living kidney donation, supporting clinical consequences from reduced endocrine reserve.

Funding: NIDDK Support

FR-PO1115
The Impact of Donor Cannabinoid Intoxication on Outcomes of Kidney Transplantation Blaithin A. McMahon, Khushleela Jagg, Edward S. Kraus, Tessa Kimberly Novick, Steven Menze, Niraj Desai, Sami Alasfah. Johns Hopkins Univ School of Medicine, Johns Hopkins Univ, Baltimore, MD.

Background: Most transplant centers now accept kidney grafts from victims who have acute drug intoxications. Despite the widespread acceptance of many of these donors the effect of the acute intoxication on graft outcome is poorly understood.

Methods: This is a single center retrospective cohort analysis of patients undergoing deceased donor kidney transplantation (DDKT). Donor and recipient characteristics and post transplantation outcomes were obtained from the institutional transplant database. Urine toxicology tests are routine, and we report the results in 115 deceased donors who underwent Neuraxone KТx from deceased donors. Details of the results are presented in Table 1. Delayed graft function (DGF) was defined as the need for dialysis during the first week after transplantation. Graft failure was defined as the need to return to dialysis.

Results: Of 300 random KTxs performed at our institution between January 2012 and October 2015, 200 were from deceased donors. 92 deceased donors (46%) were current drug users. The main toxins detectable in donor urine were alcohol (n=45, 23%), heroin (n=29, 15%), opioid/methadone (n=17, 9%), nicotine (n=46, 18%), cannabinoids (n=38, 19%), benzodiazepines (n=5, 3%), ecstasy (n=1, 0.5%), methamphetamine (n=6, 3%), LSD (n=1, 0.5%). Alcohol, heroin, nicotine, opioids/methadone, benzodiazepines, ecstasy, methamphetamine and LSD were drugs of abuse that had no significant effect on KT outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
outcomes (DGf and graft failure). However, cannabinoid use in donors had significantly higher odds of DGf (odd ratio 2.9 +/- 1.4, P = 0.05) but no effect on graft loss or death (median follow up of 1.69 years). 42 donors (n=18) who used cannabinoids had concomitant use of alcohol but there was no interaction seen.

Conclusions: Cannabinoid use is known to cause acute kidney injury. Our data suggest that cannabinoid use in kidney donors may increase the risk of DGf.

FR-POI116

Background: Kidneys grafts from UDCDD have higher ischemia injury. It develops in higher primary non-function, lower graft survival and worst renal function compared to ideal donors. The aim was to describe risk factors associated with poor renal function (PRF) in a group of renal transplants (RT) from UDCDD.

Methods: We review all RT from UDCDD performed in our center with functioning graft at 1 year. We classified grafts in two groups: Group I grafts with serum creatinine (SCr) > 2 mg/dL at 1 year from kidney transplantation and Group II with SCr < 2 mg/dL. We compared characteristics in both groups.

Results: Our center have performed 207 RT from UDCDD. We excluded 14 (7%) primary non-function and 9 (4%) grafts lost in the first year. 184 (89%) grafts were functioning at 1 year of transplantation. 13 (7%) patients were into Group I and 191 (93%) patients were into Group II. Characteristic of two groups are showed in Table.

Conclusions: The prevalence of PRF at 1 year in RT from UDCDD is low in our center although confirms a bad renal graft prognosis. PRF is associated to donor age, non-function of contralateral kidney graft, recipient weight and gender and acute rejection. A better screening of potential UDCDD, more adequate allocation of this kidneys and a lower acute rejection rate could improve the outcome of renal transplantation from UDCDD.

FR-POI117
Donation after Cardiac Death, Not Extended Criteria Donor Maria Molina, Enrique Morales, Eduardo Gutierrez-Martinez, Manuel Praga, Amado Andres. Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain.

Background: There are few experiences published about long term follow-up of renal transplant (RT) from Donation after Cardiac Death Donors (DCD) from category II of Maastricht classification (Uncontrolled DCD) (people presenting a irreversible cardiac arrest at home or on the street and despite appropriate resuscitation manoeuvres). Outcomes from grafts from Uncontrolled DCD are classically lower than organs from the Donation after Brain Death Donors (DBDD).

Methods: We reviewed all characteristics from RT from Uncontrolled DCD performed between July 2005-December 2012 in our hospital. We compared with a paired RT from DBDD, no hyperimmunized, first renal transplants with similar donor age and recipient survival among AKI and no AKI groups. Interestingly however, when we followed up a limited data regarding the factors affecting long-term graft and recipient outcomes in this kind of donors can significantly increase the number of organ recovered and improve results in kidney transplant programs, particularly for median age recipients.

Conclusions: The high incidence of delayed graft function in uncontrolled DCDD group, probably due to high ischemic stress suffering these donors, has no negative impact on graft outcome. Uncontroled DCDD is an adequate kidney donors. The expansion of this kind of donors can significantly increase the number of organ recovered and improve results in kidney transplant programs, particularly for median age recipients.

FR-POI118
Assessing Deceased Donor Quality Using the Kidney Donor Risk Index: Performance in a Canadian Setting Ann Young,1 Eric McArthur,2 Stephanie Dixon,3 Greg A. Knoll,1 Amit X. Garg,4 Charmaine E. Lok,2 Ngan Lam2, Joseph Kim,2 1Dept of Medicine, Univ of Toronto, ON, Canada; 2Inst for Clinical Evaluative Sciences, Toronto, ON, Canada; 3Div of Nephrology, Univ of Ottawa, ON, Canada; 4Div of Nephrology, Western Univ, ON, Canada.

Background: Deceased donor kidney allocation in the United States is guided by the Kidney Donor Risk Index (KDRI). The applicability of this newer allocation system in a Canadian setting is unknown.

Methods: This population-based cohort study followed deceased donor transplant recipients in Ontario, Canada from Jan 2005 to Mar 2011. Subjects were identified from Ontario’s Trillium Gift of Life Network and linked to other provincial healthcare databases. Ten donor factors were used to calculate the KDRI. Multivariable Cox proportional hazards models were used to assess the association of KDRI with graft loss or death. The role of KDRI in predicting long-term recipient outcomes, when compared to only using donor age, was explored using the likelihood-ratio test.

Results: A total of 1,299 deceased donor kidney transplants were divided into KDRI quintiles. Median follow-up time was 5.5 years. Mean donor age increased across KDRI quintiles from 27 to 64 years. A log-linear association between KDRI and total graft loss (i.e., death, return to chronic dialysis, or preemptive re-transplant) was observed. Total graft loss increased across KDRI quintiles from 3.9% to 20.2% for all patients. The adjusted hazard ratio at 95% CI from Q2 to Q5 (referent = Q1) were 1.27, (0.89, 1.80), 1.58 (1.13, 2.22), 1.43 (1.01, 2.02), and 2.15 (1.54, 2.99), respectively. Increased hazard ratios across KDRI quintiles were also observed for death-censored graft loss, but not for death. In this cohort, the KDRI significantly improved the assessment of donor quality compared to models using donor age alone (p=0.009).

Conclusions: The KDRI can be used in Canadian patients to identify kidneys at increased risk for graft loss, and can potentially inform risk assessment beyond using donor age alone. Whether the KDRI can be further refined in this population, and effectively applied in other Canadian jurisdictions, requires further study.

Funding: Government Support - Non-U.S.

FR-POI119
Risk Stratification for Optimized Utilization of Deceased Donor Kidneys with Acute Kidney Injury by KDIGO criteria Mi-Yeon Yu, Yong Chul Kim, Jung Pyo Lee, Youn Su Kim, Hajeong Lee. Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.

Background: Deceased donor kidneys with acute kidney injury (AKI) raise fear of poor graft outcomes to clinicians and consequently are often discarded. However, the growing evidence has suggested that they may be a good solution to overcome organ shortage. Although previous studies have focused on fair outcome of donor AKI, there is a limited data regarding the factors affecting long-term graft and recipient outcomes in patients received deceased donor kidneys with AKI.

Methods: We included all patients who received deceased donor kidney transplant from 2005 to 2011. We defined AKI by KDIGO criteria. Primary outcome was graft survival beyond 10 years by donor AKI stage. Secondary outcomes were 6 month, 1, 3, 5 years graft function, and 5-year recipient survival.

Results: Among a total of 413 patients, 156 received kidneys from donors with AKI including 84 stage 1, 38 stage 2, and 34 stage 3. 257 were received kidneys from donors without AKI (no AKI group). AKI developed more in ECD and hypotensive donors. There was no significant difference in delayed graft function, overall graft and recipient survival among AKI and no AKI groups. Interestingly however, when we followed up annual graft function, patients who received stage 3 AKI donor kidneys showed significantly lower 5-year graft function (median eGFR 45 [23–67] mL/min/1.73m²), compared with no AKI (median eGFR 65 [40–90]), stage 1 AKI (median eGFR 59 [39–78]), and stage 2 AKI (59 [34–84]), respectively (P=0.019). Risk factor analysis for graft survival demonstrated worsening renal function just before transplantation elevated risk of both graft failure (adjusted HR 7.65, 95% CI 1.63–35.89) and patient survival (adjusted HR 20.67, 95% CI 1.33–321.99).

Conclusions: Although deceased donor AKI was not associated with overall graft and recipient survival, stage 3 AKI had an influence on lower graft function. Moreover, worsening renal function just before transplantation was an independent risk factor for both graft and patient survival.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO1120

Differential Intragraft Gene Expression Profile of Kidney Transplant Patients on Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotenin Receptor Blocker (ARB) Christian Suarez-Fuentes, Yi Bao, Enver Akalin. Montefiore Einstein Transplant Center, Bronx, NY.

Background: Treatment with ACEI/ARB has been shown to have anti-inflammatory effects in animal models but this effect has not been investigated in kidney transplant recipients. We aimed to study the effect of ACEI/ARB treatment on intragraft gene expression profiles of transplant kidney biopsies using microarrays.

Methods: We identified near normal biopsies with chronic sum allograft injury score (ct+ci+cv) ≤ 3 for gene expression profiling. Biopsies with a diagnosis of acute or chronic rejection, glomerular disease, or polyoma nephropathy were excluded. The gene expression profiles were studied by Affymetrix HuGene 1.0 ST expression arrays. We compared 2 groups; Group 1 (n=16), patients with no exposure of ACEI/ARB treatment and Group 2 patients (n=13) with exposure to ACEI/ARB at least 6 months prior to kidney biopsy.

Results: Both groups had similar demographics characteristics in terms of age, race, sex, type of transplant, previous history of transplantation or acute rejection, panel reactive antibody levels and immunosuppressive treatment. There were no differences in acute and chronic Banff allograft injury scores between the 2 Groups. Intragraft gene expression profiles of ACEI/ARB treated Group 2 biopsies showed decreased gene transcripts of interferon-gamma and rejection-associated transcripts (GRIT) and constitutive macrophage-associated transcripts (CMAT) compared to Group 1 biopsies. There were no statistically significant differences in expression of cytotoxic T cell (CAT), regulatory T cell (TREG), B-cell (BAT), natural killer cell (NKAT), and endothelial cell-associated transcripts (ENDAT) between the 2 Groups.

Conclusions: We have shown that exposure to ACEI/ARB was associated with down-regulation of GRIT and CMAT. This anti-inflammatory effect could be an additional benefit in kidney transplant recipients.

Funding: Other NIH Support - T-32 Research Grant
SA-PO001

Epitope Sharing Causing Crossmatch Positivity in a Kidney Transplant Candidate with Very Low Pre-Transplantation Anti-Human Leukocyte Antigen Antibody Titer: A Case Report

Iris C. De Castro,1 Paul Warner,2 Christopher D. Blosser.1 1Nephrology, Univ of Washington, Seattle, WA; 2Bloodworks Northwest, Seattle, WA.

Introduction: Human leukocyte antigen (HLA) have multiple epitopes. An epitope or antigenic determinant is a part of an antigen that is capable of stimulating an immune response. Epitopes can be shared by different HLAs. HLA antibodies usually react to epitopes rather than antigens. We present a patient who, despite having very low titer HLA antibodies, repeatedly tested positive on B cell flow crossmatch (FXM) with 6 potential donors making her not suitable to receive the kidney offer.

Case Description: 62yo ABO A+, Caucasian female with 3 pregnancies, no blood transfusions and ESRD from chronic glomerulosclerosis on peritoneal dialysis. Despite cPRA 0% and single antigen bead (SAB) test showing HLA Class I and II under 1,000 MFI (positive cutoff is ~2500MFI), she tested FXM positive with 6 potential donors. On review, all HLA-DR DQ4 beads except HLA-DR7 were clustered with MFI between 300 and 950. She was found to have an antibody to a shared epitope by all HLA-DR antigens except HLA-DR7. As it was a single antibody, it only showed low level MFI on SAB making each, individually, insignificant. But, when crossmatched against non-DR7 lymphocytes, this was sufficient to yield a positive result. This was confirmed by FXM against numerous surrogate donors with different HLA-DR antigens. She had positive FXM with cells carrying any DR antigen other than DR7 and negative FXM to all HLA-DR7 homoygous donors.

Discussion: HLA antibodies that recognize broadly expressed epitopes can produce seemingly normal, low-level MFI SAB results, but FXM positive when exposed to only one of the antigens carrying the target epitope. Previous literature have reported that pre-transplantation low-level donor specific antibodies can induce severe acute antibody mediated rejection early after transplantation as a result of shared epitopes. Since the patient had persistent positive FXM against non-DR7 cells, all other DR antigens were added as unacceptable, resulting in a cPRA 99%. This case illustrates the importance of recognizing epitope sharing and its implications on kidney transplant allocation.

SA-PO002

Hyperkalemia during Voriconazole Treatment in Three Kidney Transplant Patients

Mohammed Nazmul,1 Scott G. Westphal, Clifford D. Miles. Nephrology, Univ of Nebraska Medical Center, Omaha, NE.

Introduction: Voriconazole (VOR) is a commonly used antifungal agent in renal transplant recipients who develop fungal infection. Here we present a previously unreported observation of moderate to severe hyperkalemia occurring in three patients started on VOR. In each case, the hyperkalemia developed despite adjustment in tacrolimus (TAC) dose to maintain therapeutic, low serum levels.

Case Description: We identified three kidney transplant recipients who were started on VOR for the treatment of histoplasmosis, and developed hyperkalemia following its initiation. Each patient was maintained on a TAC-based immunosuppression regimen. Hyperkalemia was not present in any of the three patients prior to starting VOR, and TAC dose was decreased to keep trough levels at 3-6 ng/ml. All patients were instructed to follow a low potassium diet and additional medications known to cause hyperkalemia were avoided. Patient #1 had several episodes of severe hyperkalemia with a peak potassium level 8.5 mEq/L occurring 2-40 days after starting voriconazole. At that time, his TAC level was 4.1 ng/ml and creatinine was 2.3 mg/dL. He ultimately was converted from TAC to everolimus, and the hyperkalemia resolved. Patient #2 had persistent hyperkalemia following initiation of VOR. His peak serum potassium reached 6.5 mmol/L occurring 75 days after starting VOR. His TAC level was 4.0 mg/dl and creatinine was 1.8 mg/dl at that time. Patient #3 had intermittent moderate hyperkalemia after starting VOR. His peak potassium level was 5.7 mmol/L which occurred 54 days after starting VOR. At the time of his peak potassium, his TAC level was 2.1 mg/ml and creatinine was 2.9 mg/dl.

Discussion: While interactions between azoles and calcineurin inhibitors are widely recognized, this is the first report describing new onset hyperkalemia following initiation of VOR in kidney transplant patients receiving TAC. In each patient, the hyperkalemia developed despite maintaining low level, therapeutic TAC levels. The mechanism behind this observation remains unclear, but may warrant further investigation. Clinicians should be vigilant for hyperkalemia when TAC and VOR are used concurrently.

SA-PO003

Autoimmune following Kidney Transplantation: A Case of De Novo Behcet’s Disease

Isabel Remedios,1 Isha Ashoor,2 Pediatrics, Louisiana State Univ Health Sciences Center, New Orleans, LA; 1Nephrology, Children’s Hospital, New Orleans, LA.

Introduction: Autoimmune disease is a rare occurrence following kidney transplant (KT). Its development may be a marker of inadequate immunosuppression secondary to altered drug pharmacokinetics or non-adherence. We present a case of Behcet’s disease (BD), a rare mucocutaneous ulcerative autoimmune condition in a non-adherent sexually active young adult KT recipient that was initially mistreated for Herpes Simplex Virus (HSV) infection.

Case Description: A 19 year-old African American female with a history of bilateral Wilms tumors, and prior failed KT due to chronic rejection presented 4 years following her second deceased donor KT with acute fever, non-bloody diarrhea, and ulcerations of the mouth, vulva, and perianal region. Her transplant course was notable for multiple rejection episodes and several sexually transmitted infections. The ulcers appeared herpetic/focal aphthous in nature. Given her chronic immunosuppression with tacrolimus, mycophenolate, and prednisone, and recent sexual encounter, disseminated HSV was suspected. She was empirically treated with IV acyclovir. After 1 week of therapy, fever and diarrhea resolved, but ulcers remained unchanged. All infectious studies returned negative. Lupus serologies and Crohn’s disease screening tests were negative. Vulvar punch biopsy showed a neutrophilic/leukocytoclastic vasculitis consistent with BD.

Discussion: Although rare, BD is an important cause of non-infectious orogenital ulcers. We describe the only KT patient in the literature with biopsy confirmed novo BD independent of pre-existing glomerulonephritis. A high index of suspicion is required to diagnose BD in this population to limit prolonged exposure to nephrotoxic medications.

SA-PO004

De Novo Post-Streptococcal Glomerulonephritis as the Cause of Transplant Acute Kidney Injury

Alexander Bullen, Mita M. Shah. Div of Nephrology-Hypertension, Univ of California San Diego, San Diego, CA.

Introduction: Acute kidney injury (AKI) is common in kidney transplant recipients (KTR) and is a risk factor for graft failure and death. We present a rare case of AKI in a KTR, acute post-streptococcal glomerulonephritis (APSGN).

Case Description: A 45-year-old male with history of ESRD secondary to unknown etiology status post living donor kidney transplant two years prior, with baseline serum Cr of 1.5 mg/dL, presented to kidney transplant clinic. He was recovering from a “cold” the week prior. His immunosuppressive regimen consisted of tacrolimus 3 mg BID, mycophenolate mofetil 750 mg BID and prednisone 10 mg QD; he had inadvertently been taking 1 mg BID of tacrolimus for several weeks. On clinical exam he was normotensive and afebrile, without graft tenderness or bruit; 3-4 mm pitting edema was noted in the lower extremities. Laboratory data showed a Cr of 2.2 mg/dL increased from 1.6 mg/dL a month prior, tacrolimus trough of 4.9, UA moderate blood, > 50 RBCs, J+ protein and urine protein/creatinine ratio of 8.2. UA a month prior did not reveal blood or proteinuria. Anti-streptolysin O antibody was elevated at 603 (0-330 IU/mL), C3 was low and C4 was normal. Biopsy revealed submembranous electron dense deposits in mainly paramesangial areas and large subepithelial electron dense deposits, consistent with APSGN and no evidence of cell or antibody mediated rejection.

A month later, Cr had decreased to 1.9 mg/dL. In three months, it had returned to baseline and proteinuria and edema had resolved.

Discussion: APSGN is caused by nephritogenic strains of group A beta-hemolytic streptococcus. The clinical spectrum ranges from asymptomatic disease to acute nephritic syndrome as in our patient. This case reveals the importance of a prompt and thorough evaluation of AKI in KTRs having a low threshold to perform a renal biopsy to assess for other entities such as APSGN.
SA-PO005

Haunted by Ghosts: An Unlikely Explanation of Hematuria in a Renal Transplant Patient

Ruchita Jariwala,1 Dia Rose Waguespack,1 William F. Glass,2 Angelina Edwards.1
1Div of Renal Diseases and Hypertension, The Univ of Texas Health Science Center at Houston, TX; 2Div of Pathology and Laboratory Medicine, The Univ of Texas Health Science Center at Houston.

Introduction: Anticoagulant use for the prevention and treatment of thrombosis is indicated in a variety of clinical settings. Anticoagulant nephropathy is a clinical entity of great importance as more anticoagulants are developed and used in broader clinical settings. We report a case of anticoagulant nephropathy in a renal transplant recipient after the initiation of warfarin for lower extremity deep vein thrombosis.

Case Description: A 62-year-old man underwent a living related donor kidney transplant for end stage renal disease secondary to Hypertension and Diabetes. He had a complicated postoperative course requiring surgical correction of ureteral leak with stent placement, repair of the transplant renal artery and anticoagulation initiation with warfarin for low to lowered international normalized ratio (INR) requiring less than 3, he had persistent microscopic hematuria with intermittent episodes of gross hematuria. Upon completion of anticoagulation, a renal transplant biopsy was performed for evaluation of elevated creatinine and persistent microscopic hematuria. Biopsy was negative for rejection but showed acute tubulointerstitial injury with red blood cell (RBC) casts and RBC ghosts suggestive of prior glomerular hemorrhage and anticoagulant related nephropathy. His hematuria resolved at follow up and his creatinine gradually improved with cessation of anticoagulation.

Discussion: Anticoagulant related nephropathy is a cause of acute kidney injury (AKI) that is frequently underdiagnosed and underappreciated. Although most cases occur with supratherapeutic INR, anticoagulant related nephropathy can occur even with modest elevations. In this case, the pathologic findings of RBC ghost casts suggest lysis and degeneration of RBCs from prior bleeding episode. Thus, anticoagulant related nephropathy can be the clinical presentation even after discontinuation of anticoagulation. This case serves to broaden the differential of AKI and hematuria in a kidney transplant patient previously on anticoagulation.

SA-PO006

An Unusual Case of Acute Myeloid Leukemia Cell Infiltration of the Renal Allograft

Sandhya Manohar,1 Insara Jaffer Sathick,1 Joseph P. Grande,2 Ziad El-Zoghby,1 Nelson Leung.1 1Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Pathology, Mayo Clinic, Rochester, MN.

Introduction: Native kidney involvement of hematological malignancies is common and can often be the presenting feature. Renal involvement is seen in about 34% of patients by autopsy studies. To our knowledge, there has been no reported case of acute myeloid leukemia (AML) infiltration in the kidney allograft and here we present such a case in a kidney transplant patient.

Case Description: A 59-year-old male presented to us for management of his recently diagnosed AML. He had a history of end stage renal disease from diabetic nephropathy and underwent deceased donor kidney transplant at an outside facility. He was maintained on a prednisone and cyclosporine regimen with a unremarkable course for 14 years. A year prior to presentation, his platelet count was 50 X 10^9 and his creatinine was 0.8. A bone marrow biopsy showed increased myeloid precursors with increased blasts (29%) consistent with acute myeloid leukemia (AML). He was sent to us for further management. We presented to us, his creatinine was 2.7 mg/dl. His urinalysis revealed mild hematuria with 24 hour urine protein of 953 mg/g of creatinine. He underwent a kidney allograft biopsy which revealed multifocal myeloid infiltrates compatible with renal involvement of AML. He was started on chemotherapy but he progressively deteriorated and passed away.

Discussion: It is well known that transplant patients are at a higher risk of developing cancers with dermatological cancers and lymphomas being the bulk of these but AML is less common. The Cincinnati Transplant Tumor registry of 1991 noted 2.7% of the cancers to be due to leukemia, of which 43% were AML. A study of autopsy cases of patients with hematological cancers had shown renal involvement in 34% of the cases. It was most common in patients with acute lymphoid leukemia (83%) but interestingly patients with hematological cancers had shown renal involvement in 34% of the cases. It was most common in patients with acute lymphoid leukemia (83%) but interestingly patients with hematological cancers had shown renal involvement in 34% of the cases.

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

SA-PO007

A Case Report - Phenytoin Overdose Treated with Hemodialysis Using a High Cutoff Filter

Jocelle Mandini,1 Monique Cormier,1 Simon Desmeules,2 Marc Ghannoum.1 1Nephrology, Hôpital de Verdun, Montreal, QC, Canada; 2Nephrology, Centre Hospitalier Unis de Québec, Québec, QC, Canada.

Introduction: The role of hemodialysis (HD) to enhance phenytoin clearance in overdose cases is uncertain. Because of phenytoin’s high protein binding (90%), it is hypothesized that dialysis using more porous filters may accentuate clearance of phenytoin. This report is the first description of phenytoin removal using a Theralfil® filter, a high cut-off filter that allows the removal of molecules with a molecular mass of up to 45 kDa.

Case Description: A 54-year-old man who ingested an unknown amount of phenytoin had a phenytoin level of 51.2 mg/L (therapeutic range 10-20mg/L) and coma, both of which remained relatively constant for 12 days. HD was prescribed to enhance elimination of phenytoin by Dury V. Despite its international normalized ratio (INR) requiring less than 3, he had persistent microscopic hematuria with intermittent episodes of gross hematuria. Upon completion of anticoagulation, a renal transplant biopsy was performed for evaluation of elevated creatinine and persistent microscopic hematuria. Biopsy was negative for rejection but showed acute tubulointerstitial injury with red blood cell (RBC) casts and RBC ghosts suggestive of prior glomerular hemorrhage and anticoagulant related nephropathy. His hematuria resolved at follow up and his creatinine gradually improved with cessation of anticoagulation.

Discussion: Anticoagulant related nephropathy is a cause of acute kidney injury (AKI) that is frequently underdiagnosed and underappreciated. Although most cases occur with supratherapeutic INR, anticoagulant related nephropathy can occur even with modest elevations. In this case, the pathologic findings of RBC ghost casts suggest lysis and degeneration of RBCs from prior bleeding episode. Thus, anticoagulant related nephropathy can be the clinical presentation even after discontinuation of anticoagulation. This case serves to broaden the differential of AKI and hematuria in a kidney transplant patient previously on anticoagulation.

SA-PO008

Renal Auto-Transplantation: An Emerging Approach to Revascularization in Takayasu Arteritis Induced Renal Artery Stenosis (TARAS)

Joelle Mardini, Catherine L. Weber, Nephrology, McGill Univ Health Center, Montreal, QC, Canada.

Introduction: Takayasu arteritis (TA) can lead to stenosis, occlusion or aneurysmal transformation of the aorta and its primary branches. Renal artery involvement is common leading to renovascular hypertension and its complications. Renal revascularization in this setting has been shown to control blood pressure and enhance long-term renal and cardiac function as well as survival. We describe a case of successful renal revascularization via renal auto-transplantation (RAT).

Case Description: A 38-year-old hypertensive female was diagnosed with TA in 2014 when CT imaging revealed diffuse wall thickening of pulmonary arteries, abdominal aorta and bilateral renal artery stenosis: 100% on the right with an atrophic kidney and 80% on the left proximal even after stent augmentation of the native renal artery. Renal angioplasty had the most dense infiltration with involvement of almost the entire kidney. But to prevent the immune response of N on the kidney transplant.

Case Description: A 62-year-old man underwent a living related donor kidney transplant for end stage renal disease secondary to Hypertension and Diabetes. He had a complicated postoperative course requiring surgical correction of ureteral leak with stent placement, repair of the transplant renal artery and anticoagulation initiation with warfarin for lower extremity deep vein thrombosis.

SA-PO009

Preserved Renal Allograft Function While Using the PD-1 Pathway Inhibitor Nivolumab

Valerie Suzanne Bart,1 Madhu C. Bhaskaran, Kenar D. Jhaveri, Nicole M. Ali, Viren G. Amin, Richard L. Barnett.1 Nephrology, Northwell Hofstra School of Medicine, Great Neck, NY.

Introduction: Treatment of malignancies in renal transplant (RT) recipients has largely consisted of targeting the cancer and reducing the immunosuppression. Newer therapies using programmed cell death protein 1 (PD-1) pathway inhibitors such as Nivolumab (N) have been associated with transplant rejection usually within 6-8 weeks of initiation. We report a living related donor (LRRT) where a pre-emptive and sirolimus (S) regimen prevented the immune response of N on the kidney transplant.

Case Description: 70 year old Caucasian male, ESRD consequent to bilateral nephrectomy in 2000 and 2007 for renal cell cancer underwent LRRT in 2010. In early 2015 he developed adenocarcinoma of the duodenal metastatic to the treated in the past year with intestinal stenting and with minimal response to multiple rounds of chemotherapy. Further disease progression led to initiation of N in 3/2016. 40mg of prednisone was initiated and prograf was replaced by S. Serum Cr was 1.35mg/dL and dipstick protein negative. S was adjusted for trough levels 4-6mg/dL. The following month upper intestinal obstruction was addressed with feeding tube and venting G tube. In 5/2016 he was successfully treated for Staphylococcus Aureus with meropenem and Cefazolin. Since N therapy his body weight has been maintained at 90kg, serum albumin 3.0g/dl, Cr DECLINED to 0.7 and urine protein/Cr was 0.3. 6/2016 donor specific antibodies were negative and CT scan revealed no disease progression.

Discussion: Checkpoint inhibitors of PD-1 class (N) and CTLA-4 antagonists have demonstrated benefit by restoring T cell mediated tumor suppression. There has been an increased risk associated with this therapy and advances in immune checkpoint inhibitors (ICIs) have been focused on improved safety, efficacy and development of novel combination regimens. In these patients lower dose steroids with calcineurin inhibitors were employed. We present a novel strategy to prevent rejection in the RT patients receiving PD-1 inhibitors using pre-emptive steroids and sirolimus.

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Underlines represent presenting author.
**SA-PO010**

**Babesiosis: An Unusual Cause of Sepsis in a Kidney Transplant Recipient**  

**Introduction:** Infections are a common cause of morbidity and mortality in solid organ transplant recipients due to the use of chronic immunosuppressive therapy necessary to prevent rejection. There is a dearth of literature regarding parasitic infections in organ transplant patients with no randomized studies. We report a unique case of babesiosis presenting as sepsis in a renal transplant recipient.

**Case Description:** This case reports a 70-year-old female with a history of deceased-donor kidney transplant who presented with a recent history of severe fatigue and intermittent fevers. Viral and bacterial screening and routine labs were normal but met criteria for sepsis with 3 of 4 systemic inflammatory response syndrome (SIRS) criteria, along with a suspected source of infection. She also had acute kidney injury (AKI) and hemolytic anemia. A thorough workup did not reveal any specific hematologic etiology, and blood and urine cultures were negative for bacterial infection. Ultimately, serology was positive for Babesia species, confirmed by PCR. The patient was successfully treated with a course of atovaquone and azithromycin and had a full recovery.

**Discussion:** Our case highlights the inherent difficulty in early recognition of babesiosis in the transplant patient population, in whom pancytopenia is a common finding with a broad differential diagnosis. Another interesting aspect of our case was the fact that our patient clinically presented with sepsis with a suspected source of infection. Parasites are usually an uncommon cause of sepsis, although it has been seen in severe malarial infections. In conclusion, our case represents the fifth reported case of babesiosis in a solid organ transplant recipient, as well as the first case of presenting with sepsis as which was successfully treated. As the solid organ transplant population has a high susceptibility to infection as well as numerous potential etiologies for the development of hemolytic anemia, it is essential for the clinician to be aware of babesiosis and consider it in the differential diagnosis in this setting.

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**SA-PO011**

**A Rare Case of Severe Emphysematous Pyelonephritis of the Transplant Kidney Successfully Treated with Percutaneous Drainage and Antibiotics**  
Abdul SA-PO011, Babesiosis: An Unusual Cause of Sepsis in a Kidney Transplant Recipient  

**Case Description:** A 41 year old lady with a history of ESRD from diabetes with a deceased donor renal transplant two years ago was transferred to our hospital after being treated for a urinary tract infection at an outside facility. She had sepsis and ongoing acute oliguric renal insufficiency and was started on intravenous antibiotics and fluids. Although her prednisone and tacrolimus were continued, mycophenolate was held due to the infection.

**Discussion:** An ultrasonogram revealed hypeerechoic foci within renal transplant corresponding to regions of air with subcapsular and peripheal fluid collections with a CT scan confirming the same. A CT guided aspiration of the biggest fluid containing area was performed the following day and purulent fluid drained. Over the next several days, her renal failure resolved and creatinine returned to baseline. She was discharged on oral antibiotics to complete a total of two weeks of antimicrobial therapy. A CT scan obtained 3 weeks later showed resolution of emphysematous changes with only trace perihepatic remaining.

**Case Description:** The described above is a rare instance of severe EPN where an allograft nephrectomy was avoided and PCD with antibiotic therapy proved successful. Although available evidence suggest that severe EPN has not been shown to respond to conservative management, early intravenous antinfectious therapy and percutaneous drainage of identifiable pockets of gas and fluid may help salvage the allograft and give a new lease of life to it. 1. Emphysematous pyelonephritis. Clinicoanatomical classification, management, prognosis and pathogenesis. Huang et al. Arch Intern Med. 2000;160(6):797-805.

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**SA-PO012**

**Furosemide Desensitization for Sulfonamide Hypersensitivity**  
Musab S. Hommos,1 Jay Jin,2 Gerald W. Velchev,3 Suzanne M. Norby,4 Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 5 Div of Allergic Diseases, Mayo Clinic, Rochester, MN.

**Introduction:** Thiazide and loop diuretics with the exception of ethacryn acid contain a sulfonamide moiety that can cause hypersensitivity reactions. While sulfonamide sensitive patients can take ethacrynic acid safely, volume management becomes challenging when ethacrynic acid is not tolerated.

**Case Description:** A 58-year-old male with systolic heart failure and chronic kidney disease stage 5 on dialysis developed pruritus while taking furosemide. Skin biopsy showed subacute dermatis with eosinophils compatible with drug reaction. A trial off his medications revealed furosemide as the probable cause of the rash. With two attempts at using ethacryn acid, severe diarrhea occurred. Trials of sulfonamide-containing bumetanide, torsemide, hydrochlorothiazide and metolazone all resulted in rash. Ten days after stopping all diuretics, he was hospitalized for decompensated heart failure and underwent ultrafiltration. Repeat skin biopsy ruled out vasculitis, lichenoid tissue reaction and immunobullous disorders. During the next week, rash, pruritus and dyspnea resolved. Furosemide desensitization procedure was performed as outlined below without recurrence of skin rash. He was dismissed from hospital on furosemide 40 mg BID.

**Discussion:** Sulfonamide hypersensitivity is a clinical diagnosis with a variety of presentations, from limited skin reactions to life threatening anaphylaxis. Providers need to be aware of the possibility of cross reactivity due to the sulfonamide moiety present in many diuretics. Although desensitization is usually done for immediate type hypersensitivity, it is also reported to be successful in cases of delayed type hypersensitivity. Desensitization is a potential option when treating patients with diuretic intolerance due to sulfonamide hypersensitivity.

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

Underline represents presenting author.

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**SA-PO013**

**Infection in the Transplanted Kidney: TB or Not TB?**  
Megha Salani, Manish Anand, Mark Lusco, Beatrice P. Concepcion, Paul Persad. Vanderbilt Univ Medical Center.

**Introduction:** Solid organ recipients with latent tuberculosis infection (LTBI) are at increased risk for TB reactivation. These patients can have variable presentations, commonly with pulmonary, lymph node, and/or genitourinary tract involvement. We present a unique case of TB reactivation limited to the renal allograft.

**Case Description:** A 38 year old Indonesian female with ESRD due to GN nephropathy underwent a deceased donor kidney transplant in 1/2015. Immediately post-transplant, she was found to have an LTBI and was treated with 9 months of isoniazid (INH). In 11/15, she presented with fever, allograft pain, and headaches. These symptoms persisted despite the use of broad-spectrum antibiotics. Initial blood and urine cultures were negative. Creatinine increased over the hospital course. The patient eventually underwent evaluation with a PET scan, which demonstrated hypermetabolic activity in the renal allograft. Kidney biopsy was performed and revealed diffuse multi-focal necrotizing granulomatous interstitial nephritis with a diffuse pleomorphic interstitial infiltrate. Bacterial, fungal, and mycobacterial stains, PCR, and cultures from the biopsy were negative. Aetiology was detected but the pattern of granulomas was not consistent with adenosvirus. Due to a high suspicion of TB based on histopathology, the patient was started on empiric INH, rifabutin, ethambutol, pyrazinamide, and moxifloxacin. After one week of therapy, her fevers resolved and her creatinine returned to baseline. She has completed 6 months of treatment and is currently without evidence of disease.

**Discussion:** Solid organ transplant recipients more commonly have extrapulmonary and disseminated TB than the general population. Our patient had a unique presentation limited to her renal allograft but was ultimately diagnosed with TB reactivation based on her history, histopathology on biopsy, and response to therapy. Given the low sensitivities of mycobacterial assays, a high index of suspicion for TB is warranted in patients with risk factors despite negative cultures or PCR. Particularly, the finding of necrotizing granulomas in a patient with prior TB exposure should prompt consideration of empiric TB treatment.

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**SA-PO014**

**Multi-Focal Tuberculous Osteomyelitis in a Renal Transplant Recipient**  
Hari Krishna Reddy Mogili,1 Boju Sangeetha Lakshmi,2 Anil Kumar Cheni Venkata,1 R. Ram,3 V. Siva Kumar,1 Abhilash Koratala.3 Sri Venkateswara Inst of Medical Sciences, India; 2Univ of Florida.

**Introduction:** Tuberculous osteomyelitis, an uncommon form of extra-pulmonary tuberculosis (EPT), accounts for 1-2% of all cases of tuberculosis (TB) and 10% of cases of EPT. Spine is the most common location of skeletal TB accounting for ~50% cases. Multifocal tuberculous osteomyelitis with involvement of metatarsals and phalanges is extremely rare. Herein, we report a case of metatarsal and pharyngeal tuberculous osteomyelitis in a kidney transplant recipient.

**Case Description:** A 26 year old Asian-Indian female presented to our institution for painful swelling in the left foot for ~10 days. She has history of End stage renal disease secondary to Lupus Nephritis and underwent deceased donor renal transplantation 3 months prior to presentation. At the time of transplant, she got Basiliximab induction and currently maintained on Tacrolimus 0.75mg bid, Mycophenolate mofetil 1000mg bid and Prednisone

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17.5 mg/day. MRI of the foot showed osteomyelitis of second metatarsal with overlying abscess. Needle aspiration of the abscess revealed numerous acid-fast bacilli (AFB) with positive Mycobacterium TB polymerase chain reaction. 3 days later, she developed painful swelling of the right thumb and little finger and aspiration showed AFB. We started her on rifampicin-free anti-TB therapy and she responded well with clinical improvement over next two weeks. Pertinent findings are shown in the figure.

Discussion: Patients with skeletal TB usually present insidiously without systemic signs such as fever, night sweats, toxicity or extreme weakness. This condition may mimic malignancy, both clinically and radiographically. It’s prudent for clinicians to consider this differential in immunocompromised patients presenting with long-term musculoskeletal pain especially those travelling from or transplanted in TB-endemic countries.

SA-PO015

Introduction: Emphysematous cystitis (EC) is a rare, but severe manifestation of urinary tract infection (UTI) characterized by spontaneous gas formation in the bladder lumen and bladder wall. Diabetes is the most common predisposing factor followed by neurogenic bladder and chronic bladder outlet obstruction. We report a case of EC in a kidney-pancreas transplant recipient on immunosuppressive therapy (IS) who is currently not a diabetic.

Case Description: 57 year old male with Diabetes mellitus type I, hypertension and ESRD status post combined Kidney-pancreas transplant 10 years ago presented with suprapubic pain, dysuria, and hematuria for 3 days. His maintenance IS included tacrolimus 6 mg bid, mycophenolate 750 mg bid and prednisone 10 mg daily. No fever. Labs showed hemoglobin 11.5 g/dL, WBC 9200 cells/cmm with 72.2% neutrophils. Serum creatinine was 1.2 mg/dL. Urinalysis showed hematuria and pyuria, urine culture revealed > 100,000 CFU/mL of Klebsiella pneumoniae. CT scan showed distended urinary bladder with abnormal urothelial enhancement and multiple foci of air in the bladder wall, suggestive of EC. Renal allograft was unremarkable and native kidneys were atrophic. Cystoscopy showed diffuse submucosal emphysematous lesions. He was treated with intravenous antibiotics and made a full recovery.

SA-PO016
Cerebral Lymphomatoid Granulomatosis (LYG) Treated Effectively with Rituximab in a Simultaneous Pancreas-Kidney (SPK) Transplant Patient Faisal Khaled Alhomayani, Muhammad A. Bukhari, David C. Holland, M. Khaled Shamseddin. Nephrology Div, Queen’s Uni, Kingston, ON, Canada.

Introduction: Lymphomatoid granulomatosis (LYG) is a rare multisystem angiocentric B-lineage lymphoproliferative disease with significant malignant potential and mortality, affecting primarily immunocompromised patients. A 51-year-old female presented with a two-day history of headache, fever, and vomiting. She had a history of Type 2 Diabetes, end stage renal disease, and SPK transplantation in 2004 (CMV: Donor negative/Recipient negative; EBV: Donor negative/Recipient positive), with normal function of both grafts. She had been induced with basiliximab then maintained on mycophenolate mofetil and tacrolimus. Post transplant course was uneventful, without any complication. Physical examination was unremarkable. Investigations: CBC, electrolytes, creatinine, urea, LFT, INR, PTT were unremarkable. An enhanced MRI head showed seven ring-enhancing brain lesions. CT chest, abdomen and pelvis were unremarkable. The mycophenolate was tapered off, tacrolimus was reduced and prednisone introduced. The patient was diagnosed with LYG based on cerebral biopsies. With switching tacrolimus to sirolimus combined with 4 weekly doses of IV rituximab, complete resolution of 5/7 lesions occurred while the other lesions decreased significantly in size on MRI one month post rituximab. She is clinically well with stable both graft functions. Her Epstein-Barr virus (EBV) viral load fell from 14,990 copies/mL to 0 at the cessation of rituximab. Post-transplant lymphoproliferative disease (PTLD) is the worst complication of solid organ transplantation occurring in 0.5-1.9% of patients. LYG is rarer than PTLD in transplant patients: both diseases may be triggered by EBV. Literature review identified seven cases of LYG in renal transplant patients. To our knowledge, this is the second report of successfully rituximab-treated cerebral LYG; the other being a renal transplant recipient with a durable (>4 years) complete remission of LYG.

Funding: Clinical Revenue Support

SA-PO017
Acute Posttransplant aHUS due to a Homozygous Deletion of CFHRI/CFHRI3 with CFH-Autoantibodies Managed by a CNI-Free Regimen with Belatacept and Eculizumab Johannes Muench, Anette Bachmann, Christof Mayer, Tom H. Lindner, Jan Halbrügger. Internal Medicine, Div of Nephrology, Univ of Leipzig, Leipzig, Germany.

Introduction: Acute renal graft failure may clinically present as atypical hemolytic uraemic syndrome (aHUS), resulting from excessive activation of the complement cascade. Mutations of the complement coding genes predispose for development of aHUS. “Second hits” (e.g. drugs, pregnancy) commonly trigger the full-blown clinical picture. As calcineurin inhibitors (CNI) are considered as one of these potential triggers, CNI-free regimens would be favorable for avoidance of aHUS manifestation and long-term toxicity. However, there is little experience regarding management of posttransplant aHUS and adequate long-term immunosuppression in these patients.

Case Description: A 58-year-old Caucasian female (ESRD of unknown origin) developed acute renal graft failure within days after transplantation, which clinically presented as aHUS (hemolytic anemia, thrombocytopenia, glomerular thrombotic microangiopathy). With complement analysis revealed autoantibodies against complement factor H (CFH), genetic testing yielded a concomitant homozygous deletion of CFHRI and CFHRI3. Therapy was switched to belatacept (blocker of T-cell co-stimulation) instead of CNI. Subsequently, renal graft function partially recovered (eGFR of 32 ml/min) and hematologic remission (absence of hemolysis) was observed for 18-month of follow up under continued administration of belatacept, eculizumab, mycophenolate mofetil (MMF) and low dose prednisolone.

Discussion: This case describes successful management of posttransplant aHUS using an individualized CNI-free immunosuppressive regimen based on eculizumab and belatacept. Especially in patients with ESRD of unknown origin, (preemptive) recognition of predisposing risk factors, such as complement abnormalities, are crucial for initiation of tailored immunosuppressive regimens and better long-term renal graft survival.

SA-PO018

Introduction: Immune reconstitution inflammatory syndrome (IRIS), first recognized in HIV patients during HAART is an intense inflammatory response from recovery of the immune system leading to deterioration in clinical status. We report a unique case of IRIS in a non-HIV, immunocompromised renal transplant recipient due to interaction between rifampin and tacrolimus (FK).

Case Description: 74 year old Asian male with history of orthotopic liver transplant 4 years ago for Hep C cirrhosis, ESRD due to calcineurin inhibitor toxicity and status post deceased donor kidney transplant a year ago was transferred to our institution for management of disseminated TB. He was on RIF (rifampin, isoniazid, pyrazinamide, ethambutol) therapy initiated at the originating hospital. Due to abdominal pain, his pyrazinamide was switched to levofloxacin with improvement of the symptom. Serum FK level at presentation was undetectable likely due to its accelerated metabolism from interaction with rifampin. He later developed fever (Tmax 104.4°F), tachycardia, tachypnea and mild hypotension. There were no localizing findings or imaging evidence suggestive of infectious source. C reactive protein (CRP) was markedly elevated on broad spectrum antibiotics after obtaining cultures. Blood and urine cultures, serology for CMV, Histoplasma, Cryptococcus were negative. He was diagnosed with IRIS, antibiotics.
were discontinued, treated with iv methylprednisolone and FK dose adjusted to achieve goal levels. He responded well and symptoms resolved. CRP trended down rapidly. His IRIS was probably due to immune system reactivation in the setting of improving infection and low FK levels.

Discussion: With the increasing immunosuppressive and immunomodulatory agents with recognized effects on the immune system in transplant patients, it is important for physicians of various specialties caring for these patients to be familiar with these drugs and their potential interactions. Rifampin is an inducer of CYP3A4 and P-glycoprotein in the liver and small bowel leading to increased metabolism of FK which may predispose to IRIS in patients with resolving TB. Timely recognition and appropriate treatment of IRIS is critical for prevention of severe complications including graft loss.

SA-PO019

Introduction: Numerous HIV-1 associated nephropathies have been described including HIVAN, HIVICK and diffuse infiltrative lymphocytosis syndrome (DILS) characterised by CDS+ interstitial deposits. Our case does not fall into any of these categories.

Case Description: A 41 year old Brazilian man presented with fever, diarrhoea, vomiting and visible haematuria. Past medical history included treated syphilis and schistosomiasis. He was newly diagnosed with HIV-1 with a viral load of 0.65x10^6 copies/ml and CD4 count of 0.32x10^9/L. Creatinine was 340 mmol/l without a previous baseline riser to 8.2. He had a history of azathioprine of 11mg/mmol without leucocyturia. No other infectious agents were identified including Zika, Chikungunya, Nipah & BK viruses. Virology revealed successful hepatitis B immunisation, previous hepatitis A and hepatitis C negative. Renal biopsy showed a diffuse proliferative glomerulonephritis with neutrophils and sparse microthrombi. Alongside high anti-streptolysin titre, this prompted amoxicillin and prednisolone which had no effect on renal function.

Further review revealed hypercellular glomeruli with tuft inflammatory cells and no evidence of collapsing glomerulopathy. The glomerular and patchy tubular infiltrate was of predominantly CD3+ CD4+ but not CD8+ lymphocytes. There were no definite immune complexes on immunohistochemistry. Electron microscopy revealed tubuloreticular inclusions but no electron dense deposits. p24 antigen stain was negative. Commencement of high active retroviral therapy elicited viral load <40 copies/ml and a concomitant fall in creatinine and urine protein excretion.

Discussion: We believe this represents a novel form of HIV-1 associated nephropathy characterised by predominantly glomerular infiltration with CD4+ cells without immune complex deposition. We term this a ‘diffuse glomerular lymphocytosis syndrome’.

SA-PO020
Rethinking Peritubular Capillary Basement Membrane Multilayering in Renal Transplant Histopathology: A Case Report Diana Maria Lopezuri, Elena N. Levchenko,1 Evelyn Lurêt,2 Noel Knoops,2 1Pediatric Nephrology and Solid Organ Transplantation, UZ Leuven, Leuven, Belgium; 2 Morphology and Molecular Pathology, UZ Leuven, Leuven, Belgium; 3Univ of Barcelona, Barcelona, Spain.

Introduction: Severe multilayering of the peritubular capillary basement membranes (ML) in kidney allografts is considered a ultrastructural hallmark of chronic antibody mediated rejection (CAMR). We describe the findings in a young man with underlying focal segmental glomerulosclerosis who underwent a living-related donor transplant procedure, questioning the specificity of this phenomenon.

Case Description: The patient received a kidney from his mother, whose donor screening was unremarkable. He developed nephrotic-range proteinuria shortly after the procedure. The post-transplant biopsies performed within the first 6 months demonstrated ML (5-6 layers), suggestive for the onset of CAMR. Since there were no other criteria for CAMR, electron microscopy was performed on the baseline biopsy, and also demonstrated ML. Seven years later the donor still has no signs of kidney disease.

A review of the literature suggest this case to be the first description of ML in a person without apparent features of kidney disease. ML is believed to result from repeated endothelial injury and is also described in native kidney disease (lupus nephritis and thrombotic microangiopathy). The severity of ML is linked to the type and duration of endothelial distress. The presence of high-grade ML (≥7) in an allograft is considered positive for antibody mediated rejection. She was treated with oral antibiotics (Abx) and her MMF dose was decreased. A repeat 1-year PBx showed no evidence of ongoing MCP but did have inflammation consistent with BANF borderline changes. Her urine cultures (UCx) remained positive, prompting a new prolonged course of intravenous Abs.

Discussion: MCP has been described in states of IS, including organ transplantation. It has been most commonly associated with E.coli UTIs and presents with obstructive uropathy. Untreated infections can lead to graft

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loss and salt wasting nephropathy. Treatment focuses on reduction of IS and prolonged Abx therapies. To our knowledge, this is the first case of MCP incidentally discovered in PBx, highlighting a unique presentation of this rare disease. While her repeat Bx was negative for MCP this may represent failure to sample a patchy process, as her UCx remains positive.

SA-PO023
Cloud-Based Connectivity Platform Allows for Remote Management of Automated Peritoneal Dialysis and Early Recognition of Catheter Dysfunction: First Swiss Experience
Valérie Jotterand Drepper,1 Pierre-Yves F. Martin,1 James A. Slonad.1 1Nephrology, Geneva Univ Hospital, Geneva, Switzerland; 2Renal Div, Baxter Healthcare Corporation, Deerfield, IL.
Introduction: Incident peritoneal dialysis (PD) patients tend to encounter more technical problems in weeks following training. Remote patient management (RPM) has the potential to detect early issues, allowing intervention prior to development of more significant problems that might lead to emergency visits, hospitalization or technique failure.
Case Description: A 23-year-old ESRD patient required hospitalization for urgent start of renal replacement therapy. Because of prior non-adherence, a newly available automated peritoneal dialysis (APD) RPM system (Sharesource) with cloud-based connectivity was implemented. Post-APD training and on return home, the patient’s treatment was both remotely observed and altered regularly. Pre-defined RPM threshold parameters were set to identify clinically relevant issues, including PD catheter drain times.
On initial home discharge, the RPM system revealed no dashboard flag alerts and normal PD cycle volume profiles (Fig1a). However, in ensuing days, red flag dashboard alerts heralded prolonged drain times (Fig1b) leading to an early diagnosis of and surgical repositioning for catheter displacement.

Discussion: RPM of APD patients with a two-way cloud-based connectivity platform allows for monitoring and adjustment of therapy, as well as early recognition and timely management of adverse clinical issues. Larger scale observational studies will determine the impact of RPM in APD technique survival and resource utilization.

SA-PO024
Refusal of Dialysis in End Stage Renal Disease Patients Residing in Skilled Nursing Facilities
Introduction: The number of ESRD pts in skilled nursing facilities (SNF) continues to grow. These pts have more comorbidities and higher mortality when compared to those not living in SNFs. SNF ESRD pts on hemodialysis (HD) undergo either conventional three times weekly (CHD) (on site or in-center) or shorter more frequent HD (DHD). DHD is utilized to allow pts to adhere to rehabilitation which may translate to improvement in functional status. When pts on HD enter a SNF that performs DHD, they are often switching from CHD to DHD. Our hypothesis is that when ESRD pts who are naïve to HD enter into a SNF that offers DHD, adherence to the more frequent sessions is low due to refusals. This may result in inadequate HD over time and could adversely affect outcomes.
Case Description: Data from nine SNFs with on-site HD programs were retrospectively compared from May-Dec 2015. Five programs delivered CHD, defined as conventional 3xs weekly HD using Fresenius equipment targeting a KT/V of 1.2. Four programs delivered DHD, defined as four or five times weekly HD using the NxStage System One, targeting a weekly KT/V of 2.0. Pts were excluded if they had been on DHD prior to entering the SNF. Missed treatments due to refusals were defined as a pt missing the entire HD session (without it being rescheduled) while residing in the SNF. Statistical analysis was performed using Fischer exact test for categorical data and Mann–Whitney for continuous data. Data was reported as mean±standard deviation.
There were a total of 335 pts who underwent 11,043 HD treatments. 171 underwent CHD treatment with 6,398 treatments and 164 underwent CHD with 5,005 treatments (p=0.074). Both groups had similar ages (DHD 70±11 yrs vs. CHD 71±12 yrs, p=0.426). Missed treatments due to refusals were higher in DHD compared to CHD (DHD, 40.6±42% vs. CHD, 11.4±28%, p<0.0001).
Discussion: In our experience with HD in the SNF, there was a significant increase in percentage of missed treatments due to patient refusals in DHD. This lack of adherence to the dialysis prescription could adversely affect outcomes.

SA-PO025
Care of Kidney Transplant Recipients in Syrian War Zones
Kamel Hatahet,1 Nada Alalach,2 Crystal A. Gadgebeku,1 Sami Alasfar.2 1Temple Univ Hospital, Philadelphia, PA; 2The John Hopkins Univ, Baltimore, MD.
Introduction: Care of kidney transplant recipients is complex and requires an organized infrastructure. The current Syrian conflict has led to deterioration in medical care for these patients. The information on management and outcome of such patients in Syrian war zones is lacking.
Case Description: prospective observational study of 138 kidney transplant recipients in the Syrian northwestern provinces, which are greatly affected by the war. Data on the patients are collected during the patients’ clinic visits to two physicians involved in their care. Median follow up is 1.5 years. Patients are seen every month if their transplant >6 months old. Routine labs checked includes CBC, BMP, UA, and drug levels.

Clinical parameters
N=138
Mean age at transplantation (yr) 40 +/- 10.9
Gender (M) 77%
Cause of original kidney disease
Dialysis 7%
Hypertension 21%
Glomerulonephritis 24%
Other/Unknown 48%
Donor’s type
Living related 60%
Living unrelated 40%
Immunosuppression
Tacrolimus 51%
Cyclosporine 49%
Mean most recent Creatinine 1.35 ± 0.67
Mean most recent CSA level 254 ± 215
Mean most recent FK level 5.8 ± 1.9
Mean distance from clinic (KM) 36 ± 21
Mean time from clinic (Min) 49 ± 28
Rejection (n) 4
Graft loss (n) 0

Complicated cases are referred to one nephrologist in the area or discussed through social media means with nephrologists in the US. Major Barriers to care identified as following: 1-availability of the immunosuppressions; 2-Cost of drug monitoring; 3- Lack of security during transportation. 4- Fear of targeting doctors. 5- Limited medical staff and ancillary studies. 6-Time needed to obtain results of lab and imaging studies.
Discussion: Despite many barriers and poor infrastructure, teamwork between physicians in Syrian war zones, Syrian American Nephrologists, and humanitarian organizations has translated into a life saving support to the Syrian renal transplant patients. More sustained effort and financial aid is needed for optimal management of these patients.

SA-PO026
Extracorporeal Treatments to Enhance Dapsone Elimination: A Case Report
Amelie Bernier-Jean,1 Marc Ghannoum,2 Monique Cormier,2 Dave Brindamour,1 Clement Deziel,1 Josée Bouchard. 1Hôpital du Sacré-Coeur de Montréal, Canada; 2Hôpital Verdun, Canada.
Introduction: Intentional dapsone intoxication can be life-threatening. There is very limited data on the effect of extracorporeal treatments (ECTRs) on dapsone elimination. We describe a case of severe dapsone toxicity and report clearance, quantification and half-life of dapsone and its metabolites with different ECTRs.
Case Description: A 23 year-old woman was admitted 2.5 hours after ingesting 2.2 g of dapsone. On admission, the patient complained of headache, and the physical exam was remarkable for cyanosis. She developed severe methemoglobinemia (39.9%) and showed signs of toxicity (hemodynamic instability and slow processing) despite multiple-activated charcoal, methylene blue, vasopressors, and endotracheal intubation. Continuous venovenous hemofiltration (CVVH) was initiated after 4 hours, followed by intermittent hemodialysis with hemoperfusion (HDF-HP) for 4 hours, and CVVH for another 48 hours. The platelet count dropped three hours after IHD-HP (nadir was 32 X 109/L). The elimination half-life of dapsone was 2.0 hours during HD-HP, and 14.2 hours during CVVH. Mean dapsone clearance with IHD was 62 ml/min and with CVVH, 22 ml/min. Renal clearance was 6ml/min. IHD removed 95.3 mg, and CVVH removed 67.8 mg over 3.8 hours. The sieving coefficient of dapsone was 0.24-0.30. No rebound occurred following ECTR cessation. The toxicokinetics of dapsone metabolites were also accelerated during ECTR. The patient was extubated after 3.5 days and discharged without sequelae after 7 days.
Discussion: Contrary to previous reports and despite its high protein binding, dapsone appears to be dialyzable due to improvements in dialysis filters and catheters. In addition, ECTRs can accelerate dapsone elimination compared to multiple-activated charcoal alone. Although we obtained a shorter elimination half-life by combining IHD and HP, it remains unclear if this benefit is worth the costs and the risk of severe thrombocytopenia compared to IHD alone. We suggest that IHD with or without HP be considered following massive dapsone ingestion with life-threatening manifestations and high methemoglobinemia levels.

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SA-PO027

Recurrent Acute Hypotension with Initiation of Dialysis and Ventricular Interdependence Sumeet Munjal,1 Asma Mursleen,2 Alberto Morales,1 1Div of Cardiology, Univ of South Florida; 2Div of Nephrology, Univ at Buffalo, NY.

Introduction: Ventricular interdependence is the mechanism whereby right heart failure (RHF) can cause left heart dysfunction. The primer bolus used before initiating dialysis can lead to an acute right ventricular volume overload. We report a case where primer bolus lead to acute RHF causing mobilization of interventricular septum towards the left, reducing cardiac output and lead to recurrent severe hypotension and syncope.

Case Description: 44 yo AAF with history of ESRD, DM, Non-ischemic cardiomyopathy (EF 15%) s/p AICD, presented after an episode of syncope while on dialysis. Patient had similar episode 2 weeks back and was started on midodrine before dialysis. Work up showed gram negative bacteria due to infected catheter and was treated for septic shock with fluids, pressors and antibiotics. Patient recovered from sepsis but became volume overload requiring daily dialysis. However with each dialysis, she would become acutely unresponsive and apneic within 4-6 minutes after initiating dialysis causing early termination of sessions. Various interventions including albumin, lowering diastolic temperature and step sodium profiling was used to avoid hypotension, without any success. EEG negative for any seizure. Patient underwent TEE during dialysis which revealed worsening right ventricular dilatation, severe hypokinesia and septal bouncing within minutes after starting dialysis. This was accompanied with drop in SBP from 128 to 78mm Hg. The septum shifted to the left consistent with right ventricle volume overload, ventricular interdependence accompanied with severe hypotensive. Hemodialysis was stopped and patient was given nesnephritine with improvement in BP. We concluded that primer bolus was sufficient to cause ventricular interdependence leading to severe hypotension. Dialysis was reinitiated but primer bolus was purged, patient successfully completed dialysis without any hypotension or syncope.

Discussion: Our case illustrates that 300cc of primer bolus is enough to cause acute RHF with subsequent LHF, causing recurrent severe hypotension and syncope. Simple purging of primer bolus allowed the patient to undergo dialysis repeatedly without any complications.

SA-PO028

Single-Pass Albumin Dialysis during Continuous Renal Replacement Therapy for Severe Hyperbilirubinemia Nathan T. Beins,1 Marita Thompson,2 Darcy K. Weidemann,1 Rebecca M. Greene,2 Utem Garg,1 Vinal Chadhda.1 1Nephrology, Children’s Mercy Hospital and Clinics, Kansas City, MO; 2Critical Care Medicine, Children’s Mercy Hospital and Clinics, Kansas City, MO.

Introduction: Severe hyperbilirubinemia (SHB) is uncommon in critically ill children with multi-organ dysfunction syndrome (MODS). SHB can be a surrogate marker of hepatic failure and is associated with increased mortality. Furthermore, SHB can interfere with laboratory assays and near-infrared spectroscopic (NIRS) monitoring. While CRRT is commonly utilized for the management of acute kidney injury and fluid/electrolyte issues in children, it does not clear serum bilirubin. Molecular adsorbent recirculating system (MARS) has been successfully used for the management of hepatic failure, but is not FDA approved for SHB, and is unavailable in most centers. There are few case reports of single-pass albumin dialysis (SPAD) enhancing bilirubin clearance in children.

Case Description: A 7 month old male infant presented with MODS (underlying disease - autoimmune hemolytic anemia and hemophagocytic histiothymocytosis) who developed SHB (peak total serum bilirubin 51.5 mg/dL). While he received CRRT and intermittent plasmapheresis, the serum bilirubin levels continued to remain significantly elevated. We performed SPAD (1.85% albumin in dialysate bag) for two consecutive days. Serum and dialysate bilirubin concentrations were monitored and are shown below;

Discussion: Our experience shows >10-fold increase in bilirubin clearance with SPAD during CRRT. While SPAD is effective in decreasing serum bilirubin and possibly other protein-bound toxins, its impact on removal of nutrients and medications is unknown and needs to be carefully explored. Large scale studies are needed to see if SPAD can improve patient outcomes.

SA-PO029

Using Ultrasound to Detect Non-Occlusive Mesenteric Ischemia in a Hemodialysis Patient Sean Verma,1 Alfredo M. Peguero,2 Jorge A. Lamaracho,2 Craig S. Courville,2 Marina Antar-Shultz,2 Mohamed M. Taha.2 1Internal Medicine, Univ of South Florida; 2Nephrology, James A. Haley Veterans’ Hospital.

Introduction: Non-occlusive mesenteric ischemia (NOMI) is a rare disorder seen in the hemodialysis (HD) population that carries a high mortality rate. The risk for NOMI in HD patients is estimated to be 44 times the risk of the average population. Ultrasound (US) is an adjunct diagnostic tool to diagnose NOMI in an HD patient.

Case Description: A 62-year-old woman with ESRD, malnourishment, and hypertension was admitted for failure to thrive. Vitals showed tachycardia and blood pressure 116/70 mmHg. Physical exam revealed cachexia and anasarca. Labs showed albumin 1.2 g/dL. She had prolonged intra and post dialytic hypotension associated with abdominal pain. A bedside US showed a collapsed inferior vena cava and gas (arrows) in the portal vein. Also, extraluminal fluid accumulation, thinning of the bowel wall, and ileus were seen on US. Labs showed leukocytosis 10.99 x109/L, lactic acid 3.5 mg/dL, and anion gap metabolic acidosis. CT scan showed portal venous gas and pneumatosis of the gastric fundus with patent of the mesenteric arteries suggestive of NOMI. She was not felt to be a surgical candidate due to her comorbidities. She was treated with albumin, fluids, and empiric antibiotics but expired 4 days later.

Discussion: Common NOMI findings include abdominal pain, fever, metabolic acidosis, and leukocytosis following intradialytic hypotension. Portal vein gas and/or mesenteric gas are ominous but late signs that are most consistent with mesenteric ischemia. US hasn’t conventionally been used to detect NOMI and evaluate for portomesenteric gas, as CT scan has been the imaging of choice. However, bedside US is quicker and comparable in sensitivity. US with clinical suspicion for NOMI in ESRD patients may allow for a more prompt diagnosis via earlier CT scan ordering, and earlier initiation of treatment.

SA-PO030

An Extreme Case of Tumoral Calcinosis in End Stage Renal Disease Sean Verma,1 Tambi Jarri.1 1Internal Medicine, Univ of South Florida, Tampa, FL.

Introduction: Tumoral Calcinosis is a rare and severe sequela of end stage renal disease (ESRD) patients on hemodialysis (HD) in which calcium salt deposits occur in periarticular soft tissue, typically around large joints such as the shoulder, elbow, and wrist.

Case Description: A 19-year-old woman with ESRD due to hemolytic uremic syndrome on HD presented for right shoulder and left elbow masses. She had a living related donor transplant at age fourteen with rejection two years later. Physical exam revealed right shoulder mass with overlying telangiectasias and left elbow mass with seropurulent, gritty drainage. Labs were notable for calcium 10.5 mg/dL, phosphorus 6.3 mg/dL, and intact parathyroid hormone 955 pg/mL. Right shoulder MRI revealed a periaricular heterogeneous mass with cystic and calcific components, consistent with tumoral calcinosis. Given the extent of her disease, the patient underwent parathyroidectomy for tumoral calcinosis due to tibary hyperparathyroidism. In addition, she was treated with HD with low-calcium dialysate for five days per week. Upon two month follow up her calcium masses had decreased significantly in size.
Discussion: Tumoral calcinosis tends to occur more frequently in patients with high calcium-phosphate product, secondary-tertiary hyperparathyroidism, or hyperphosphatemia. Treatment involves intensification of HD with low-calcium dialysate, non-calcium containing phosphate binders, parathyroidectomy for secondary or tertiary hyperparathyroidism, and possible surgical removal of the calcium depositions. Surgical excision of the masses has often been shown to be ineffective long term as they are prone to recur, unless biochemical correction of calcium-phosphate product can be achieved. Tumoral calcinosis is difficult to treat but has been shown to resolve after successful kidney transplantation.

SA-PO031
Apparent Picture of Dialysis Catheter in Chest CT
Mariusz Kuształ, Tomasz Golebiowski, Krzysztof Letachowicz, Magdalena Krajewska, Marian Klinger. Nephrology and Transplantation Medicine, Wrocław Medical Univ, Wrocław, Poland.

Introduction: Unintentionally leaving dialysis catheter in the central vein is almost impossible. Here we present the case of a female patient with a history of dialysis catheter placement when chest CT scans strongly suggested migrated portion of central venous catheter (CVC).

Case Description: 44yo female with a 15 y history of SLE with poststeroidal arthropathy – a complication of vertebroplasty occurring in 10-60% of such cases. Features distinguishing CVC from cement on CT scans are as follows: hollow and equal outline of CVC (usual diameter range of CVC 3.8-6mm). Based on measurements taken from 10 other patients with CVC in the chest, mean Hounsfield units were 1309 (range 1000-1585). Subsequently, she became pyrexial and started cough. After admission to the pulmonology clinic, chest CT revealed a small lung abscess and a “portion of dialysis catheter”.

After a failed endovascular attempt to retrieve the catheter, the patient was prepared for thoracotomy. Because the nephrologist was sure of the complete catheter removal initially, an alternate explanation of the findings was proposed. Through differentials and scrutiny in anamnesis (i.e. review of various chest CT scans from patients with implanted CVC) revealed that the catheter-like picture was in fact cement embolism in the right pulmonary artery – a complication of vertebralplasty occurring in 10-60% of such cases. Features distinguishing CVC from cement on CT scans are as follows: hollow and equal outline of CVC (usual diameter range of CVC 3.8-6mm). Based on measurements taken from 10 other patients with CVC in the chest, mean Hounsfield units were 1309 (range 1000-1585). Cement embolism in this case had an unequal outline (3.8-4.5 mm in diameter) and 1880 (1670-2020) Hounsfield units.

Discussion: This case is notable because two independent radiologist suggested catheter left in the chest as its implantation was reported in medical files, however cement embolism with high glare was the case.

Funding: Government Support - Non-U.S.

SA-PO032
Encapsulating Peritoneal Sclerosis in Peritoneal Dialysis with Kidney Transplant
Arun Kottaratara, Matthew Abramson, Yezina T. Nigatu, Nand K. Wadhwa. 1Dept of Nephrology, Stony Brook Univ Medical Center; 2Dept of Medicine, Stony Brook Univ Medical Center.

Introduction: Encapsulating peritoneal sclerosis (EPS) is a complication of long term peritoneal dialysis (PD) following discontinuation of PD. We present two cases of EPS occurring following kidney allograft receiving steroid free immunosuppressive protocol.

Case Description: Case 1: A 41-year-old woman with End Stage Renal Disease (ESRD) secondary to hypertension nephrosclerosis. On PD for 10 years she received a living related kidney allograft. 10 days post transplant (PT) S Cr was 1.3 mg/dl. PD catheter was removed 1 week PT. She developed nausea, vomiting and diffuse abdominal pain, and physical examination unremarkable. CT abdomen showed dilated small bowel and treated conservatively. S Cr was 0.8 mg/dl. 3 days later, she was readmitted with nausea, vomiting and abdominal pain. CT abdomen revealed distended small bowel. GI follow through showed atonic small bowel. 23 days PT, she underwent exploratory laparotomy which revealed extensive brownish yellow peritoneum encapsulating entire bowel. She received IV prednisolone followed by oral prednisone in addition to tacrolimus and mycophenolic acid with complete resolution of symptoms in 4 weeks. She is prednisone 5 mg daily since and has been symptom free for 8 years.

Case 2: A 48 year-old woman with ESRD of unknown etiology, on PD for 6 years received a deceased kidney allograft. 3 days PT, her S Cr was 3.0 mg/dl. 11 days PT, she had recurrent nausea, vomiting and diarrhea. CT abdomen revealed distended small bowel engulced in fibrinous inflammatory membrane suggestive of abdominal cocoon. She needed nasogastric decompression and IV prednisolone, transitioned to oral prednisone. Prednisone 5 mg was continued with mycophenolic acid and tacrolimus. She has been symptom free for 13 months.

Discussion: Both patients had excellent outcomes with bowel rest and steroids. Our institution’s transplant protocol involves alendroutumab induction and steroid withdrawal within 3 days post-transplant. We suggest that PD patients undergoing renal transplant remain on immunosuppressive regimen including steroids to prevent EPS.

SA-PO033
Calciphylaxis after Acute Kidney Injury: A Mysterious Case of Painful Skin Necrosis
Elizabeth Upton, Vinmal K. Derebail. UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC.

Introduction: We describe a case of calciphylaxis in an individual without end-stage renal disease (ESRD) who had recovered from an episode of acute kidney injury (AKI).

Case Description: A 43-year old female with history of prior Roux-en-Y gastric bypass surgery, non-alcoholic steatohepatitis, and former alcohol abuse presented with 8 weeks of skin necrosis on her abdomen, buttocks, and thighs. Three months prior to evaluation, she was admitted for sepsis complicated by liver and kidney failure not requiring dialysis. Admission labs included creatinine of 0.6 mg/dL, ALT 15 U/L, ALT 25 U/L, PTH 44 pg/ml, and calcium phosphate product of 57. Skin biopsy demonstrated calcium deposition in the subcutaneous tissue and vessels, dermal and subcutaneous fat necrosis, and neutrophil and lymphocyte infiltration, consistent with calciphylaxis. Hypercoagulable, autoimmune, and infectious workups were negative. After therapy with intravenous sodium thiosulfate 25 g thrice weekly, oral sevelamer, and topical silver sulfadiazine, she had dramatic improvement over 6 months.

Figure 1: Necrotic skin lesion secondary to calciphylaxis.

Discussion: Calciphylaxis occurs rarely in patients without ESRD with other risk factors including female sex, obesity, primary hyperparathyroidism, malignancy, alcoholic liver disease, corticosteroid use, protein C/S deficiency, or a history of a Roux-en-Y surgery. Defects in vascular calcification pathways such as fetuin-A and matrix Glα protein and increased serum levels of matrix metalloproteases contribute to calciphylaxis. Patients with underlying liver disease with AKI may be especially susceptible. Progression remains poor with mortality approaching 50%. Further studies are needed to elucidate the pathogenesis of all forms of calciphylaxis to develop specific treatments.

SA-PO034
Atypical Mycobacterial Peritoneal Dialysis Catheter Related Infections in Pediatric End-Stage Renal Disease Patients: A Case Series
Jackson Londero, Donald K. Murphy, David H. Simon, Kartik Pillutla. 1Pediatric Nephrology, Dell Children’s Medical Center of Central Texas, Austin, TX; 2Pediatric Infectious Diseases, Dell Children’s Medical Center of Central Texas, Austin, TX; 3Univ of Texas at Austin Dell Medical School, Austin, TX.

Introduction: Atypical Mycobacterium peritoneal dialysis catheter related infections are rare and serious infections complications. We report three cases of catheter related infections in our pediatric nephrology practice.

Case Description: Case #1: A 10 month-old male with ESRD secondary to bilateral renal agenesis on peritoneal dialysis presented with an exit site and tunnel infection. His culture grew Mycobacterium fortuitum.

Case #2: A 12 month-old with ESRD secondary to urethral agenesis on peritoneal dialysis presented with an exit site infection. His culture grew Mycobacterium fortuitum.

Case #3: An 18 month-old with ESRD secondary to obstructive uropathy on peritoneal dialysis presented with peritonitis. His peritoneal culture grew Mycobacterium abscessus.

Discussion: All three patients were treated with antimicrobial therapy and catheter removal.

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Infection control was consulted. Patients were non-ambulatory, began peritoneal dialysis in infancy and had gastrostomy tubes. Catheters were well healed and caregivers demonstrated appropriate technique. Exit site care consisted of washing site with soap and tap water followed by topical gentamicin daily. As atypical mycobacterium are found in the natural environment tap water contamination was suspected. Our policy was changed to clean the exit site with chlorhexidine gluconate in place of tap water for non-ambulatory patients.

SA-PO035

Longest Survival on Hemodialysis: 47 Continuous Years and Counting
Centrefold

Introduction: We report a case of uninterrupted hemodialysis for 47 years and counting, which is the longest recorded in the published literature. This case illustrates the advances of hemodialysis over the years in technique, vascular access, treatment of bone disease and anemia. In the era of multi-modality renal replacement therapies, it also highlights a case of successful single modality hemodialysis for an exceptionally long period of time.

Case Description: The patient is a 57 year old man who developed end-stage renal disease at the age of 10 months secondary to congenital bladder neck obstruction. He was started on home hemodialysis in 1969 at age 11 and was the first pediatric patient to be dialyzed in Canada. His initial access was an ankle AV shunt. He had an AV fistula created in 1983 which lasted 23 years and undoubtedly contributed to his longevity on hemodialysis. He started dialysis with a Kil dialyzer which required long treatments and sterilization. The introduction of hollow-fiber dialyzers improved dialysis efficiency and his quality of life by shortening his required dialysis time. Over time, he developed fractures due to osteitis fibrosa cystica and fluorosis from fluorinated city water. He was treated with subcutaneous parathyroidectomy and addition of a deionizer to his water treatment system. He was later found to have significant aluminum on bone biopsy from exposure to aluminum-based phosphate binders. He was transfusion dependent until the development of ESA in 1989. The patient was never a candidate for renal transplantation or peritoneal dialysis and despite being on hemodialysis for most of his life he completed his education, studied architecture at a technical college and participated in the workforce for 28 years. He continues on center dialysis three times per week via a tunneled cather.

Discussion: This case parallels the history of advances in hemodialysis from innovations in vascular access, dialyzers and water treatment to the development of non-aluminum phosphate binders and erythropoietin stimulating agents. It illustrates that single modality hemodialysis can be associated with excellent outcomes, including exceptional longevity and quality of life, in some patients.

SA-PO036

Hemodialysis Associated Thrombocytopenia Corrected with Changing Membrane Sterilization Method
Sharica Brooks, Juan Pablo Arroyo, Ed Gould, Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.

Introduction: Hemodialysis (HD) associated thrombocytopenia (TCP) is a rare, but serious complication which needs to be identified quickly to prevent further morbidity and mortality in HD dependent patients. While a variety of membrane and sterilization techniques have been associated with the development of TCP, we present the first case of HD associated TCP which resolved after switching from electron beam sterilized to steam membrane sterilization.

Case Description: A 40-year-old Caucasian female with Polycystic Kidney Disease was admitted for initiation of dialysis in advance of bilateral nephrectomy to prepare for renal transplantation. Her platelet count was 226 x 10^3/μL, and then 14 x 10^3/μL, after each consecutive dialysis session with the electron beam sterilized polysulfone HD membrane. A work-up for causes of TCP, including heparin induced thrombocytopenia, bleeding, and auto-immune disorders returned negative. Following platelet recovery, re-challenge with the same membrane once again led to decline in platelet count to 76 x 10^3/μL. The HD membrane was changed to a steam sterilized dialysis membrane. With that change, the platelet count (118 x 10^3/μL) post (110 x 10^3/μL) HD platelet counts remained stable. Surgery was postponed, and her platelets recovered to 232 x10^3/μL while receiving ongoing HD.

Discussion: Platelet half-life can be directly impacted by the dialysis membrane. HD membrane sterilization techniques, e.g., ethylene oxide, gamma-ray or electron-beam, and steam, are varied and may alter their biocompatibility. In our patient the switch from electron-beam sterilization to steam sterilization corrected the TCP. Previous case reports switched to either electron-beam or gamma-ray sterilization, we present the first reported case of platelet recovery after switching from electron beam to steam sterilization. This has only been previously reported to improve HD associated leuopenia and not TCP. It is important to note that although changes in biocompatibility are rare, early identification and management are essential to improving the care of the HD dependent patient.

SA-PO037

A Successful Case of Peritoneal Dialysis-Related Pleuroperitoneal Communication Diagnosed by Contrast-Enhanced Ultrasoundography and Treated by Thorascopic Surgery
Mimiko Matsamura, Takaaki Higashihara, Rie Uti, Hideki Takano, Dept of Nephrology, Tokyo Teishin Hospital, Tokyo, Japan.

Introduction: Peritoneal reperitonial communication is a famous complication of peritoneal dialysis (PD). It is difficult to diagnose and treat because there may be no way to identify the pleural holes certainly. Here, we present a successful case of pleureperitoneal communication.

Case Description: A 66-year-old woman with ESRD due to chronic glomerulonephritis was admitted to our hospital to start PD. After the PD cather was inserted successfully, right-sided hydrothorax occurred caused by pleureperitoneal communication. Immediately after injecting of Perflubutane into abdominal cavity through PD cather, we could detect high echoic area around the pleural holes by contrast-enhanced ultrasonography. To prevent fluid reaccumulation, video-assisted thoracic surgery (VATS) was performed. Under an infrared light thorascoscope, the flow through holes in the diaphragm was clearly confirmed with the fluorescence color of indocyanine green (ICG) contained in the PD solution (figure 1). The holes in the diaphragm were removed with surgical stapling devices. She subsequently resumed automatic PD without recurrence for 6 months before undergoing kidney transplantation from a living donor.

A thorascopic view showing holes of the diaphragm (A), and an infrared light thorascopic view showing the inflow of indocyanine green (B).

Discussion: Contrast-enhanced ultrasonography using Perflubutane is a safe way for detection of the leakage and VATS is a feasible method for treating pleureperitoneal communication.

SA-PO038

Case Report of Hypophosphatemia Occurring with the Use of Filgrastim in a Patient on Hemodialysis
Sarath G. Nadh, Vadim Abramov, Moro O. Salifu, Mary C. Mallappallil, Medicine, SUNY Downstate Medical Center, Brooklyn, NY.

Introduction: Hypophosphatemia is an electrolyte disturbance in which there is abnormally low level of phosphate in the blood. Hypophosphatemia is most commonly seen in malnourished patients. Hypophosphatemia is rare in patients with end stage renal disease (ESRD) who are on hemodialysis (HD). Filgrastim is a granulocyte colony-stimulating factor analog used to stimulate the proliferation and differentiation of granulocytes that can result in hypophosphatemia. We report a rare case of severe hypophosphatemia 0.9 mg/dl after use of filgrastim in a HD patient being treated for neutropenia that was caused by use of carbamazepine.

Case Description: A 69 year old man with hypertension, seizure disorder, ESRD on HD, presented to the emergency room with a temperature of 101 Fahrenheit from his dialysis center. Admission laboratory were significant for white cell count (WBC) of of 0.81 x10^3/μL and phosphate of 0.9 mg/dl. Chemistry was repeated to show the value to be real. He was supplemented with phosphate while he continued to receive filgrastim as laboratory was noted for WBC count of 29.97 x10^3/μL, and phosphate of 0.9 mg/dl. He received 5 doses of filgrastim before it was stopped as laboratory was noted for WBC count of 29.97 x10^3/μL, and phosphate of 0.9 mg/dl. He was continued to receive filgrastim as scheduled. He had rapid resolution of his fever and quickly resumed his usual diet. He was not on phosphate binders and not on any medications which could cause hypophosphatemia. His serum calcium levels were 8.3mg/dl and his intact parathyroid hormone level was 208pg/mL.

<table>
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He was never on Valproic acid (which has been noted to cause hypophosphatemia via Fanconi’s syndrome).

Discussion: Hypophosphatemia is a possible outcome with filgrastim use in a dialysis patient. Possible mechanism includes the combination of dialysis and consumption of phosphate in the process of rapid cell turnover of white cells. We report a case of severe hypophosphatemia that was case with filstagtrim use in a patient on HD.

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

Underline represents presenting author.
SA-PO039
Chylorperitoneum in a Neonate with ESRD on Peritoneal Dialysis: A Case Report

Introduction: Chylorperitoneum (CP) is a rare complication of peritoneal dialysis (PD). CP is diagnosed when triglyceride (TG) level (>110 mg/dL) in the PD effluent is elevated. Treatment is by changing to medium chain triglyceride (MCT) based diet as MCTs are absorbed by the intestine & transported by the portal system bypassing lymphatics, allowing the chylous fistula to heal naturally. We report a case of CP in an neonate on PD successfully managed with diet change alone.

Case Description: A 5 wk old male infant with ESRD due to bilateral cystic renal dysplasia initiated on manual PD at low exchange volume (EV) (10 ml/kg) at 12 days old, wt 3.5 kg & cr 6.69 mg/dL. EV slowly increased by 10 ml every 5-7 days. Milky PD effluent (Fig1) developed without any other signs of infection 3 weeks after initiation of PD. PD effluent TG 184 mg/dL. Diet at diagnosis was expressed breast milk (EBM) supplemented with Similac PM 60/40, Duocal & Beneprotein. It was changed to skimmed EBM with MCT oil to 1 ml/kg/day while waiting for MCT based formula. PD was continued. Within 12 hrs of formula change, milky appearance cleared & by 24 hrs, TG level returned to normal (< 10 mg/dL). Commercial formula with high % MCT (Enfaport) supplemented with Solcarb and Beneprotein added to sEBM & MCT oil once available. Regular EBM slowly reintroduced after 10 days. He tolerated transition to full formula change after day 4 (4.7mEq/L) while [Na+] remained between 136 and 130mEq/L on day 3. He continued to be hyperkalemic and both the pre- and post-filter [K+] were normalized. He started using the HeRO catheter within 3 weeks after placement. Despite few thrombotic episodes, the HeRO catheter remains functional and provides a reasonable hemodialysis access in this patient for the last 5 years. It is worth mentioning that this patient is non-compliant with warfarin therapy used to treat protein C deficiency, which could explain the recurrent thromboses of the dialysis access.

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Underline represents presenting author.

SA-PO041
Thigh HeRO Catheter: The “Last Resort” Dialysis Vascular Access
Alian Albalas,1 Ahmed Kamel Abdel Aal,2 Ammar Almehmi,3 Nephrology, UAB, Birmingham, AL; 1Radiology, UAB, Birmingham, AL; 3Nephrology and Radiology, UAB, Birmingham, AL.

Introduction: Thigh vascular access is commonly employed in dialysis patients with upper extremity central venous system occlusive disease. On the other hand, Hemodialysis Reliable Outflow (HeRO) catheters have been used in tunneled catheter-dependent patients who have exhausted other access options. However, thigh HeRO catheter is rarely utilized as a possible vascular access option in those patients.

Case Description: This is a 34-year-old African American male with known history of end-stage renal disease due to hypertension, protein C deficiency who was started on hemodialysis via neck tunneled catheter 12 years ago. Multiple graft and fistula accesses on both upper extremities failed due to recurrent stenotic lesions and thromboses. In 2004, he underwent deceased kidney transplant that remained functional for 7 years. In 2011, he presented with acute kidney injury due to graft rejection (due to non-compliant with immunosuppressive medications), volume overload and respiratory failure that required renal replacement therapy via left femoral vein catheter. Due to the limited available vascular estate in this patient, the decision was to proceed with left thigh HeRO catheter placement.

Fig1: Milky PD effluent.

Discussion: CP is a rare complication of PD. Prompt diagnosis is important as it can be easily managed with change of diet to MCT based formula without cessation of PD. Regular formula can be slowly reintroduced after 1 wk. A 5 wk old male infant with ESRD due to bilateral cystic renal dysplasia was initiated on manual PD at low exchange volume (EV) (10 ml/kg) at 12 days old, wt 3.5 kg & cr 6.69 mg/dL. EV slowly increased by 10 ml every 5-7 days. Milky PD effluent (Fig1) developed without any other signs of infection 3 weeks after initiation of PD. PD effluent TG 184 mg/dL. Diet at diagnosis was expressed breast milk (EBM) supplemented with Similac PM 60/40, Duocal & Beneprotein. It was changed to skimmed EBM with MCT oil to 1 ml/kg/day while waiting for MCT based formula. PD was continued. Within 12 hrs of formula change, milky appearance cleared & by 24 hrs, TG level returned to normal (< 10 mg/dL). Commercial formula with high % MCT (Enfaport) supplemented with Solcarb and Beneprotein added to sEBM & MCT oil once available. Regular EBM slowly reintroduced after 10 days. He tolerated transition to full feeds with EBM over 1 wk without recurrence of CP. PD EV advanced to full prescription (35 ml/kg) over the next 3 months without recurrence of CP. He was discharged home at 5 months on CCfPD, on EBM + Similac PM 60/40 with Beneprotein without further problems.

SA-PO042
Using Stent Grafts for Fistula Aneurysms Exclusion: Case for Caution
Alian Albalas,1 Ahmed Kamel Abdel Aal,2 Ammar Almehmi,3 Nephrology, UAB, Birmingham, AL; 1Radiology, UAB, Birmingham, AL; 2Nephrology and Radiology, UAB.

Introduction: Dialysis fistula aneurysms are commonly encountered in clinical practice. Most of the fistula aneurysms do not require direct intervention other than making sure that the draining veins are adequate and the fistulae are not pressurized. Direct surgical interventions, are warranted only when there are associated clinical issues, such as active bleeding, skin defect/erosion, mural thrombosis, infection, and significant cosmetic issues.

Case Description: This is a 70-year-old hemodialysis patient with a left brachiocephalic arteriovenous fistula presented with low fistula flow and difficult cannulation. Six months prior to the current presentation, a fistogram revealed multiple aneurysmal formations of the fistula vein.

The stenosis between the aneurysms was treated with balloon angioplasty. Ten days prior to current presentation, the patient was hospitalized for thrombosed fistula, where he underwent thrombectomy as well as a stent graft placement in the fistula vein.

On current presentation, the physical examination disclosed diffuse infiltration over the fistula body and weak thrill. Additionally, large aneurysmal formations of the fistula body were noted. Angiographic exam revealed a long stent graft in the fistula vein. When viewed from a different angle, the distal end of the stent graft was kinked within the aneurysm and the lateral wall of the distal stent graft was blocking fistula blood flow.
Further endovascular intervention was unsuccessful due to the kinked stent graft and the fistula flow was not sufficient for dialysis. Consequently, the patient necessitated tunneled dialysis catheter insertion in order to continue his dialysis therapy.

Discussion: A high degree of caution is needed for the “off-label” use of stent grafts to manage fistula aneurysms and their associated complications, as stent grafts may create more problems than they are intended to solve.

SA-PO043

Development of Pancreatitis in an ESRD Patient with Preceding Sodium Thiosulfate Usage

Introduction: Sodium thiosulfate is a drug with few known medical indications including cyanide poisoning, calciphylaxis and extravasation management in some chemotherapeutic regimens. Herein we present a case of acute pancreatitis in an ESRD patient with recent sodium thiosulfate usage with calciphyaxis. Sodium thiosulfate is a drug used frequently in calciphylaxis management in ESRD patients, but has not been previously documented to be associated with pancreatitis.

Case Description: A 58 year old female with past history significant for ESRD on HD, presented to the hospital with 1 week history of nausea, vomiting, and epigastric pain. She was started on IV sodium thiosulfate with HD for calciphylaxis ten days prior to the admission. Full workup for typical etiologies of pancreatitis including alcohol use and cholelithiasis was negative. Labs were significant for a lipase of 1160 on admission. Triglyceride level was 152. Calcium level was 9.0. Abdominal CT study documented changes consistent with acute pancreatitis. Patient underwent MRCP to evaluate pancreatic ducts with no pathology found. Patient was treated conservatively and Sodium thiosulfate was discontinued due to potential for drug-induced pancreatitis (no other medications of concern identified). No subsequent episodes of pancreatitis reported after discontinuation.

Discussion: Various etiologies have been identified in acute pancreatitis, with heavy alcohol consumption and gallstones being top culprits. Drug induced pancreatitis reflects a smaller portion of the total cases, estimated at 0.3 to 1.4%. The temporal relationship between initiation of a drug and development of pancreatitis is unclear, as some drugs demonstrate more immediate effects and others after weeks. There have not been any major studies involving sodium thiosulfate and its effects on the human pancreas to date. Based upon extensive review, sodium thiosulfate was believed to contribute to our patient’s presentation. Withholding the suspected drug and conservative measures were all that was required for management. As the prevalence of ESRD continues to rise, consideration of sodium thiosulfate as a contributor to acute pancreatitis may become a prudent differential diagnosis.

SA-PO044

Use of Tencoff Catheters in Diagnosing Abdominal Malignancies

Introduction: Tencoff catheters have been used for peritoneal dialysis since 1968. Peritonitis, traumatic chylous effusions, exit site infections, migration of the catheter and omental obstructions are common complications.

Case Description: We present a case of an 82-year-old male with a history of long standing uncontrolled hypertension leading to progressive chronic kidney disease (CKD). A clinical decision was made to initiate renal replacement therapy based on progressive fatigue standing uncontrolled hypertension leading to progressive chronic kidney disease (CKD). A clinical decision was made to initiate renal replacement therapy based on progressive fatigue leading to progressive CKD. A delay in diagnosis and management of CKD led to the development of end stage renal disease (ESRD). Upon presentation, the patient was afebrile with normal vital signs. Physical examination revealed a soft, non-tender abdomen with mild tenderness to deep palpation. Laboratory studies revealed a normal complete blood count and biochemistry panel. Urinalysis was normal. A computed tomography (CT) scan of the abdomen revealed a mass lesion in the distal ileum with surrounding mesenteric fat stranding. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) of the lesion was performed. The specimen was sent for cytological analysis. Cytological examination of the aspirate revealed epithelial cells with abundant amphophilic cytoplasm and moderate pleomorphism. Immunohistochemical staining showed positivity to BerEp4, CK7, EpCAM, CEA and CA19.3. These results were strongly suggestive of a pancreatic, upper GI or a biliary malignancy. Further diagnostic workup revealed elevated serum CA 19-9 levels (1383 U/ml). A subsequent PET-CT scan showing a hyper metabolic mass in the pancreatic body, confirming the diagnosis of pancreatic adenocarcinoma.

Discussion: This case demonstrates the diagnostic potential of cytologic analysis of peritoneal dialysis effluent in the diagnosis of peritoneal malignancy. It highlights the importance of prompt diagnosis and management of peritoneal dialysis catheter-related infections to prevent serious complications.

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Underline represents presenting author.

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SA-PO045

Two Tunnels for One Peritoneal Dialysis Catheter! A Rare Delayed Surgical Complication

Introduction: Catheter tunnel infection (CTI) is a known cause of adverse outcomes in peritoneal dialysis (PD)-related peritonitis. Extension of exit site infection is the most common reported reason for CTI. We report a case of PD-related peritonitis due to a delayed surgical complication.

Case Description: A 54 year old man with a history of end stage renal disease due to polycystic kidney disease (PKD) was treated with continuous PD for the past 5 years. He presented with fever, abdominal pain, and cloudy PD effluent. His abdomen was diffusely tender. Except for extruded external cuff, the PD catheter exit site was unremarkable. Serum drainage was noted one inch from the exit site where the trocar was inserted for laparoscopic PD catheter placement. The patient reported increasing drainage for 4 weeks prior to presentation. Laboratory studies were consistent with PD-related peritonitis. Broad spectrum antibiotics were initiated. Abdominal ultrasound confirmed a 1.5 inch sinus tract connecting the surgical trocar insertion site to the inner segment of the catheter tunnel.

The patient deteriorated rapidly but removal of the PD catheter resulted in progressive improvement in his clinical condition. This case is notable for a number of teaching points.

Discussion: In addition to its rarity, this case is notable for a number of teaching points. Patients with PKD are at risk for early PD fluid leak due to increased intra-abdominal pressure. Although uncommon, such complications can appear later and create a diagnostic dilemma. Moreover, this case shows importance of ultrasound imaging in evaluation of unexplained PD-related peritonitis even without overt symptoms of exit site infection. If technically feasible, it is prudent to insert the surgical trocar as far as possible from the exit site and the catheter tunnel. Finally, sinus formation should be considered when a previously healed scar develops abundant drainage.

SA-PO046

Diffuse Dermal Angiomatosis; an Unusual Cause for Painful Ulcerative Lesions in Patients with End Stage Renal Disease

Introduction: Diffuse Dermal Angiomatosis (DDA) is a benign vascular condition associated with peripheral vascular disease (PVD) and calciphylaxis in End Stage Renal Disease (ESRD) patients and presents as painful, ulcerative skin lesions. We describe two patients with ESRD who presented with painful ulcers and found to have DDA by skin biopsy. Given that DDA is hypothesized to be secondary to underlying hypoxia and ischemia, we treated each patient with topical Nitroglycerin and witnessed improvement in wound healing.

Case Description: Case 1: A 51 year old African American female with a history of end stage renal disease due to diabetes mellitus, hypertension and end stage renal disease on peritoneal dialysis; who presented with worsening of peritonitis and advanced surgical complication. We report a case of PD-related peritonitis due to a delayed surgical complication.

Case Description: Case 2: A 36 year old African American female with a history of poorly controlled diabetes mellitus, hypertension and end stage renal disease on peritoneal dialysis due to peripheral vascular disease (PVD). Given the patient's history of advanced peripheral vascular disease (PVD), we hypothesized that the lesion was secondary to underlying hypoxia and ischemia.

Discussion: DDA is a rare, benign, acquired disease. It is characterized clinically by very painful erythematous to violaceous patches with central ulceration and histologically by diffuse vascular endothelial cell proliferation within the dermis. It has been thought to be caused by local hypoxia and described in association with PVD. Revascularization is very effective and treatment with steroids and isotretinoin had been successful occasionally. In our two patients; we used topical Nitroglycerin with good wound healing. The proposed mechanism of action for Nitroglycerin is improvement of local perfusion.
SA-PO047

Shunt Nephritis and Pyogenic Spondylitis with a Positive PR3-ANCA Associated with Chronically Infected Ventriculo-Arterial Shunt

Hiroaki Ono, Seiji Kishi, Taizo Inagaki, Masanori Tamaki, Taichi Murakami, Kojiro Nagai, Hideharu Abe, Toshio Doi. *Nephrology, Tokushima Univ Hospital, Tokushima, Japan.*

**Introduction:** Shunt nephritis is a rare complication mostly described in the setting of chronic infection of ventriculo-atrial (VA) shunts. Although shunt nephritis is a well-recognized entity, diagnosis can be challenging and may be overlooked.

**Case Description:** A 56-year-old Japanese man presented with a persistent low grade fever for 4 months, hematuria and proteinuria and progressive kidney dysfunction. He had a history of secondary hydrocephalus associated with non-HIV cryptococcal meningitis at the age of 50, which was treated with ventriculo-venous-peritoneal (VP) shunt, followed by replacement with VA shunt because of intraduodenal abscesses. On admission, physical examination was unremarkable except for mild lower back tenderness. Laboratories revealed renal insufficiency (serum creatinine 2.35 mg/dl, baseline 0.86 mg/dl), hypocoomplementemia (CH50: 17 U/ml, elevated C3 and CRP) (3.53 mg/dl), positive PR3-ANCA (67.4U/ml), proteinuria (1.63 g/24h) and hematuria (100 erythrocytes/HPF). Blood culture and CSF culture were both returned positive for Staphylococcus capitis. Transcranialic echo showed no vegetation. Lumbar-spine magnetic resonance imaging demonstrated findings consistent with pyogenic spondylitis. There was increased uptake in both kidneys on gallium scintigraphy. VA shunt was removed and antimicrobial therapy was immediately started. He had resolution of proteinuria and hematuria, improvement of renal function and hypocoomplementemia, and normalization of CRP. He didn’t show symptoms related to hydrocephalus again after VA shunt and signs or symptoms of Wegener’s granulomatosis. We didn’t perform renal biopsy because urinalysis and renal function began to improve after treatment.

**Discussion:** We successfully treated a patient with shunt nephritis with antibiotic treatment and hematuria, proteinuria and progressive kidney dysfunction all improved. Physicians should be aware of the risks of infection-related GN in patients with VA shunts as early diagnosis and treatment initiation with antibiotics and shunt removal is a key to the successful management.

SA-PO048

Babesiosis Mimicking Hemolytic Uremic Syndrome as Cause of Hemolytic Anemia in an End Stage Renal Disease Patient

Ayantika Chenna, Pradeep Reddy Thodima, Mauricio Alexander Pedroza, Rasib Raja, Imara Dissanayake. *Nephrology, Albert Einstein, Philadelphia, PA.*

**Introduction:** Babesiosis is a tick borne disease and is seen in patients with recent history of travel to endemic areas. Since the advent of erythropoetic agents in ESRD patients, the number of cases of babesiosis have diminished. We present a case of severe hemolytic anemia from babesiosis in ESRD patient from blood transfusion being misdiagnosed as IUGR. There have been cases of babesiosis reported in HIV, splenectomy and renal transplant recipients. This is the first case described in ESRD patient to the best of our knowledge.

**Case Description:** 52 year old male with h/o ESRD recently started on hemodialysis, HTN, CHF with EF<15% was admitted with low Hemoglobin (Hb) of 6.5 gm/dl ( baseline about 8-9 gm/dl). During previous admission for gastrointestinal bleeding, he received 1 unit of PRBC before discharge. During the current admission, physical exam was significant for Jaundice, ejection systolic murmur, pedal edema and splenomegaly. Vital signs were normal. Labs showed – Hb 6.5 g/dL, BUN/Cr 8.7 and Ptt count of 52x10^3/mL. Na134, K 3.7, Cl97, HCO3 22 mmol/L, BUN 78 and Cr 5.9 mg/dL. Coombs test was negative. LDH 724 IU/L with Haptoglobulin low at 8 mg/dL. Peripheral Blood smear was positive for occasional schizocytes. He was started on plasmapheresis and steroids for presumed HUS/ITP per hematology. ADAMTS 13 was pending. After receiving 3 sessions of plasmapheresis, due to persistent anemia and thrombocytopenia, hematology repeated peripheral blood smear. It showed intra and extra erythrocytic ring forms concerning for parasitic infection. Plasmapheresis was thus discontinued. Patient was started on atovaquone and azithromycin for infectious disease. Babesia PCR was sent out. There was improvement in LDH, BUN and thrombocytopenia following the treatment.

**Discussion:** It is very rare to see hemolytic anemia from babesiosis in ESRD patients. Babesiosis and other anthrophob born illnesses should be considered in ESRD patients even in the absence of localizing symptoms if patients are not improving with the standard treatment.

SA-PO049

Actinomycosis Peritonitis: A Novel Therapy and Case Review

Aaron P Coulon, Rahul V. Kumat, Ashwin P. Jaikishen, Mihran V. Naljayan. *Dept of Medicine, Section of Nephrology and Hypertension, LSUHSC School of Medicine, New Orleans, LA.*

**Introduction:** Peritonitis is a leading complication of peritoneal dialysis (PD). Actinomycosis is a very rare cause of PD peritonitis, and each of the previously reported cases employed a different management plan. We chose a unique, simplified approach using ceftriaxone without catheter removal.

**Case Description:** The patient is a 40-year-old female with end stage renal disease on PD for 2 months. She was on apixiban for a deep venous thrombosis and presented to the dialysis unit with a three-day history of pink effluent. Cell count, gram stain, and cultures were obtained, and she was empirically given vancomycin 1 gram intraperitoneal (IP). Initially, the patient showed WBC 771 and BCR <10,000. She was admitted to the hospital and found to have leukopenia (4.1 x10^9/L) and anemia (hemoglobin 6.6 g/dL) with a normal abdominal exam. Repeat peritoneal fluid analysis showed WBC 266 and RBC 730, which decreased to 0 and 2, respectively, on hospital day three. A repeat culture grew gram positive rods (Diptherioids), and the initial culture grew Actinomyces. We decreased apixiban and started ceftriaxone 1 gram IP daily for three weeks with a six-hour dwell and fluconazole 200 mg every other day. All follow up cultures were negative and effluent was clear.

**Discussion:** Actinomycosis can cause abdominal and pelvic infections, but peritonitis is rare. Infection classically follows mucosal compromise and causes fibrosis, abscesses, and fistulas. Penicillins are the cornerstone of therapy. The four previous PD peritonitis cases that used antibiotics chose penicillin, amoxicillin, or clindamycin either as primary treatment or to prevent relapse. Ceftriaxone has been successfully used in cases involving various organ systems, but no one had used IP ceftriaxone for peritonitis. We had success with three weeks of ceftriaxone IP and fluconazole for fungal prophylaxis. In this case, removal of the PD catheter and penicillin were not necessary. This case is one of a rare disease, actinomyces PD peritonitis, treated in a novel way. It is the first report of treatment with ceftriaxone alone, and it provides another example of successful treatment with catheter preservation.

SA-PO050

A Case of Tuberculous Peritonitis Diagnosed at the Onset of Omental Torsion after Six Years of the Cessation of Peritoneal Dialysis

Makoto Ono, Naoki Sugano, Ai Katsuma, Izumi Yamamoto, Nanae Matsuo, Yudo Tanno, Ichiro Okhidko, Keitaro Yokoyama, Takashi Yoko. *Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.*

**Introduction:** It is well-known that the incidence and prevalence of tuberculosis in patients with chronic kidney disease, especially dialyzed patients, is extremely higher than those of non-renal patients. Furthermore, dialyzed patients had a high percentage of extrapulmonary tuberculosis and it makes the diagnosis difficult for a nephrologist. A 67-year-old man was admitted with complaints of pyrexia, abdominal pain, and acute inflammatory reaction. He initiated peritoneal dialysis for end-stage renal disease due to nephrosclerosis ten years ago, and transferred to hemodialysis because of underdialysis six years ago. He had no history of peritonitis as well as encapsulating peritoneal sclerosis. Subsequent abdominal computerized tomography (CT) showed right inguinal hernia, and it contained omentum mucus.

We performed an emergency hernia operation. We diagnosed as omental torsion and remove damaged omentum. Then patient became asymptomatic. We suspected tuberculous peritonitis as the cause of omental torsion, because epididymal granuloma was found in the specimen from resected omentum and ascites concentration of adenosin deaminase (ADA) was high. We initiated antituberculous agents without diagnostic confirmation from bacteriological examination. Tuberculosis bacterium was detected from the peritoneum six days after Six Years of the Cessation of Peritoneal Dialysis. We suspected tuberculous peritonitis as the cause of omental torsion, because epithelioid granuloma was found in the specimen from resected omentum and ascites concentration of adenosin deaminase (ADA) was high. We initiated antituberculous agents without diagnostic confirmation from tubercle bacillus from the resected omentum, and aborted the administration of antituberculous agents. On admission, the patient was on several antibiotics, including clindamycin, azithromycin, and ceftriaxone, and he was taking several antituberculous agents. We initiated antituberculous agents and tuberculate peritonitis was diagnosed as the cause of omental torsion and removed the omentum with granuloma. We also performed a laparoscopy with specimens for histological examination. Histological examination of the resected omentum showed granulomatous inflammation with epithelioid cells, Langhans giant cells, and multinucleated giant cells. We also performed a laparoscopy with specimens for histological examination. Histological examination of the resected omentum showed granulomatous inflammation with epithelioid cells, Langhans giant cells, and multinucleated giant cells.

**Discussion:** We treated the patient with ceftriaxone without catheter removal. Culture of the peritonitis fluid showed Actinomyces. We decreased apixiban and fluconazole for fungal prophylaxis. In this case, removal of the PD catheter and penicillin were not necessary. This case is one of a rare disease, actinomyces PD peritonitis, treated in a novel way. It is the first report of treatment with ceftriaxone alone, and it provides another example of successful treatment with catheter preservation.
SA-PO052
Survival among Patients with End Stage Renal Disease in Low versus High Serum FLC Levels
Yoonkyung Song, Jieun Kim, Gang Jee Ko, Young-Joo Kwon. Div of Nephrology, Korea Univ, Seoul, Republic of Korea.

Introduction: Approximately 500 mg/day polyclonal free light chain (FLC) is released into the blood in chronic inflammatory disease. Serum polyclonal FLC levels may reflect the activity of the adaptive immune system and is cleared by the kidney and reticular system. Moreover, some recent studies reported an association between polyclonal FLC level and mortality rate in end-stage renal disease (ESRD) patients undergoing dialysis.

Case Description: Initially, 432 ESRD patients who started hemodialysis or peritoneal dialysis after 2005 were enrolled. The levels of serum total FLC, FLC kappa, FLC lambda were determined at the start of dialysis. Of the 432 patients, only 300 patients whose status, whether alive or dead, was available in the data from Korean Society of Nephrology were included in this study.

Of the 300 patients, 75 were dead and 225 were alive at the start of this study. Patient’s survival status had no significant influence on the mean FLC levels. Furthermore, the levels of FLC as well as other serum parameters, including hemoglobin, phosphate, calcium, albumin and creatinine, and PTH, showed no correlation with survival rate. For the group analysis, the patients were assigned to one of two groups based on age: ≥60 years and above 60 years. In the ≥60 years group, significant difference was observed in the mean FLC levels of surviving and non-surviving patients. In Cox regression analysis, elevated total FLC levels were significantly correlated with overall mortality and reduced kidney survival according to the five-fold upper limit of reference values (P = 0.015, exp(B) 3.7). FLC lambda showed significant difference, the patients were assigned to one of two groups based on age: ≤60 years and above 60 years. FLC lambda showed significant upper limit of reference values (P = 0.015, exp(B) 3.7).

Discussion: FLC levels were positively correlated with mortality in young patients (<60 years old). This finding highlights the importance of FLC level measurement for dialysis patients.

Case Conclusion: Four of twenty-six patients that have been exposed to NxStage dialysis in British Columbia developed platelet counts of <100 x10^9/L within the first week following transition from conventional HD as outlined in figure below. They did not experience any symptoms suggesting hypersensitivity or any clinical events related to thrombocytopenia. No changes, other than exposure to a new dialysis system, were made in these patients. The study was an observational study. Although an alternate cartridge allows manual replacement of the dialyzer, this negates much of the advantage of the cartridge system. HHD programs using NxStage should monitor for thrombocytopenia and consider the platelet threshold at which patients require a dialyzer or machine change.

SA-PO053
Gentamicin-Resistant Gram Negative Exit Site Infection in a Peritoneal Dialysis Patient Salma Elbehary,1 Anupkumar Shetty,2 Nephrology, Baylor Univ Medical Center, Dallas, TX; 2Nephrology, Dallas Nephrology Associates, Dallas, TX.

Introduction: Infection is the most common complication of peritoneal dialysis (PD). Prevention of exit site infection (ESI) is an important component of care of patients on PD. Bernardini et al. showed that topical prophylaxis at the exit site with gentamicin results in reduction of infections in patients with Gram-positive and Gram-negative organisms including Pseudomonas. Since publication of this paper, most dialysis centers have been using gentamicin 1% cream instead of mupirocin to prevent ESI.

Case Description: A 52 year old non diabetic African American male with end-stage renal disease was started on PD in November 2012 and he was using topical gentamicin cream to the exit site with each dressing change to prevent ESI. In April 2014, he was treated for gentamicin sensitive coagulase- negative Staphylococcus epidermidis exit-site infection with antibiotics. After completing treatment, we continued prophylactic gentamicin cream with dressing changes. He was doing well until April 2015, when he developed ESI. Culture grew pseudomonas aeruginosa resistant to gentamicin. He received oral Levquin. Patient had unusually large amount of crust with underlying proud flesh that needed frequent cauterization with silver nitrate. More recently exit site swab in March 2016 grew gram positive bacilli. He continues to have large amount of crust and proud flesh. We switched to topical mupirocim cream along with topical sodium hypochlorite.

Discussion: There is a potential risk of developing gentamicin resistance which would limit antibiotic options for the treatment of ESI. Use of gentamicin cream alternating with mupirocin cream for prevention of PD related ESI needs to be investigated.

SA-PO054
Potential Role of Plasmapheresis in Severe CMV Infection with Ongoing Immune-Mediated Hemolysis and Low Complement Levels Yougandhar et al.,1 Swetha Rani Kanduri,2 Arnoldo F. Lopez-Ruiz,1 Tibor Fulop.1 Div of Nephrology, Univ of Mississippi Medical center, Jackson, MS; 2Div of Transplantation, Univ of Debrecen, Jackson, MS.

Introduction: Symptomatic CMV infection in patient with no previous history of immunosuppressive therapy is rare and it has only been reported after long hospitalization.

Case Description: We report the atypical case of young woman with ESRD who has developed a CMV infection resulting in liver damage and multiple systemic complications.

Case Conclusion: A 33 year old woman with type 2 diabetes chronic anemia and end-stage renal disease was admitted for acute diarrhea, elevated liver enzymes, and vaginal candidiasis. She was on hemodialysis for four months prior to admission. She had unexplained lower extremity weakness for same duration. C. diff testing by polymerase chain reaction was negative on three consecutive occasions. stool and blood cultures for bacteria, fungi and parasites were negative. Serology for HIV, acute hepatitis, autoimmune hepatitis or SLE were also negative. However, she was found to have low C3 and CH50 and low IgM. Hemolytic work-up revealed ongoing hemolysis with low haptoglobin level and direct Coombs positivity. In the context of chronic unexplained wasting, persistently low albumin, chronic diarrhea and elevated liver enzymes, CMV serum PCR was obtained, revealing massive elevation at 9 million copies/ml. While CMV IgG titer was positive, IgM titer was negative repeatedly. CSF analysis was unremarkable including negative CMV PCR. Bone marrow biopsy was normal. Given Pt was unstable and has elevated viral load, pt had plasmapheresis for three sessions, CMV immune globulin and L.V ganciclovir. After 2 weeks of therapy with ganciclovir, CMV decreased to 2600 viral copies/cm³. But she developed unilateral blindness and right hemiparesis.

Discussion: This case was very unusual for the profound viresence without neutropenia and this case of CMV-mediated hemolysis with low complement level and negative IgM antibody during the illness and broadens our horizon of potential CMV-associated illnesses. Timely initiation of PLEX and CMV immune globulin infusion may contributed to recovery in our case.

SA-PO055
Basement Membrane Nephropathy Like Phenotype in a Family with an ARHGAP24 Mutation Known to Cause Familial FSGS Elizabeth Kotzen,1 Gzentzon Hall,2 Megan Chyrst-Ladd,1 Guanghong Wu,1 Brandon M. Lane,1 WCR. Bone marrow biopsy was normal. Given Pt was unstable and has elevated viral load, pt had plasmapheresis for three sessions, CMV immune globulin and L.V ganciclovir. After 2 weeks of therapy with ganciclovir, CMV decreased to 2600 viral copies/cm³. But she developed unilateral blindness and right hemiparesis.

Introduction: Apoport Syndrome (AS), other glomerular basement membrane (GBM) disorders, and focal segmental glomerulosclerosis (FSGS) are major causes of glomerular disease worldwide. The pathogenesis and phenotypic spectrum of these conditions is not completely known, however recent genomic discoveries have demonstrated significant phenotypic overlap. In this study, we report a family with a mutation in the FSGS gene ARHGAP24 and predominant GBM defects on renal biopsy.

Case Description: We identified a 3-year-old Hispanic female with persistent microscopic hematuria and proteinuria. Renal biopsy was performed. Light microscopy showed unremarkable glomeruli with no sclerosis or significant GBM thickening or duplication. Immuno-fluorescence staining showed patchy, discontinuous IgM deposits on the GBM and minimal deposition of C3 and -5 chains of type IV collagen and electron microscopy revealed areas of thinning and thickening suggesting an AS phenotype. Audiologic and opthalmologic evaluation were normal. Targeted sequencing of the COL4A3, COL4A4, COL4A5, and MTHF9 genes was performed.

Discussion: There is a potential risk of developing gentamicin resistance which would limit antibiotic options for the treatment of ESI. Use of gentamicin cream alternating with mupirocin cream for prevention of PD related ESI needs to be investigated.
Akihiko Hypertension and Renal transplantation, Univ of Florida.

Disease A Fatal Complication (Hemoperitoneum) of Acquired Cystic Kidney SA-PO057

Jong Q158R was previously reported as a cause of hereditary FSGS in a Hispanic kindred. We normal. Whole exome sequencing (WES) revealed the Q158R mutation in an unidentified functional deep intronic sequence variant in a COL4A4 gene. These findings emphasize the need for a multifaceted approach to glomerular disease classification that integrates clinical, morphologic, and genomic data.

SA-PO0056 Andersen Tawil Syndrome Presented with Hypokalemic Periodic Paralysis Jong-Hwan Jung, Seon-Ho Ahn. 1 Div of Nephrology, Dept of Internal Medicine, Wonkwang Univ College of Medicine, Iksan, Jeonlabukdo, Korea.

Introduction: Hypokalemic periodic paralysis is often developed in clinical settings, such as thyrotoxicosis, renal tubular dysfunction, and channelopathies related with potassium. The channelopathy of inward rectifier K+ channel, IKS, is a disorder associated with mutations in an ion channel gene. Andersen Tawil syndrome associated with the channelopathy is characterized by dysmorphic features, ventricular arrhythmia, and hypokalemic periodic paralysis.

Case Description: A 25-year-old male visited our hospital due to lower legs paralysis. He took a medicine to control fever by acute pharyngotonsilitis for recent three days. He has a history of this condition, including potential complications e.g. malignancy/bleeding can be better predicted.


Introduction: Acquired Cystic Kidney Disease (ACKD) in patients with advanced chronic kidney disease (CKD) and end stage renal disease (ESRD), unlike other forms of cystic renal diseases, is largely considered a benign pathology with no clear recommendations for follow up care. We present a unique complication due to ACKD resulting in death of a patient.

Case Description: A 48 year old man with ESRD on hemodialysis (HD) for 14 years developed acute abdominal pain during his outpatient HD session and was sent to the ER. He was found to be hypotensive requiring fluid resuscitation and vasopressors and acute anemia with hemoglobin of 8.5 g/dL. Abdominal CT revealed large Hemoperitoneum with a right perinephric sentinel clot, bilateral multiple renal cysts, and features suspicious of bleeding originating from the upper anterior pole of right kidney. Renal angiogram showed active ongoing extravasation from multiple branches of the right renal artery.

Selective right renal artery embolization was unsuccessful. An emergent laparotomy revealed a torn right renal capsule with subcapsular hemorrhage and a 1.4 cm ragged defect in the inferior portion of the kidney. He underwent right nephrectomy and pathology was negative for malignancy. Because of religious reasons, patient refused blood transfusion and unfortunately died of hemorrhagic shock after the surgery.

Discussion: Our case shows a fatal and potentially preventable complication due to ACKD. Without clear guidelines for follow up and majority of the studies on cystic renal diseases excluding patients with ACKD, the true incidence of complications in these patients is not known. We believe an observational cohort study on the lines of Bosniak classification in patients with advanced CKD/ESRD should be considered such that natural history of this condition, including potential complications e.g. malignancy/bleeding can be better predicted.

SA-PO0058 Improvement of Kidney Function by Everolimus in a Patient with Kidney Angiomyolipoma due to Tuberous Sclerosis Complex Hideki Matsumura,1 Akira Ashida,1 Hyogo Nakakura,1 Yoko Fujii,1,2 Akihiro Shirasu,1 Satoshi Yamazaki,1 Motoshi Hattori,1 Hiroshi Tamai.1,2 Pediatrics, Osaka Medical College, Osaka, Japan; 1Internal Medicine, Kanazaki Municipal General Hospital, Hyogo, Japan; 2Pediatric Nephrology, Tokyo Women’s Medical Univ, Tokyo, Japan.

Introduction: Tuberous sclerosis complex (TSC) is a multisytemic genetic disorder characterizing growth of hamartomas in various organs throughout the body, including the brain, kidney, and skin. In the kidney, angiomyolipomas occur in most patients with TSC and can lead to kidney failure. Recently, clinical trials with mTOR inhibitors have demonstrated promising results for several indications, such as renal angiomyolipoma, subependymal giant cell astrocytoma. Here we report for the first time a case of kidney angiomyolipoma due to TSC in which kidney function improved after administration of an mTOR inhibitor, everolimus.

Case Description: The patient was a 39-year-old man who had been diagnosed as having TSC associated with facial angiofibromas, brain subependymal nodules and angiomyolipoma in the kidney and liver. He also had neurological symptoms including intellectual disability and seizures. Both kidneys were fully filled with angiomyolipomas, and kidney function had decreased gradually to eGFR 13.7 mL/min/1.73 m2. Because of his intellectual disability, it had been expected that initiation of dialysis would present many difficulties for him and his family. Therefore, we administered everolimus to preserve the patient’s kidney function and to delay the initiation of renal replacement therapy. Although the rate of eGFR decline had been -4.6 mL/min per year before everolimus treatment, the eGFR recovered to 20.3 mL/min/1.73 m2 (+4.7 mL/min per year) after four months of everolimus administration.

Discussion: Although everolimus has been approved as a new treatment option for TSC patients with kidney angiomyolipoma and is effective for reduction of tumor size, no previous report has indicated that it can improve kidney function. Although this is only a single case report based on short-term observation, everolimus therapy may be a promising new option for TSC patients with kidney insufficiency.

SA-PO0059 Gastroparesis in a Patient with ADPKD David M. Dewolfe,1 Vinod Raman,1 Andrew A. Wagner,2 Theodore I. Steinman.1,3 Nephrology, Beth Israel Deaconess Medical Center; 1Urology, Beth Israel Deaconess Medical Center, Boston, MA.

Introduction: ADPKD is associated with cystic enlargement of the kidneys and has rarely been reported to cause mechanical bowel obstruction. Here, we document the first case of a kidney cyst causing gastroparesis in a patient with ADPKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
A Mutation of the Gene KLHL3 as a Cause of Gordon Syndrome

Introduction: Hyperkalemic hypertension (Gordon Syndrome or pseudohypokalemia renal type) can be defined by elevated serum potassium (K+), sodium wasting, magnesium wasting, and absence of aldosterone reabsorption. There have been several gene mutations including a gain of function in WNK1 (With No lysine 1) or a loss of function in the thiazide sensitive NaCl co-transporter (NCC). There have been several gene mutations implicating, including a gain of function in WNK1 (With No lysine 1) or a loss of function in the thiazide sensitive NaCl co-transporter (NCC). Here, we report a case of adult hypertension and hyperkalemia, without offending agent. Family history was significant for hypertension but without obvious magnesium wasting, are most commonly associated with maturity-onset diabetes of the nuclear factor-1-beta (HNF1B) gene.

Case Description: A 39 year-old female is referred for chronic hypomagnesemia. 24hr urine: 700ml; Cre 629mg; Mg 50mg; Ca 59mg; K 103 mmol/l, bicarbonate 21 mmol/l, BUN 18 mg/dl, creatinine 1.32 mg/dl. Plasma renin was suppressed at 0.24 ng/ml and aldosterone was 7.8. Transtubular potassium gradient was 2.3, consistent with aldosterone deficiency. Urinalysis was consistently 5.8-5.9 mmol/l. Medication list was without offending agent. Family history was significant for hypertension but without obvious inheritance pattern. Laboratory tests showed serum Na+ 143 mmol/l, Cl 103 mmol/l, bicarbonate 21 mmol/l, magnesium 1.22 mmol/l. Plasma renin was suppressed at 0.24 ng/ml and aldosterone was 7.8. Transtubular potassium gradient was 2.3, consistent with failure to appropriately excrete potassium. Given this constellation, a presumptive diagnosis of Gordon syndrome was made and he was started on hydrochlorothiazide 12.5 mg 3x per week and sodium restriction. This led to improved blood pressure and serum K+ values. During this course, results of genetic testing done several months prior revealed a dominant mutation in the KLHL3 gene.

Discussion: Gordon syndrome involves abnormalities in WNK kinases, proteins affecting their degradation can lead to unregulated chloride reabsorption in the distal tubule. Without luminal electronegativity, the driving force for aldosterone mediated potassium and chloride reabsorption is lost. Here, we report a case with high clinical suspicion of Gordon syndrome, confirmed with a discovered mutation in the KLHL3 gene, one such protein known to impair degradation of WNK kinases, leading to cellular accumulation.

SA-PO060

A Mutation of the Gene KLHL3 as a Cause of Gordon Syndrome

Introduction: A 60 yo female with a history of ADPKD was referred with one pole cyst. 24hr cardiac monitoring: frequent PVCs. Differential included occult diuretic abuse. No family history of renal disease, electrolyte abnormalities or diabetes. Hypomagnesemia was previously mistakenly attributed to laxative or diuretic abuse. This case underscores the importance of maintaining a broad differential diagnosis and avoiding premature closure, particularly in a patient with a confounding history.

Case Description: A 26 year old male with a history of recurrent pneumothorax presented with progressive left flank pain. A computed tomography angiography (CTA) demonstrated a typical “string of beads” appearance with dissections of bilateral renal arteries and infarctions of bilateral kidneys. On day 8, he suddenly felt left, side abdominal pain. His hemoglobin decreased from 15.9 g/dl to 11.0 g/dl, and serum creatinine increased from 0.69 mg/dl to 1.52 mg/dl. He received blood transfusion and CTA, showing large retroperitoneal hemorrhage from ruptured left RAA. He was treated with a coil embolization of left renal artery, and then right RAA was embolized two days later with endovascular stent emplacement in right renal artery dissection. His renal function has markedly recovered. Two years later, he underwent video-assisted thoracoscopic bullectomy for the recurrence of pneumothorax. The diagnosis of von Hippel-Lindau disease was considered due to the long standing history of recurrent pneumothorax. Postoperative serum K+ was 19.5 mg/dl. Renal ultrasonography: 8.3cm right kidney; 8.5cm left kidney, with 2cm upper pole cyst. 24hr cardiac monitoring: frequent PVCs. Differential included occult diuretic abuse or Gitelman's. Genetic analysis: heterozygous whole gene deletion of the hepatocyte nuclear factor-1-beta (HNF1B) gene.

Discussion: HNF1B variants, which present with hypomagnesemia due to renal magnesium wasting, are most commonly associated with maturity-onset diabetes of the young with renal cysts (MODY5). Variants have also been associated with abnormal renal development or multiple simple renal cysts. Our case phenomenologically resembles Gitelman’s. It is a rare presentation with an HNF1B mutation giving the absence of significant structural abnormalities or diabetes. Hypomagnesemia was previously mistakenly attributed to laxative or diuretic abuse. This case underscores the importance of maintaining a broad differential diagnosis and avoiding premature closure, particularly in a patient with a confounding history.

SA-PO062

2,8-Dihydroxyadenine Crystalline Nephropathy: A Forgotten Cause of Renal Allograft Dysfunction

Introduction: We describe a case of 2,8-dihydroxyadenine crystalline nephropathy (DHACN) in renal allograft leading to graft dysfunction. This disease is under-recognized and frequently missed. Complications in renal allograft can be prevented by prophylaxis with allopurinol prior to kidney transplant (txp).

Case Description: 39 F with ESRD due to presumed HTN received a deceased donor kidney. A month after transplant, pt developed AKF with Cr of 5 mg/dl. Renal txp US showed moderate hydronephrosis, not relieved by foley catheter. Kidney biopsy showed no evidence of acute rejection but brown, polarizable, crystalline material within tubular epithelium and lumina consistent with 2,8-DHA crystals. No crystals were identified on urine sediment. Urinary stone risk panel showed elevated oxalate and decreased citrate. Pt was started on allopurinol and sodium citrate. She required anterograde ureteral stent removal as stent broke during cystoscopy. Cr leveled off at 2.4 mg/dl at 4 months. Pt never had personal or familial history of kidney stones and was not on triamterene. Pt was found to have hyperuricemia (uric acid >5mg/dl). APRT deficiency was considered and genetic testing revealed a missense base mutation in the APRT gene (c.3193G>A(p.Gly1065Arg)), which controls the production and assembly of type III collagen.

Discussion: APRT deficiency is a rare AR disorder of purine metabolism. In the absence of APRT, adenine is oxidized by xanthine dehydrogenase to 2,8-DHA, which is poorly soluble and forms crystals at physiological pH resulting in 2,8-DHA nephrolithiasis and crystalline nephropathy. APRT deficiency is frequently missed, owing to the absence of specific manifestations and lack of awareness of the disease among physicians. In kidney txp pts who are not on prophylactic treatment, 2,8-DHACN can recur in the kidney txp leading to allograft loss in more than 25% of cases. To date, only a few cases of recurrent 2,8-DHA nephropathy were reported. In a series of 9 pts with 2,8-DHACN, diagnosis was missed in all cases prior to txp. 2,8-DHACN after kidney txp can manifest as delayed graft function or primary graft non-function. Management of APRT deficiency includes allopurinol which reduces the generation of 2,8-DHA, fluid intake, and avoidance of purine-rich diet.
Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**SA-PO065**

**Rare Association of Autosomal Dominant Polycystic Kidney Disease (ADPKD) with Chromophobe Cell Carcinoma in a Young Patient**

_Elena Bezenja,1 Andreae Andronesi,2 Raluca Bobeica,3 Bogdan Constantin Haineala,4 Monica Gratiai Hortopan,5 Emi Marinela Preda,6 Nephrology, Fundeni Clinical Inst, Bucharest, Romania; 2Urology, Fundeni Clinical Inst, Bucharest, Romania; 3Pathology, Fundeni Clinical Inst, Bucharest, Romania._

**Introduction:** ADPKD is one of the most common genetic diseases caused by the mutation of PKD1 and PKD2 genes. There are very few cases described of ADPKD-chromophobe cell carcinoma association.

**Case Description:** A 24-year-old patient, aged 32, without significant medical history, is admitted for pain in the lumbar left spine and pollakiuria. A CT-scan was done before in another medical facility which revealed ADPKD and a tumor 35 mm in diameter in the right kidney (RK), incompletely characterized by CT (angiomyolipoma? oncocytoama?). Other abdominal imaging (US, MRI) did not show anything abnormal, as the lesion was not visible. Serum creatinine and urinalysis were normal. There were no inflammation, anemia, or changes in the clotting factors. Immunological assessment and tumor markers were negative MRI was done confirming the polycystic kidneys with cortical cysts type Bosniak I, II and IF, and a RK medreno-renal solid mass, possible an oncocyoma or a renal carcinoma with chromophobe cells. A total RK nephrectomy was done in the Urology department. The histological exam established the positive diagnosis of chromophobe cell kidney carcinoma (the clear and eosinophilic variant).

**Discussion:** We present the case of a special association between a genetic kidney disease with a very rare histological type of kidney malignancy in the absence of hypertension, hematuria, or family history of kidney cancer.

**SA-PO066**

**Polycthemia and Peribular Capillary Rarefaction in Two Adolescents Born Prematurely with Extremely Low Birth Weight**

_Nariaki Sugano,1 Naoki Sugano,2 Nobuo Furutani,3 Yoichi Miyazaki,4 Makoto Ogura,5 Gorou Tokudome,6 Takashi Yokoo._

**Nephrology and Hypertension, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.**

**Introduction:** Premature decrease of tubular VEGF causes peritubular capillary rarefaction in renal function. In X-8, he was referred to our department of outpatient. Since the 2015, VEGF expression becomes reduced with exposure to extratubular relative hypoxia after premature birth. Placental insufficiency also suppresses VEGF in the embryonic kidney. We therefore considered that the capillary rarefaction seen in our patients was caused by premature delivery and/or LBW.

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

**SA-PO067**

**A Case of Epstein Syndrome with Slow Development of Kidney Impairment**

_Kuniaki Takanori,1 Yoichi Andronesi,2 Daisuke Tsukahara,3 Nariaki Sugano,4 Naoki Sugano,2 Nobuo Furutani,3 Yoichi Miyazaki,4 Makoto Ogura,5 Gorou Tokudome,6 Takashi Yokoo._

**Nephrology and Hypertension, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.**

**Introduction:** It is estimated that there are about 200 patients suffered from Epstein syndrome (ES) around the world. This is an autosomal dominant hereditary disease characterized by sensorineural hearing loss and deterioration in renal function. In X-8, he was referred to our department of outpatient. Since the 2015, VEGF expression becomes reduced with exposure to extratubular relative hypoxia after premature birth. Placental insufficiency also suppresses VEGF in the embryonic kidney. We therefore considered that the capillary rarefaction seen in our patients was caused by premature delivery and/or LBW.

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

**SA-PO068**

**Everolimus Can Induce Regression of Inferior Vena Cava Aml**

_Edward J. Seg,1 Simon T. Wood,2 Nicole Isbel.1_1Dept of Nephrology, Princess Alexandra Hospital, Brisbane, Australia; 2Dept of Urology, Princess Alexandra Hospital, Brisbane, Australia.

**Introduction:** Tuberous sclerosis complex (TSC) is a genetic disorder characterised by multi-organ hamartomatous lesions, which frequently involve the kidney. The most common renal manifestation is angiomylipoma (AML). Tumour thrombus invasion into the inferior vena cava (IVC) is a rare complication of angiomylipoma. The role of everolimus in complicated renal AML is not clearly defined. The aim of this study was to report a case of a 19-year-old female with tuberous sclerosis complex (TSC) manifesting as bilateral renal AMLs with normal biochemical function; cortical tufts with frequent sequestrum and neurofibromatosis deficits; myoccardial involvement without outflow tract obstruction; and facial angiofibromas. She had previously experienced a life threatening retroperitoneal haemorrhage which required embolisation. On surveillance imaging, she was found to have extension of her right renal AML into the renal vein and IVC. There were no features to suggest renal cell carcinoma. To avoid the risks associated with extensive surgery, she was commenced on everolimus 10mg daily. Within 3 months, she experienced improvement in seizure frequency, neurocognitive function and cutaneous disease. The dose was increased to 15mg daily in split dosing to achieve trough levels of 5-10. At 6 months, partial regression of the IVC tumour was demonstrated on MRI. By 12 months, there was complete resolution of the IVC and renal vein tumour and reduction in the size of the intrarenal AML. Drug toxicity included mouth ulcers and intermittent mild neutropenia.

**Discussion:** This is the first reported case of tumour thrombus regression with everolimus in complicated renal AML. Traditionally, vascular invasion has been managed surgically due to the risk of cardiac or pulmonary tumour embolus, however operative intervention of this nature involves significant morbidity. Treatment with mTORi in patients with aggressive disease including tumour thrombus warrants consideration.

**SA-PO069**

**Rothia mucilaginosa Peritonitis**

_Khurram Mehtabdhin, Mala Sachdeva._

**Div of Nephrology and Hypertension, Northwell Health, Great Neck, NY.**

**Introduction:** Peritonitis is a known complication in patients who are on peritoneal dialysis (PD) and is usually caused by Staphylococcus species, Escherichia Coli, and Pseudomonas Aeroginosa. Physicians should be aware of uncommon causes of bacterial peritonitis. We report a rare case of _R. mucilaginosa_ peritonitis requiring catheter removal. To our knowledge, we have only reported cases of _R. mucilaginosa_ peritonitis, formerly known as Stomatococcus mucilaginosus associated with PD.
Case Description: We report an 80 year old male on PD for eight years, with a history of bilateral lower extremity edema, prior who presented with fever, vomiting, abdominal pain, and cloudy effluent. His baseline creatinine was 0.9mg/dl per day. He was not volume depleted, not septic. There were no new medications. He was placed and Warfarin was stopped. He presented to the ED 10 days later with bilateral lower extremity edema, gross hematuria and acute oliguric renal failure. His baseline creatinine was 0.9mg/dl but his presentation was 3.4 mg/dl. Creatinine continued to rise by 1mg/dl per day. He was not volume depleated, not septic. There were no new medications. A: Hematocyt in the urine was also noted. An ultrasound was performed which revealed a 6.5cm soft tissue collection. She was re-admitted with a fever and growing flank mass. Repeat CT scan (Figure 2) revealed a soft tissue mass at her left flank, which CT scan reported as a 6.5cm soft tissue collection. She was emergently taken to the OR for an abscess drainage. The abscess was drained in the OR and sent for culture. The culture was again positive. Due to refractory peritonitis, his PD catheter was removed and the catheter was placed and Warfarin was stopped. He continued to report malaise, weakness, and lack of appetite. Day 8 counts showed total nucleated cell count of 43, 85% polys; however the culture was negative. Due to refractory peritonitis, his PD catheter was removed and he began hemodialysis.

Discussion: Stomatococcus mucilaginosus is an encapsulated gram-positive, coagulase negative organism found in pairs, clusters and tetrads. It is considered to be part of the normal flora of the oral cavity in dental caries and plaques, indwelling catheters, leukemia, valvular disease, intravenous drug use, severe neutropenia or immunocompromised state. Prior cases have demonstrated this organism to be susceptible to penicillins. Despite treatment, the patient presented had refractory peritonitis, requiring removal of the PD catheter. Our case illustrates the importance of quick diagnosis and timely treatment in patients with rare organisms causing peritonitis.

SA-PO070 IVC Filter Migration Associated with Bilateral Renal Vein Thrombosis Treated with Thrombolytic therapy Arouna Senthilkumar, Benjamin Ling, Julia Schneider. Nephrology and Hypertension, Hines VA Hospital, Hines, IL.

Introduction: Little is known about the migration of IVC filters. Here we present a case of dislodged IVC filter, bilateral renal vein thrombosis with acute renal failure successfully treated with tissue plasminogen activator (tPA).

Case Description: 87 year old man with history of PE twice and a lower extremity DVT in 2014 treated with Warfarin but complicated by GI bleeding. VenaTech IVC filter was placed and Warfarin was stopped. He presented to the ED 10 days later with bilateral lower extremity edema, gross hematuria and acute oliguric renal failure. His baseline creatinine was 0.9mg/dl but presentation was 3.4 mg/dl. Creatinine continued to rise by 1mg/dl per day. He was not volume depleated, not septic. There were no new medications. A: Hematocyt in the urine was also noted. An ultrasound was performed which revealed a 6.5cm soft tissue collection. She was re-admitted with a fever and growing flank mass. Repeat CT scan (Figure 2) revealed a soft tissue mass at her left flank, which CT scan reported as a 6.5cm soft tissue collection. She was emergently taken to the OR for an abscess drainage. The abscess was drained in the OR and sent for culture. The culture was again positive. Due to refractory peritonitis, his PD catheter was removed and the catheter was placed and Warfarin was stopped. He continued to report malaise, weakness, and lack of appetite. Day 8 counts showed total nucleated cell count of 43, 85% polys; however the culture was negative. Due to refractory peritonitis, his PD catheter was removed and he began hemodialysis.

Discussion: Stomatococcus mucilaginosus is an encapsulated gram-positive, coagulase negative organism found in pairs, clusters and tetrads. It is considered to be part of the normal flora of the oral cavity in dental caries and plaques, indwelling catheters, leukemia, valvular disease, intravenous drug use, severe neutropenia or immunocompromised state. Prior cases have demonstrated this organism to be susceptible to penicillins. Despite treatment, the patient presented had refractory peritonitis, requiring removal of the PD catheter. Our case illustrates the importance of quick diagnosis and timely treatment in patients with rare organisms causing peritonitis.

SA-PO071 A Case Report of Erdheim-Chester Disease Involving the Kidney and Retropitoneum Vinay Srinivas. Medicine, Gold Coast Univ Hospital, Gold Coast, Queensland, Australia.

Introduction: Erdheim-Chester Disease (ECD) is a rare non langerhans cell histiocyotosis neoplasm, that has multi organ involvement The renal and retropitoneum can be the primary sites of involvement and account for 30% of cases. We present an interesting case report of a gentleman who presented with multiple episodes of obstructive oliguric acute kidney injury with hydronephrosis who required repeat ureteric stenting. CT with non contrast revealed soft tissue thickening surrounding the left kidney. Open biopsy of this tissue showed features of ECD. Interestingly our case had a right nephrectomy for non renal disease.

Case Description: Our patient initially presented to the nephrology outpatient clinic with deteriorating renal functions that were previously normal. He had multiple episodes of acute kidney injury with associated hydronephrosis on renal ultrasound. Ureretic stents were placed and his renal functions improved. CTKUB scan revealed a 15mm soft tissue thickening around the left kidney which was not present in his initial CT scan. Open biopsy of the perinephric tissue showed features of ECD marked by histiocytes within the perinephric tissue. The biopsy was tested for the BRAF V600 mutation and was positive. He was commenced on Dabrafenib, an oral BRAF inhibitor.

Discussion: Since its first description in 1930, over 500 cases of ECD have been reported. Common clinical manifestations include bone pain, diabetes insipids and neurological complaints. Hydronephrosis, abdominal pain and dysuria are chief renal complaints. Retropitoneal fibrosis illustrates retroperitoneal involvement. CTKUB reveals perinephric and peri-ureteric thickening giving the hairy kidney sign. Biopsy reveals xanthogranulomatous inflammation that may be BRAF mutation positive. BRAF mutation positive status has important implications; it is a tumour responsive mutation. Good response rates have been achieved using oral BRAF inhibitors. It is a potent therapeutic agent that can improve survival to a disease that was previously fatal.
SA-PO074
Renal Manifestations of Leptospirosis
Josef Bautista, Andrew Rogers, Jie Tang.
Section of Hypertension and Nephrology, Dept of Medicine, Rhode Island Hospital - Brown Univ, Providence, RI.

Introduction:
In the setting of infection, acute kidney injury is usually secondary to renal hyperperfusion and cytokine-induced inflammation, but not the infectious organism itself. Rarely, however, the infectious organism can directly injure the glomeruli and renal tubules. The net results are decreased glomerular filtration and electrolyte and acid-base disorders. In this case we present a patient with severe leptospirosis who developed acute kidney injury (AKI), hypokalemia, glucosuria, and non-anion gap acidosis. We also review the existing literature regarding the effect of leptospirosis on the renal tubules.

Case Description:
A 55-year-old male with no significant past medical history presented with jaundice, myalgia and malaise. He had no oliguric acute kidney injury with a creatinine of 10 ml/dl, thrombocytopenia, transaminitis, hyperbilirubinemia and rhabdomyolysis. Physical examination revealed normotension, icterus, pulmonary crackles and no rales. Notable laboratory findings included serum potassium of 3.1 mg/dl, bicarbonate of 11 meq/L with anion gap of 10, and a urinalysis showing glucosuria with normal serum glucose. Urine microscopy showed muddy brown casts and renal tubular epithelial cells. He was treated with ceftriaxone for presumed leptospirosis, which was later confirmed on follow-up his hypokalemia and glucosuria resolved.

Discussion:
This case highlights the several renal manifestations of leptospirosis, i.e. hypokalemia, proximal tubular dysfunction and acute tubular necrosis. While it is well known that Leptospira sp can directly injure the renal tubule and interstitium, more recent evidence also showed that Leptosiral infection could lead to altered expressions of renal hypoperfusion and cytokine-induced inflammation, but not the infectious organism itself. Recent evidence also showed that Leptosiral infection could lead to altered expressions of renal hypoperfusion and cytokine-induced inflammation, but not the infectious organism itself. This case was recently started on hemodialysis (HD) via a tunneled catheter in her right internal jugular vein. She has a history of RCC managed with a total right nephrectomy and radiation therapy twenty years before starting HD. Shortly after starting HD, she complained of dysphagia, as well as a new neck mass. Examination revealed a rapidly-enlarging thyroid nodule. All lab results, including thyroid function studies, were unremarkable. Ultrasound (US) guided fine needle aspiration of the nodule yielded non-discrete results leading to surgical excision. The patient underwent total thyroidectomy, subsequent pathological identification of 3.5x5.5x7.5cm hypervascular mass in the right lobe of the thyroid. Sectioning and staining of the mass confirms the recurrence of RCC, which was positive for CD10 and PAX-2, along with a having classic chicken-wing vascular appearance and clear cells on histologic analysis. US of the remaining kidney and whole-body PET/CT scan did not delineate further areas of malignancy, suggesting the recurrence of RCC was confined to the thyroid.

Discussion:
While the bulk of RCC recur within five years of curative nephrectomy, long-term recurrence has been reported after a decade. Our patient is unique, as she presented with a thyroid nodule that was the discreet recurrence of her RCC excised two decades prior. Although RCC has been shown to metastasize to the thyroid, recurrence of RCC solely in the thyroid has not been reported in English literature. The findings of the case support the notion that any new mass in a patient treated for RCC should be considered a potential recurrence of the disease, even beyond the five-year active surveillance window.

SA-PO077
Atypical Presentation of Primary Renal Lymphoma
Syed Rizwan A. Bokhari, 1
Abeer Ansari, 2 Maria Rizwan Bokhari. 2
Nephrology, Doctors Hospital and Medical Center, Lahore, Pakistan; 1Radiology, Jinnah Hospital, Lahore, Pakistan.

Introduction:
Primary renal lymphoma (PRL) is a very rare disease, accounting for less than 1% of extra nodal lymphomas. Usually renal tissue is devoid of lymphoid tissue, but it can be involved in cases of disseminated disease. We present a case of a young patient with bilaterally enlarged kidneys.

Case Description:
A 21-year-old male medical student presented with a 4-month history of left shoulder pain, continuous fever (100-101)°F and weight loss (13 lbs in 4 months) down to 53 kg. He developed dull, generalized abdominal pain a week before presentation. There was no previous history of diabetes, hypertension, cardiovascular, hepatic, pulmonary or kidney disease. Patient received multiple courses of antibiotics, antibiotics, steroids and NSAIDs from local practitioners with no improvement. Personal and family history were insignificant. Examination did not have any significant physical findings.

Laboratory data showed complete blood count within normal limits, chemistry panel and renal function tests within normal limits. Urinalysis showed bilaterally enlarged kidneys with grade 1 echogenicity, size had increased compared to a prior scan. Percutaneous renal biopsy revealed B cell CD 20, Ki-67, CD3 and Tdt positive lymphoblastic Non Hodgkin Lymphoma (NHL). CT scan of chest, abdomen and pelvis revealed bilateral diffuse enlargement of kidneys with heterogeneous enhancement.

Discussion:
No mediastinal or abdominal lymphadenopathy was noted. Patient was referred for chemotherapy for NHL chemotherapy treatment. Patient is on regular follow up after chemotherapy with creatinine of 1.2.

Discussion:
Although PRL is quite uncommon, it should be distinguished from other causes of renal enlargement, mainly renal cancer and infectious etiology apart from metastatic involvement. Prompt diagnosis and timely management can help as promising outcome.

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

648A
SA-PO078
IgG4-Related Kidney Disease in a Patient with Plasma Cell Dyscrasia
Chandrashekar Kashyap,1 Anees Quyyumi,1 Alton Brad Farris,2 Kyle Bradley.2 1Dept of Nephrology, Emory Univ, Atlanta, GA; 2Dept of Pathology, Emory Univ, Atlanta, GA.

Introduction: IgG4-related disease (IgG4-RD) is an immune-mediated disease with manifestations in various organs. IgG4-RD has been increasingly recognized in nephrology for its role in causing acute or chronic renal failure. We report a case of a 80 year old male with plasma cell dyscrasia who presented with progressive renal failure. Kidney biopsy showed IgG4 related tubulointerstitial nephritis.

Case Description: An 80 year old Black man was referred to the Renal Clinic for evaluation of worsening renal function. Past medical history included plasma cell dyscrasia (diagnosed in 2013) with bone marrow biopsy, hypertriglyceridaemia, hypertension, chronic pancreatitis and lymphadenopathy. He was asymptomatic with normal physical exam and blood pressure of 140/78. Lab Results: Baseline SCr was 0.89mg/dL in Aug 2014. SCr ranged from 3.1 to 3.7mg/dL from Oct 2015 to Jan 2016. SCr was 6.7mg/dL in Feb 2016. Computerized tomography and bone scan were normal. Complement levels were low. Autoimmune screen, hepatitis panel and HIV were negative; Serum Ig level was high at 10250mg/dL. Kidney biopsy revealed IgG4-RD.

Discussion: IgG4-RD can masquerade many infectious, malignant and inflammatory conditions. This case illustrates the need to consider IgG4-related kidney disease as a potential differential in the workup of CKD and AKI. Thorough history and physical exam is vital as it can affect multiple organs. Early identification is necessary as it is a potentially treatable disorder.

SA-PO079
Diffuse Large B-Cell Lymphoma Localized in Peritubular Capillaries Diagnosed by Percutaneous Kidney Biopsy
Kenji Harada,1 Kosuke Masutani,2 Kazuhiko Tsuruya,1 Hitotosei Kanai.1 1Div of Nephrology, Kokura Memorial Hospital, Kitakyushu, Fukuoka, Japan; 2Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan.

Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin’s lymphoma, and gastrointestinal DLBCL is a frequent form of extranodal lymphoma. We hereby report a rare case of DLBCL showing various neurological symptoms and diagnosed by kidney and bone marrow biopsy.

Case Description: A 38-year-old Japanese male developed disturbance in gait, general fatigue, and nausea. He also developed urinary disturbance, and saw a neurologist. A proteinuria of 652mg/24hr was noted on 24 hr urine study. Kidneys showed normal size and echogenicity with no hydronephrosis on Renal ultrasound. A 3.5 x 3.5 x 3.2 cm cyst was seen in the interpolar right kidney. Kidney biopsy in Mar 2016 confirmed IgG4 related tubulointerstitial nephritis. Key biopsy findings were: Lymphoplasmacytic infiltration, eosinophils and storiform fibrosis. Immunohistochemistry showed 50-100 IgG4+ plasma cells high power field. IgG4/IgG ratio > 40%. Patient was started on prednisone at 40mg/day.

Discussion: IgG4-RD can masquerade many infectious, malignant and inflammatory conditions. This case illustrates the need to consider IgG4-related kidney disease as a potential differential in the workup of CKD and AKI. Thorough history and physical exam is vital as it can affect multiple organs. Early identification is necessary as it is a potentially treatable disorder.

SA-PO081
Development of a Functional Glomerulus at the Organ Level on a Chip to Mimic Hypertensive Nephropathy
Mengyin Zhou,1 Dept of Nephrology, The First Affiliated Hospital of Dalian Medical Univ, Dalian, Liaoning, China.

Introduction: To develop a microfluidic rapid evaluating multi-inducers device to reproduce glomerular structure and function of glomeruli. By applying this microfluidic chip, the expression of F-actin, CD-31, vWF of glomeruli and podocytes was detected by immunofluorescence and the expression of F-actin, CD-31, vWF of glomeruli and podocytes was detected by fluorescence microplate, the expression of F-actin, CD-31, vWF of glomeruli and podocytes was detected by immunofluorescence microplate. Consequently, this work provides an reappearance of the hypertransfusion, high filtration and high transmembrane pressure in glomerular capillary when hypertension leads to renal disease and also decompensation of the glomerular epithelial barrier. The potential for glomerular microfluidic device which confirmed directly that the abnormal hemodynamic factors can degrade GFB function by injuring the skeleton of endothelial cells and podocytes and ligandin between cells.

Funding: Government Support - Non-U.S.

SA-PO082
Mamood Elsayed1,2 Ahmed Alghali,1 Alzate O’Farrell,1 Austin G. Black,1,3 Graduate Entry Medical School (GEMS), Univ of Limerick, Limerick, Ireland; 1Dept of Nephrology, Univ Hospital Limerick, Limerick, Ireland; 2Dept of Health Research Inst (HRI), Univ of Limerick, Limerick, Ireland.

Introduction: Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized by the presence of non-caseating granulomas. Hypercalcemia associated with sarcoidosis exhibits seasonal variability with peak incidence during summer months associated with elevated production of 1,25 (OH)2 vitamin D. The impact of this on short-term and long-term kidney function and the extent to which it can be managed with corticosteroid treatment is poorly understood.

Case Description: Herein, we report on the case of a 64-year male who presented to our unit with acute kidney injury (AKI) (peak creatinine was 1.39 mg/dL) and moderate hypercalcemia (peak calcium 13.2 mg/dL) on a background of sarcoidosis, chronic kidney disease (CKD) and type II diabetes. Serum calcium levels failed to normalize despite two-weeks of high dose oral corticosteroid therapy and high volume normal saline infusion. Treatment with oral ketoconazole (200mg once daily) resulted in an immediate and sustained reduction in serum calcium levels with subsequent resolution of his AKI.

A careful review of the patient’s previous ten-year medical history revealed a seasonal pattern to his hypercalcemic episodes, corresponding with maximum daylight hours and triggering severe AKI.

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

469A
Monophosphoryl Lipid A Prevents Inhibition of Bicarbonate Absorption by LPS in Medullary Thick Ascending Limb (MTAL) Through a TLR4-Pleckstrin-KAkt Pathway

Bruns A. Watts,1 Thampi George,1 Edward R. Sherwood,2 David W. Good.1 1Univ TX Medical Branch; 2Vanderbilt Univ Medical Center.

Background: Monophosphoryl lipid A (MPLA) is a detoxified derivative of LPS that is used as a vaccine adjuvant in humans due to its immunomodulatory properties. MPLA functions as a TLR4 agonist to augment the innate host response to infection and pretreatment with MPLA reduces inflammation and increases survival in models of sepsis and endotoxemia. Whether MPLA may protect against sepsis- or LPS-induced kidney dysfunction is not known. Previously we demonstrated that LPS inhibits HCO₃⁻ absorption in the MTAL by a basolateral TLR4-ERK signaling pathway. Here we examined whether pretreatment of MTALs with MPLA would attenuate the effect of LPS to inhibit HCO₃⁻ absorption and the mechanisms involved.

Results: MTALs from rats were perfused in vitro with MPLA (1 µg/ml) in bath and lumen or bath alone for 2 hr, then LPS was added to (and MPLA removed from) the bath solution. Pretreatment with MPLA eliminated the effect of LPS to inhibit HCO₃⁻ absorption. In contrast, in MTALs pretreated with MPLA plus a phosphatidylinositol 3-kinase (PI3K) or Akt inhibitor, LPS decreased HCO₃⁻ absorption by 26%. Treatment with MPLA increased Akt phosphorylation 1.4-fold in dissected MTALs. The activation of Akt by MPLA was eliminated by a PI3K inhibitor and in MTALs from TLR4-deficient mice. Pretreatment of MTALs with MPLA prevented LPS-induced ERK activation; this effect of MPLA was eliminated by a PI3K inhibitor. Thus, blocking activation of PI3K or Akt by MPLA restored the ability of LPS to activate ERK and inhibit HCO₃⁻ absorption in MPLA-treated MTALs. MPLA alone had no effect on HCO₃⁻ absorption, indicating an ability of MPLA to convey resistance to LPS without inherent toxicity.

Conclusions: We conclude that pretreatment with MPLA prevents the effect of LPS to inhibit HCO₃⁻ absorption in the MTAL. This effect is mediated through MPLA stimulation of a TLR4-Pleckstrin-KAkt pathway, which prevents LPS-induced ERK activation. These studies show that MPLA induces protection against LPS in MTAL cells and identify TLR4-based immunomodulators as potential novel therapeutic agents to prevent or treat sepsis-induced renal tubule dysfunction.

Funding: NIDDK Support

SA-PO085

The NH₃-H⁺ Transport Stoichiometry of Human SLC4A11 Xuesi Max Shao,2 Liyo Kao,3 Ira Kurtz.1 1David Geffen School of Medicine, UCLA, Los Angeles, CA; 2Dept of Neurobiology, UCLA, Los Angeles, CA.

Background: SLC4A11 was reported to be capable of functioning as a NH₃-H⁺ co-transporter (Zhang et al. 2015) with a transport stoichiometry of 1 NH₃-2 H⁺, and a role in acid-base regulation in renal ammonia handling. The use of conventional reversal potential (Eᵣ) methods without a specific inhibitor to estimate the transport stoichiometry can be inaccurate due to currents mediated by other plasma membrane endogenous channels/electrogenic transporters.

Methods: HEK-293 cells expressing SLC4A11 were whole-cell voltage clamped, and steady state currents were measured at various voltages to obtain the I-V relationships. We first analyzed the I-V relationship using the delta current method (Shao et al. 2014). The NH₃ concentration in the patch pipette ([NH₃]ᵣ) was 1 mM, and the bath NH₃ concentration ([NH₃]ᵢ) was switched from 1 mM to 3 mM. The NH₃⁺-H⁺ transport stoichiometry was also estimated by recording the I-V relationship of HEK-293 cells expressing SLC4A11 and the I-V relationship of mock-transfected cells, with 1 mM [NH₃]ᵢ and 3 mM [NH₃]ᵣ. The SLC4A11-specific IV curve was obtained by subtracting the mean I-V curve of the mock-transfected cells from the mean IV curve of SLC4A11-expressing cells.

Results: Using the delta current method, the NH₃⁺-H⁺ transport stoichiometry calculated according to: 2RT/[Eᵣ(ln(∆I/V₁=0))₋(ln(∆I/V₂=0))], was 1 NH₃⁺:2.94 H⁺ (n = 14) or ~1:3, where ∆I/V₂ is the delta current at V₂ ~ -10 mV, and ∆I/V₁ is the delta current at V₁ ~ 0 mV. In the second series of experiments, the Eₒ of the SLC4A11-specific I-V curve (SLC4A11-expressing cells, n = 14; mock-transfected cells, n = 8) was ~8.6 mV which approximates the expected Eₒ value of ~9.3 mV for a 1 NH₃:3 H⁺ stoichiometry calculated according to: RT/(Eᵣ(ln(∆I/V₁=0))₋(ln(∆I/V₂=0))), where q is the stoichiometry of H⁺ when p = 1 and q = 3; where p is the stoichiometry of NH₃, q is the stoichiometry of the H⁺, Zᵣ is the valence of NH₃ ([Zᵣ = 0], and Zᵣ is the valence of H⁺ (Zᵣ = 1).

Conclusions: We used two independent methods to determine the NH₃⁺-H⁺ stoichiometry of SLC4A11 that correctly for bias due to endogenous channel/transporter currents. Our results consistently demonstrate that the SLC4A11 transport stoichiometry is 1 NH₃⁺:3 H⁺.

SA-PO086

Normal Intrinsic Na/HCO₃ Cotransport Activity but Altered Plasma Membrane Abundance of Phosphomimetic NBCe1-A Mutants

Evan J. Myers, Aniko Marshall, Mark Parker. Physiology and Biophysics, SUNY at Buffalo, Buffalo, NY.

Background: Renal phosphoproteomic studies by others have revealed two in-vivo phosphorylation sites (Ser982 and Ser985) on the cytosolic C-terminus of the renal Na/HCO₃ cotransporter NBCe1-A that can exhibit a phosphorylated state either individually (pSer982 or pSer985) or in tandem (pSer982/pSer985). Others have suggested that phosphorylation of Ser982 can change the Na:HCO₃ stoichiometry from 1:2 (as observed in most heterologous expression systems) to 1:3 (as predicted, but rarely observed, in kidney cells).
Methods: In order to probe the phosphorylation status of the NBCe1-A/C-term in our expressed proteins, we generated novel phospho-specific antibodies that recognize singly phosphorylated state pS982/985 or the doubly phosphorylated state pS982/pS985. We also created a series of EGFTagged phosphomimetic mutants D982/A985, D982/D985, A982/D985, and A982/A985. To investigate the consequence of phosphorylation, we performed western blotting on cell extracts, two-electrode voltage clamp on Xenopus oocytes heterologously expressing NBCe1-A, and immunofluorescence on MDCK-II cells. Results: We detected both phosphorylation states of NBCe1-A in mouse kidney and Xenopus oocytes. Our electrophysiological studies reveal that all phosphomimetic mutants exhibit inward current (iNa),-dependent cotransport activity and a reversal potential consistent with a 1:2 stoichiometry. However, biotinylation assays and fluorescence microscopy on oocytes reveal significant differences in plasma membrane abundance among the mutants, notably A982/D985 was least abundant (75% less abundant than D982/ D985). In pooled MDCK-II cell extracts except A982/D985 consistently localized to the basolateral membrane; 3 of 6 cells transfected with A982/D985 exhibited evidence of intracellular NBCe1-A retention. Conclusions: Our data confirm that Ser982 and Ser985 are phosphorylated in vivo and suggests that the phosphorylation status of Ser982 influences plasma membrane abundance but not activity. Our antibodies will allow us to probe changes in the phosphorylation state of these two residues in response to physiological and pathological cues.

SA-PO087
Proximal Tubule Glutamine Synthetase Expression Is Necessary for the Normal Response to Dietary Protein Restriction
Hyun-Wook Lee,1 Gunars Osis,1 Mary E. Handlogten,1 Chao Chen,1 Jill W. Verlander,1 I. David Weiner,1,2 "Nephrology, Univ of Florida College of Medicine, Gainesville, FL; 1Nephrology and Hypertension Section, NF/SGVHS, Gainesville, FL.

Background: Dietary protein restriction has multiple benefits in kidney disease. Because protein intake is a major determinant of endogenous acid production, it is important that decreased protein excretion decreases during protein restriction. Glutamine synthetase (GS) catalyzes the reaction of NH3 and glutamate, which regenerates the essential amino acid, glutamine, and can decrease net ammoniagenesis. GS is highly expressed in the proximal tubule, and its expression increases during dietary protein restriction. This suggests ammonia recycling via GS during protein restriction could decrease net ammoniagenesis and decrease ammonia excretion. The current study’s purpose was to determine proximal tubule GS’s role in the normal response to protein restriction.

Methods: We generated mice with proximal tubule-specific GS deletion (PT-GS-KO) using Cre-loxP techniques. Cre-negative control (C) and PT-GS-KO mice in metabolic and molecular biology experiments to support the findings obtained from the analyses.

Results: We performed Gene Ontology (GO) and motif analyses for low pH-induced gene transcripts obtained from TSS-Seq using a rat intercalated cell line (IN-IC cells) that are incubated either in pH 7.4 or 7.0 for 24h. To evaluate ubiquitin-proteasome pathway, cells were incubated either in pH 7.4 or 7.0 for 12h, then further incubated in the presence of N32, a proteasome inhibitor. Western blotting was performed to determine antibodies for specific mRNAs after cells were incubated either in pH 7.4 or 7.0.

Results: GO analysis showed the enrichment of genes that are classified into “programmed cell death”: Fzd2, Jag2, Tgm2, and Gck. Those genes are known to be involved in renal fibrosis. We found many ubiquitin-proteasome system (UPS)-related genes up-regulated by low pH: six ubiquitin protein ligases, five ubiquitin conjugating enzymes, two deubiquitinating enzymes, and four other genes involved in UPS. Western blot showed that low pH induced global ubiquitination of protein. Motif analysis predicted motif sequences associated with low pH-induced transcription that possibly interact with specific transcription factors such as EGR1, SP1, and KLF5. We found that the expression of EGR1 mRNA was immediately increased by low pH in 2h.

Results: The results implied various possible mechanisms that are involved in acid-induced renal injury.

Funding: Government Support - Non-U.S.

SA-PO090
Why Does SLC26A7 Not Compensate the Loss of kAE1 in Distal Renal Tubular Acidosis? A_K_M. Shahid Ullah,1 Rawad Lashhab,1 Jennifer C. King,1 Valentina Pelch,2 Johannes M. Herrmann,1 R. Todd Alexander,1 Emmanuelle Cordat,1 1Dept of Physiology, Univ of Alberta, Edmonton, AB, Canada; 2Cellular Biology, Univ of Kaiserslautern, Kaiserslautern, Germany; 1Univ of Calgary, Calgary, AB, Canada.

Background: SLC26A7 and kidney anion exchanger 1 (kAE1) proteins are Cl-/HCO3- exchangers that are both expressed at the basolateral membrane of the α-intercalated cells in the medullary collecting duct of the kidney. Mutations in the kAE1 gene or knockouts of the SLC26A7 gene can cause distal renal tubular acidosis (dRTA) in humans and mice, respectively. This study aimed to clarify the role of the SLC26A7 protein in renal epithelial cells under physiological or pathological conditions. We hypothesized that the SLC26A7 activity is impaired in dRTA patients due to the loss of kAE1.

Methods: MDCK cells expressing SLC26A7 were grown in either normal, hypertonic or acidic growth conditions to mimic the medulla and dRTA environment, respectively, and the protein were examined by immunoblot. kAE1 or SLC26A7 functions were examined using the pH-sensitive fluorescent probe BCECF-AM.

Results: Comparison of SLC26A7 and kAE1 abundance when expressed in Madin-Darby Canine Kidney (MDCK) cells grown in normal or hypertonic conditions showed that, in contrast with kAE1, SLC26A7 is upregulated by hypertonic conditions. Functional assays showed an increase in the SLC26A7 anion exchange activity after incubation in hypertonic conditions. However, growing MDCK cells under acidic conditions, as occurs in dRTA patients, resulted in decreased abundance of SLC26A7 suggesting that in dRTA patients, SLC26A7 is downregulated and unable to compensate for the loss of kAE1 protein. Furthermore, total anion transport was reduced in cells co-expressing both SLC26A7 and kAE1 R901X dRTA mutant compared to cells expressing individual proteins, suggesting an inhibitory effect of one protein on the other when co-expressed.

Conclusions: This study provides insight into the physiological role of SLC26A7 in kidney epithelial cells under various hypertonic or low extracellular pH conditions and thus provides information for the interpretation of the compensatory effect of SLC26A7 in dRTA patients.

Funding: Government Support - Non-U.S.
Involvement of Aldosterone and the Ubiquitin-Proteasome System in the Regulation of Expression of an Ammonia Transporter, Rhesus Blood Group C Glycoprotein, in the Intercalated Cells

Koji Eguchi, Yuichiro Izumi, Yushi Nakayama, Hideki Inoue, Yutaka Kakizoe, Takahige Kuwabara, Naomi Matsu, Terumasa Nakagawa, Masashi Mukoyama. Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.

Background: Acid-base balance is regulated by aldosterone which stimulates acid secretion in the intercalated cells of the collecting ducts of the kidney. Rhesus blood group C glycoprotein (Rhcg) is an ammonia transporter which cooperates with H⁺-ATPase to secrete H⁺ from the intercalated cells. We presented in Kidney Week 2015 that aldosterone induces the expression of Rhcg in membrane fraction in vivo and in vitro. In the present study, we further investigated the regulation mechanism of Rhcg.

Methods: We established a cell population of IN-IC cells (a rat intercalated cell line) stably expressing mouse Flag-tagged Rhcg (Rhcg-Flag). Cells were treated with aldosterone (10⁻⁶ M) for 2, 24, and 48 h, and then membrane fraction was extracted. To see whether the ubiquitin-proteasome system (UPS) is involved in the regulation of Rhcg, cells were treated with MG132, a proteasome inhibitor, and whole cell lysates were extracted. Immunoprecipitation using anti-Flag antibody was performed to examine communoprecipitation with ubiquitin. Western blotting was applied with anti-Flag and anti-ubiquitin antibodies.

Results: Treatment with aldosterone increased the expression of Rhcg-Flag in membrane fraction by 30, 120, and 50 % at 2, 24, and 48 h, respectively.

Conclusions: These results indicate that aldosterone and UPS should regulate the expression of Rhcg protein, suggesting a crosstalk between aldosterone and UPS in the intercalated cells.

The Stimulus of Ammoniagenesis Plays an Important Role in the Development of Renal Hypertrophy in Diabetes Mellitus

Hassane Amlal, Sihame Amlal, Sulaiman Sheriff. Internal Medicine, Univ of Cincinnati, Cincinnati, OH.

Background: Studies have shown that total ammonia (NH₃, + NH₄⁺) causes renal cell hypertrophy in vitro and that diabetes mellitus (DM) is associated with an early increase in kidney mass. However, whether hyperglycemia-induced ammoniagenesis plays a role in the development of early renal hypertrophy in DM remains elusive.

Methods: Rats treated with streptozotocin (STZ) and Akita mice and their wild-type (Type I DM); ob/ob mice and their lean controls (Type II DM) and adenine-treated rats (model of renal failure) and their controls were housed in metabolic cages for food and water balance studies. Urinary NH₃ excretion was analyzed and correlated with changes in kidney mass (kidney weight/BW). Results: STZ-treated rats exhibited a significant increase in kidney mass, which correlated with a 4-fold increase in urinary NH₃ excretion as early as 6 days of hyperglycemia. The stimulation of ammoniagenesis in Akita mice, corrected by insulin treatment. Hyperglycemic Akita mice showed a 4-fold increase in NH₃ excretion at 4 weeks and kidney mass doubled at 9 weeks of age vs. wild-type mice. Similarly, ob/ob mice exhibited a sharp hyperglycemia which correlated with a 7-fold increase in NH₃ excretion with significant increase in kidney mass at 9 weeks of age vs. lean mice. Lastly, normoglycemic adenine-treated rats exhibited a sharp increase in ammoniagenesis with 32% increase in kidney mass after 1 week of treatment vs. controls.

Conclusions: The development of renal hypertrophy correlates with early hyperglycemia-induced ammoniagenesis in both type I and type II DM models. The stimulation of ammoniagenesis also correlated with early renal hypertrophy in the adenine-fed rat model known to progress to renal failure. Hence, ammoniagenesis likely contributes to the development of early renal hypertrophy, which subsequent progresses to kidney disease in diabetes mellitus and in the adenine-fed animals.

Interaction of the Renal NH₃/NH₄⁺ Transporters Rh Glycoproteins with Cellular Proteins in Acid-Base Homeostasis

Nazih L. Nakhoul, L. Lee Hamm, Karen Brown, Solange Abdulnour-Nakhoul. Medicine, Tulane Medical School, New Orleans, LA; SEVFHCS.

Background: Renal excretion of NH₃, accounts for almost two-thirds of net acid excretion and increases significantly during acid loads. In the collecting duct, two Rh glycoproteins, Rhbg and Rhcg, expressed in the intercalated cells are involved in trans-cellular NH₄⁺ and NH₃ transport. Our earlier studies showed that Rhbg transported NH₃, and NH₄⁺, whereas Rhcg predominately transported NH₃. Little is known about regulation of these transporters. Recent data indicate that Rh proteins may interact with other cellular proteins. In this study, we examined whether Rhbg and Rhcg associate with specific membrane proteins known to affect acid-base transport.

Methods: We determined the association of Rhbg with pendrin (both at the apical membrane) and Rhbg and Rhcg with carbonic anhydrases (CA IV & CA II). We used immunohistochemistry to co-localize Rhbg, CA IV, CA II and pendrin in mouse kidney sections. We then used co-immunoprecipitation of kidney lysates from either medulla or cortex to investigate the association of the specific proteins with Rh transporters.

Results: We used Rhbg antibody (Rhbg-ab) bound to activated magnetic beads to pull down CA IV and Rhbg-ab to pull down pendrin. The reverse configuration and appropriate controls were also used. The eluates were examined by Western analysis. The blots showed positive staining for Rhbg in the eluates when Rhbg or CA IV antibodies were coupled to the beads, and positive staining for CA IV when CA IV or Rhbg antibodies were on the beads. Similar results were obtained with pendrin and Rhbg. Immunoprecipitating Rhbg with ATPas was negative. To confirm the co-IP results we demonstrated that pulled-down Rhbg band was glycosylated (at 50 KD) and that it can be de-glycosylated (to 37 KD) similar to the native Rhbg in kidney lysates. Lastly, using pH measurements by microelectrodes we showed that co-expressing Rhbg with CA IV in frog oocytes attenuated NH₃/NH₄⁺ transport by Rhbg.

Conclusions: These data are consistent with association of Rhbg with CA IV and Rhbg with Pendrin. It is likely that this interaction may affect expression, trafficking or regulation of NH₃/NH₄⁺ by the Rh proteins.

Insulin Stimulates Renal Proximal Tubule Sodium Transport via Akt2/mTORC2 Pathway

Motonobu Nakamura, Masumi Suzuki, Nobuhiko Satoh, Go Y. Schulman, Shigeo Atsushi Suzuki, Yasuhiro Sato, Yukio Homma, Shoko Horita, Masaomi Nangaku. Dept of Internal Medicine, The Univ of Tokyo Hospital; 1Yaizu City Hospital; 2Dept of Urology, The Univ of Tokyo Hospital.

Background: We found that the IRS2/PI3K-dependent stimulation of renal proximal tubule (PT) sodium transport by insulin is preserved even in insulin resistance or overt diabetic nephropathy (JASN 16, 2005, Kidney Int 87, 2015, BBRC 461, 2015), indicating that hyperinsulinemia, by facilitating sodium retention, may contribute to hypertension associated with these pathological conditions. The roles of Akt isoforms or mammalian target of rapamycin (mTORC1) complex have been well established in insulin-stimulated glucose uptake into adipocytes. However, the roles of these protein kinases in insulin-mediated PT sodium transport regulation remain unknown.

Methods: By monitoring cell pH decrease in response to bath HCO₃⁻ reduction with a pH-sensitive dye BCECF, we measured Na-HCO₃ cotransporter (NBCe1) activity in freshly-isolated rat PTs or human PTs obtained during surgery for renal cell carcinoma. For rat PTs, we also measured NBCe1 activity after 24-hr incubation with siRNA against Akt1, Akt2, Raptor (an mTORC1 component), or Rictor (an mTORC2 component). Results: In freshly-isolated rat and human PTs 10⁻⁶ M insulin induced 50-80% increase in NBCe1 activity above baseline, and this stimulation was completely suppressed by Akt1/2 inhibitors. Furthermore, incubation with siRNA against Akt2, but not Akt1, completely suppressed the stimulatory effect of insulin on rat PTs. When an mTORC1/2 inhibitor (PP242 completely suppressed the insulin-mediated NBCe1 stimulation in rat and human PTs, an mTORC1-specific inhibitor rapamycin failed to affect the insulin effect. Moreover, siRNA against Rictor, but not Raptor, completely suppressed the insulin-mediated NBCe1 stimulation in rat PTs. Consistent with the essential roles of Akt2 and mTORC2, Akt1 inhibitor VIII and PP242, but not rapamycin, strongly suppressed the insulin-induced Akt Ser473 phosphorylation in renal cortex of rats and humans.

Conclusions: Stimulation of PT sodium transport by insulin is mediated via Akt2/mTORC2 pathway, which may be a therapeutic target for hypertension in metabolic syndrome.

Gpr56 - A Renal GPR Involved in Systemic pH Homeostasis

Premraj Rajkumar, Boyong Cha, Mark Donowitz, Jennifer L. Pluznick, 1 Physiology, Johns Hopkins SOM, Baltimore; 2Medicine & Physiology, Johns Hopkins SOM, Baltimore; 3Molecular Membrane Neuroscience, RIKEN Brain Science Inst, Japan.

Background: Recent studies have identified orphan G-protein coupled receptors (GPRs) as sensors of physiological metabolites. Our goal is to elucidate the functional role of an understudied renal GPR, Gpr56, which we previously found to be highly expressed in the kidney (Rajkumar et al., 2014).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
SA-PO096
Decreased Renal Threshold for Urinary Excretion of Ammonia Underlies Pseudohypoaldosteronism Type II in TASK2-Channel-Deficient Mice

Background: TASK2 (TWIK-related acid-sensitive K+ channel)-deficient (task2−/−) mice showed metabolic acidosis (Warth et al, 2004) and may be a good model for proximal renal tubular acidosis (pRTA). We also investigated the TASK2-α-intercalated cell (α-IC) phenotype and on immunostainings of cardiac anion hydride type II (CAII) and phosphoenolpyruvate carboxykinase (PEPCK) in the kidney.

Methods: In task2−/− (WT) and task2−/− (KO) mice, we investigated the effects of acid/alcali-containing diet on blood and urine data to evaluate the maximum capacity of the renal-ammoniagenesis. We also investigated the TASK2-α-IC phenotype and on immunostainings of cardiac anion hydride type II (CAII) and phosphoenolpyruvate carboxykinase (PEPCK) in the kidney.

Results: We confirmed that KO mice fed normal diets showed hyperchloremic metabolic acidosis (pH 7.24 ± 0.10 vs. 7.37 ± 0.10 in KO mice, n = 2, p = 0.07). In addition, the blood pH of KO mice trended acidic compared to WT in unanesthetized mice (WT: 7.44 ± 0.04, n = 6; KO: 7.34 ± 0.02, n = 6; p = 0.07). P < 0.005. Furthermore, in an in vitro assay Gprc5c increased sodium proton exchange under alkaline conditions (pH 10) by 1.6 fold compared to vector controls (p > 0.05); this increase is Tenapanor-sensitive, implying that it is mediated via NHE3 (a transporter which localizes apically in the renal PT).

Conclusions: Gprc5c localizes to the renal PTs apically where it contributes to systemic pH homoeostasis via modulation of NHE3 function.

Funding: Private Foundation Support

SA-PO097
Targeted Deletion of the NCOA7 Gene Results in Incomplete Distal Renal Tubular Acidosis in Mice
Maria Merkulova,1,2 Teodor G. Paunescu,1,2 Anil V. Nair,1,2 Chia-Yu Wang,1,2 Sylvie Breton,1,2 Dennis Brown,1,2 Div of Nephrology, Mass. Gen. Hospital; 1Harvard Medical School, Boston, MA.

Background: Primary renal tubular acidosis (dRTA) is a rare disease with various levels of severity from growth retardation in its complete form to almost asymptomatic when it is incomplete. Three genes, SLC4A1, ATP6V1B1 and ATP6V0A4, are known to cause this disease in humans. However in some dRTA cases no mutations in any of them have been found, suggesting that other genes are involved. By generating a renal V-ATPase interaction, we recently discovered that several novel proteins (including NCOA7, nuclear receptor coactivator-7 of unknown function) interact with ATP6V1B1 and may regulate V-ATPase function.

Methods: To study if deletion of the NCOA7 gene can cause dRTA, blood pH and bicarbonate (HCO3) levels, and urine pH were compared in wild-type (WT) mice and NCOA7 knockout (KO) mice fed a standard rodent diet and after acid loading with ammonium chloride (NH4Cl) for 3 days. Kidney intercalated cells were examined by immunofluorescence microscopy with anti-V-ATPase antibody.

Results: We found a significant difference between WT and KO mice in blood pH (7.26 ± 0.07 vs 7.26 ± 0.06) and HCO3 level (20.3 ± 2.79 vs 20.4 ± 2.79 mM), but urine pH was significantly higher in KO than in WT (6.98 ± 0.56 vs 6.15 ± 0.39). At the microscopic level, intercalated cells in the inner stripe of outer medulla were larger and formed continuous rows in NCOA7 KO compared to WT mice, a phenotype previously associated to PHAII. When WT and KO mice were chatted with NH4Cl, their blood pH was slightly reduced to a similar degree (7.23 ± 0.08 and 7.22 ± 0.10 respectively). HCO3 levels were reduced in WT but even more in KO mice (15.7 ± 0.31 and 14.7 ± 1.37 mM). Urine pCO2 levels were also lower in NCOA7 KO (36.4 ± 6.14 vs 43.4 ± 6.04 mmHg). Urine pH was not reduced after NH4Cl treatment in both WT and KO mice, but was still higher in KO mice (5.88 ± 0.10 vs 5.60 ± 0.15).

Conclusions: NCOA7 KO mice do not maximally acidify their urine and demonstrate incomplete dRTA. This suggests that the NCOA7 gene may play a role in regulating V-ATPase-induced primary acidification.

Funding: NIDDK Support

SA-PO098
Maternal Acidosis Directs Intercalated Cell Subtype Distribution in Young Rabbits
Peggy M. Parker,1,2 Alexandra N. Marasco,1 George J. Schwartz.

Pediatrics, Univ of Rochester Medical Center, Rochester, NY.

Background: In the cortical collecting duct (CCD), modifications of acid-base balance are mediated by α and β intercalated cells, α-intercalated cells (IC) secrete protons via a basolateral AE1 and apical B1-VATPase, whereas β-IC secrete bicarbonate via apical pendrin and basolateral H+ATPase. A previous study in rats suggested that maternal acid-base status during pregnancy influences intercalated cell differentiation (Narbitz et al. AJP 264:F415, 1995).

Methods: To confirm and extend this study maternal acidosis was induced in pregnant rabbit does via administration of ammonium chloride in water and food during the 3rd-4th week of gestation, and its effect on intercalated cell differentiation in rabbit progeny at one to three weeks was studied. The numbers of AE1+ (α-IC), PND+ (β-IC) and B1- (total IC) per unit length (i.e. 100 µm) of CCD were determined in images of immunofluorescent stained kidney sections.

Results: The normal IC subtype distribution in the adult rabbit CCD is ecf, 23% and 77% for α- and β-IC, respectively. In normal pregnant rats the number of α-IC was reduced (26% at week 2, 28% at week 3) in normal control rats. In contrast, maternal acidosis (5 days) reduced the number of β-IC from 7.0 ± 0.5 to 5.0 ± 0.5 per 100 mm at 1 week and from 9.0 ± 1.5 to 5.9 ± 0.2 in 3 week old pups (p < 0.05 Normal/Maternal acidosis). In normal kits and acidotic kits, there were 2.6 ± 0.1 α-IC/100 µm (p < 0.005) whereas maternal acidosis increased this number to 3.0 ± 0.3 and 3.1 ± 0.1 in one and three old kits (p < 0.05 Normal/αMaternal acidosis) such that the IC subtype distribution was 37% α-IC and 63% β-IC, respectively.

Conclusions: The influence of maternal acidosis on IC subtype differentiation persists for at least several weeks. Whether postnatal acid-base status overrides developmental programming and promotes differentiation of β- over α-subtypes to compensate for the alkaline-rich diet is currently under investigation.

Funding: NIDDK Support

SA-PO099
The Pseudohypoaldosteronism Type II-Causing Mutant Cul3 Protein Forms Dimer with KLH3 and Inhibits the Degradation of WNK4 with a Dominant-Negative Effect
Yuya Araki,1 Tatsumitsu Kai,2 Eisei Sohara,2 Takayasu Mori,2 Yuichi Inoue,2 Tuforo Mori,2 Shinichi Uchida.2 Dept. of Nephrology, Ome Municipal General Hospital, Ome, Tokyo, Japan; 2Dept. of Nephrology, Tokyo Medical and Dental Univ, Bunkyo-Ku, Tokyo, Japan.

Background: Pseudohypoaldosteronism type II (PHAII) is a hereditary hypertensive disease caused by mutations in four different genes: WNK1 and 4, KLHL3, and cullin 3 (Cul3). Cul3 and KLH3 form an E3 ligase complex that ubiquititates and reduces WNK4 protein. PHAII causing mutation in culin 3 gene results in the production of Cul3 protein with a 57-amino acid deletion (Cul3Δ57). However, precise mechanism how Cul3Δ57 causes PHAII is unclear. And it is not clear whether Cul3Δ57 is a gain-of-function mutation or loss-of-function mutation.

Methods: We generated and studied the mice which express Cul3Δ57 in the kidney. To study if deletion of the NCOA7 gene can cause dRTA, blood pH and bicarbonate (HCO3) levels, and urine pH were compared in wild-type (WT) mice and NCOA7 knockout (KO) mice fed a standard rodent diet and after acid loading with ammonium chloride (NH4Cl) for 3 days. Kidney intercalated cells were examined by immunofluorescence microscopy with anti-V-ATPase antibody.

Results: We successfully generated Cul3Δ57 mice. These mice had the phenotype similar to PHAII, hyperkalaemia, metabolic acidosis and hypertension. Cul3Δ57 mice revealed that Cul3Δ57 were highly neddylated and the expression level of Cul3Δ7 was suppressed than wild type mice. Co-IP assays revealed that Cul3Δ57 formed a dimer with Cul3Δ7 and KLH3. While neddylation is generally required for efficient ubiquitination, Cul3Δ57 mutant also interfered the degradation of WNK4 by Cul3Δ7/7. However, this dominant-negative inhibition was not dependent on neddylation of Cul3r. This may explain why Cul3Δ57 causes a more severe phenotype than other mutations.

Funding: Government Support - Non-U.S.
Valenti, Gerardo - Bueno.
The Corticosteroid-Repressible Protein DCNL4 Promotes WNK Kinase Degradation via the KLHL3/CUL3 Complex

Background: WNK kinases regulate NaCl and K transport in the distal nphron. Abundance of these kinases is controlled by the KLHL3/CUL3 complex, a cullin-RING E3 ligase (CRL) that ubiquitylates the WNKs, marking them for degradation. Little is known about the mechanisms that physiologically regulate KLHL3/CUL3 activity. Mammalian DCN-like (DCNL) proteins are a family of 5 CRL co-activators that promote cullin activity through neddylation. Of these proteins, DCNL4 was identified as a candidate stimulator of KLHL3/CUL3 activity and WNK substrate turnover, as a kidney RNAseq database noted DCNL4 expression in the distal tubule, and 4 independent prediction algorithms identified DCNL4 as a target of miR-27, a corticosteroid-induced microRNA whose activity is linked to cardiovascular disease. Thus, we hypothesized that corticosteroid-mediated repression of DCNL4 might downregulate KLHL3/CUL3 activity, increasing WNK expression and activity in the distal nphron.

Methods: We evaluated DCNL4 expression in the mouse kidney by RT-PCR, IF, and Western. DCNL4 was transiently coexpressed with KLHL3/CUL3 and WNKs in 293 cells to assess CUL3 neddylation and WNK turnover by ChlI chase. mCCD cells were treated with ald50mm or a miR27 mimic and DCNL4 mRNA was quantified by qRT-PCR.

Results: Renal DCNL4 was detectable by RT-PCR & immunoblot. Under standard diet, DCNL4 antibodies recognized a strong proximal and distal tubule-specific signal. In 293 cells, DCNL4 enhanced CUL3 neddylation. Compared to KLHL3/CUL3, KLHL3/CUL3/DCNL4 antibodies recognized a strong proximal and distal tubule-specific signal. In 293 cells, DCNL4 enhanced CUL3 neddylation. Consistent with KLHL3/CUL3 dependency, DCNL4 did not reduce WNK4 abundance when it was coexpressed with FHHt-associated KLHL3 mutants that disconnect WNK4 from CUL3. In mCCD cells, ald50mm reduced DCNL4 mRNA by 50%.

Conclusions: These data support a model in which DCN-like proteins trigger the degradation of WNK kinases by potentiating KLHL3/CUL3 complex activity through neddylation. MicroRNA-mediated downregulation of active KLHL3/CUL3/DCNL4 complexes might represent a novel mechanism by which corticosteroid hormones can augment WNK signaling in the distal nphron. Funding: NIDDK Support, Other NIH Support - NHLBI, VA Support

SA-POI102

A Novel Regulatory Mechanism of WNK4 Activity Involving Canonical Angiotensin II-PKC or PKA Mediated Phosphorylation R. Maria Castañeda-Bueno.

Background: The With-No-lysine kinase 4 (WNK4) regulates activity of the thiazide-sensitive Na+-Cl cotransporter (NBC) by phosphorylating the kinases SPAK (Ste20-related Proline Alanine rich Kinase) and OSR1 (Osmotic Stress Responsive kinase), which in turn phosphorylate and activate NBC. WNK4 levels are regulated by binding to KLHL3, which targets WNK4 for ubiquitination and degradation. This activity is regulated by phosphorylation of KLHL3 via protein kinase C (PKC), downstream of Angiotensin II (AngII) or via PKA, likely downstream of vasopressin.

Methods: We tested whether these signaling pathways also have effects on phosphorylation and activity of WNK4 using mass spectrometry, pharmacological inhibitors, site-specific phosphoantibodies, in vitro kinase assays and mouse studies.

Results: By tandem mass spectrometry we identified several WNK4 phosphorylation sites, five of which are phosphorylated by PKC in vitro and in mammalian cells, downstream of AngII (S47, S64, S116, S118, S119). They are also target phosphorylation for PKA. Elimination of these phosphorylation sites prevents WNK4-mediated activation of SPAK in HEK293, which is attributable to loss of phosphorylation at S64 and S119 in WNK4. Loss of phosphorylation at these sites markedly reduces activation of WNK4 kinase via autophosphorylation of the kinase T-loop at S122. Thus, AngII signaling leads to phosphorylation of WNK4, which stimulates kinase’s activation, inducing downstream signaling. We further show that phosphorylation occurs in vivo in mouse with AngII stimulation, primarily in the distal convoluted tubule, where phosphorylated WNK4 co-localizes with SPAK.

Conclusions: AngII activates WNK4 through direct phosphorylation of key sites in WNK4-C- and N-terminal domains. Activated WNK4 subsequently activates activation of SPAK/OSR1-NCC, resulting in increased Na+ and Cl- reabsorption. Funding: NIDDK Support, Private Foundation Support

SA-POI103

Distal Convoluted Tubule Aggrephagy Involving WNK Kinases Is a Response to Metabolic Stress Causing NCC Activation

R. Maria Castañeda-Bueno.

Background: The With-No-lysine kinase 4 (WNK4) regulates activity of the thiazide-sensitive Na+-Cl cotransporter (NBC). Early work, using cultured cells, suggested that osmotic stress leads to the accumulation of WNK kinases in vesicular structures representing the trans-Golgi network. In vivo, hypokalemia induced by OSR1 knockout or low K+ diet, also leads to SPAK/WNK4 puncta. Here, we tested whether stress generates unique cellular structures.

Methods: Mice received high salt/low K+ (HS/LK) or control diets for 10 days. Rats received furosemide or vehicle via osmotic minipump for 7 days. WNK1-transfected HEK293 cells were exposed to vehicle or hypertonic stress (0.2 M NaCl). Immunostaining for WNK1, WNK4, SPAK, S383-phospho-SPAK, and autophagy markers was performed.

Results: Both HS/LK and furosemide led to accumulation of WNKs and SPAK in perinuclear puncta within DCT cells. These puncta were undetectable in mice on high NaCl or control diets. The autophagy marker ATG5 colocalized in the puncta, whereas standard lysosomal markers did not. Electron microscopy revealed abundant aggresome-like structures adjacent to autophagosomes in kidneys from HS/LK or furosemide-treated animals, but not in controls. In transfected cells, hypertonic stress-induced formation of similar, WNK1/ATG5-positive puncta, with markers suggesting that they are not autophagosomes. In control cells, WNK1 and ATG5 did not co-localize and were, instead, diffusely expressed in the cytoplasm.

Conclusions: Activation of the DCT induces formation of perinuclear, autophagosome-like structures containing WNK kinases and enhanced K+ homeostasis during periods of metabolic stress, through WNK kinases and enhanced thiazide-sensitive NaCl cotransporter (NBC). Early work, using cultured cells, suggested that osmotic stress leads to the accumulation of WNK kinases in vesicular substructures representing the trans-Golgi network. In vivo, hypokalemia induced by OSR1 knockout or low K+ diet, also leads to SPAK/WNK4 puncta. Here, we tested whether stress generates unique cellular structures.

Funding: NIDDK Support

SA-POI104

WNK4 Regulates Adipocyte Differentiation in 3T3-L1 Cells


Molecular Physiology Unit, INCNMSZ-JIB-UNAM, Mexico City, Mexico.

Background: WNK kinases regulate NaCl and K transport in the distal nphron. WNK kinases are a family of 5 CRL co-activators that promote cullin activity through neddylation. MicroRNA-mediated downregulation of active KLHL3/CUL3/DCNL4 complexes might represent a novel mechanism by which corticosteroid hormones can augment WNK signaling in the distal nphron. Funding: NIDDK Support, Other NIH Support - NHLBI, VA Support

SA-PO101

RFxV Motif Analysis in WNK4: Mechanistic Insights into the WNK4-SPAK Pathway

Alejandro Rodriguez-Gama, Adrián de Murillo-de-Ozones, Silvana Bazua-Valenti, Gerardo Gamba, Maria Castañeda-Bueno.

Molecular Physiology Unit, INCNMSZ-JIB-UNAM, Mexico City, Mexico.

Background: WNK kinases modulate activity of SPAK/OSR1 kinases which in turn regulate metabolic stress. The With-No-lysine kinase 4 (WNK4) regulates activity of the thiazide-sensitive Na+-Cl cotransporter (NBC). Early work, using cultured cells, suggested that osmotic stress leads to the accumulation of WNK kinases in vesicular substructures representing the trans-Golgi network. In vivo, hypokalemia induced by OSR1 knockout or low K+ diet, also leads to SPAK/WNK4 puncta. Here, we tested whether stress generates unique cellular structures.

Methods: Mice received high salt/low K+ (HS/LK) or control diets for 10 days. Rats received furosemide or vehicle via osmotic minipump for 7 days. WNK1-transfected HEK293 cells were exposed to vehicle or hypertonic stress (0.2 M NaCl). Immunostaining for WNK1, WNK4, SPAK, S383-phospho-SPAK, and autophagy markers was performed.

Results: Both HS/LK and furosemide led to accumulation of WNKs and SPAK in perinuclear puncta within DCT cells. These puncta were undetectable in mice on high NaCl or control diets. The autophagy marker ATG5 colocalized in the puncta, whereas standard lysosomal markers did not. Electron microscopy revealed abundant aggresome-like structures adjacent to autophagosomes in kidneys from HS/LK or furosemide-treated animals, but not in controls. In transfected cells, hypertonic stress-induced formation of similar, WNK1/ATG5-positive puncta, with markers suggesting that they are not autophagosomes. In control cells, WNK1 and ATG5 did not co-localize and were, instead, diffusely expressed in the cytoplasm.

Conclusions: Activation of the DCT induces formation of perinuclear, autophagosome-like structures containing WNK kinases and enhanced K+ homeostasis during periods of metabolic stress, through WNK kinases and enhanced thiazide-sensitive NaCl cotransporter (NBC). Early work, using cultured cells, suggested that osmotic stress leads to the accumulation of WNK kinases in vesicular substructures representing the trans-Golgi network. In vivo, hypokalemia induced by OSR1 knockout or low K+ diet, also leads to SPAK/WNK4 puncta. Here, we tested whether stress generates unique cellular structures.

Funding: NIDDK Support

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

Underlines represent presenting author.

654A
differentiation, and development. However, neither their metabolic functions nor their extrarenal roles are clear, especially in case of WNK4. In the present study, we report a novel role of WNK4 as a regulator of adipogenesis in 3T3-L1 cells.

Methods: We stimulated 3T3-L1 fibroblasts and induced adipogenesis with differentiation medium, containing insulin, dexamethasone, and 3-isobutyl-1-methylxantine. The effect of knockdown on WNK4 in the differentiated 3T3-L1 cells was examined. These experiments using siRNA specific to WNK4 (si-WNK4). The effect of WNK4 inhibition on 3T3-L1 adipocytes was examined by Oil-red O staining, qRT-PCR, and immunoblotting.

Results: The expression level of WNK4 mRNA in the undifferentiated 3T3-L1 cells was low. However, when adipogenesis was induced, WNK4 expression was markedly increased to 44 fold in the very early phase of adipocyte differentiation, preceding the expression of key transcriptional factors PPARα and C/EBPβ. When the differentiated cells were transfected with siWNK4, they exhibited impaired lipid accumulation and PPAR expression was downregulated by immunoblot analysis. It was also indicated that involvement of WNK4 with adipocyte differentiation was independent of WNK4 kinase activity and the known downstream effector, OSR1/SPAK-NKCC1 signaling cascade.

Conclusions: We found a novel role of WNK4 as a regulator of adipocyte differentiation in 3T3-L1 cells and have offered novel insights into the relationship between WNKs and adipogenesis. Our results also indicate that WNK4 inhibition might be beneficial in the management of both hypertension and obesity.

Funding: Government Support - Non-U.S.

SA-PO105
Phosphorylation of KLHL3 at Serine 433 Impairs Its Interaction with the Acidic Motif of WNK4: A Molecular Dynamics Study
Lingyun Wang, Ji-Bin Peng. Div of Nephrology, Dept of Medicine, Nephrology Research and Training Center, Univ of Alabama at Birmingham, Birmingham, AL.

Background: Interaction between the acidic motif (AM) of protein kinase WNK4 and the Kelch domain of KLHL3 are involved in the pathogenesis of pseudohypoaldosteronism type II, a hereditary form of hypertension. This interaction is disrupted by some disease-causing mutations in the Kelch domain of KLHL3 or by angiotensin II and insulin-induced phosphorylation of KLHL3 at serine 433, which is also a site frequently mutated in patients. However, the mechanism by which this phosphorylation disrupts the interaction is unclear.

Methods: In this study, we approached this problem using molecular dynamics simulation with structural, dynamical and energetic analyses.

Results: Results from independent simulations indicate that when S433 was phosphorylated, the electrostatic potential became more negative in the AM binding site of KLHL3 and therefore was unfavorable for binding with the negatively charged AM. In addition, the intermolecular hydrogen bond network that kept the AM stable in the binding site of KLHL3 was disrupted, and the forces for the hydrophobic interactions between the AM of WNK4 and KLHL3 were also reduced. As a result, the weakened interactions were no longer capable of holding the AM of WNK4 at its binding site in KLHL3.

Conclusions: In conclusion, phosphorylation of KLHL3 at S433 disrupts the hydrogen bonds, hydrophobic and electrostatic interactions between the Kelch domain of KLHL3 and the AM of WNK4. This study provides a key molecular understanding of the KLHL3-mediated regulation of WNK4, which is an integrative regulator of electrolyte homeostasis and blood pressure regulation in the kidney.

Funding: NIDDK Support

SA-PO106
Molecular Dynamics Simulation Unveils Impaired Interactions between the Acidic Motif of WNk4 and Klh3 Carrying Disease-Causing Mutations on the Surface of the Kelch Domain
Lingyun Wang, Ji-Bin Peng. Div of Nephrology, Dept of Medicine, Nephrology Research and Training Center, Univ of Alabama at Birmingham, Birmingham, AL.

Background: Mutations in Kelch-like 3 (KLHL3) and without-lysin [K] kinase 4 (WNK4) are found in patients with pseudohypoaldosteronism type II, a hereditary form of hypertension. At least ten disease-causing mutations are localized in the Kelch domain of KLHL3, which is involved in the interaction with WNK4, an important step for WNK4 ubiquitination and degradation. However, the mechanism by which these mutations disrupt the interaction between KLHL3 and WNK4 are not well understood.

Methods: To approach this problem, molecular dynamics simulations with structural, dynamical and energetic analyses were performed based on the crystal structure of the Kelch domain of KLHL3 in complex with the acidic motif of WNK4.

Results: Significant increases in the distance between the acidic motif and the Kelch domain were observed for mutations on the surface of the Kelch domain, including Q309R, S352N, S433N, R528H, and S433L. These mutations altered the electrostatic potential in the binding site for the acidic motif and disrupted the hydrogen bonds and hydrophobic interactions between the Kelch domain and the acidic motif. In addition, S432, S433, and R528 of KLHL3 form hydrogen bonds with residues in the acidic motif of WNK4; and R528 of KLHL3 by the mutations on the surface of the Kelch domain. Further studies are needed to determine the impairments caused by the mutations buried in the Kelch domain.

Funding: NIDDK Support

SA-PO107
Single-Cell RNA Sequencing Reveals Transcriptions of Four Cell Types Isolated from the Mouse Renal Collecting Duct

Background: The renal collecting duct contains principal cells (PCs) and at least two types of intercalated cells (ICs). These cell types bear different molecular signatures and mediate different physiological functions. The development of next generation DNA sequencing techniques offers the ability to carry out RNA sequencing (RNA-Seq) in single cells. Here, we use this technology to profile transcriptomic profiles of all cell types in the renal collecting duct.

Methods: We isolated cells from mouse kidney cell suspensions using reagents that recover co-corted by duct cell surface markers to enrich collecting duct cells, viz. c-kit for ICs and Dolichos biflorus agglutinin (DBA) for PCs. The resulting cells were used for single cell RNA-Seq using a microfluidic single-cell isolation device (Fluidigm) followed by reverse transcription, initial amplification, and library preparation with bar coding, prior to sequencing on an Illumina HiSeq platform.

Results: We profiled transcriptions in 66 individual cells with an average of 10.9M reads, and 95% of mapped reads and 78% uniquely mapped reads per cell. The average transcriptome depth was 3386 genes (RPM=1). We classified each of the 66 cells, based on canonical markers for each cell type, as follows: 21 PCs, 13 ICs, 3 c-kits, 14 hybrid ICs, 4 fibroblasts, one distal convoluted tubule cell, and 10 unclassified cells. The “hybrid” ICs are of particular interest. These cells expressed IC-specific H-ATPase subunits plus a combination of a and β IC markers. Interestingly, seven of the 30 cells classified as ICs also expressed aquaporin-2 at low, but readily detectable levels, suggesting that aquaporin-2 expression is not an exclusive characteristic of PCs or connecting tubule cells.

Conclusions: In conclusion, single cell RNA-Seq in mouse renal collecting duct cells showed the presence of intermediate cell types that are not clearly identifiable as PCs, ICs, or hybrid ICs based on standard markers. The single cell RNA-Seq method, more broadly applied, has the potential of identification of the mechanisms of cell-type specific gene expression and physiological regulation in the collecting duct.

Funding: Other NIH Support - NHLBI

SA-PO108
Empagliflozin Lowers Blood Pressure and Inhibits NHE3 Activity in Hypertensive Rats
Adriana C.C. Girardi, Corina De Albuquerque Silva, Regiane Cardoso Castelo Branco, Renato C版权归原著, Gerhard Malnic, Wevertor M. Luchi. 1Heart Inst, Univ of Sao Paulo Medical School, Sao Paulo, Brazil; 2Hospital Univ Cassiano Antonio de Moraes, Federal Univ of Sao Paulo, Sao Paulo, Brazil; 3Physiology and Biophysics, Univ of Sao Paulo, Sao Paulo, Brazil.

Background: SGLT2 inhibitors have clinically significant antihypertensive effects in patients with type 2 diabetes. In the proximal tubule, SGLT2 co-locates with the major apical sodium transporter NHE3. The aim of this study was to test the hypothesis that inhibition of SGLT2 by empagliflozin reduces blood pressure and inhibits proximal tubule NHE3 activity in an experimental model of hypertension not associated with hyperglycemia.

Methods: Fourteen-week-old male spontaneously hypertensive rats (SHR) were treated with empagliflozin (10 mg/kg/day) or vehicle (control) for two weeks. Blood pressure and renal function were measured before (baseine) and after treatment (post-treatment). Post-treatment proximal tubule NHE3 activity and expression were determined by stationary microperfusion and real time reverse transcriptase-polymerase chain reaction, respectively.

Results: Blood pressure decreased in empagliflozin-treated SHRs (188 ± 4 vs. 177 ± 5 mm Hg, p < 0.05) and increased in vehicle-treated SHRs (187 ± 4 vs. 200 ± 6 mm Hg, p < 0.05, post-treatment vs. baseline). Urinary flow, sodium and glucose excretion were similar between the two groups of rats at baseline, increased significantly after treatment with empagliflozin and remained similar with baseline in vehicle-treated rats. Proximal tubule NHE3-mediated bicarbonate reabsorption was remarkably lower in empagliflozin-treated SHRs compared to control (0.67 ± 0.09 vs. 1.18 ± 0.09 mmol/cm²·min, p < 0.001). No differences were observed on renal cortical NHE3 protein expression between the two groups of rats.

Conclusions: Collectively, these results indicate that inhibition of SGLT2 reduces blood pressure in euglycemic hypertensive rats. Inhibition of NHE3 activity by empagliflozin may contribute to the antihypertensive effect of empagliflozin in hypertension.

Supported by FAPESP.

Funding: Government Support - Non-U.S.

SA-PO109
Claudins along the Cortico-Medullary Axis of the Thick Ascending Limb of Henle’s Loop
Nina Himmelk, 1 Vera C. Wulfmeyer, 1 Hoor Arewell, 2 Kerim Mutig, 3 Tilman Breiderhoff, 2 Jianghui Hou, 1 Markus Bleich, 1 Dorothee Günzel, 1 Susanne Milatz. 1Inst of Physiology, Christian-Albrechts- Univ, Kiel, Germany; 2Dept of Anatomy, Charité – Universitätsmedizin, Berlin, Germany; 3Inst of Clinical Physiology, Charité – Universitätsmedizin, Berlin, Germany; 2Dept of Internal Medicine – Nephrology, Hannover Medical School, Schloß Clinic, Schloß Clinic, M. Wilhelmshaven, Germany.

Background: The thick ascending limb of the loop of Henle (TAL) fulfills distinct physiological tasks in the kidney: (a) Being water tight but actively transporting NaCl it is considered to be the motor which drives the counter current mechanism and the concentration ability of the kidney. (b) Providing a lumen-positive transepithelial potential for NaCl, it is considered to be an important determinant of lumen-positive transepithelial potential.
It is one of the main sites of divalent cation reabsorption through the tight junction (TJ). The TJ consists of different claudins which interact within the same plasma membrane (cis-interaction) and between neighboring plasma membranes (trans-interaction) resulting in the formation of a complex TJ strand meshwork.

Methods: Electrophysiological measurements of transcellular and paracellular transport were performed in freshly isolated cortical and medullary TAL in combination with claudin expression analyses by subsequent immunostaining and confocal laser-scanning microscopy. Cis- and trans-interaction of the relevant TAL claudins was examined by means of live cell imaging and Förster/resonance energy transfer (FRET) in an overexpression system.

Results: Cortical and medullary TAL differed regarding their paracellular permeability properties and their equipment with claudins 3, 10, 11, 16, and 19. A clear correlation between dominance of specific claudins within the TJ and ion selectivity was observed. Not all claudins were expressed in the same TJ in native TAL and some of them failed to interact with each other in cis- or trans-configuration in the overexpression system.

Conclusions: We reveal a specific claudin expression pattern in the TAL which can be explained by the particular interaction capabilities of different claudins. On that basis, we suggest the existence of at least two spatially distinct types of paracellular pores with different preferences for Na\(^{+}\), Ca\(^{2+}\), and Mg\(^{2+}\) in the TAL.

Funding: Other NIH Support - R01DK084059, Government Support - Non-U.S.

SA-PO110

Identification and Functional Characterization of CLCNKB Mutations in Patients with Classic Bartter’s Syndrome Shih-Hua P. Lin, Jen-Chi Chen, Yi-Fen Lo, Chih-Jen Cheng. Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Background: Classic Bartter’s syndrome (cBS) is caused by mutations in the gene encoding voltage-gated chloride ClC-Kb channel. More than 50 gene encoding voltage-gated chloride ClC-Kb channel. More than 50

Results:

Conclusions: We first did co-immunoprecipitation (Co-IP) which showed 14-3-3γ binding to NCC. 14-3-3γ belongs to a family of multifunctional regulatory proteins that can mediate endocytosis and trafficking of megalin and cubilin. However, little is known about the functional molecular regulation of this channel. Previous study only demonstrated the interaction between CLC-5 and kinesin family member 3B (KIF3B) using yeast two-hybrid strategy (Am J Physiol 298: F365-F380, 2010). In this work, we aimed to identify novel associated proteins with CLC-5 more effectively than yeast two-hybrid screening.

Methods: We generated specific anti-peptide antibodies (Ab) against a synthetic peptide corresponding to the C- or N-terminal of CLC-5. Following to immunolocalisation of CLC-5-bearing vesicles using the magnetic beads, we performed the analysis by LC-MS/MS and immunoprecipitation assays to identify specific binding partners. Furthermore CLC-5 and co-localization with associated proteins were imaged using confocal microscopy.

Conclusions: The integration of immunoprecipitation assays with analysis by LC-MS/ MS might be advanced approach to elucidate a novel regulation of channel trafficking. The interaction between AP3 and phosphor-mimic or phosphor- defective NCC was tested in vitro. We also generated and analyzed both the kidney tubule-specific cadherin gene promoter driven flag-tagged mouse AP3S1 (KSP-Flag-mAP3S1) transgenic (Tg) and AP3S1 heterozygous (He) knockout mice. The phenotype and expression of NCC and other interested targets were evaluated at age of 10-12 weeks fed with normal rat chow.

Results: In AP3S1 Tg mice, normal serum electrolytes but an enhanced urine K\(^{+}\) and Ca\(^{2+}\) excretion as well as an attenuation of total and phosphor-NCC expression were observed. While urine K\(^{+}\) and Ca\(^{2+}\) excretion was increased, hyperkalemia were not observed. In AP3S1 He mice, an enhanced total and phosphor-NCC were found in AP3S1 He knockout mice. AP3S1 and NKnk1/4 abundance was not significantly changed in both AP3S1 Tg and He knockout mice. We also observed that the phosphorylation status of NCC T60 residue, which locates in one of the putative canonical YYXX (YNXX) binding motifs of the \( \mu \) subunit of AP complexes, could affect its binding ability with AP3. Leupetin (a lysosyme inhibitor) could enhance the membrane expression of phosphor-defective T60M/NCC in MDCK cells and NCC T85M knock-in mice.

Conclusions: AP3 could regulate NCC abundance and phosphorylation of NCC T60 residue, the most important phosphor acceptor site of SPK/OSR1 kinase, might play a role on affecting AP3-realized lysosomal degradation of NCC.

Funding: Government Support - Non-U.S.

SA-PO113

Identification and Functional Characterization of CLCNKB Mutations in Patients with Classic Bartter’s Syndrome Shih-Hua P. Lin, Jen-Chi Chen, Yi-Fen Lo, Chih-Jen Cheng. Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Background: Classic Bartter’s syndrome (cBS) is caused by mutations in the gene encoding voltage-gated chloride ClC-Kb channel. More than 50 gene encoding voltage-gated chloride ClC-Kb channel. More than 50

Results:

Conclusions: We first did co-immunoprecipitation (Co-IP) which showed 14-3-3γ binding to NCC. 14-3-3γ belongs to a family of multifunctional regulatory proteins that can mediate endocytosis and trafficking of megalin and cubilin. However, little is known about the functional molecular regulation of this channel. Previous study only demonstrated the interaction between CLC-5 and kinesin family member 3B (KIF3B) using yeast two-hybrid strategy (Am J Physiol 298: F365-F380, 2010). In this work, we aimed to identify novel associated proteins with CLC-5 more effectively than yeast two-hybrid screening.

Methods: We generated specific anti-peptide antibodies (Ab) against a synthetic peptide corresponding to the C- or N-terminal of CLC-5. Following to immunolocalisation of CLC-5-bearing vesicles using the magnetic beads, we performed the analysis by LC-MS/MS and immunoprecipitation assays to identify specific binding partners. Furthermore CLC-5 and co-localization with associated proteins were imaged using confocal microscopy.

Conclusions: The integration of immunoprecipitation assays with analysis by LC-MS/ MS might be advanced approach to elucidate a novel regulation of channel trafficking. The interaction between AP3 and phosphor-mimic or phosphor- defective NCC was tested in vitro. We also generated and analyzed both the kidney tubule-specific cadherin gene promoter driven flag-tagged mouse AP3S1 (KSP-Flag-mAP3S1) transgenic (Tg) and AP3S1 heterozygous (He) knockout mice. The phenotype and expression of NCC and other interested targets were evaluated at age of 10-12 weeks fed with normal rat chow.

Results: In AP3S1 Tg mice, normal serum electrolytes but an enhanced urine K\(^{+}\) and Ca\(^{2+}\) excretion as well as an attenuation of total and phosphor-NCC expression were observed. While urine K\(^{+}\) and Ca\(^{2+}\) excretion was increased, hyperkalemia were not observed. In AP3S1 He mice, an enhanced total and phosphor-NCC were found in AP3S1 He knockout mice. AP3S1 and NKnk1/4 abundance was not significantly changed in both AP3S1 Tg and He knockout mice. We also observed that the phosphorylation status of NCC T60 residue, which locates in one of the putative canonical YYXX (YNXX) binding motifs of the \( \mu \) subunit of AP complexes, could affect its binding ability with AP3. Leupetin (a lysosyme inhibitor) could enhance the membrane expression of phosphor-defective T60M/NCC in MDCK cells and NCC T85M knock-in mice.

Conclusions: AP3 could regulate NCC abundance and phosphorylation of NCC T60 residue, the most important phosphor acceptor site of SPK/OSR1 kinase, might play a role on affecting AP3-realized lysosomal degradation of NCC.

Funding: Government Support - Non-U.S.
SA-PO114
Site Specific Ubiquitylation of the Thiazide Sensitive Sodium Chloride Cotransporter NCC Is Important for Plasma Membrane Abundance and Function  
Lena Lindtoft Rosenbek,1 Federica Rizzo,3 Olivier Staub,3 Robert A. Fenton.2 1Dept of Neuroscience and Pharmacology, Univ of Copenhagen, Denmark; 2Dept of Biomedicine, Univ of Aarhus, Denmark; 3Dept of Pharmacology and Toxicology, Univ of Lausanne, Switzerland.

Background: A critical role for phosphorylation to modulate NCC function is well established, but recent findings indicate that NCC is ubiquitylated on at least 11 conserved lysine residues. Although the role of each of these sites is not established, we have recently demonstrated that an inverse relationship between NCC phosphorylation and ubiquitylation corresponds with the levels of NCC in the apical cell membrane. The aim of this study was to systematically assess the role of various ubiquitylated lysines in NCC for modulation of NCC function.

Methods: Novel tetracycline inducible MDCKI cell lines stably expressing human wt NCC and various K-R mutants were generated and characterized using immunoprecipitation coupled to biotin-based membrane abundance assays and phospho-specific antibodies. A Na22 uptake assay was developed to measure NCC activity in these polarized cell lines.

Results: Relative to wt NCC, 4 mutants (K706R, K828R, K885R, and K909R) had significantly higher abundance in the apical plasma membrane under basal conditions. Low chloride stimulation significantly increased membrane abundance of these and additional K128R and K706R mutants, to similar or greater levels than wt NCC. Under basal conditions K828R, K909R and K948R mutants had detectably lower ubiquitylated NCC in the plasma membrane, and all mutants displayed reduced NCC ubiquitylation following low chloride stimulation. Thiazide-sensitive Na22 uptake assays verified elevated transport activity in the K828R and K909R mutants.

Conclusions: Several specific ubiquitylation sites in NCC are important for modulation of NCC function.

Funding: Government Support - Non-U.S.

SA-PO115
A New Ubiquitylation Site Plays a Role in the Regulation of the Sodium/ Chloride Cotransporter NCC  
Federica Rizzo,1 Lena Lindtoft Rosenbek;2 Robert A. Fenton,3 Olivier Staub.3 1Univ of Lausanne, Switzerland; 2Univ of Copenhagen, Denmark; 3Univ of Aarhus, Denmark.

Background: The Na-CI Cotransporter (NCC) is expressed in cells of the Distal Convoluted Tubule (DCT), where it plays an important role in NaCl reabsorption and maintaining the blood pressure. NCC is intricately regulated by a variety of post-translational modifications such as glycosylation, phosphorylation and ubiquitylation. In this study we aimed to address the role of ubiquitylation in the modulation of NCC function.

Methods: A UbScan assay on mouse kidney lysates and analysis of human/rat urinary proteins identified several ubiquitylated lysines (K) in NCC. These individual sites in NCC were mutated to arginine (R), and the WT NCC and various mutants expressed in HEK293 and MDCK cells to examine NCC localization and activity.

Results: Biotinylation assays determined that four NCC K-R mutants were of greater abundance in the plasma membrane compared to WT NCC when transiently expressed in HEK293 cells. In particular K828R NCC was increased about 50% in the membrane compared to NCC WT. This result was confirmed in tetracycline-inducible NCC expressing MDCKI cell lines. In these cells the quantity of K828R NCC in the apical membrane in normal chloride conditions is comparable to the amount of NCC WT in the apical membrane after low chloride stimulation, which has been previously demonstrated to dramatically increase function and membrane expression of the cotransporter. Furthermore the increase of the mutant in the apical membrane is coupled with a reduction in the basolateral one suggesting an involvement of the ubiquitylation in lysine 828 in the trafficking of NCC. Na22 uptake demonstrated increased NCC activity in the K828R mutant relative to WT NCC, which correlates well with its increased membrane expression.

Conclusions: Our data indicate that at least one ubiquitylated lysine in NCC has an important role in the trafficking, membrane expression and activity of the cotransporter. To our knowledge, this is the first identification of an ubiquitylation site directly involved in the regulation of the cotransporter.

SA-PO116
Synergistic and Profound Diuretic Effect of Hydrochlorothiazide/ Probenecid Combination  
Sharon L. Barone,1,2 Jie Xu,3 Marybeth Brooks,1 Kamyar A. Zahedi,1,2 Manoocher Soleimani,1,2 1Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; 2Research Services, Veterans Affairs Medical Center, Cincinnati, OH.

Background: Concomitant deficiency of Na-CI co-transporter (NCC) and pendrin leads to significant salt wasting and diuresis. Probenecid is an inhibitor of the organic anion transporters, OATs and MCTs, in the kidney proximal tubule and a uricosuric agent. Probenecid is also an inhibitor of pendrin in mammalian cells. The diuretic effect of HCTZ, which is a specific inhibitor of NCC, is significantly blunted due to compensatory salt absorption by pendrin. We hypothesized that pre-treatment with probenecid will downregulate pendrin, therefore enhancing the diuretic effect of HCTZ.

Methods: The effect of probenecid treatment on pendrin-transfected HEK-293 cells and male Sprague Dawley rats (200-225 g) was examined.

Results: Probenecid (0.5 mM) significantly inhibited pendrin-mediated Cl-/HCO3 exchange in transfected HEK293 cells as measured by the pH sensitive dye, BCECF.

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

SA-PO117
Reverse Feeding with High Salt Impairs Diurnal Variation of Sodium Excretion  

Background: Night shift work increases risk of cardiovascular disease associated with an altered time of day feeding behavior. Elevating this risk is the overall increase in salt intake observed in the typical Western diet. Our lab has shown that high salt intake alters renal circadian rhythms that has been shown to affect Na handling. Normally, renal Na excretion has a distinct diurnal pattern, independent of time of intake, yet the interaction between circadian rhythm of intake and sodium intake has not yet to be determined. The hypothesis of the current study is that reversed feeding (RF, food restricted to inactive period) in addition to high salt feeding will disrupt the diurnal rhythm of renal Na+ excretion.

Methods: Male Sprague Dawley rats were placed on either normal (NS 0.49% NaCl) or high (HS, 4% NaCl) salt diet. Rats were housed in metabolic cages and allowed food ad libitum or subject to RF. Urine was collected every 12 hours. Data is expressed as mean ± SEM of the inactive to active ratio (UA).

Results: As expected, rats fed NS and allowed food ad libitum had a diurnal rhythm in Na+ excretion (0.37±0.08 IU/A). Interestingly, the rhythm in Na+ excretion was not significantly different after 5 days of RF compared to ad libitum (0.42±0.12 IU/A). In response to HS, the diurnal rhythm in Na+ excretion (0.26±0.07 IU/A) was similar to NS fed rats, but was abolished after 5 days of reverse feeding (1.5±0.4 IU/A). In addition, RF significantly reduced the diurnal variation in urinary aldosterone excretion in both NS (0.33±0.05 vs. 0.85±0.19, ad libitum vs. RF) and HS (0.36±0.06 vs. 1.21±0.30, ad libitum vs. RF) fed rats. There was no difference in 12 hour mean arterial pressure as measured by telemetry.

Conclusions: These data support the hypothesis that high salt intake impairs circadian mechanisms associated with renal Na+ excretion. Finally, these data suggest that consuming food during one’s typical inactive phase impairs diurnal variation in aldosterone production and provide a possible mechanism for increased cardiovascular risk in night shift workers.

Funding: Other NIH Support - NHLBI

SA-PO118
Sodium Intake Affects Excretion over Short Time Periods in Steady-State C57Bl/6J Mice  
Jonathan Nizar,1 Lise Bankir,2 Vivek Bhalla.1 1Nephrology, Stanford Univ, Palo Alto, CA; 2Centre de Recherche des Cordeliers, INSERM, Paris, France.

Background: Homeostatic balance of sodium is a criterion for the study of channel/ transporter-specific tubular transport or any physiological process that regulates sodium excretion. Traditionally, animals are thought to balance sodium over 12 to 24 hours, with relatively little effect of sodium intake during shorter time periods. We tested the hypothesis that in mice with tight control of sodium intake over days, small amounts of sodium intake over 2-4 hours would not influence sodium excretion.

Methods: To accomplish this, adult C57BL/6J mice were fed a high sodium diet as gel food over two weeks. In metabolic cages, mice consumed 2.6 +/- 0.05 mmoles Na+ / day for at least three days before undergoing intraperitoneal injection with saline or one of several diuretics and urine collection over 4 hours. Results: After each diuretic and saline injection, sodium excretion varied predictably with the diuretic or vehicle treatment and significantly varied with the amount of ingested sodium during the collection period (p<0.001, linear regression compared to slope = 0), despite nearly identical intake over the prior 24 hours. Daily treatment of rats with probenecid (250mg/kg) for 6 days significantly reduced pendrin expression and increased Na+ excretion, but not affecting diuresis. While treatment of rats with HCTZ (40mg/kg) alone caused a very mild diuresis (12.5 to 14 ml/24 hrs after 4 days of HCTZ, p<0.05). However, co-administration of HCTZ and probenecid to rats that were pre-treated with probenecid for 6 days caused a significant increase in urine output (15.3 ml/ day in rats treated with probenecid for 10 days vs 35 ml/day in rats treated with probenecid for 6 days and then with HCTZ plus probenecid for 4 additional days). Compared to either probenecid or HCTZ treatment animals, rats pre-treated with probenecid for 6 days and then given probenecid plus HCTZ for 4 days exhibited enhanced kidney renin expression and volume depletion. While probenecid partially interfered with HCTZ secretion into the urine, the higher HCTZ blood levels were unlikely to be responsible for the profound diuresis. 

Conclusions: Despite being considered a mild agent, we propose that HCTZ could be a potent diuretic when administered in individuals pre-treated with probenecid.

Funding: VA Support
Solid line indicates linear regression of all drugs in aggregate. 


text continue: The results highlight the technical challenges of balance experiments in mice and warrant the need to adjust excretion data for intake, even during short collection intervals. 

Funding: NIDDK Support

SA-PO119

Dietary Salt Impacts Active Sodium Transport and Metabolic Sensing along the Kidney Tubule

Khalid Udwany,1 Ahmed Abed,1 Carla Bettoni,2 Isabelle Roth,2 Carsten A. Wagner,3 Eric Feraille.1 1PHYME, Univ of Geneva, Geneva, Switzerland; 2Inst of Physiology, Univ of Zurich, Zurich, Switzerland.

Background: Variations of dietary sodium intake induce adaptive changes in renal sodium handling in order to maintain sodium balance. Both glomerular filtration rate and tubular reabsorption process are modulated in response to dietary sodium load. The physiological changes in active sodium reabsorption by tubular cells are associated with changes in ATP and oxygen consumption. These changes may modulate the activity of metabolic sensors such as HIF and AMPK promoting anaerobic glycolysis.

Methods: We used micro-dissected kidney tubules to identify segment-specific effect of salt intake on ion transport systems and metabolic sensor pathways such as HIF and AMPK. Control mice were placed on low (LSD 0.06%), normal (NSD 0.18%) or high (HSD 1.26%) sodium diet for 7 days.

Results: LSD increased the GFR but paradoxically decreased the total expression levels of most Na+ transporters in both kidney cortex and medulla. However, analysis of the expression levels and activity of Na,K-ATPase as well as the activation levels of AMPK in renal epithelial cells. Patch-clamp and epithelial voltage supplies are limited enough to trigger both HIF and AMPK signaling pathways.

Conclusions: From our experiments, we conclude that the actual Na+ transport in different segments of the nephron is better reflected by the expression level of Na,K-ATPase and the activation level of metabolic sensors, rather than the expression levels of apical Na+ transporters alone. Our results show that under physiological conditions, ATP and oxygen supplies are limited enough to trigger both HIF and AMPK signaling pathways.

Funding: Government Support - Non-U.S.

SA-PO120

Role of βPix in the Regulation of ENaC by AMPK

Pei-Yin Hsu,1 Hui Li, Tengis S. Pavlov,2 Lei Cheng,2 Robert A. Fenton,3 Alexander Staruschenko,2 Kenneth R. Hallow.1 1Medicine, USC Keck School of Medicine, Los Angeles, CA; 2Physiology, Medical College of Wisconsin, Milwaukee, WI; 3Biomedicine, Aarhus Univ, Aarhus, Denmark.

Background: AMP-activated protein kinase (AMPK) inhibits the epithelial Na+ channel (ENaC) by increasing binding of Nedd4-2 to ENaC. The Rho-GEF protein βPix promotes Nedd4-2 targeting of ENaC by impairing the 14-3-3/Nedd4-2 association. We hypothesized that AMPK may enhance ENaC degradation by regulation of βPix and the Nedd4-2/14-3-3 association.

Methods: Mass spectrometry (MS) and in vitro phosphorylation assays were used to detect AMPK phosphorylation sites in βPix. Wild-type and mutant βPix were overexpressed in lentivirally transduced collecting duct mPCkCδ, cells. Co-immunoprecipitation (co-IP) assays were used to examine modulation of βPix/14-3-3/Nedd4-2 interactions by AMPK in renal epithelial cells. Patch-clamp and epithelial volt-ohmmeter (EVDOM) studies were performed in CHO and mPCkCδ, cells co-expressing ENaC and various βPix and AMPK constructs.

Results: AMPK directly phosphorylates βPix in vitro, and at least two potential AMPK phosphorylation sites were detected by MS. AMPK stimulation by metformin inhibited the binding of Nedd4-2 to 14-3-3 proteins but did not modulate 14-3-3/βPix interaction in MDCK cells. Whole-cell ENaC currents were decreased by the AMPK activator AICAR or by βPix over-expression in CHO cells, but these effects were not additive. Co-expressing βPix mutant unable to bind 14-3-3 protein (Δ602-611) abolished the ENaC current inhibition by AICAR or overexpression of a constitutively active AMPK mutant. Finally, overexpression of βPix/14-3-3 increased, whereas wild-type/βPix decreased ENaC short-circuit currents in mPCkCδ, cells, supporting the results found in CHO cells.

Conclusions: The regulation of ENaC by AMPK requires both functional Nedd4-2 and βPix. AMPK reciprocally stimulates Nedd4-2-ENaC binding and inhibits Nedd4-2-14-3-3 binding, thereby promoting ENaC degradation. βPix participates in this regulation, but the mechanisms involved are currently unclear. The potential role of AMPK phosphorylation of βPix in the regulation of ENaC will be assessed through additional mutagenesis studies.

Funding: NIDDK Support

SA-PO121

Regulation of the Epithelial Sodium Channel by Paraoxonase-2

Shuji Shi, Carol L. Kinlough, Allison L. Marciszyn, Rebecca P. Hughey, Thomas R. Kleyman. 1Renal-Electrolyte Div, Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: Paraoxonase-2 (PON-2) is a membrane-bound lactonase with unique anti-oxidative property. PON-2 shares key structural elements with C. elegans ME-6, an endoplasmic reticulum-residency/chaperone that is indispensable for the worm’s gentle touch response. ME-6 is required for proper folding and assembly of ME-4, a pore-forming subunit of the mechanosensitive ion channel in C. elegans touch receptor neurons. ME-4 belongs to the same family as the epithelial Na+ channel (ENaC), a key mediator of Na+ uptake in the aldosterone-sensitive distal nephron. As the overall structures are highly conserved between ME-4 and ENaC subunits, we hypothesized that mechanisms by which these ion channels are regulated are also evolutionally conserved and that PON-2, like ME-6 by analogy, regulates ENaC activity.

Methods: We therefore examined PON-2 expression in mouse kidney, and its interaction with ENaC subunits in HeK293 cells. The function of PON-2 on ENaC activity was assessed in Xenopus oocytes.

Results: We found tubular-specific expression of PON-2 in mouse kidney, including principle cells and intercalated cells of distal nephron segments. When co-expressed with ENaC in Xenopus oocytes, PON-2 reduced amiloride-sensitive whole cell Na+ currents, but not K+ currents mediated by ROMK, the renal outer medullar potassium channel. As ENaC activity is tightly regulated by a variety of endogenous or external factors that affect channel biogenesis or gating, the inhibitory effect of PON-2 could reflect a reduction in channel βPix or the number of channels on the cell surface. We found that PON-2 did not alter ENaC gating in response to extracellular Na+, flow-mediated shear stress, or α-chymotrypsin, suggesting that channel αPix was not altered by PON-2. In contrast, surface expression of ENaC was reduced by PON-2 co-expression. Additionally, we found that PON-2 interacted with ENaC subunits in HeK293 cells and PON-2 inhibited ENaC activity in a dose-dependent manner.

Conclusions: In summary, our results suggest that PON-2 functions as a chaperone to regulate the surface expression of ENaC.

Funding: NIDDK Support

SA-PO122

Effect of ENaC Inhibition on Na+ Reabsorption Is Partially Compensated by a Reduction in Paracellular Secretion: A Modeling Study

Anita T. Layton,1 Aurelie Edwards,2 Volker Vallon.3 1Dept of Mathematics, Duke Univ, Durham, NC; 2Centre National de la Recherche Scientifique, Centre de Recherche des Cordeliers, Paris, France; 3Dept of Medicine and Pharmacology, Univ of California San Diego, San Diego, CA.

Background: The amiloride-sensitive Na+ channel (ENaC) is expressed on the apical membrane of the principal cells in the distal nephron. Together with the basolateral Na+-K+-ATPase, ENaC regulates Na+ reabsorption and plays a major role in total body salt and water homeostasis and blood pressure control. We aimed to investigate to the extent to which ENaC inhibition alters urinary solute excretion and Na+ transport (TNaCl) efficiency.

Methods: We developed a multi-nephron computational model that represents detailed transcellular and paracellular transport processes along the nephron of a rat kidney. Using that model, we simulated the inhibition of ENaC.

Results: Under baseline conditions, ENaC was predicted to mediate ~7% of renal TNaCl. ENaC-mediated Na+ reabsorption was accompanied by substantial paracellular Na+ secretion. Consequently, ENaC-mediated T NaCl exceeded total Na+ reabsorption along the distal nephron segments. ENaC inhibition was predicted to significantly impact connecting tubule TNaCl. However, the fractional reduction in active NaCl transport was substantially lower than the fractional inhibition of ENaC. That discrepancy can be attributed to the elevated luminal Na+, which increased the driving force for transmembrane Na+ reabsorption and attenuated paracellular Na+ secretion. Connecting tubule TNaCl, given by the number of moles of Na+ reabsorbed per moles of O2 consumed, decreased from 4.5 (baseline) to 1.6 (full ENaC inhibition). Additionally, ENaC inhibition lowered K+ secretion, most notably into the connecting tubules, since Na+ reabsorption generates the transmembrane potential difference that drives K+ secretion. When ENaC was fully inhibited, urinary Na+ and K+ excretion was predicted to increase by ~3.5 folds and to decrease by ~80%, respectively.

Conclusions: ENaC inhibition has a major impact on both transcellular and paracellular TNaCl along the distal nephron, and on K+ secretion and excretion.

Funding: NIDDK Support, VA Support

SA-PO123

Exaggerated Urinary Sodium Excretion by Mineralocorticoid Receptor (MR) Antagonists in Rats when Tested Against Fluorocortisone Rather Than Aldosterone


Background: Electrolyte effects of MR antagonists in man are typically assessed by analysing urinary sodium secretion after single doses in presence of the orally administered mineralocorticoid fluorocortisone (Hydron) in preclinical settings, effect of single dose MR antagonists on urinary sodium secretion is typically assessed in presence of subcutaneously administered aldosterone (aldo) or after a three day low salt diet to elevate endogenous aldo. A309977 is a novel MR modulator which in preclinical testing dissociates organ protective

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 658A
Electrolyte Homeostasis in AQP-2-Principal-Cell-Targeted Insulin Receptor (IR) and Mammalian-Target-of-Rapamycin (mTOR) Knockout (KO) Mice under LSD. Plasma K+ levels tended to be lower in the KO (both antagonists when tested against fludro rather than aldo indicates differences in the mode of action of fludro vs aldo. It remains to be established whether this is true also in man.

**Funding:** Pharmaceutical Company Support - AstraZeneca R&D

**SA-PO124**

Electrolyte Homeostasis in AQP-2-Principal-Cell-Targeted Insulin Receptor (IR) and Mammalian-Target-of-Rapamycin (mTOR) Knockout (KO) Mice under Low- and Normal-Sodium Diets

**Diabetes**

**Jhunjhunwala**

**Washington, DC**

**Sanjay Gandhi Post-Graduate Inst of Medical Sciences, Lucknow, India.

**Background:** Insulin has been shown to increase the reabsorption of sodium in the renal collecting duct (CD), but less is known about its effects on potassium or chloride handling at this site. Dysregulation of these key electrolytes can affect acid-base homeostasis and blood volume. Previous studies have demonstrated that mTOR may play a role in activation of ENaC by insulin in the collecting duct.

**Methods:** We assessed the impact of low-sodium (Na+) diet (0.05%), LBSD) on blood chemistry and urine excretion in male AQP2-principal-cell-targeted insulin receptor and mTOR knockout (IRKO and mTORKO) mice, as compared to their respective wild-type (WT) littermates. Urine (24-hr) was collected on days 1-3 and 7 of LBSD. Volume and electrolyte excretion was measured. In a separate experiment, mice were randomized to receive the LBSD or control diet (0.5% Na+). One week, mice were euthanized, and blood was analyzed by iSTAT (EG8 cartridge) for chemistry profile.

**Results:** No obvious differences in urine Na+ excretion were found between genotypes; however, hematocrit was significantly (p < 0.05) higher (4-6%) in the IRKO and mTORKO versus their WT littermates under LBSD. Plasma K+ levels tended to be lower in the KO (both types) on either control or LBSD, while plasma Cl- was significantly reduced by LBSD in the KO, but not WT. Furthermore, mTORKO had mild alkalosis as determined by significantly elevated blood pH, HCO3-, base excess, and reduced pCO2, relative to WT, independent of diet. These differences were absent in the IRKO mice.

**Conclusions:** Overall, these results support a role for CD IR and mTOR in electrolyte homeostasis and blood volume control. Increased hematocrit in both KO lines suggested mild volume contraction under LBSD, absent in WT mice. Similarities between the phenotypes with regard to plasma electrolyte profile suggest that IR may indeed be working in the kidney to maintain homeostasis. Differences in acid-base status suggest additional roles for CD mTOR independent of IR.

**SA-PO125**

A Mathematical Model of the Rat Kidney: K-Induced Natriuresis

**Alp, Mark; Steinberg, Physiolog and Biophysics, Weill Medical College of Cornell, New York, NY.

**Background:** Increased K intake is associated with natriuresis, but the renal locus of this effect is uncertain.

**Methods:** A model of the rat nephron (Am. J. Physiol. 308:F1098, 2015) has been extended with the addition of mediulary vasculature. Within outer medulla (OM), the model specifies 20000 short descending vasa recta (DVR) and 4000 long DVR; within inner medulla (IM), long DVR coalesce, halving their number with each mm of medullary depth; cortical medullary rays (MR) are supplied by 7200 DVR. In all regions, ascending vasa recta (AVR) are twice the number of DVR, which provides for slower AVR flows, and secures equilibration of AVR and interstitial concentrations. Blood vessels contain all 15 solutes from the nephron model (Na+, K+, Cl-, HCO3-, H2CO3, CO3, urea, phosphate, ammonia, formate, and glucose), plus 14 additional species from the model of Atherton et al. (Am. J. Physiol. 247:F61, 1984), which represent hemoglobin buffering. For this kidney model, the global unknowns are initial proximal tubule pressures and flows (plus connecting tubule pressure) from the nephron model, plus medullary interstitial pressures and solute concentrations. With partitioning of OM into 2 sections, of IM into 5 sections, and a single MR section, there are 128 interstitial variables, yielding a total of 141 unknowns for the full kidney model.

The advantage of the model under antidiuretic conditions predicts OM interstitial gradients for Na+, K+, Cl-, HCO3-, and NH4+, such that at OM-IM junction, the respective concentrations relative to plasma are 1.2, 3.0, 2.9, and 8.0; within IM, there is high urea and low HCO3-, with concentration ratios of 11 and 0.5 near the papillary tip. When plasma K+ is increased from 5.0 to 5.5 mm Na+ and K+ excretion are predicted to increase 2.5- and 1.3-fold. The natriuresis derives from a 4% decrease in proximal Na+ reabsorption, and K+ excretion was stimulated with a 30% increase in connecting tubule Na+ delivery.

**Conclusions:** Thus, in the absence of other regulation, this model favors the importance of proximal over distal events in K+-induced diuresis.

**Funding:** NIDDK Support

**SA-PO126**

The Distal Convoluted Tubule Requires Kir4.1 to Sense Plasma Potassium and Regulate Potassium Homeostasis Properly

**Catherine A. Cuevas, James A. McCormick, Chao-Ling Yang, WenHui Wang, David H. Ellison, Medicine, Oregon Health & Science Univ, Portland, OR; Renal Section, Portland VA Medical Center, Portland, OR; Pharmacology, New York Medical College, Valhalla, NY.

**Background:** Urinary potassium excretion is mediated by secretion along the connecting tubule and collecting duct, but a key role for the upstream segment, the distal convoluted tubule has been recently recognized. The potassium channel, Kir4.1, which appears to be the dominant potassium conductive pathway in these cells, appears to play a key role. We recently developed a mouse model in which Kir4.1 can be deleted along the nephron in adult mice. The mice exhibit hypokalemia and decreased thiazide-sensitive NaCl cotransporter (NCC) abundance.

**Methods:** To test whether Kir4.1 is essential for the physiological response to a dietary K+ challenge, kidney-specific Kir4.1 knockout (KS-Kir4.1 KO) mice were fed with diets deficient in K+ (0% K+), rich in K+ (5% K+, HW) and with normal K+ (0.8% K+, NK) for 4 days each.

**Results:** On NK, KS-Kir4.1 KO mice were hypokalemic and alkaline (K+ 1.0±0.1 mmol/l) along with even more marked metabolic alkalosis (35±0.8 CO2 mmol/l), accompanied by continued urinary K+ wasting. Even HK failed to normalize plasma K+ in KS-Kir4.1 KO mice (1.2±0.1 mmol/l). The mechanism for K+ wasting in the KS-Kir4.1 KO mice was revealed by analysis of NCC abundance. In contrast to wild type mice in which NCC abundance correlates inversely with dietary K+ intake, NCC abundance was nearly undetectable in KS-Kir4.1 KO mice and unaffected by diet.

**Conclusions:** Together, these data show that Kir4.1 is required for the kidney to sense plasma K+ and that NCC activity is required to maintain K+ balance, even under usual diet conditions.

**Funding:** NIDDK Support, VA Support

**SA-PO127**

Disturbed Renal K Handling in Carriers of the Gly40Ser Mutation of the Glucagon Receptor Suggests a Role for Glucagon in K Homeostasis

Lise Bankir, Antonio Barbato, Ornella Russo, Gilles Cranbret, Roberto Iacone, Nadine Bouvy, Pasquale Strazullo, INSERM Unit 1138-E2, Centre de Recherche des Cordeliers, Paris, France; *Clinical Medicine*, *Federico II Univ*, *Naples, Italy.

**Background:** Clearance studies in rats showed that iv glucagon (Gluc) infusion increases urinary K excretion dose-dependently and reversibly (Aloshly, AJP Renal, 295:F632, 2013). The present study investigated these electrolyte changes in all taking advantage of the Gly40Ser mutation of the Gluc receptor that has been shown to induce a partial loss of function (lesser CAMP release by rat hepatocytes in vitro; lesser rise in plasma glucose after Gluc infusion in humans).

**Methods:** In the Olivetti cohort (male workers), 25 subjects who carried this mutation were matched 1:4 to 100 non-carriers for age (mean 57y) and weight (mean BMI 27.8 kg/m2). Estimated osmolality (Osm) of plasma and 24h urine was calculated as ([Na+K+]2/2 * glucose/urea). Transubtral K gradient (TTKG) reflecting the intensity of K secretion in distal nephron was calculated as [(urine K/serum K)/(urine Osm/serum Osm)].

**Results:** There was no significant difference in blood pressure, serum insulin, serum or urine urea and Na excretion. Urine volume was slightly higher and Osm slightly lower in carriers than non-carriers (but NS).

**Means (interquartile range)**

<table>
<thead>
<tr>
<th></th>
<th>Non-Carriers (n=100)</th>
<th>Carriers (n=25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creat.Clear (ml/min/1.73m²)</td>
<td>86 (82-90)</td>
<td>88 (81-95)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum K (mmol/l)</td>
<td>4.3 (4.4-4.6)</td>
<td>4.5 (4.3-4.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum K (mmol/l)</td>
<td>47 (45-51)</td>
<td>38 (34-43)</td>
<td>p=0.030</td>
</tr>
<tr>
<td>K excretion (mmol/d)</td>
<td>68 (64-73)</td>
<td>66 (57-74)</td>
<td>NS</td>
</tr>
<tr>
<td>TTKG</td>
<td>5.0 (4.3-7.2)</td>
<td>4.2 (3.9-4.6)</td>
<td>p=0.015</td>
</tr>
</tbody>
</table>

The difference in urine K and TTKG remained statistically significant after adjustments for serum insulin and 24h K and Na excretion.

**Conclusions:** These results in humans, along with previous observations in rats, strongly suggest that Gluc stimulates K secretion in the distal nephron. Infusion of K+ has been shown to stimulate both insulin and Gluc secretion in conscious dogs (Santusansio, Table2, Circ Res 81:M89-973). Thus, besides insulin (that favours K entry into muscle cells), glucagon most likely also participates in K homeostasis by promoting renal K excretion, as hypothesized recently [Bankir, AJP-Renal in press].

**Funding:** Government Support - Non-U.S.
Role of Cilia in Ca2+-Dependent Flow-Induced K Secretion (FIKS) in Rabbit Cortical Collecting Duct (CCD) Rolando Carrizoza-Gaytan,1 Carlos Schreck,1 Thomas R. Kleyman,2 Lisa M. Satin.1 Pediatrics, Icahn SOM at Mount Sinai, New York, NY; 2Medicine, Univ of Pittsburgh SOM, Pittsburgh, PA.

Background: BK channels, present in both CCD principal (PC) and intercalated (IC) cells, mediate Ca2+-dependent FIKS. PCs possess an apical cilium which responds to manipulation with an increase in cell Ca2+ concentration [Ca2+]i, and are considered to mediate transepithelial Na absorption and K secretion. Immunoperfusion of rabbit CCDs with anti-BKα Ab revealed robust immunodetectable protein in PC cilia (MS in preparation).

Methods: To test whether cilia BK channels mediate FIKS, net transepithelial transport (Jx) of Na and K was measured in microperfused control or deciliated (by luminal perfusion with 1 mM dibucaine, 30 min) CCDs isolated from NZW rabbits. Flow-stimulated JNa (70±4.5 and 53±2.7 pmol/min:mm; p=0.12) and JFIKS (21±2.6 and 1.9±0.3 pmol/min:mm; p=0.63) were similar in control and deciliated CCDs (n=4 and 5, respectively). The detection of FIKS in deciliated CCDs suggested that a flow-increased increase in [Ca2+]i must be preserved in absence of cilia. To test this, flow-induced [Ca2+]i transitions, inferred from fluorescence intensity ratios (FIKS), were measured in control, deciliated or suramin (100 μM; nonspecific P2 receptor antagonist) pretreated CCDs loaded with fura-2. In control CCDs, a rapid increase in tubular fluid flow rate led to a typical high amplitude peak increase in FIKS in both PC and IC, presumably reflecting release of Ca2+ from internal stores and influx of Ca2+ from the extracellular space, followed by gradual decay to a plateau value, considered to be mediated by luminal Ca2+ entry. Deciliation led to loss of the flow-induced Ca2+ peak, but the plateau elevation in FIKS above baseline was retained during a period of sustained high flow. Suramin-treated CCDs subject to acute increase in flow exhibited a slow increase in [Ca2+]i to a sustained plateau, but no early peak response.

Results: We conclude that cilia BK channels do not mediate FIKS in the CCD, and speculate that apical BK channels in CCDs that mediate FIKS are activated by elevations in [Ca2+]i elicited by mechanoactivated cilium- and P2 receptor-independent signaling.

Funding: NIDDK Support

Transgenic Mice with High Endogenous Omega-3 Fatty Acids Are Protected from Ischemia-Reperfusion-Induced Acute Kidney Injury via Basal Autophagy Activation Won Min Hwang, Se-Hee Yoon, Sung-Ro Yoo. Dept of Nephrology, College of Medicine, Kyongng Univ. Daegon, Republic of Korea.

Background: Several studies found that omega-3 fatty acid diet reduces kidney dysfunction followed by ischemic injury. However, the effects of omega-3 PUFA on IR-induced AKI were evaluated in terms of serological marker for kidney function, kidney injury marker, morphology and inflammatory cell infiltration. Finally, autophagy status in renal tubular cells with or without IR-induction was assessed by confocal microscopic observation. These data demonstrate that DN T cells in the kidney have similarities but also unique MHC restriction compared to other lymphoid organs. Microarray analysis demonstrated further insightful differences. Further dissection of kidney DN T cell biology will help us understand the pathogenesis of AKI and other immune mediated kidney diseases.

Funding: NIDDK Support

Kidney CD4-CD8- Double Negative T Cell Development Is MHC Dependent Mohanraj Mohanraj, Sanjeev FoxP3-1,3 Tregs in acute kidney injury (AKI) pathogenesis. Several studies found that omega(ω)-3 fatty acid diet reduces kidney dysfunction followed by ischemic injury. However, the effects of ω-3 PUFA on IR-induced AKI were evaluated in terms of serological marker for kidney function, kidney injury marker, morphology, and inflammatory cell infiltration. Finally, autophagy status in renal tubular cells with or without IR-induction was assessed by confocal microscopic observation. These data demonstrate that ω-3 PUFA has advantages in ischemia/reperfusion (IR)-induced AKI using fat-1 transgenic mice. In addition, we investigated the involvement of autophagy process as a possible underlying mechanism of these protection. Bilateral kidneys of experimental animals (fat-1 and C57BL/6 mice) were subjected to 30 min of warm ischemia. After 24hrs and 72hrs of reperfusion, animals were sacrificed. The effects of ω-3 PUFA on IR-induced AKI were evaluated in terms of serological marker for kidney function, kidney injury marker, morphology, and inflammatory cell infiltration. Finally, autophagy status in renal tubular cells with or without IR-induction was assessed by confocal microscopic observation. These data demonstrate that DN T cells in the kidney have similarities but also unique MHC restriction compared to other lymphoid organs. Microarray analysis demonstrated further insightful differences. Further dissection of kidney DN T cell biology will help us understand the pathogenesis of AKI and other immune mediated kidney diseases.
SA-PO132

Interaction between miR-21 and Hypoxia Induced Factors (1α and 2α) in Ischemia/Reperfusion Induced Acute Kidney Injury

Nana Song,1,2 Xiuxian Xu,1,2 Ping Jia,1,2,3 Yi Fang,1,2,3 Xiaoxia Dong.1,2,3

*Div of Nephrology, Zhongshan Hospital, Fudan Univ, Shanghai, China; 1Shanghai Key Laboratory of Kidney and Hemodialysis, Shanghai, China; 2Shanghai Inst of Digestion and Dialysis, Shanghai, China.

Background: Accumulating evidence suggests that miR-21 is importantly involved in the pathological process of ischemia/reperfusion (IR) injury. It was reported that overexpression of miR-21 and hypoxia-inducible factor (HIF) induced by hypoxia preconditioning protected against kidney I/R injury. However, it is little known whether miR-21 and HIF interact with each other in the process of kidney I/R injury.

Methods: In this study, we applied in vitro hypoxia (1%O2 + 5%CO2 + reoxygenation/21% O2 + 5%CO2, H/R) and in vivo [schematic (renal pedicle were clamped for 35 min)/reperfusion (24hrs), I/R] experimental models to investigate the feedback loop between miR-21 and HIF. We demonstrated that expression of miR-21, HIF1α and HIF2α were increased by I/R in vitro and I/R in vivo. Inference expression of HIF1α and HIF2α was modulated by miR-21.

Results: The results revealed that expression of miR-21, HIF1α and HIF2α increased with I/R in vitro and I/R in vivo. Vimentin expression was increased by I/R in vitro and I/R in vivo. Inference expression of HIF1α and HIF2α was modulated by miR-21.

Conclusions: In summary, our finding indicated that HIF regulated expression of miR-21 and miR-21 interacted with HIFα by AKT/mTOR pathway in turn. The feedback loop between miR-21 and HIFα increased susceptibility to I/R injury and may be a potential therapeutic target for I/R induced acute kidney injury. Additionally, the up-regulation of miR-21, HIFα during acute kidney injury may imply a self-protection mechanism of the kidney.

Funding: Government Support - Non-U.S.

SA-PO133

Transcriptional Profile in Kidneys Subjected to Ischemia Reperfusion Injury Modified by CHBP and Caspase-3 siRNA

Yuangyan Wu,1,2 Yufang Zhang,1,2 Aileen Liu,1,2 Bin Yang.1,2,3

Infection, Immunity and Inflammation, Univ of Leicester, United Kingdom; 1Basic Medical Research Centre, Nantong University, China; 2Nephrology, Affiliated Hospital of Nantong University, China.

Background: Ischemia reperfusion (IR) injury is an major cause of acute kidney injury (AKI) without effective treatment. Identifying the etiology and mechanism of AKI may facilitate individualized intervention timely. Here, transcriptional profiles were investigated in mouse IR injury kidneys, with or without etoricoxib derived cytokines like BAP (CHBP) or caspase-3 small interfering RNA (C3siRNA).

Methods: Genomic profiling in IR injury kidneys with other injury parameters was detected in mouse kidneys subjected to 30-min bilateral renal occlusion followed by 48-h reperfusion. Comparison was performed in 4 groups: IR, IR+24 mmol/kg CHBP, IR+CHBP+C3siRNA and CHBP+C3siRNA.

Results: CHBP altered 97 genes expression in the IR kidneys, while differentially expressed genes between C3siRNA and NCsiRNA in the IR+CHBP kidneys increased to 228, with only 5 genes in common such as PDK4 (1.5-fold, p<0.05). These genes broadly involved in proliferation, repair and repair processes and 28 genes were highly correlated to renal-related injury. 8 genes such as CALCA and CYPA31 positively and MYO5A and FG1 negatively associated with tubulointerstitial damage (TID), with CALCA also positively related to serum creatinine (Scr) and apoptosis; and additional 7 genes related to apoptosis and caspase-3 activation, which were all reduced by CHBP. On the other hand, due to additional C3siRNA, PD4, GREM1 and TIMEM100 negatively related to TID; additional 13 genes, APLN and TMSF21 positively associated with Scr, rest 11 genes such as GREM1, TIMEM100 and CHER2 negatively related to Scr and apoptosis.

Most interestingly, attributed to C3siRNA+CHBP treatment, TEMEM100 and COL1A1 positively related to all Scr, apoptosis, TID and caspase-3 activation.

Conclusions: IR injury might be closely related to genes involving in vascular integrity and renal cell survival, which was improved by CHBP and further enhanced by C3siRNA. Candidate genes such as PDK4, CALCA, TIMEM100 and COL1A1, as potential biomarkers and therapeutic targets, need to be further validated.

Funding: Government Support - Non-U.S.

SA-PO134

The Endothelial Hypoxia-Inducible Factor -1 and -2 Mediate Protection from Acute Kidney Injury in the Context of Endothelial Prolyl Hydroxylase Domain 2 Deficiency

Ganeshkumar P. Shanmugam, Michael P. Schonfeld, Pinelopi P. Kapsisiotou. Nephrology Div, Univ of Kansas, Kansas City, KS.

Background: Prolyl-hydroxylases (PHD) have emerged as safeguards of cellular metabolism through their oxygen sensing function, which enables them to regulate the activity of hypoxia-inducible factors (HIF). Previous researches have previously reported that loss of endothelial PHD2 protected from renal ischemia reperfusion injury (IRI) but the molecular mechanisms remain undefined. Here, we investigated the contribution of HIF in renal protection in endothelial phospho-D2 blocking and examined the impact of HIF-activation in endothelial cell (EC) mechanism.

Methods: EC-specific HIF activation was achieved by crossing Vacularin (Cdh5)Cre transgenic PHD2 floxed mice with the contribution of isolated kidney isolated was generated by double knockout lacking both PHD2 and HIF1 (PHD2HIF1) or PHD2 and HIF2 (PHD2HIF2). IRI was induced by unilateral renal artery clamping. Metabolic profiling was conducted by LC/MS and GC/MS while bioenergetic analysis was performed using a Seahorse Extracellular Flux Analyzer.

Results: Deletion of either endothelial HIF1 or HIF2 in endothelial PHD2 deficient background reversed the renoprotection conferred by endothelial PHD2 loss as indicated by histological injury scores and KidM mRNA levels in kidney homogenates (Day 3 post IRI, n=8 mice/group). Metabolic analysis of ECs exposed to PHD inhibitor revealed significant increase in glycolytic metabolites with simultaneous reduction in TCA cycle metabolites suggesting that HIF activation led to glycolytic shift and suppression of mitochondrial metabolism (n=5), also indicated by reduction in oxygen consumption rate on bioreactor analysis. In contrast, pre-conditioning of ECs with PHD inhibitor abolished the significant defects in mitochondrial metabolism triggered by hypoxia-reoxygenation (H/R).

Conclusions: Our data establish that both HIF-1 and HIF-2 are required in endothelial PHD2 mediated renoprotection. Furthermore, we show that the PHD/HIF axis leads to alterations in EC metabolism with critical consequences in response to H/R. Therefore, endothelial HIF may promote resistance to kidney injury by reprogramming EC metabolism.

Funding: Other NIH Support - P20 GM104936, Private Foundation Support

SA-PO135

Similar Serum Creatinine, but Non-Overlapping Gene Expressions

Katherine Xu,1 Paul Rosenstiel,1 Neal A. Paragas,2 Christian Hinze,3 Kai M. Schmidt-Ott,1 Paolo Guerrieri,1 Jonathan M. Barash,4 Dept of Medicine/Nephrology, Columbia Univ Medical Center, New York, NY; 3Nephrology, Charite, Berlin, Germany.

Background: Acute kidney injury (AKI) is currently diagnosed by the rise in serum creatinine (Scr) or a decrease in urine output without emphasis on its potential etiologies or on its clinical heterogeneity. While any etiology of AKI worsens patient outcomes, it remains unknown how hemodynamic or volume-responsive (vAKI) is related to intrinsic AKI with tubular damage (iAKI).

Methods: To clarify their relationship, we performed renal transcriptional profiling in mouse models of vAKI and iAKI with matched sCr levels.

Results: We found thousands of genes specifically to vAKI or to iAKI with limited overlap. These genes sets activated different signaling pathways, were functionally unrelated, and were expressed in different regions of the kidney. Moreover some of these proteins encoded by these genes demonstrated distinctive patterns in human urine. A cytokeration was increased in human iAKI urine but not in vAKI urine, while a plasma-associated protein that may play a role in salt-sensitive volume stress, was expressed in human vAKI urine, but was absent in iAKI due to its proteolysis, demonstrating the potential loss of a protective mechanism. This distinct pattern of vAKI and iAKI in human urine has a number of clinical applications including the possible utility of a new class of biomarkers responsive to reversible volume stresses.

Conclusions: Consequently, despite similar sCr levels, vAKI and iAKI in our models were biologically distinct, implying that these tests could refine and enhance current definitions of acute injury, implying of the kidney. Funding: NIDDK Support

SA-PO136

Regulation of IL-17 mRNA Expression by Elevated Sodium and Ang II in AKI Primed Cd4+ T Cells Is Dependent on Cytosolic Ca+2 Signaling

Purvi Mehrotra, Seth D. McKinney, Stacey L. Dineen, Michael Sturek, David P. Basile. Cellular and Integrative Physiology, Indiana School of Medicine, Indianapolis, IN.

Background: Th17 cells have been implicated in the pathogenesis of immune-mediated diseases and in acute kidney injury (AKI). We have shown that during the AKI-chronic kidney disease (CKD) transition, the number of Th17 cells increased 2-4 fold in addition, post ischemic rats on high salt diet when treated with angiotensin receptor (AT1) blocker, losartan significantly reduced IL-17 cell infiltration as compared to vehicle control. To investigate IL-17 responses in post ischemic rats, Cd4+ T cells isolated from injured rats were treated with both Ang II (10 m&mu;L) and elevated Na+ (170 mM) in vitro. IL-17 mRNA expression significantly increased 1.5 fold when treated with both elevated Na+ and Ang II and no to either elevations when only Ang II alone. Interestingly, no IL-17 response was measured in Cd4+ T cells isolated from sham-operated rats. The IL-17 response was significantly reduced by 2-aminoethoxydiphenyl borate (2-ABP) (93%; p<0.05) an inhibitor of store-operated Ca2+ channel and the L-type Ca2+ channel inhibitor, Nifedipine (1µM) (85%). In contrast there was no induction of IL-17 expression when sodium was raised to the same degree by mannitol or choline chloride, suggesting the response was specific to extracellular Na+. Multiple studies suggest that T cell receptor stimulation and Ang II independently increase intracellular free Ca2+ concentration, which induces proliferation and cytokine secretion. We hypothesize that elevated Na+ and Ang II may enhance a Ca2+ influx in T cells leading increased IL-17 secretion.

Methods: Fura-2 was used to measure Ca2+ in renal Cd4+ T cells isolated from post-ischemic or sham operated rats 7 days post-surgery.

Results: Interestingly, elevated Na+ and Ang II induced a sustained elevation of calcium influx, measured at the single cell level. The increase in Ca2+ response in post ischemic rats was present in 50% of the cells, whereas <1% of the sham-operated cells showed any effect.

Conclusions: Taken together, these data suggest that IL-17 gene regulation in AKI-prone cells is dependent on increased cytosolic Ca2+ via Ca2+ influx. Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO137
Protective Role of Endothelin B Receptor against the Development of Tunicamycin-Induced Renal Apoptosis
Carmen De Miguel, Janet Hobbs, Pamela K. Carmines, David M. Pollock, Jennifer S. Pollock.
Medicine/Nephrology, Univ of Alabama at Birmingham, Birmingham, AL; Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE.

Background: Renal injury is normally preceded by renal tubular apoptosis and loss of nephrin. The vasoactive peptide endothelin-1 (ET-1) is upregulated in cardiovascular and renal disease; however, the exact mechanisms by which ET-1 leads to renal injury are unclear. These studies were designed to determine the role of ET-1 receptors in the development of renal apoptosis in response to the acute kidney injury inducer tunicamycin (TM; 2.2 mg/kg body weight i.p.).

Methods: ET-1, deficient (-/-) or transgenic (TG) control rats were pre-treated with the ET receptor antagonist ABT-627 (500mg/kg/day, drinking water) or vehicle for 1 week prior to TM injection. 24 hours after TM administration kidneys were collected and renal apoptosis assessed by TUNEL assay. TUNEL+ cells were counted in cortex and medulla of TG control and ET-1+/- def rats 24 hours after TM administration.

Results: Pre-treatment of TG control rats with ABT-627 almost completely obliterated TM-induced apoptosis in renal cortex (decreasing from 13.5±1.6 to 1.3±0.4 TUNEL+ cells/field; n=5-6/group; p<0.05), indicating that ET-1 receptor activation is critical for the development of renal apoptosis. In contrast, ABT-627 failed to prevent TM-induced cortical and medullary apoptosis in ET-1+/- control rats (cortex: 17.6±2.0 TUNEL+ cells/field; medulla: 39.0±4.4 TUNEL+ cells/field), highlighting the important protective role of the ET-1 receptor against development of renal apoptosis. Examination at high magnification revealed that the TUNEL+ cells in renal tissue are interstitial cells located between tubules and/or near vasculara.

Conclusions: Taken together, these results underscore the involvement of the ET-1 receptor in the development of TM renal apoptosis and highlight the ET system as a potential therapeutic target against acute kidney injury. Funded by NIH T32 DK075455 to CDM and P01 HL59499 and P01 HL69999 to DMP and JSP.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO138
Macrophages Regulate the Expression of Stromal Cell-Derived Factor 1 via Indoleamine 2,3-Dioxygenase after the Renal Acute Ischemia–Reperfusion Injury
Xin Wang, Changchun Cao. Dept of Nephrology, Nanjing First Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: To observe the expression of indoleamine 2,3-dioxygenase(IDO) and stromal cell-derived factor 1(SDF-1) in the kidney after ischemic reperfusion injury(IRI), and explore the relationship between IDO, SDF-1 and macrophage by depleting macrophages before the IRI.

Methods: A total of 32 healthy C57BL/6 male mice were used to establish renal IRI model by clamping unilateral renal pedicle for 60 minutes followed by reperfusion. Kidney tissue samples were collected at indicated time points. Renal histological changes were estimated. The expression of SDF-1 and IDO were determined by immunohistochemistry, ELISA and real-time PCR. In LC group, after the liposomal clodronate was injected intraperitoneally, the location of CD68 was observed by immunofluorescence. In 1-MT group, IDO was evaluated by immunofluorescence after injecting intraperitoneally with 1-MT.

Results: Compared with sham-operated group, classical tubular damage was found in IRI group, accompanied by a lot of inflammatory cells infiltrate. The expression of total renal SDF-1 and IDO peaked on day 1 and decreased to normal levels after two weeks. IDO doesn’t express in healthy kidneys, while SDF-1 in healthy kidney was localized at cortex and expand to the other area of the kidney during IRI. Compared with IRI group, elimination of macrophageby injection of liposomal clodronate alleviated renal IRI and down-regulated the expressions of CD68 while up-regulating SDF-1. In 1-MT group, which IDO was depleted by using 1-MT, the expression of CD68 was normal while SDF-1 was up-regulated.

Conclusions: SDF-1 expression is up-regulated in IRI kidney and is associated with macrophage expression with IDO. SDF-1 may play a role in the early phase of acute kidney injury and IDO inhibitor can be a new medicine in therapy of AKI.

Funding: Government Support - Non-U.S.

SA-PO139
Inhibiting PERK Phosphorylation Prevents Expression of the Pro-Apoptotic Protein CHOP
Rachel Carlisle, Jeffrey G. Dickhout. Div of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.

Background: Acute kidney injury (AKI) is a major cause of morbidity and mortality in North America, and is regularly associated with endoplasmic reticulum (ER) stress. Tunicamycin, a nucleoside antibiotic, is often used as a mouse model of ER stress-mediated kidney injury. Tunicamycin induces an increase in the expression of the tumor necrosis factor-related apoptosis inducing ligand (TRAIL), an apoptosis-inducing ligand. Our studies show that tunicamycin and decrease in the expression of Sirt1, an NAD+-dependent deacetylase, markers, including GRP78 and CHOP. Interestingly, transgenic knock out of the pro-apoptotic protein CHOP prevented tunicamycin-mediated renal damage, implicating CHOP in the pathogenesis of AKI. GS2606414 inhibits the phosphorylation of PERK, which upstream of CHOP. We hypothesized that inhibiting PERK phosphorylation with GS2606414 would prevent tunicamycin-induced CHOP expression and AKI.

Methods: Immortalized human proximal tubular cells were treated with vehicle, tunicamycin (1 μM), tunicamycin and GS2606414 (1 μM), or GS2606414 alone, for 4 or 24 hrs. RT-PCR was performed for CHOP and Western blotting for CHOP and GRP78. Male wild type C57BL/6 mice were treated with a single dose of tunicamycin (0.5 mg/kg I.P.) or co-treated with tunicamycin and daily GS2606414 (50 mg/kg) oral gavage. Mice were sacrificed after 3 days, and kidneys were subsequently stained for CHOP.

Results: These results demonstrate that tunicamycin significantly increased CHOP mRNA and protein expression in proximal tubular cells; inhibiting PERK phosphorylation with GS2606414 prevented this increase. Mice treated with tunicamycin exhibited an increase in nuclear CHOP staining. Mouse kidneys were protected from increased CHOP expression by treatment with GS2606414.

Conclusions: These results suggest that CHOP plays a significant role in ER-stressed induced renal damage, and attenuating its expression may provide new therapeutic strategies to protect against certain forms of AKI. Funding - Dr Dickhout is a Krescent New Investigator.

Funding: NIDDK Support

SA-PO140
Niclosamide Relieves Renal Ischemia-Reperfusion Injury by Promoting Fatty Acid Oxidation in Tubular Epithelial Cells
Jining Wu, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Acute kidney injury (AKI) induced by ischemia/reperfusion (IR) injury is one of major clinical challenges with increasing morbidity and mortality. Defective fatty acid oxidation (FAO) was evident in IR, which is fatal to tubular epithelial cells. It was recently reported that niclosamide, a mitochondrial uncoupling agent, could promote FAO in liver cells. However, whether niclosamide could reduce I/R injury via improving FAO is largely unknown.

Methods: Male C57BL/6J mice were subjected to renal I/R. Niclosamide was given orally from 1 day before the surgery till the end of the study. Renal function, kidney histological abnormalities and FAO disorders were examined.

Results: Compared to vehicle control, niclosamide treatment markedly relieved renal dysfunction 6 h after reperfusion for 1 day after I/R as demonstrated by reduced the increase of blood urea nitrogen. Histological examination showed the relief of tubular injury in cortex and outer medulla by niclosamide. I/R-induced fatty acid deposition in tubular epithelium was almost diminished in niclosamide-treated mice. The reduced expressions of enzyme and transcription factor that mediates and regulates FAO (CPT1 and PPAR-a) after I/R were largely restored by niclosamide.

Conclusions: In this study, it was demonstrated that niclosamide protects IR-induced AKI by promoting FAO. Our results raised the possibility that correcting the defective FAO may be useful for preventing and treating acute kidney injury.

Funding: Government Support - Non-U.S.

SA-PO141
NAD+ Degradation in the Injured and PGC1α-Deficient Kidney
Mei T. Tran, Samir M. Parikh. Div of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.

Background: NAD+ is a key regulator of cellular energy metabolism. The kidney expends large amounts of energy in its main functions of reabsorption and secretion. Recent work showed that total NAD+ is markedly reduced in the kidney following ischemia reperfusion injury. Genetic induction of PGC1α activated de novo biosynthesis of NAD+, resulting in faster recovery from ischemic injury. Whether biosynthesis, reduced consumption from NAD-dependent enzymes, or a critical balance of both confers this NAD-related protection requires further investigation.

Methods: Genetic mice null (KO) or overexpressing PGC1α in the kidney (NephPGC1α) underwent 20 min of bilateral renal ischemia, then 24h of reperfusion. Organs were harvested at 24h post-injury. Wildtype C57BL6 mice were injected with niacinamide (Namp, 400 mg/kg). Total NAD and Sirt1 activity were measured by colorimetric and fluorometric assays. Gene expression was measured by qPCR.

Results: Enzymes involved in NAD+ biosynthesis were upregulated in NephPGC1α mice, but remained elevated in NephPGC1α KO mice. NAD+ had lower basal expressions of these enzymes, which were further depleted in IRI. The rise and fall of these enzymes coincided with total NAD. To address if NAD+ fluctuations were due to increased NAD+ consumption, rather than reduced NAD+ biosynthesis, sirtuin expression and activity levels were measured in Nam-treated wildtype mice. Total NAD+ was elevated in Nam-treated mice, with no change in Sirt1 activity. Following IRI, NAD+ levels and Sirt1 activity decreased across all conditions. Relative to injured controls, total NAD+ was still greater in injured Nam-treated mice, and unexpectedly, Sirt1 activity was similarly elevated.

Conclusions: Results suggest that depletion of NAD+ in the injured or PGC1α-deficient kidney may not be due to greater NAD+ consumption, but as recent work proposes, inability to synthesize NAD+. Furthermore, though Nam is known to inhibit Sirt1, these studies suggest that Sirt1 activity in vitro was unchanged with systemic Nam administration. Even more surprising is that Sirt1 activity is higher in the injured Nam-treated mice, suggesting that sirtuin activity reflects overall kidney health.

Funding: NIDDK Support
SA-PO142

Pannexin1 Deletion Protects Kidneys from Ischemia-Reperfusion Injury in Mice

Jukab Jankowskia, Heather M. Perry, Liping Huang, Hong Ye, Brant Isaksnon, Koki S. Ravichandran, Mark D. Okusa, 1 Div of Nephrology: Center for Immunity, Inflammation and Regenerative Medicine, Univ of VA; 2 Dept of Molecular and Cellular Physiology, Univ of VA, 3 Dept of Microbiology, Immunology, and Cancer Biology, Univ of Virginia, Charlottesville, VA.

Background: Extracellular ATP can contribute to inflammation following cell death or damage through its action as a danger molecule on P2X and P2Y receptors. The cellular mechanism of ATP release and its impact on kidney ischemia-reperfusion injury (IRI) are largely unknown. Pannexin1 (PANX1), a transmembrane channel, can be activated to release ATP yet its impact on kidney IRI is not known. We hypothesize that deletion of PANX1 and reduction of ATP release is protective in kidney IRI. We predict this effect may be mediated by PANX1 in proximal tubules (PT), as they are a rich source of ATP and highly susceptible to IRI.

Methods: Global PANX1 (Pannx1−/−, n=10) and PT-specific PANX1 (PepckCrePannx1f/f, n=4) KO mice and appropriate controls (n=9 and 3 respectively) were subjected to 26' bilateral kidney IRI or sham operation and 24h of reperfusion. Kidney function was assessed by plasma creatinine (Cr) and kidney injury by stereological quantification of acute tubular necrosis (% of outer medulla area) of HE stained kidney sections. Proinflammatory markers were quantified by real-time PCR of whole kidney lysates. Apoptosis was assessed by detection of cleaved caspase3 by immunohistochemistry.

Results: Increased Cr (mg/dL) in WT mice after IRI was blunted in Pannx1−/− mice (1.4 ± 0.2 vs WT 7.1 ± 0.01, p<0.001). Fewer cleaved-caspase 3 positive tubule cells. The increase in kidney mRNA of proinflammatory cytokines (Icam1, Sele, Selp) and leukocyte adhesion molecules (Icam1, Select, Selp) in WT mice after IRI was attenuated in Pannx1−/− mice. Lastly, the increase in Cr in controls after IRI was markedly reduced in PepckCrePannx1f/f mice (1.8 ± 0.16 respectively).

Conclusions: These results show that both global and PT loss of PANX1 protect mouse kidneys from IRI and suggest that PANX1 may serve as a therapeutic target in AKI.

SA-PO143

Drp1-Dependent Mitophagy Protects against Cisplatin-Induced Apoptosis of Renal Tubular Epithelial Cells by Improving Mitochondrial Function

Yanjuan Yang, Ningning Wang, Huijuan Mao, Chang Ying Xing. Dept of Nephrology, The First Affiliated Hospital of Nanjing Medical Univ; Nanjing, Jiangsu, China.

Background: Mitochondrial dysfunction plays an important role in cisplatin induced nephrotoxicity. Degradation of damaged mitochondria is carried out by mitophagy. Little is known of the precise role of mitophagy and its molecular mechanisms during cisplatin induced death. Also, little evidence that activation of mitophagy improved renal function is lacking. Furthermore, several evidences have shown that mitochondrial fission coordinates with mitophagy. The aim of this study was to investigate whether activation of mitophagy protects against mitochondrial dysfunction and renal tubular cells injury during cisplatin treatment. The effect of mitochondrial fission on mitophagy was also investigated.

Methods: Autophagy was evaluated by autophagy markers and mRFP-GFP-LC3 adenovirus. Mitophagy was determined the co-localization of mitochondria with lysosome. ROS levels were determined by DCFDA and MitoSOX. Mitochondrial morphology was visualized by using MitoTracker Red. siRNAs were used to knock down mitophagy machinery. Knock-down efficiency of each siRNA was firstly examined before acute I/R injury. Proximal tubule specific UCP2 knockout mice were created by Cre-LoxP recombinant enzyme system. Mice were fed standard diets with conjugated linoleic acid (CLA) to upregulate UCP2. Cells were transfected with siRNA for TXNIP reduced changes of these enzymes in NRK-52E cells.

Results: Increased Cr (mg/dL) in WT mice after IRI was blunted in Pannx1−/− mice (1.4 ± 0.2 vs WT 7.1 ± 0.01, p<0.001). Fewer cleaved-caspase 3 positive tubule cells. The increase in kidney mRNA of proinflammatory cytokines (Icam1, Sele, Selp) and leukocyte adhesion molecules (Icam1, Select, Selp) in WT mice after IRI was attenuated in Pannx1−/− mice. Lastly, the increase in Cr in controls after IRI was markedly reduced in PepckCrePannx1f/f mice (1.8 ± 0.16 respectively).

Conclusions: These results show that both global and PT loss of PANX1 protect mouse kidneys from IRI and suggest that PANX1 may serve as a therapeutic target in AKI.

SA-PO144

Thioredoxin-Interacting Protein (TXNIP) Regulates Mitochondrial Function of Renal Tubular Cells and Prognosis of Ischemia/Reperfusion-Induced Acute Kidney Injury

Shigeru Nojima, Tatsuki Matsumoto, Koh Takahashi, Hirofumi Nishikawa, Yoshio Shimamura, Kosuke Inoue, Yoshinori Taniguchi, Taro Horino, Shimpai Fujimoto, Yoshio Terada. Dept of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi Univ, Nankoku, Kochi, Japan.

Background: Thioredoxin-interacting protein (TXNIP) has been found to regulate the cellular reduction-oxidation (redox) state by binding to and inhibiting thioredoxin in a redox dependent manner. Little is known about the role of TXNIP in mitochondrial function and acute kidney injury (AKI) pathogenesis.

Methods: We evaluated the role of TXNIP in renal function in bilateral renal ischemia (27 min of ischemia injury during transposning TXNIP knock-out mice using Bax or Bcl-2 (a marker for apoptosis and peroxynitrite (r = 0.32; p=0.03), Bax: Bcl-2 and peroxynitrite (r=0.48; p=0.01). We found higher Bax

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

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levels in PTX (5.75±0.71) than the RL (3.75±1.77) and PTX groups (5.75±0.71; p<0.001). BCL-2 immunohistochemical levels were higher in Sham group (5.50±1.69) than in the other groups (p<0.001). The Bax/Bcl-2 ratio was higher in PTX (3.25±0.89) than HSSPTX group (2.38±0.92; p<0.009). TUNEL immunohistochemical levels were lower in HSS (18.56±9.33) and HSSPTX (10.72±7.77) groups than in the other groups (p<0.001). We did not observe difference in the concentration of MDA between the groups (p=0.62).

**Conclusions:** HSSPTX attenuated oxidative stress and decreased the immunohistochemical markers of apoptosis in sepsis-induced AKI.

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**SA-PO147**

**Preconditioning with a Pharmacologic Activator of Adenine Monophosphate-Activated Kinase Reduces Apoptosis of Proximal Tubular Cells Exposed to Metabolic Stress:** Role of Akt and Glycogen Synthase Kinase Wilfried Lieberthal,1 Jerrold S. Levine,1,2 Medicine, Stony Brook Medicine, Stony Brook, NY;1 Medicine, Univ of Chicago at Illinois, Chicago, IL.

**Background:** We have reported that preconditioning proximal tubular cells (PTCs) with A-769662, an activator of adenine monophosphate-activated kinase (AMPK), ameliorates stress-induced apoptosis by preserving cell ATP stores (AIP: In Press). We now examine the role of Akt, a pro-survival kinase, and of glycogen synthase kinase-3b (GSK-3b) a pro-apoptotic kinase, in mediating the pro-survival effects of A-769662.

**Methods:** After preconditioning, PTCs were subjected to metabolic stress induced by anticycin without dextrose. Apoptosis was evaluated by FACS, the activity of Akt, GSK-3b, BAD and BAX by immunoblotting and cell survival using the MTT assay.

**Results:** Preconditioning with A-769662 reduced stress-induced apoptosis, increased the activation of Akt (by phosphorylating Thr-308 and Ser-473) and inhibited the activation of GSK-3b (by phosphorylating Ser-9). Preconditioning with A-769662 also inhibited the activation of BAD by phosphorylating Ser-136 (an effect mediated by Akt), and inhibited the allosteric activation of BAX, (an effect mediated by inhibition of GSK-3b). Knocking down AMPK activity reduced all these effects of A-769662 suggesting that they are mediated by AMPK activation. The increase in stress-induced cell survival by preconditioning with A-769662 alone, was reduced by preconditioning with A-769662 + MK-22-2 (an Akt inhibitor). Post-stress cell survival after preconditioning with MK-2202 alone, was lower than cell survival after preconditioning without A-769662 or MK-2202. The increased stress-induced cell survival by preconditioning with A-769662 alone, or with A-769662 + TAZD-8 (an inhibitor of GSK-3b) was comparable, while the post-stress cell survival after preconditioning with TAZ alone was lower than that after preconditioning with A-769662 + TAZD-8, but higher than that after preconditioning without A-769662 or TAZD-8.

**Conclusions:** The pro-survival effects of preconditioning PTCs with A-769662 before exposing them to stress is mediated, in part, by the activation of Akt and the inhibition of GSK-3b.

**Funding:** VA Support

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**SA-PO148**

**Vascular Adhesion Protein-1 Promotes Neutrophil Infiltration via Hydrogen Peroxide Generation in Renal Ischemia-Reperfusion Injury** Shintaro Tanaka, Tetsuya Tanihara, Keisuke Saito, Hisako Saito, Rehim Magi, Masasumi Nangaku, Div of Nephrology and Endocrinology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan.

**Background:** Vascular adhesion protein-1 (VAP-1) acts as an adhesion molecule as well as an ectoenzyme catalyzing oxidative deamination of primary amines to generate hydrogen peroxide in extracellular space. While VAP-1 is implicated in leukocyte trafficking in various inflammatory diseases, its role in acute kidney injury is incompletely characterized. Thus, we examined the effect of VAP-1 inhibition in a rat model of renal ischemia-reperfusion (IR) injury.

**Methods:** Rats were subjected to left renal ischemia for 45 min after right nephrectomy, followed by reperfusion for 48 h. A specific VAP-1 inhibitor, Compound A (R-Tech Ueno, Tokyo, Japan; 40 mg/kg/day, in feed), or vehicle was administered to rats from 7 days before IR surgery.

**Results:** Immunofluorescence analysis suggested that VAP-1 was predominantly expressed in pericytes of rat kidneys. Primary mouse kidney pericytes expressed and released enzymatically active VAP-1. In vivo, Compound A administration significantly suppressed VAP-1 enzyme activity in the whole kidneys (70.61.3 vs 0.90.1 pmol/mg protein/min), which was accompanied by better renal function (BUN: 139±19 vs 69±6 mg/dL, Cr: 2.5±0.2 vs 1.4±0.1 mg/dL; p<0.01). TUNEL immunohistochemical levels were lower in HSS (18.56±9.33) and HSSPTX (10.72±7.77) groups than in the other groups (p<0.001). We did not observe difference in the concentration of MDA between the groups (p=0.62).

**Conclusions:** HSPPTX attenuated oxidative stress and decreased the immunohistochemical markers of apoptosis in sepsis-induced AKI.

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

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**SA-PO149**

**Methionine Sulfoxide Reductase A (MsrA)-Gene Deletion Aggravates Cisplatin-Induced Nephrotoxicity in Mice** Mi Ra Noh,1 Jee In Kim,2 Kwon Moo Park.1 1Dept of Anatomy and BK21 Plus, Kyungpook National Univ School of Medicine, Daegu, Korea; 2Dept of Molecular Medicine and MRC, Keimyung Univ School of Medicine, Daegu, Korea.

**Background:** Methionine sulfoxide reductase A (MsrA) catalyzes stereospecifically the reduction of methionine-S-sulfoxide, and plays an antioxidant enzyme that scavenges reactive oxygen species (ROS). Cisplatin is the most widely used for the treatment of solid tumors. However, its side effects including nephrotoxicity limit use. In the present study, we investigated the role of MsrA in cisplatin-induced nephrotoxicity using MsrA gene-deleted (MsrA−/−) and wild-type (MsrA+/+) mice.

**Methods:** Mice were administered with vehicle or cisplatin (10 mg/kg, i.p.) for 5 days.

**Results:** Cisplatin-induced renal functional and morphological impairments were greater in the MsrA−/− than in MsrA+/+ kidneys. Cisplatin increased superoxide anion formation, hydrogen peroxide (H2O2) production, lipid peroxidation, and the ratio of cystathionine-β-synthase (CBS) to total glutathione (GSH) in the kidneys. These increases were much higher in MsrA−/− than in MsrA+/+ kidneys. Cisplatin reduced the expression and activity of MsrA and MsrBs in the kidneys. Cisplatin reduced the expression of cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE), both of which are H2S-producing enzymes, in the kidneys. Cisplatin exacerbated mitochondrial dysfunction, reducing the levels of mitochondrial fission (Fis1), promoter of mitochondrial fission. Cisplatin also enhanced the pro-apoptotic response and increased the number of apoptotic cells. MsrA deficiency increased the cisplatin-induced mitochondrial dysfunction and apoptosis in the kidneys.

**Conclusions:** Taken together, these results demonstrate for the first time that cisplatin reduces MsrA activity and MsrA gene deletion exacerbates cisplatin-induced nephrotoxicity via increased oxidative stress, mitochondrial dysfunction, and apoptosis. It suggests that MsrA plays a crucial role in the pathogenesis of cisplatin-induced acute kidney injury (AKI) and may be a useful target protein to prevent cisplatin-induced nephrotoxicity.

**SA-PO150**

**Mitochondrial Function during Injury and Recovery from AKI:** Mark Hopkoski, Elanore Hall, Hai Pham, Ying Li, Prabhleen Singh, Medicine, UC San Diego and VADSHS, San Diego, CA.

**Background:** Renal tissue hypoxia is a common link between AKI and CKD. The kidney has high mitochondrial oxidative metabolism, and is exquisitely sensitive to hypoxic injury. Mitochondria play a central role in cell injury and their dysfunction has been implicated in various forms of AKI, but information on mitochondrial function during recovery from AKI is limited.

**Methods:** We performed 5 min- and 15-min of bilateral renal artery clamping (IR) in mice and then serial GFR measurement by FITC inulin kinetics at days 1, 3, 7, 14 and 28 after ischemia and protein expression of mitochondrial oxidative phosphorylation complexes (Ox phos), fission, fusion and AMPK at the same time points.

**Results:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Ox Phos Complexes</th>
<th>Fission</th>
<th>Fusion</th>
<th>AMPK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>Highest</td>
<td>Low</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>IR</td>
<td>Decreased</td>
<td>Increased</td>
<td>Decreased</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Serial GFRs:** In the 10-min group, GFR was significantly lower at days 1 and 3 but improved significantly to levels similar to sham at days 15-28. In the 15-min group, GFR was dramatically reduced with partial recovery over 4 weeks. Ox Phos expression: Significant reduction in expression for both 10 and 15 min IR at 1-2 weeks for most complexes, with recovery in expression for 4 weeks for 10-min, but persistent reduction for 15-min IR. Mitochondrial Proteins-4 weeks, 15-min IR showed significant reduction in MtF2 and increase in Fis1 expression. AMPK expression was increased at day 1, but no increase in pAMPK was seen in the 15-min IR kidney. In 10 min IR, pAMPK was increased at 24 hrs and persisted at 4 weeks.
Conclusions: Our findings show duration of IR corresponding with severity of injury and impaired recovery in GFR, and mitochondrial dysfunction with decreased O2 phos proteins and altered dynamics with impaired AMPK activation in IR kidneys, corresponding to severity of injury, but in some instances despite functional recovery. These may be important in transition of AKI to CKD. Additional studies to compare these two models when manipulated with maneuvers to worsen or improve recovery from IR are ongoing.

Funding: NIDDK Support, VA Support

SA-PO151

Antrum Maculos Protein-18 Prevents Cisplatin-Induced Acute Kidney Injury in Mice

Patrick Cunningham, Bradley K. Hack, Peili Chen, F. Gary Toback. Section of Nephrology, Univ of Chicago, Chicago, IL.

Background: Cisplatin induced nephrotoxicity is a frequent complication which limits the use of platinum based chemotherapy and increases morbidity in cancer patients. Antrum maculos protein-18 (AMP-18) is a protein produced in the stomach which has mitogenic and protective effects on epithelium, mediated in part by strengthening intercellular tight junctions, previously demonstrated in cell culture and models of intestinal injury. We hypothesized that AMP-18 would provide protection against cisplatin-induced nephropathy and improve recovery from renal injury in mice, which causes severe injury to the tubular epithelium (acute tubular necrosis, or ATN).

Methods: C57BL/6 mice were given daily injections of AMP-18 peptide (25 mg/kg) starting two days before cisplatin administration. At day zero, mice were given cisplatin (30 mg/kg). AMP-18 injections were continued until sacrifice at 72 h after cisplatin (n = 6 per group). Serum was analyzed for BUN, and kidneys were collected for light microscopic staining and analysis of protein and mRNA.

Results: Mice in the cisplatin alone group had significant renal failure, but AMP-18 injected mice were profoundly protected (BUN 11.8 +/- 2.1 mg/dl in cisplatin + vehicle group, versus 39.8 +/- 5.2 mg/dl in cisplatin + AMP-18, p < 0.01). Mice injected with AMP-18 also had significantly less tubular necrosis on light microscopy (injury score 5.1 +/- 1.0 v. 1.0 +/- 0.2, p < 0.003), which correlated tightly with BUN readings. AMP-18 injected mice also had significantly less albuminuria (84.1 +/- 3.8 v. 185 +/- 84.4, p < 0.015), as well as fewer apoptotic nuclei as seen by TUNEL staining. Immunofluorescence showed relatively preserved tight junctions in the tubular epithelium in AMP-18 treated mice.

Conclusions: In summary, AMP-18 peptide showed a strong protective effect in preventing cisplatin-induced nephrotoxicity. This finding may ultimately lead to therapies which could prevent cisplatin nephrotoxicity in patients.

Funding: NIDDK Support

SA-PO152

Renoprotection of CHBP against Ischemia Reperfusion-Related Renal Injury Associated with Inhibiting Endoplasmic Reticulum Stress

Wu Seong Jang,1 Babu J. Pandanaram,1,2 * Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE; 2Internal Medicine, Section of Nephrology, Univ of Nebraska Medical Center, Omaha, NE.

Background: Damage of proximal tubule cell by chemotherapeutic agent cisplatin causes kidney injury and dysfunction. However, the underlying mechanism of cisplatin-induced tubular injury remains to be elucidated.

Methods: Since cyclophilin D (CypD) plays a critical role in necrotic cell death, we investigated whether proximal tubule-targeted deletion of CypD prevents cisplatin-induced kidney injury.

Results: Loss of proximal tubule CypD preserved mitochondrial morphology and function and prevented downregulation of mitochondrial biogenesis and expression of mitochondrial metabolism-related genes. Fatty acid metabolism was impaired in wild type mice, but was preserved in mice with proximal tubule deletion of CypD after cisplatin treatment. Consistent with mitochondrial damage, proximal tubule-targeted deletion of CypD suppressed cisplatin-induced tubular necrosis, apoptosis, inflammation, and kidney dysfunction. Pharmacological inhibition of CypD using Sanglifeherin A also prevented cisplatin-induced kidney injury. However, inhibition of ferroptosis by ferrostatin-1 did not protect, rather worsened, cisplatin-induced kidney injury, suggesting a dispensable role of CypD in ferroptosis. When manipulated with maneuvers to worsen or improve recovery from IR are ongoing.

Conclusions: Collectively, targeting CypD prevents cisplatin nephrotoxicity through preservation of mitochondrial metabolism, and may be developed as a potential therapeutic strategy for cisplatin nephrotoxicity.

Funding: NIDDK Support, Private Foundation Support

SA-PO155

Renal Cold Storage plus Transplantation Alters Mitochondrial Dynamics: Involvement of Oxidants? (SA-PO155)

Lee Ann MacMillan-Crow, Nirmala Parajuli, Stephen Shrum. Pharmacology/Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR.

Background: A major hurdle in the field of renal transplantation is the shortage of suitable donor kidneys. Renal transplantation using living donors organ performs better when compared to deceased donor kidneys that were exposed to cold storage (CS) prior to transplantation (TX). We recently reported that 4 hr CS compared to autotransplantation resulted in more severe mitochondrial and renal damage (J. Kidney, 2: 114, 2016). The purpose of the current study was to evaluate whether mitochondrial dynamics (fusion/fission pathways) were altered during CS and TX and to dissect the molecular pathways involved.

Methods: Male (n = 6) kidneys from C57BL/6 donors were isolated anoxically, exposed to 4 hr cold storage, and then transplanted in a naïve Lewis rat followed by right nephrectomy. Mitochondrial function was assessed via high resolution respirometry and ATP measurement. Mitochondrial dynamics were monitored using western blotting and electron microscopy (EM).

Results: In the EM data revealed marked mitochondrial fragmentation following CS+Tx Likewise, mitochondrial function was inhibited at complexes I, II, and III. Interestingly, CS alone led to impaired mitochondrial fusion (loss of long form of Opa1, which is critical for inner membrane fusion). CS+Tx also showed impaired Opa1 processing and decreased mitofusion expression (critical for outer membrane fusion). The mitochondrial protease, Oma1, has been shown to be activated by stress (and oxidants) which can lead to increased Opa1 processing and impaired mitochondrial fusion. Early studies show altered Oma1 activity during CS+Tx.

Conclusions: In summary, these studies suggest that renal CS initiates a defect in mitochondrial dynamics that likely involves increased oxidant-induced Oma1 protease function which then impairs mitochondrial fusion. Further studies designed to blunt Oma1 activity may protect donor kidneys from CS-mediated damage prior to transplantation.

Funding: NIDDK Support, Other NIH Support - R01 support (DK089659); T32 support (DK061921 and GM106999)

SA-PO154

Proximal Tubule-Specific Deletion of Cyclophilin D Prevents Cisplatin Nephrotoxicity

Hsieh-Seeong Jang,1 Babu J. Pandanaram,1,2 * Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE; 2Internal Medicine, Section of Nephrology, Univ of Nebraska Medical Center, Omaha, NE.

Background: Damage of proximal tubule cell by chemotherapeutic agent cisplatin causes kidney injury and dysfunction. However, the underlying mechanism of cisplatin-induced tubular injury remains to be elucidated.

Methods: Since cyclophilin D (CypD) plays a critical role in necrotic cell death, we investigated whether proximal tubule-targeted deletion of CypD prevents cisplatin-induced kidney injury.

Results: Loss of proximal tubule CypD preserved mitochondrial morphology and function and prevented downregulation of mitochondrial biogenesis and expression of mitochondrial metabolism-related genes. Fatty acid metabolism was impaired in wild type mice, but was preserved in mice with proximal tubule deletion of CypD after cisplatin treatment. Consistent with mitochondrial damage, proximal tubule-targeted deletion of CypD suppressed cisplatin-induced tubular necrosis, apoptosis, inflammation, and kidney dysfunction. Pharmacological inhibition of CypD using Sanglifeherin A also prevented cisplatin-induced kidney injury. However, inhibition of ferroptosis by ferrostatin-1 did not protect, rather worsened, cisplatin-induced kidney injury, suggesting a dispensable role of ferroptosis in cisplatin nephrotoxicity.

Conclusions: Collectively, targeting CypD prevents cisplatin nephrotoxicity through preservation of mitochondrial metabolism, and may be developed as a potential therapeutic strategy for cisplatin nephrotoxicity.

Funding: NIDDK Support, Private Foundation Support

SA-PO155

Effect of Mitochondrial NADP+-Dependent Isocitrate Dehydrogenase (IDH2) on Cisplatin-Induced Nephrotoxicity

Min Jung Kong,1 Sang Jun Han,1 Jee In Kim,1 Kwon Moo Park.1 *Dept of Anatomy and BK21 Plus, Kyungpook National Univ School of Medicine, Daegu, Korea; 2Dept of Molecular Medicine and MRC, Keimyung Univ School of Medicine, Daegu, Korea.

Background: Mitochondrial NADP+-dependent isocitrate dehydrogenase (IDH2) is a major producer of NADPH which is critical for maintenance of glutathione (GSH) levels and is considered a possible protective factor against oxidative stress. Cisplatin is one of the most common anticancer drugs. However, its nephrotoxicity due to a reduction of intracellular levels of glutathione by formation of cisplatin-GSH complex limits its use. Here, we investigated the role of IDH2 in cisplatin-induced nephrotoxicity using IDH2 gene-deleted (IDH2−/−) and wild type (IDH2+/+) mice.

Methods: Mice were administrated intraperitoneally cisplatin (20 mg/kg body weight). Some mice were treated Mitox-Tempo, a mitochondria-specific antioxidant, before cisplatin injection.

Results: IDH2 deficiency aggravated cisplatin-induced renal functional and morphological impairments. MT reduced those cisplatin-induced renal functional and morphological impairments both IDH2−/− and IDH2+/+ mice. Cisplatin reduced NADPH levels in the kidney. This cisplatin-induced reduction of NADPH levels was greater in the IDH2−/− mice (p < 0.05). These results suggested that IDH2 deficiency exacerbates cisplatin-induced renal injury.

Conclusions: In summary, these studies revealed marked mitochondrial fragmentation following increased hydrogen peroxide, lipid peroxidation and GSSG total GSH ratio. These increases were
greater in the IDH2−/− mouse kidneys than IDH2+/− mouse kidneys. MT reduced those cisplatin-mediated effects of Drp1, and induced mitochondrial fragmentation and apoptosis, and GSSG/total GSH ratio both IDH2−/− and IDH2+/− mouse kidneys. Mitochondrial damage and renal cell death after cisplatin injection were greater in the IDH2−/− than IDH2+/− mouse kidneys. MT reduced those cisplatin-induced mitochondrial damage and cell death both IDH2−/− and IDH2+/− mouse kidneys. Above effects of MT were greater in IDH2−/− mouse kidneys when compared with IDH2+/− mouse kidneys.

Conclusions: These results indicate IDH2 deficiency aggravates cisplatin-induced nephrotoxicity by increasing mitochondrial oxidative damage, suggesting that IDH2 plays a crucial role in the pathogenesis of cisplatin-induced acute kidney injury (AKI).

SA-PO156
Deletion of Sirtuin 7 Ameliorates Cisplatin-Induced Acute Kidney Injury Through Regulation of Inflammatory Response Yazishika Miyasato, Tatsuya Yoshizawa, Terumasa Nakagawa, Yutaka Kakizoe, Yuichiro Izumi, Takashi Kawanabe, Masataka Adachi, Eva Bober, Masashi Mukoyama, Kazu Yamaagata. 1Medical Biochemistry, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; 2Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; 3Cardiac Development and Remodeling, Max-Planck-Inst for Heart and Lung Research, Bad Nauheim, Germany.

Background: Sirtuin 7 (SIRT7) is an NAD+/NADH+-dependent histone deacetylase. It is reported that SIRT7 has significant roles in disease conditions such as hepatic steatosis, cardiac dysfunction, and cancer. However, very little is known about the functional roles of SIRT7 in kidney diseases. Therefore, we investigated the role of SIRT7 in acute kidney injury.

Methods: Acute kidney injury was induced by intra-peritoneal cisplatin administration (20mg/kg body weight) in SIRT7 deficient (SIRT7−/−) and wild-type (WT) mice. Mice were sacrificed at day 3 after cisplatin administration. Knockdown of SIRT7 in NKG52E, a renal proximal tubular cell line, was induced by short hairpin RNA (shRNA).

Results: SIRT7−/− mice showed significantly lower serum creatinine levels compared with WT mice (0.30±0.25 vs 0.85±0.38 mg/dL, p<0.05). Histological analysis revealed lower kidney injury score and macrophage accumulation in SIRT7−/− mice. The number of TUNEL positive cells was also significantly low. The survival rate of SIRT7−/− mice was significantly higher than WT mice at day 7 after cisplatin administration (Log-rank test, p<0.01). There were significant decreases in inflammation-related gene expression (TNF-α, IL-1β, IL-6, MCP-1, and CXCL-1) in SIRT7−/− mice compared to WT mice. In addition, the number of inflammatory infiltrates were reduced in nCDase−/− mice as compared to that of the WT. Additionally, western blot analysis revealed that nCDase−/− mice exhibited reduced markers of ER stress (PERK, pJNK, IRE1α, CHOP, cleaved caspase 12).

Conclusions: Data presented indicate that loss of nCDase protects the kidney from the nephrotoxic effects of cisplatin treatment and thus inhibiting this enzyme is a potential renal protective strategy during cisplatin chemotherapy.

Funding: NIDDK Support

SA-PO157
Silencing Numb Exacerbates Cisplatin-Induced Acute Kidney Injury by Promoting Mitochondrial Fragmentation Ze Liu, Jing Nic. The Key Laboratory of Organ Failure Research, Nanfang Hospital, Southern Medical Univ, Guangzhou, China.

Background: Numb is a multifunctional protein involved in diverse cellular processes. We previously studied that Numb is expressed in proximal tubules. Depletion Numb from proximal tubular cells attenuated interstitial fibrosis. The aim of the present study is to determine whether depletion Numb in acute renal injury.

Methods: Scramble siRNA or Numb siRNA was injected into male BALB/C mice (18-20g) through tail vein. Cisplatin was administrated 24 h after siRNA injection and mice were sacrificed at day 3 after cisplatin injection. Renal function was evaluated by the level of serum creatinine. Renal morphology was examined by Hematoxylin and eosin staining. The apoptosis of tubules was tested by TUNEL assay, flow cytometry and western blotting. The mitochondrial morphology was assessed by electron microscopy (EM) and immunofluorescence staining. The mitochondrial damage was evaluated by the release of cytochrome c.

Results: The expression of Numb was significantly upregulated after cisplatin administration both in vivo and in vitro. Silencing Numb exacerbated cisplatin-induced renal injury as shown increased Scr (2.0±0.4mg/dL vs 1.0±0.3mg/dL, P<0.05) and more severe morphological damage. TUNEL assay and flow cytometry analysis demonstrated that Numb deficiency dramatically increased cisplatin-induced apoptosis both in vivo and in vitro. EM showed that there was more mitochondrial fragmentation in Numb siRNA injected mice after cisplatin treatment. Similarly, compared with scramble siRNA transfected cells, mitochondrial fragmentation and cytochrome C release were more severe in Numb siRNA transfected NRK-52E cells after cisplatin treatment. Western blot analysis revealed that silencing Numb increased the protein level of Drp1, a key mitochondrial fission protein, after cisplatin stimulation both in vivo and in vitro. Pretreatment with mdivi-1, a pharmacological inhibitor of Drp1, attenuated cisplatin-induced mitochondrial fragmentation and apoptosis in Numb siRNA transfected NRK-52E cells.

Conclusions: Our data suggest that Numb plays a crucial role in cisplatin-induced acute kidney injury by suppressing mitochondrial fragmentation, and the subsequent tubular cell apoptosis.

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SA-PO158
Loss of Neutral Ceramidase in Mice Protects from Cisplatin-Induced Acute Kidney Injury Deanna L. Snoe, Tess Dupre, Mark A. Doll, Sierra Sharp, Kumar Saurabh, Judit Megyesi, Ashley J. Snider, Lina M. Obeid, Yufii A. Hannum, Levi J. Beverly,2,3 Leah J. Siskind.1,3 Pharmacology and Toxicology, Univ of Louisville, Louisville, KY; 2Medicine, Univ of Louisville, Louisville, KY; 3JG Brown Cancer Ctr, Univ of Louisville, Louisville, KY; Internal Medicine, Univ of Arkansas for Medical Sciences/Central Arkansas Veterans Healthcare Sys, Little Rock, AR; 4Medicine, Stony Brook Cancer Center, Stony Brook Univ, Northport Veterans Affairs Medical Center, Stony Brook, NY; 5Medicine, Stony Brook Cancer Center, Stony Brook Univ, Stony Brook, NY.

Background: Acute kidney injury (AKI) resulting from the use of the chemotherapeutic agent, cisplatin, remains a dose- and treatment-limiting obstacle for many patients. Sphingolipids, especially ceramide, play a central role in regulating the toxic effects of cisplatin on the kidney. Neutral ceramidase (nCDase) deficiency has been shown to exacerbate cisplatin-induced metabolic loss and metabolism of this enzyme has been proven to be protective in traumatic injuries of both the brain and heart. We hypothesized that loss of nCDase would offer protection for cisplatin-induced AKI.

Methods: In this study we utilized a transgenic mouse whereby expression of nCDase has been depleted (nCDase−/−) in combination with an established murine model of cisplatin-induced AKI. Nine week old nCDase−/− and wild-type (WT) C57BL/6 mice were used for this study.

Results: Our data indicate that loss of nCDase protects the kidney from cisplatin injury as evidenced by improved markers of kidney function (BUN, Serum Creatinine), reduced markers of kidney injury (NGAL), and improved kidney pathology. Expression levels of pro-inflammatory chemokines and cytokines (TNF-α, IL-1β, IL-6, MCP-1, and CXCL-1) and the number of inflammatory infiltrates were reduced in nCDase−/− mice as compared to that of the WT. Additionally, western blot analysis revealed that nCDase−/− mice exhibited reduced markers of ER stress (PERK, pJNK, IRE1α, CHOP, cleaved caspase 12).

Conclusions: Data presented indicate that loss of nCDase protects the kidney from the nephrotoxic effects of cisplatin treatment and thus inhibiting this enzyme is a potential renal protective strategy during cisplatin chemotherapy.

Funding: NIDDK Support

SA-PO159
Renoprotective Effect of Prothymosin α-Derived Hexapeptide against Cisplatin-Induced Acute Kidney Injury Kenta Torio,1 Yoko Obata,1 Miki Sawa,1 Satoru Oka,1 Takehiko Koji,1 Hiroshi Ueda,1 Tomoya Nishino,1 1Dept of Nephrology, Nagasaki Univ Hospital, Nagasaki, Japan; 2Dept of Histology and Cell Biology, Nagasaki Univ Graduate School of Biomedical Sciences, Nagasaki, Japan; 3Dept of Pharmacology and Therapeutic Innovation, Nagasaki Univ Graduate School of Biomedical Sciences, Nagasaki, Japan.

Background: Prothymosin alpha (ProTa) is reported to exert neuroprotective actions against ischemia and hypoxia, and is a common clinical event leading to high mortality and development of chronic kidney disease. However, to date, no effective treatment for AKI have been established. In this study we investigated the renoprotective effect of P α against cisplatin-induced AKI.

Methods: 8 week old male Wistar rats were divided into 3 groups: vehicle-treated group, cisplatin (8mg/kg)-treated group, cisplatin-treated group with P α (30mg/kg) injection. Cisplatin was injected intraperitoneal once for 30 minutes before cisplatin treatment. Renal function was assessed at 1, 3, 5, 7, 9 days after cisplatin treatment by measuring serum creatinine. Renal histological change was assessed by PAS staining, and apoptosis of renal tubular cell was assessed by TUNEL staining.

Results: Serum creatinine level peaked at 5 days after cisplatin treatment. Histologic examination revealed extensive tubular damage such as tubular epithelial cell swelling, vacuolar degeneration, and desquamation in cisplatin-treated rats. Cisplatin treatment also increased the number of TUNEL-positive apoptotic cells at day 5, P α injection significantly suppressed cisplatin-induced AKI and apoptosis of tubular cells.

Conclusions: We showed the renoprotective effect of ProTa-derived hexapeptide against cisplatin-induced AKI via suppression of apoptosis. Our results suggest that ProTa-derived hexapeptide may become a preventive drug for cisplatin-induced AKI.

SA-PO160
Ir8 Regulated by DNA Methylation Contributes to Cisplatin-Induced Acute Kidney Injury Chunyuan Guo,1,2 Xiao Xiao,1,2 Qingjing Wei,1,2 Huidong Shi,1,2 Zheng Dong,1,2 1Dept of Cellular Biology and Anatomy, Augusta Univ, Augusta, GA; 2Cell Lineage Research Center, Augusta, GA; 1Dept of Biochemistry and Molecular Biology, Augusta Univ, Augusta, GA.

Background: Acute kidney injury (AKI) is a major side effect of cisplatin chemotherapy in cancer patients. The pathogenesis of cisplatin-induced AKI remains largely unclear. This study was designed to determine the role of DNA methylation in cisplatin-induced AKI and identify the specific genes regulated by DNA methylation.

Methods: Reduced representation bisulfite sequencing (RRBS) was performed to determine the genome-wide DNA methylation changes in cisplatin-induced AKI. We also examined the effects of the DNA methylation inhibitor–5-aza-2′-deoxycytidine
(5-aza) on cisplatin-induced AKI in vitro. Furthermore, we determined the involvement of specific genes, such as Irf8, with methylation changes in cell culture model of kidney tubular cell injury.

**Results:** The genome-wide DNA methylation analysis showed aberrant DNA methylation alterations in cisplatin-induced AKI. DNA methylation inhibitor 5-aza sensitized RPTC cells to cisplatin-induced apoptosis. To identify the key genes regulated by DNA methylation which are involved in cisplatin-induced AKI, we analyzed the genome-wide DNA methylation data and found Irf8 showed hypomethylation at 5' UTR. This hypomethylation was associated with a marked increase of Irf8 expression in both mRNA and protein levels in cisplatin-induced AKI. Moreover, in RPTC cells, inhibition of DNA methylation by 5-aza upregulated Irf8 expression with or without cisplatin. And silencing Irf8 in RPTC cells inhibited cisplatin-induced apoptosis.

**Conclusions:** These results suggest that DNA methylation plays an important role in cisplatin-induced AKI by regulating specific genes, such as Irf8.

**Funding:** NIDDK Support, VA Support

**SA-PO161**

**Mechanisms of Decreased Acute Kidney Injury (AKI) and Decreased Tumor Growth by Mitogen-Activated Extracellular Signal-Regulated Kinase (MEK) Inhibition**

**Kameswaran Ravichandran,** Aklesh Juni, Raphael A. Nemenoff, Charles L. Edelstein.

**Univ Colorado Denver.**

**Background:** The pathogenesis of cisplatin (Cis) AKI involves the MEK/ERK pathway. The MEK inhibitor U0126 blocks ERK activation. The effect of U0126 on AKI and tumor growth was determined in a 4 wk model of cisplatin AKI in tumor bearing mice.

**Methods:** Mice were injected with lung cancer cells. 10 days later, Cis (10 mg/kg/wk) and U0126 (5 mg/kg 2X/wk) were given for 4 wks. RIP3, a marker of necroptosis, cleaved caspase-3 (CC-3), a marker of apoptosis, PD-L1, an immune system suppressor, p-INK and p-ERK (MAPK signaling) were measured by immunoblot. MAPK signaling RT² Profiler™ PCR Array was used to profile genes in the kidney.

**Results:** U0126 resulted in a significant decrease in BUN, SCr in mice with or without tumor. In kidney, U0126 protected against AKI despite increasing RIP3. ERK regulated cell cycle genes specifically cyclins, cyclin-dependent kinases (Cdk) and Cdk inhibitors were up to 78-fold increased by Cis and reduced by U0126. U0126 decreased tumor weight, potentiated the effect of cisplatin, increased CC-3, decreased p-ERK and p-INK, had no effect on PD-L1 in tumor.

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>No cancer BUN</th>
<th>No cancer SCr</th>
<th>Cancer BUN</th>
<th>Cancer SCr</th>
<th>Kidney RIP3</th>
<th>Tumor wt (g)</th>
<th>Tumor PD-L1</th>
<th>Tumor p-INK</th>
<th>Tumor p-ERK</th>
<th>Kidney gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeh/10 U0126</td>
<td>29</td>
<td>.14</td>
<td>27</td>
<td>1</td>
<td>+</td>
<td>1.8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Fold increase by Cis</td>
</tr>
<tr>
<td>Cis</td>
<td>23</td>
<td>.12</td>
<td>27</td>
<td>.1</td>
<td>++</td>
<td>1.0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Fold decrease by U0126</td>
</tr>
<tr>
<td>Cis+U0126</td>
<td>33 *</td>
<td>25 *</td>
<td>50 *</td>
<td>3 *</td>
<td>+++</td>
<td>.9 *</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>**P&lt;0.05 vs. Vehicle; **P&lt;0.05 vs. Cis</td>
</tr>
</tbody>
</table>

**Conclusions:** The effect of U0126 to decrease AKI and tumor growth is independent of the presence of tumor. In kidney, U0126 increased RIP3 and the large increase in gene expression of cell cycle proteins regulated by ERK was decreased by U0126. Cell cycle proteins regulated by ERK signaling in AKI and cancer merits further study.

**Funding:** VA Support

**SA-PO162**

**Doxycycline Ameliorates Cisplatin-Induced Nephrotoxicity in Mice Through Directly Acting on Proximal Tubular Cells and Promoting Cell Viability**

**Terumasa Nakagawa,**1 Yutaka Kakizoe,2 Naoki Suena,1 Yuki Narita,3 Yoshikazu Miyasato,1 Teruhiko Mizumoto,1 Manabu Hayata,1 Yuichiro Izumi,2 Takashige Kusawara,1 Masataka Adachi,1 Hirofumi Jono,1 Hideyuki Saito,1 Kenji Hori,1 Katamura,2 *Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; Internal Medicine III, Univ of Yamanashi School of Medicine, Yamanashi, Japan; Clinical Pathological Sciences, Kumamoto Univ Graduate School of Pharmaceutical Sciences, Kumamoto, Japan.

**Background:** Cisplatin (CDDP) is a widely used anticancer agent but its use is sometimes limited by nephrotoxicity. We reported in Kidney Week 2015 that doxycycline (Dox) suppressed CDDP-induced acute kidney injury in mice through its anti-inflammatory, anti-oxidative and enzyme-inhibiting effects. In this study, in order to further explore the mechanism, we investigated the effect of Dox on the accumulation of CDDP in kidney tissue. Furthermore, we studied whether Dox attenuates cell injury caused by CDDP using cultured renal tubular cells.

**Methods:** C57BL/6J mice were divided into three groups: 1) Control, 2) CDDP (20mg/kg, intraperitoneally) and 3) CDDP+Dox (2mg/ml in drinking water). 7 days later, pretreatment of Dox, CDDP was administered, and animals were sacrificed 24 hr later. The amount of platinum in the kidney tissue was measured by ICP-MS. Next, after cultured proximal tubular cells (NRK52E) were treated with CDDP and Dox, cell viability (WST-1) and mRNA expressions of cell injury markers were assessed.

**Results:** Renal accumulation of CDDP was not inhibited by treatment with Dox (CDDP:21.16±1.1 vs CDDP+Dox:21.5±1.2mg/g tissue), indicating that Dox may not affect pharmacokinetics of CDDP but exert protective effects by inhibiting detrimental reactions caused by CDDP within tubular cells. In NRK52E cells, CDDP reduced cell viability and induced mRNA expressions of IL-6, MCP-1, p67phox and Fas. These changes were mitigated significantly by treatment with Dox.

**Conclusions:** Dox suppressed CDDP-induced nephrotoxicity not only through inhibiting CDDP accumulation but through directly attenuating detrimental reactions within tubular cells, suggesting that Dox could become a potential therapeutic strategy against CDDP-induced nephrotoxicity.

**SA-PO163**

**Exacerbated Cisplatin-Induced Renal Injury in NHERF1 KO Mice Is Associated with NF-E2 Regulation**

**Sanjana Rane,** Shunying Jin, Caryl Conklin, Michelle T. Barat, Kenneth Gagnon, Eleanor D. Lederer, Madhavi J. Rane, Eleanor D. Lederer. Medicine, Univ of Louisville.

**Background:** Cisplatin, an effective chemotherapeutic drug, is highly nephrotoxic, limiting its use. Cisplatin toxicity is associated with acrolein accumulation in the cytosol of damaged renal tubules, yet the precise mechanisms underlying these events are unknown. Acrolein is known to modulate sodium-phosphate co-transport in renal cells, of which sodium-hydrogen exchange regulatory factor 1 (NHERF1) is a key mediator. Preliminary studies demonstrate renal regulation of Nuclear Factor Erythroid-derived 2 (NF-E2) by acrolein. Therefore, we hypothesized that mice treated with cisplatin induces kidney damage and fibrosis by modulating NF-E2 expression in a NHERF1-dependent manner.

**Methods:** Wild-type (WT) and NHERF1 knockout (NHERF1 KO) mice were mice were treated with saline or cisplatin (20 mg/kg body weight) and sacrificed after 72 hours. Kidney homogenates and plasma samples were immunoblotted with appropriate antibodies. Kidney tissue sections were subjected to H&E staining and NF-E2 immunohistochemistry.

**Results:** Renal NF-E2 expression decreased in NHERF1 KO mice, compared to WT mice, which decreased further after cisplatin treatment, while cleaved-Cas-3 and Connective Tissue Growth Factor (CTGF) expression increased further. Cisplatin treatment resulted in loss of NF-E2 expression from the renal brush-border membrane in WT mice kidneys which was decreased further in cisplatin treated NHERF1 KO mice. Interestingly, NF-E2 was detected in the plasma of NHERF1 KO mice which was enhanced further after cisplatin treatment. Furthermore, NHERF1 KO mice were sensitized to more renal damage after cisplatin treatment compared to WT mice.

**Conclusions:** NHERF1 expression regulates intracellular and extracellular NF-E2 expression. Thus, NF-E2 could serve as a biomarker of AKI alleviating need for biopsies. NHERF1 could serve as a therapeutic target to modulate NF-E2 expression and treat AKI halting its progression to ESRD, in addition to potentially blocking cisplatin’s nephrotoxic effects.

**Funding:** Other NIH Support - NIAID R01AI075212, VA Support
MAP3K14 Promotes Acute Kidney Injury

MAP3K14 targets in tubular cells, thus identifying potential mediators of the deleterious effect of kidney injury.

MAP3K14 activity-deficient aly/aly mice revealed RelB/NFkB2, and proteins involved in NFkB2 p100 ubiquitination and proteasomal degradation. Data are mean±SEM.

MI+RC (intrafemoral iopamidol 2.9g/kgBW iodine, n=15), MI+4F (10 mg/kgBW i.p. 4F, n=15). MI+RC+4F reduced LDL oxidation.

Hypercholesterolemia decreases nitric oxide availability, aggravating myocardial infarct size. Apolipoprotein A-I Protects against Post-Myocardium Infarct Cell Injuries in Murine Renal Ischemia Reperfusion and Cisplatin Induced Nephropathy.

Background: Contrast-Induced acute kidney injury (CI-AKI) is a common adverse effect in patients with chronic kidney disease. CI-AKI promotes renal vasoconstriction, hypoxia, activation of inflammatory cascade, oxidative cell damage and impaired renal function. This study evaluated the renoprotection of resveratrol (RSV), a polyphenol with vasodilating and anti-inflammatory properties in nephrectomized rats treated with iodinated contrast (IC).

Conclusions: Association between chronic kidney disease with CI-AKI predisposes to severe kidney injury. Resveratrol ameliorates renal function in CI-AKI by modulating renal hemodynamics in Nx rats.

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

SA-PO165

Apolipoprotein A-I Protects against Post-Myocardium Infarct Radiocontrast-Induced Acute Kidney Injury

Background: Contrast-Induced acute kidney injury (CI-AKI) is a common adverse effect in patients with chronic kidney disease. CI-AKI promotes renal vasoconstriction, hypoxia, activation of inflammatory cascade, oxidative cell damage and impaired renal function. This study explored the renoprotection of resveratrol (RSV), a polyphenol with vasodilating and anti-inflammatory properties in nephrectomized rats treated with iodinated contrast (IC).

Conclusions: Association between chronic kidney disease with CI-AKI predisposes to severe kidney injury. Resveratrol ameliorates renal function in CI-AKI by modulating renal hemodynamics in Nx rats.

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

SA-PO168

Indole Analog MA-5 Protects against Contrast-Induced Renal Injury

Background: Contrast-induced nephropathy (CIN) is the most common cause of the iatrogenic and drug-induced kidney injury, but the therapeutic procedures have not been established. The renal hypoxia and the direct toxic effects of contrast media on renal tubular cells are postulated as the pathophysiologic mechanisms of CIN. Recently we reported mitochondria-targeted indole-derivative mitochondrial acid-5 (MA-5) increased intracellular ATP, decreased mitochondrial ROS and improved cell survivals of fibroblasts form mitochondrial disease patients. MA-5 also improved the renal function and tubular cell injuries in murine renal ischemia reperfusion and cisplatin induced nephropathy models. The aim of this study is to examine the protective effects of MA-5 on CIN (Suzuki T. JASN 2015).

Methods: Immunolabeled human proximal tubular cell line HK-2 cells were cultured to 80% confluence and MA-5 10μM final concentration for 24h without serum and then added radiocisternal sodium diatrizoate, Iopamidol and iohexol at 75mg iodine/ml for another 1h. Cell viability and cytotoxicity were assessed by WST-8 assay and LDH assay respectively. Male CD-1 cell, Body weight 30-35g were left-nephrectomized (Nx) and MA-5 was administered, at 50mg/kg body weight by gavage, to mice 2hr before they injected with an inhibitor of prostaglandin synthesis (indomethacin, 10 mg/kg) intraperitoneally before iohexol (300 mg iodine/ml, 2 g iodine/kg ) intravenously injection. 24hr after iohexol injection, mice were sacrificed, serum creatinine (Cr), urinary Neutrophil gelatinase-associated lipocalin (NGAL) and renal pathology were examined.

Results: MA-5 improved cell viabilities and reduced injured cell derived LDH activity in culture medium in Sodium diatrizoate, Iopamidol and iohexol treated HK-2 cells. Serum Cr at 24hr after iohexol injection was not significantly different between MA-5 and control group. Urinary NGAL was significantly decreased in MA-5 treated animals compared to vehicle gavage mice.

Conclusions: MA-5 exhibited improved viability in contrast medium treated HK-2 cells as well as reduced renal injury marker NGAL in CIN model mice. MA-5 might have the therapeutic potency on CIN.

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

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

Underline represents presenting author.

668A
Methods: Plasma and urinary U1 were measured by RIA, neutrophil gelatinase-associated lipocalin (NGAL) and retinol-binding protein 4 (RBP4) were measured by ELISA, immunohistochemistry and western blot were conducted on the kidney tissues of CIN with U1 receptor gene knock-out mice (KO-CIN) , CIN with wild type mice (WT-CIN), and wild type control mice. Apoptosis of renal cells were detected by TUNEL methods.

Results: Plasma creatinine was significantly increased in WT-CIN group and KO-CIN group in comparison to control group; however, plasma creatinine was significantly lower in KO-CIN group than in WT-CIN. Renal U1 expression, urinary U1, NGAL and RBP4 significantly increased in WT-CIN and KO-CIN group in comparison to normal control, whereas NGAL and RBP4 levels were significantly decreased in KO-CIN than those of WT-CIN. Apoptosis is increased in renal tubular epithelial cell in WT-CIN mice than that of normal control; however, apoptosis is inhibited in KO-CIN in comparison to WT-CIN mice. Expression of LC3-II is increased and P62 is reduced in comparison to that of the normal control, while expression LC3-I is decreased and P62 is increased in KO-CIN mice in comparison to WT-CIN.

Conclusions: U1 plays important roles in CIN and it can aggravate renal tubular epithelial cell injury. It can alleviate renal tubular epithelial cell injury in CIN if we interfere with U1 action. The mechanisms involve inhibiting apoptosis and inhibiting overactive autophagy of renal tubular epithelial cells.

SA-PO169
Thymoquinone Prevents Contrast-Induced Nephropathy
Murat H. Sipahioglu, 1 Serkan U. Topaloglu, 1 Cevat Yazici, 1 Cagri Sakalar, 1 Ismail Kocyigit, 1 Aydin Uнал, 1 Sedat Sezen, 1 Bulent Tokgoz, 1 Oktay Oymak. 1
1Nephrology, Erciyes Univ, Kayseri, Turkey; 2Biochemistry, Erciyes Univ, Kayseri, Turkey.

Background: Thymoquinone (TQ), the main constituent of the volatile oil from Nigella sativa seeds, is reported to possess strong anti-oxidant and anti-inflammatory properties. Pathophysiology of contrast induced nephropathy (CIN) associates multiple factors such as renal vasoconstriction, oxidative stress and increased inflammatory responses. In view of this, we hypothesized that TQ can attenuate renal injury in the rat experimental contrast induced nephropathy (CIN) model.

Methods: CIN was induced by injection of the radiocontrast medium diatrizoate in addition to inhibition of prostaglandin and nitric oxide (NO) synthesis after 2 days of water deprivation. Rats were divided into 7 groups: control (C), L-NAME+ INDO (NG-nitro-L-arginine+ indomethacin), contrast media (CM), TQ (1 mg/kg/day), TQ 1.75 (1.75 mg/kg/day), TQ+CM, TQ 1.75+CM. TQ was given at two different doses (1 or 1.75 mg/kg/day) for 4 days intraperitoneally before the contrast injection.

Results: Administration of 1 mg dose of TQ significantly attenuated the resulting renal dysfunction and inflammatory process (table 1) and histologic renal injury in the light microscopy.

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>L-NAME+INDO</th>
<th>CM</th>
<th>TQ1</th>
<th>TQ1.75</th>
<th>TQ1+CM</th>
<th>TQ1.75+CM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.3±0.03</td>
<td>0.56±0.27</td>
<td>2.03±0.28</td>
<td>0.29±0.02</td>
<td>0.28±0.02</td>
<td>0.41±0.06</td>
<td>2.23±0.08</td>
<td>0.004</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td></td>
<td></td>
<td>70.7±6.3</td>
<td>9.7±1.4</td>
<td>6.7±4.7</td>
<td>9.7±0.6</td>
<td>1.9±8</td>
<td>2.12±0.6</td>
</tr>
<tr>
<td>NF-KB expression</td>
<td></td>
<td></td>
<td>100±10</td>
<td>100±10</td>
<td>100±10</td>
<td>100±10</td>
<td>100±10</td>
<td>100±10</td>
</tr>
<tr>
<td>iNOS expression</td>
<td></td>
<td></td>
<td>100±10</td>
<td>100±10</td>
<td>100±10</td>
<td>100±10</td>
<td>100±10</td>
<td>100±10</td>
</tr>
</tbody>
</table>

Serum malondialdehyde and superoxide dismutase levels did not show any significant difference between the groups.

Conclusions: This study suggests that administration of thymoquinone may have potential as a new therapeutic approach to prevent CIN.

SA-PO170
Megalin Blockade with Cilastatin Suppresses Drug-Induced Nephrotoxicity
Shou Kawahara, 1 Michihiro Hosojima, 1 Ryouhei Kaseda, 1 Sawako Goto, 1 Tomomichi Iida, 1 Akhikko Saito, 1 Applied Medical Medicine, Niigata Univ, Niigata, Japan; 2Clinical Nutrition Science, Niigata Univ, Niigata, Japan; 3Clinical Nephrology and Rheumatology, Niigata Univ, Niigata, Japan.

Background: Nephrotoxicity induced by anti-microorganism or anti-cancer drugs is a serious clinical problem. Megalin, an endocytic receptor expressed at the apical membranes of proximal tubules, mediates the nephrotoxicity of aminoglycosides (AGs) and colistin (CLT), which are key antimicrobials for multidrug-resistant organisms. The mechanisms underlying the nephrotoxicity induced by vancomycin (VCM), an antibiotic for methicillin-resistant Staphylococcus aureus, and cisplatin (CDDP), an important anti-cancer drug, are unknown, but the nephrotoxicity of these drugs and of gentamicin (GM), an AG, is known to be suppressed experimentally with cilastatin (CS), which was developed originally to inhibit megalin-mediated nephrotoxicity with CLT, VCM, and CDDP. We used quartz-crystal microbalance (QCM) analysis to examine the binding of these drugs to megalin in the presence or absence of CS. Kidney-specific mosaic models were used to investigate megalin-mediated nephrotoxicity with CLT, VCM, and CDDP. C57BL/6J mice were used to analyze the suppression of CLT-induced nephrotoxicity by CS. We performed agar disk diffusion analysis to assess whether CS affects the anti-bacterial activity of GM, VCM, and CDDP.

Results: QCM analysis revealed that megalin is also bound by VCM and CDDP, and that the binding of GM, CLT, VCM, and CDDP to megalin is competed with CS. In addition, the nephrotoxicity induced by CLT, VCM, and CDDP was found to depend on megalin expression in the proximal tubules. CLT-induced nephrotoxicity in C57BL/6J mice was suppressed by concomitant CS administration. CS did not inhibit the anti-bacterial activity of GM, CLT, and VCM in vitro, just as CS was previously found not to affect the anti-cancer activity of CDDP.

Conclusions: Megalin blockade with CS efficiently suppressed the nephrotoxicity induced by GM, CLT, VCM, and CDDP.

Funding: Government Support - Non-U.S.

SA-PO171
Reduced Glomerular Number in a Juvenile Rabbit Model of AKI Detected by MRI
Jennifer R. Charlton, 1 Edwin Baldelemon, 1 Valeria M. Pearl, 1 Kevin M. Bennett. 1 University of Virginia; 2Univ of Hawaii.

Background: There is a strong association between low nephron endowment and CKD. MRI techniques have made it possible to measure whole-kidney glomerular endowment (Nglomer) and volume (Vglomer) in the intact kidney, revealing pathology not detected by traditional biomarkers. Here we applied cationic ferritin enhanced-MRI (CFE-MRI) to investigate nephron loss from acute kidney injury (AKI) in a juvenile rabbit model.

Methods: New Zealand rabbits received 4 days of indomethacin (5 mg/kg) and gentamicin (100 mg/kg) during nephroprotection at 1 wk of life. At 6 wks the AKI and controls received horse CF (1.92 mg/100 g BW, n=3/group). Ninety minutes after the injection, the animals were euthanized. Images of intact kidneys were acquired with a 7T ClinScan (gradient echo: TE/TR: 80/20, 3 averages, resolution: 59x59x200 microns, slice thickness: 170 µm). Nglomer and Vglomer were determined using custom software.

Results: The AKI group weighed less than controls (diff: 655 g, p=0.004) and there was no difference the serum creatinine between the groups at 6 wks. Median Nglomer by CFE-MRI in the AKI group was 100,932.5 (75,726-127,783) and in the controls median Nglomer was 191,652 (138,417-251,180).

Conclusions: CFE-MRI was used to detect glomerular morphology in the intact juvenile kidney. Induced AKI in neonatal rabbits causes a significant decrease in Nglomer but no observed change in Vglomer over 6 weeks of age, possibly due to the short duration from injury to evaluation. AKI in rabbits, induced by common medications and monitored through noninvasive MRI, provides an important model to study the impact of AKI on renal development later in life.

SA-PO172
Ferreptosis, but Not Necroptosis, Plays an Important Role in Nephrotic Folic Acid Induced Acute Kidney Injury
Diego Martin-Sánchez, 1 Olga Ruiz Andrés, 1 Jonay Poveda, 1 Susana Carrasco, 1 María D. Sanchez-Niño, 1, 2 Marta Ruiz-Ortega, 1 Jesús Egido, 1, 2 Andreas Linkermann, 1 Alberto Ortiz, 1 Ana Bellen Sang, 1, 2 Div of Nephrology, BF- Fundación Jiménez Díaz, Madrid, Spain; 1Nephrology, School of Medicine, Autonoma Univ, UAM, Madrid, Spain; 2Clinic for Nephrology and Hypertension, Christian-Albrechts-Univ Kiel, Kiel, Germany.

Background: Acute kidney injury is characterized by necrotic cell-death and inflammation. Diverse pathways of regulated necrosis have been reported to contribute to AKI but there is no agreement on the molecular regulators involved. We explored the contribution of ferroptosis and necroptosis to folic acid (FA) AKI in mice. FA-AKI in mice is associated with lipid peroxidation and downregulation of glutathione metabolism proteins, features that are typical of ferroptotic cell death.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We induced AKI with an overdose of folic acid in wild type, RIP3K-KO and MLKL-KO mice. Renal function was measured by plasma creatinine and BUN levels. Protein studies were assessed by western blot and immunohistochemistry, mRNA analyzing by real-time PCR. For cell death detection we used TUNEL.

Results: We demonstrate that ferrostatin-1 (Fer-1), an inhibitor of ferroptosis, preserved renal function and decreased histological injury, oxidative stress and tubular cell death in this model. With respect to the immunogenicity, we demonstrate that Fer-1 prevented the upregulation of IL-33, an alarm that is linked to necroptosis, and other chemokines and cytokines, as well as macrophage infiltration, suggesting that Fer-1 prevents renal inflammation by inhibiting necroptosis. By contrast, the non-caspase inhibitor VAD-fmk was not protective. Additionally, although FA-AKI resulted in increased protein expression of the necroptosis mediators RIP3K and MLKL, targeting necroptosis with the RIPK1 inhibitor necrostatin-1, or genetic deficiency of RIPK3 or MLKL did not prevent renal injury. MLKL KO mice displayed more severe AKI. By contrast, inflammation was milder in RIPK1 KO mice.

Conclusions: These data suggest that ferroptosis is the primary cause of FA-AKI, and that immunogenicity secondary to ferroptosis may further worsen the damage, while necroptosis related proteins may play additional roles in AKI.
The Renoprotective Effect of 5-Aminolevulinic Acid in Murine Rhabdomyolysis-Induced Acute Kidney Injury Is Independent of Heme Oxygenase-1 Activation

Atsushi Uchida, Minoru Satoh, Tamaki Sasaki, Naoki Kashihara. Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.

Background: Rhabdomyolysis often occurs after severe skeletal muscle injury, and high morbidity and mortality have been reported for the acute kidney injury (AKI). 5-aminolevulinic acid (ALA) is the naturally occurring metabolic precursor of heme and serves as a protein material related to energy production. A previous study showed that ALA has the potential to prevent cisplatin-induced AKI via induction of heme oxygenase. In the present study, we investigated if ALA has renoprotective effects in another model of acute kidney injury, rhabdomyolysis-induced AKI.

Methods: Male C57Bl/6 mice were used. Mice were subdivided into 4 groups: (1) control group, (2) Rhabdomyolysis group, (3) Rhabdomyolysis+ ALA group, and (4) Rhabdomyolysis+ ALA+ ZapPβX (HO-1 inhibitor) group. Rhabdomyolysis-induced AKI was caused by intramuscular injection of glycerol. ALA and ZapPβX were administered each day at 48 h before glycerol administration. These mice were euthanized 72 h after glycerol injection, and the blood and renal tissues were collected.

Results: Serum creatinine, blood urea nitrogen, and urine neutrophil gelatinspecific alcinor excretion increased in the Rhabdomyolysis group compared to that in the control group. ALA significantly attenuated these changes. ALA also ameliorated glycerol-induced morphological tubular damage. Excretion of urinary 8-hydroxy-2'-deoxyguanosine, an oxidative stress marker, was suppressed by ALA. ALA significantly attenuated macrophagic infiltration and expression of proinflammatory cytokines. Notably, these changes did not disappear in the Rhabdomyolysis+ ALA+ ZapPβX group.

Conclusions: ALA has a renoprotective effect and prevents tubular injury in rhabdomyolysis-induced AKI. It is already used for tumor diagnosis and fluorescence-guided minimally invasive surgery. Therefore, the safety and efficacy of this drug has been proven in clinical practice. ALA treatment may be a new therapeutic target in rhabdomyolysis-induced AKI, but the mechanism is independent of HO-1. The renoprotective mechanisms of ALA in AKI should be elucidated.

SA-PO178

Quantitative Phosphoproteomic Analysis of Rat Renal Cortical Tubules in Response to Phospholipase A2 from Russell’s Viper Venom

Kavee Limbutara, 1,2 Poohrichaya Somparrn, 1 Narumol Pakmanee, 2 Lawan Chanhom, 3 Orawan Khon, 2 Narongsak Chaiyabun, 3 Visith Siptiraj, 3 Khumjai Rattanapan, 3 Petcharat Maneerat. 1,3 Department of Nephrology, Medicine, Chulalongkorn Univ, Thailand; 2 Systems Biology Center, Faculty of Medicine, Chulalongkorn Univ, Thailand; 3 Queen Saovabha Memorial Inst, The Thai Red Cross Society, Thailand.

Background: Russell’s viper is a medically important snake causing multiple effects and high morbidity and mortality have been reported for the acute kidney injury (AKI). Phospholipase A2 from Russell’s viper venom (RVV) and possibly mediates the nephrotoxicity. The Thai Red Cross Society, Thailand.

Methods: The aim of this study is to clarify mTORC1-S6 kinase pathway involvement in the development of glomerulosclerosis in human IgA nephropathy. First, 12 human IgA nephropathy cases derived from three men and nine women aged 15 to 63 years (mean ± SD, 32.8 ± 16.9 years) were analyzed. Immunohistochemistry of phosphorylated ribosomal protein S6 (phospho-rpS6) (a surrogate marker of mTORC1-S6 kinase pathway) was performed. Next, mesangium-specific mTORC1 activation was induced by ablation of an upstream negative regulator, Tuberous sclerosis complex 1 (TSC1), using tamoxifen-induced Foxd1-Cre mice to clarify the role of mTORC1-S6 kinase pathway in the development of glomerulosclerosis.

Results: Phospho-rpS6 was detected in mesangial area of human IgA nephropathy. Mesangium-specific TSC1 ablation in mice (MsKOTSC1) caused rpS6 phosphorylation in mesangial area confirmed by immunohistochemistry and westernblot analysis. MsKOTSC1 showed IgA nephropathy features, including the increase of collagen IV accumulation at 12 weeks of age and collagen I and alpha smooth muscle actin upregulation at 1 year of age in glomeruli. However, MsKOTSC1 did not exhibit significant albuminuria. Furthermore, mesangium-specific mTORC1 activation by ablation of an upstream negative regulator, Tuberous sclerosis complex 1 (TSC1), using tamoxifen-induced Foxd1-Cre mice to clarify the role of mTORC1-S6 kinase pathway in the development of glomerulosclerosis.

Conclusions: Mesangium-specific mTORC1-S6 kinase pathway activation could develop glomerulosclerosis in mesangial area, which mimics human IgA nephropathy. However, the activation of mTORC1-S6 kinase pathway was not enough to cause albuminuria. Mesangium-specific Cre-Ioxp system is useful to clarify the mechanism of human IgA nephropathy.

Funding: Government Support - Non-U.S.

SA-PO181

Vitamin D Receptor Contributes to Disparate Effects during the Initiation and Progression of HIV-Associated Nephropathy (HIVAN)

Xiqian Xiang, 1,2 Waqar Khawar, 1,2 Manoj K. Temhrab, 1,2 Judith Eng, 1,2 Seyed Shadafarin Marashi Shohistari, 1,2 Hanan K. Tawadrous, 1 Anil K. Mongolia, 1 Ashwani Malhotra, 1 Pravin C. Singhal. 1 Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; 2 Pediatrics, Down State Medical Center, Brooklyn, NY.

Background: Renin angiotensin system plays a role in the progression of HIV-associated nephropathy (HIVAN). Since angiotensinogen (Agt) is a substrate for renin, we hypothesized that mice with enhanced expression of Agt would display an enhanced progression of HIVAN. We evaluated the effect of different copies of Agt in the initiation and progression of renal lesions in genetically engineered HIVAN mice (tg26/Tg26). Methods: Control and Agt mice with 2 (Tg26/Agt-2/2) and 4 (Tg26/Agt-4/4) copies of Agt were evaluated for severity of renal lesions, arteriosclerosis and hypertension at 8 weeks and 16 weeks. Renal cortical sections were stained with Sirius red and PAS. RNA was extracted from renal tissues and probed for AT1, AT2, PAI-1, VDR, and molecules of interest. Results: Tg26/Agt-2/2 showed higher blood pressure vs. Tg26/Agt-4/4 wks. Tg26/Agt-4/4 wks displayed attenuated expression of PAI-1 vs. Tg26/Agt-2/2 wks.; however, Tg26/Agt-4/4 wks showed 3-fold greater PAI-1 expression than to Tg26/Agt-2/4 wks.

Funding: Government Support - Non-U.S.
To identify the significance of autophagy in lupus nephritis (LN), we counted the number of autophagosomes in podocytes and evaluated the expression of multiple molecular markers associated with autophagy in LN specimens.

**Background:** To define the significance of autophagy in lupus nephritis (LN), we counted the number of autophagosomes in podocytes and evaluated the expression of multiple molecular markers associated with autophagy in LN specimens.

**Methods:** Autophagosomes in podocytes were counted using transmission electron microscopy. Beclin-1, microtubule-associated protein light chain 3 (LC3), autophagy-related gene 7 (Atg7), and UNC-51-like kinase 1 (ULK1) expression levels were measured using immunohistochemistry in renal biopsy specimens from 90 patients with LN and 15 healthy controls.

**Results:** The number of autophagosomes in patients with LN types III, IV, and combined V-IV type were significantly higher than in controls (p<0.0001; p=0.0001; p=0.0009, respectively). However, expression patterns were reversed at 16 wks. Tg26/Agt-2/8wks displayed attenuated expression of AT1 and AT2 and down regulation of Tert, TGF-β, Snail, and vimentin when compared to Tg26/Agt-2/8wks. However, all these markers were comparable between these groups at 16 wks of age. Tg26/Agt-2/8wks developed renal lesions which were more advanced than Tg26/Agt-4/8wks. Conversely, Tg26/Agt-4/16wks displayed more advanced renal lesions vs. Tg26/Agt-2/16wks.

**Conclusions:** VDR dynamics determined the initiation and acceleration of renal lesions in Tg26/Agt-1 and Tg26/Agt-2 mice both at early and later time periods.

**Funding:** NIDDK Support

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**SA-PO184**

**Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) Is Required for Regulated Protein Degradation Through the Ubiquitin Proteasome System in Murine Kidneys in Health and Immune-Complex Nephritis**

**Background:** UCH-L1 is a major deubiquitinating enzyme of the nervous system. In the human kidney, UCH-L1 is expressed in tubular and parietal epithelial cells and in the setting of glomerulonephritis UCH-L1 is upregulated in the tubular compartment and de novo expressed in podocytes. Biochemically, UCH-L1 is thought to regulate the intracellular pool of monoubiquitinated, required for ubiquitinatation procedures. Nothing is known about the significance of UCH-L1 in the kidney in health and disease.

**Methods:** We generated constitutive UCH-L1-deficient mice which were phenotypically characterized by histological and biochemical assays. Anti-podocyte antibodies (APN), an immune-complex glomerulonephritis, was induced by injection of anti-podocyte antibodies and clinical and morphological disease development was monitored.

**Results:** Naïve UCH-L1-deficient mice developed systemic hypotension and urine retention in the bladder due to over-all neurodegeneration. The renal and glomerular pool of polyubiquitinated and of oxidative-modified proteins was increased. Simultaneously, prostasomal activity was decreased and the balance between the 26S and the 19S proteasomal content was altered in both whole kidney and in isolated glomeruli.

**Conclusions:** UCH-L1-deficient mice developed proteinuria and podocytes showed signs of stress despite an inconspicuous overall glomerular morphology. Induction of APN in wild-type mice demonstrated that similarly to human glomerulonephritis, UCH-L1 is up-regulated in tubular cells and in glomerular cells such as podocytes and endothelial cells. UCH-L1-deficient mice exhibited an exacerbated course of disease with increased tubulointerstitial and glomerular damage and nephrotic syndrome. UCH-L1-deficient mice failed to upregulate the proteolytic effective 26S proteasome resulting in decreased prostasomal activity and accumulation of oxidative-modified and of K48-polyubiquitinated proteins in whole kidney and glomeruli.

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

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**SA-PO185**

**Evaluation of DLK1 Absence in Unilateral Ureteral Obstruction Model**

**Background:** The Notch signaling molecular pathway is involved in kidney embryonic development. Notch expression is virtually absent in adult human kidneys, whereas overexpression of ligands and receptors have been described in many human chronic renal diseases. There are several non-canonical Notch ligands that can activate or inhibit Notch signaling. The non-canonical ligand DLK1 (Delta-like homologue 1) has been suggested as a Notch inhibitor in Drosophilia and mammal cells in vitro, regulating several processes, including adiopogenesis, differentiation and angiogenesis. However, its role in renal injury is unknown.

**Methods:** The role of DLK1 in renal damage was evaluated using a Dlk1-null mice in the model of unilateral ureteral obstruction (UUO).

**Results:** In obstructed kidneys, activation of the canonical Notch/Jagged-1 pathway was found at 2 days, determined by nuclear translocation of active Notch-1, production of Jagged-1 and increased gene expression of the effector Hes-1, as previously described. Interestingly, upregulation of the non-canonical ligands Dlk1 and DLK2 gene expression was observed after 5 days, later than Notch/Jagged-1 activation. In several tissues and pathological conditions, DLK1 deletion was associated to over-activation of the Notch pathway. However, neither control nor obstructed kidneys of Dlk1-null mice presented further renal Notch/Jagged-1 activation than wild-type mice. Only hey-1 and DLK2 gene levels were significantly elevated in Dlk1 null mice compared to wild-type. In obstructed kidneys of Dlk1-null mice a marked gene expression of renal injury biomarkers was found, but there were no significant differences compared to wild-type mice, at any time evaluated until 14 days. Moreover, there were no significant changes in inflammatory parameters or renal fibrosis between wild-type and Dlk1-null mice.

**Conclusions:** Our data suggest that Dlk1 is not acting as an endogenous Notch inhibitor, at least in the experimental model of unilateral ureteral obstruction.

**Funding:** Government Support - Non-U.S.
SA-PO186
Rapamycin Attenuates Parietal Epithelial Cell Proliferation in a Model of Collapsing Focal Segmental Glomerulosclerosis
Bart Smeets,1 Shagun Sharma,2 Jack F. Wetzels,3 Brigit Willemsen,1 Marinka Bakker-van Bebber,2 Marcus J. Moeller,1 Hendrik Dijkmans,3 Johan van der Vlag,3 Pathology, Radboud Univ Medical Center, Netherlands; 1Nephrology, Radboud Univ Medical Center, Netherlands; 2Nephrology and Clinical Immunology, RWTH, Unv. of Aachen, Germany.

Background: Th-11 transgenic mice develop glomerular lesions that mimic human collapsing FSGS. We questioned whether the mTOR inhibitor rapamycin (sirolimus) could prevent the development of these lesions and if protection is related to glomerular epithelial cell proliferation.

Methods: Anti-Thy-1.1 injected mice (day 0) were treated with sirolimus (oral gavage, 4mg/kg, qod) by day 6 to prevent the development of the glomerular lesions (early treatments from day -3 to days 4, 7, and 21). In addition, we treated mice twice after development of the collapsing FSGS lesions (late treatment from day 11 to day 31). We compared kidney function, the development of glomerular lesions and kidney cell proliferation, between sirolimus- and vehicle-treated mice. In addition, the direct effects of rapamycin on cell activity (MTT assay) and growth of mouse primary parietal epithelial cells were examined.

Results: Early treatment with sirolimus from day -3 to days 4, 7 and 21 attenuated the development of glomerular lesions, whereas, late treatment from day 11 did not. The reduced number of glomerular lesions was associated with a significantly less activation (CD44 expression) and proliferation (Ki-67) of parietal epithelial cells, at day 4 and after anti-Thy-1.1 injection. Interestingly, at these time points sirolimus treatment did not have an effect on albuminuria, blood urea nitrogen and podocyte injury reflected by the expression of desmin. In cell culture, we observed dose dependent reduction of the activity and growth of mouse primary parietal epithelial cells.

Conclusions: Inhibition of mTOR, attenuates the development of experimental collapsing FSGS. We propose that the effects are related to the ability of rapamycin to reduce parietal cell proliferation.

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

SA-PO187
Knocking Down Thymosin ß4 in Endothelial Cells Impairs Recovery after Acute Tubular Injury, with Decreased Peritubular Capillary Number and Function
Jianyong Zhang,1,2 Haichun Yang,1,2 Agnes B. Fogoly,1,2 Pathology, Microbiology and Immunology, Vanderbilt Univ Medical Center, Nashville, TN; 2Pediatric Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.

Background: Thymosin ß4 (Tß4) is a G-actin sequestering protein expressed ubiquitously, which affects cell proliferation, migration and angiogenesis. We previously demonstrated that knockdown of thymosin ß4 in endothelial cells results in decreased endothelial cell number and impaired function, which decreases recovery of tubular injury.

Methods: Tß4 expression in endothelial cells was significantly reduced in Tß4 KD vs Cont mice. Tß4 KD 1.84±0.20%, P<0.01). Dextran was infused iv, with more dextran leakage to interstitial areas in Tß4 KD than Cont mice. Tß4 KD mice had significantly higher collagen 1 (Tß4 KD 2.48±0.40 vs. Cont 1.2±0.12, P<0.05) and TFGR mRNA expression vs. Cont (Tß4 KD 1.1±1.0 vs. Cont 0.7±1.07, P<0.05), but Coll 1 protein, assessed by IHC, was not different between the groups. Urinary NGAL, a marker of tubular injury, was also higher in Tß4 KD vs Cont mice. Tß4 KD mice had significantly higher collagen I (Tß4 KD 2.48±0.40 vs. Cont 1.2±0.12, P<0.05) and NGAL expression vs. Cont (Tß4 KD 1.1±1.07 vs. Cont 0.7±1.07, P<0.05), but Coll 1 protein, assessed by IHC, was not different between the groups.

Conclusions: Inhibition of mTOR, attenuates the development of experimental collapsing FSGS. We propose that the effects are related to the ability of rapamycin to reduce parietal cell proliferation.

Funding: NIDDK Support

SA-PO188
Potassium Chloride in Hypoelectrolytic Isoosmotic Solution for Infusion Prevents an Artifact of Electron Microscopic Morphology for Fresh Renal Biopsy Specimen
Kensuke Joh. Tohoku Univ Graduate School of Medicine, Dept of Pathology, Sendai, Miyagi, Japan.

Background: Wrapping fresh kidney biopsy specimens in saline-soaked gauze in order to avoid drying of renal tissue and preservation could be the major factor of artifacts. Hypoelectrolytic isoosmotic solution for infusion (SOLDEM 3A) instead of saline for soaking gauze prevents artifacts in electron micrograph(Pathol Int 2015 Nakamura et al). Concerning an underlying mechanism,high glucose concentration for maintaining osmolality or potassium chloride lack has been reported as factors contributing to an artifact in morphology. Therefore, the purpose was to provide an evidence for a finding of preventing an artifact.

Methods: Before fixation with 2.5% GA in PB, fresh small cubes of the tissue from male mice were treated in group A(SOLDEM 3A 90 mEq/L-L-Lactate 20 mEq/L-Osmotic pressure ratio 1) or in group B(SOLDEM 3A Na 35 mEq/L-K 20 mEq/L-L-Lactate 35 mEq/L-L-Lactate 20 mEq/L-Osmotic pressure ratio 1) for 10 min or 30 min. Thereafter, the samples were processed by 1% OsO4 and embedded for observation. Each group was composed of five pieces of kidney tissue, respectively. In control group, the tissues were dropped directly into the fixative.

Results: In group A(SOLDEM 1 lacking potassium chloride), swollen endothelium and podocyte showing a dilatation of endoplasmic reticulum, mesangium showing a swollen condition, but not in group B. The border of the tubules were seen after 10 min. maceration.These findings became prominent after 30 min. maceration. Foot processes were relatively preserved.In group B(SOLDEM 3A with potassium chloride), no abnormal findings,which were identical with those of control group, were seen after 10 min. and 30 min. maceration.

Conclusions: Since ATP driven sodium potassium pump link the export of sodium and import of potassium ions from the cell and their respective electrochemical gradients,we suspect that a buffer containing potassium can help the maintenance of morphological architecture of the specimens, even after a cessation of the ion pump due to a removal of the tissue from the body.

SA-PO189
Hyaluronidase Treatment Blocks the Glomerular Homing of Memory T Cells and Improves Proteinuria and Survival Rate in the NZM Mouse Model of Lupus Nephritis
Hiroaki Kaduya1, Chaum O. Jacob,2 Janos Peti-Peterdi,3 1Physiology and Biophysics, Univ of Southern California, Los Angeles, CA; 2Medicine/Rheumatology, Univ of Southern California, Los Angeles, CA.

Background: Lupus Nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus. The exact pathomechanism of LN has been elusive, and therefore current non-specific therapies are limited to general immunosuppression. The present study aimed to test the hypothesis that an interplay between cellular components of the immune system (activated memory T cells) and local kidney fibrosis (the CD44 ligand hyaluronic acid (HA) in the glomerular endothelial glyocalyx) is critically important in the glomerular homing of T cells, and therefore in the development and potential therapy of LN.

Methods: Intravital imaging with serial multiphoton microscopy (MPM) was used to track the fate of exogenous FACS sorted spliced activated memory T cells (10+10 cells) injected iv, or endogenous T cells labeled with anti-CD3 and anti-CD44 antibodies in vivo in New Zealand mixed (NZM) mice.

Results: In glomerular size, sclerosis and albuminuria were significantly increased at 4 weeks old NZM mice compared with control healthy mice. Activated memory T cells (the vast majority of all immune cells found in LN kidney) homed into affected glomeruli in LN mice and in a model of endothelial dysfunction (two weeks after L-NAMETreatment and on high salt diet), but not into healthy kidneys. On average, we observed 30-40 CD44+CD44+ T cells perglomerulus sticking to endothelial cells within glomerular capillaries of LN mice, but not in control healthy mice. In a robust effect, a single iv injection of hyaluronidase (200 U/mg) significantly reduced (by ~40%) the number of homed CD44+ cells in glomeruli already within 1 hour after injection, and improved albuminuria and survival rate of NZM mice with high proteinuria.

Conclusions: Our results support the major importance of HA in the endothelial glycocalyx in the glomerular homing of T cells in the development and pathology of LN. Hyaluronidase treatment is a promising new therapeutic approach for LN.

SA-PO190
Transmembrane Protein 144A1 is Differently Expressed in Human Proteinuric Renal Diseases
Josephine Bornmairer, Ramzi Khalil, Jan A. Brijn, Hans J. Baede. Pathology, Leiden Univ Medical Center.

Background: Identifying individual components of the glomerular filtration barrier that are involved in the development of proteinuria can help to find new potential therapeutic targets for CKD. We previously showed that transmembrane protein 144A (TMEM14A) is involved in the development of proteinuria. In this study, we aim to assess its localization in the glomerulus and whether it is differentially expressed in human proteinuric renal disease and spontaneously proteinuric rats.

Methods: TMEM14A protein expression was assessed by immunohistochemistry in glomeruli of patients with IgA nephropathy, lupus nephritis, minimal change disease, and healthy controls. Renal tissue of spontaneously proteinuric Dahl rats and non-proteinuric SHR rats were also stained for TMEM14A protein. Furthermore, QPCR was performed to investigate TMEM14A mRNA expression inpodocytes, HEK, and HuvEc and compared to renal tissue.

Results: TMEM14A was primarily localized in podocytes, as shown by immunohistochemistry and qPCR. Expression was significantly higher (p<0.05, chi-square test) in glomeruli of proteinuric patients compared to controls. In Dahl rats, TMEM14A expression was significantly diminished (p<0.05, mann-whitney u-test) in Dahl rats aged 2 and 4 weeks of age compared to SHR rats, before onset of proteinuria.

Conclusions: Here, we show that TMEM14A protein expression is primarily expressed by podocytes and is differentially expressed under proteinuric circumstances. Interestingly, TMEM14A protein expression in Dahl rats is decreased before onset of proteinuria, similar to our previous findings in mRNA expression. In contrast with the findings in our rat model, we found that TMEM14A protein expression changes significantly higher in patients with various proteinuric renal diseases. Based on the results of this study, we hypothesize that TMEM14A is part of a regulatory system that is involved in the development of proteinuria.
Role of Non-Adrenergic α(2A)-Adrenoceptors in Renal Fibrosis

Johannes Stegbeaun, 1 Steven D. Crowley, 2 Lars C. Rump, 1 Sebastian Alexander Pothoff, 1 Lydia Herin, 1 1Nephrology, Medical Faculty, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany; 2Nephrology, Duke Univ Medical Center, Durham, NC.

Background: Increased sympathetic tone leads to progression of chronic kidney disease (CKD). α2A-adrenoceptors (α2A-AR) in adrenergic neurons are known for regulating sympathetic tone by a negative feedback mechanism. Not much is known about their function on non-adrenergic cells. Here, we investigate the impact of α2A-AR on the development of renal fibrosis.

Methods: Unilateral peripheral obstruction (UUO) was performed in α2A-AR knockout (KO) and wild-type (WT) mice on a FVB background. Immunohistochemistry and gene expression analysis were performed 7 days after UUO.

Results: Despite increased renal sympathetic neurotransmission release, fibrosis, assessed by Sirius red/fast green collagen staining (p<0.05) and collagen-1 expression (p<0.001), was attenuated in kidneys of KO compared to WT mice 7 days after UUO. Moreover, expression of the pro-inflammatory and pro-fibrotic cytokines and chemokines TNF-α, TGF-β, CCL2 and CCL5 (p<0.05) were reduced in KO compared to WT mice. In order to dissect between adrenergic and non-adrenergic effects, we also generate α2A-AR-KO mice in which α2A-ARs are restored in adrenergic cells under the control of the human dopamine beta-hydroxylase (DbH-KO). In DbH-KO, renal sympathetic neurotransmission was significantly reduced compared to KO but similar to WT mice suggesting functional presynaptic α2A-ARs in DbH-KO mice. Beside fibrosis, macrophage infiltration was significantly reduced in α2A-AR-KO compared to WT but similar to total KO suggesting a crucial role of non-adrenergic α2A-AR on immune cells in fibrosis. Indeed, stimulation of isolated macrophages from WT mice with the α2-A agonist UK14,304 (0.1μM) increased TNF-α expression of TNF-α (p<0.05).

Conclusions: Although adrenergic α2A-ARs are considered as a negative regulator of sympathetic tone, they also seem to promote inflammation and fibrosis in response to injury. These effects seem to be mediated by non-adrenergic α2A-AR which might be a good candidate for reducing the progression of CKD.

The Role of Resistance Training (Exe), before and after Nephrectomy (5/6Nx) Reduce Mortality and Prevent the Increase of Proteinuria in Rats with Chronic Kidney Disease

Alejandro Sáadel, Rafael DaSilva Luiz, Edson Andreade Pessoa, Nектор Schoor. Nephrology Div, Escola Paulista de Medicina/UNIFESP, São Paulo, Brazil.

Background: The aim of this study was to evaluate the Exe effects on renal function and mortality rate in rats with 5/6Nx.

Methods: Adult Wistar rats were divided in two groups (n=8): Previous Exercise + Nx 5/6 + exercise (EXE-EXE), Previous exercise + Nx 5/6 + exercise (EXE-SED). The protocol was performed in 5/6Nx rats after 7 days from the surgical procedures, 6 to 12 limbs/day, 5 days/week, 40 a 60% of maximal loading, 8 weeks total (4 before surgery, 5 and 4 weeks after) for the group EXE-EXE and 4 weeks for SED group (only 4 weeks after surgery). It was evaluated mean arterial pressure (MAP), creatinine clearance (CrCl), proteinuria (μProt), blood urea nitrogen (BUN) as well mortality rate.

Results: The Exe diet did not modify the increment in proteinuria but prevent the increase in proteinuria rate (43,2±2,9 vs 82,1±5,2 mg/24h, p<0.0001) and mean BUN in EXE-EXE was higher compared with EXE-SED (114,2±8,4 vs 76,9±2,0 mg/dl, p<0.0001). A higher mortality rate was observed in EXE-EXE (50%) vs EXE-SED (0%).

Conclusions: * vs. EXE-SED.

Results: Conclusions suggested that the EXE minimize the impact of 5/6Nx, with much lower increase in BUN (28%), proteinuria (48%) and lower mortality in EXE vs EXE-SED. Minor impact of 5/6Nx on CrCl indicate that exercise could have a protective effect, especially under this experimental protocol. Thus, it is reasonable to suggest that EXE could be an additional strategy to be employed in CKD.

Meprin Expression/Activity Impacts Metabolite Profiles in Kidney Tissue of Mice with STZ Induced Type 1 Diabetes

Jessica Moi ge, Saud Andrade, Maria Grazia Bidwell, Steven Marie Gooding, Albert J. Unge, Marie Crowley, V., Cameron M. Behringer, Natalya Mezenina. Dept of Biology, Ball State Univ, Muncie, IN.

Background: Meprin metalloproteinases are the most abundantly expressed proteins in the brush border membranes of proximal kidney tubules. Meprins have been shown to play a role in the pathophysiology of diabetic nephropathy (DN) in humans and mice. In vitro and in vivo studies have identified several meprin targets in the kidney which include cytoskeletal proteins, tight junction proteins, extracellular matrix proteins, and cell signaling molecules. It’s not known how proteolytic processing of these and other targets by meprins impacts metabolic pathways in the kidney. This knowledge is important in delineating the mechanism(s) by which meprins modulate the progression of DN.

Methods: Low dose streptozotocin (STZ) was used to induce type 1 diabetes in 8 week old male wild-type (WT) and meprin β knockout (βKO) mice. The mice were sacrificed at 8 weeks post-STZ injection and kidney tissue harvested for metabolomics analysis. Biochemical assessment of kidney injury utilized ELISAs for creatinine, neutrophil gelatinase associated lipocalin (NGAL), and kidney injury molecule-1 (KIM-1). Lyophilized kidney proteins were reconstituted in 95:5 acetone/ethyl and loaded onto a UPLC-QTOF system for separation by HILIC chromatography and detection in MS² mode.

Results: Metabolomics analysis found more than 200 compounds associated with diabetes in WT and meprin βKO mice, including two annotated as the osmolytes glycerophosphocholine and betaine. One of the metabolites STZ only affected in WT, is N-Methyl-pyridine-carboxamide. It’s isomers, 4- and 2-PA, are markers of peroxisomal proliferation and inflammation and correlate with creatinine clearance as well as glucose concentration in oral glucose tolerance tests. Importantly, the anti-diabetic drug, Viglumide, lowered the concentrations of both isomers in urine.

Conclusions: The meprin β-associated changed metabolites (e.g. N-methyl-4-pyridine-3-carboxamide) have been implicated in kidney injury suggesting that meprins impact metabolic pathways that influence the progression of DN.

Funding: NIDDK Support, Other NIH Support - NIH/NIGMS # SC3GM102049; NIH Center Grant # U24DK097193; NIH/NH/NIH award # UL1TR001111; and NIGMS # K01GM109320

Changes in Malondialdehyde Levels with Age in the Nucleus, Cytosol and Mitochondria from Rat Kidney Cortex and Medulla

Mariana J. Zamla-tuski, Cameron M. Behringer, Natalya Mezenina. Dept of Biology, Ball State Univ, Muncie, IN.

Background: Oxidative stress caused by free radicals generated in aerobic metabolism contributes to cell injury and dysfunction seen with age. Malondialdehyde (MDA) is a product of lipid peroxidation of cell and organelle membranes by free radicals, and is used as an indicator of oxidative stress. The present study was undertaken to investigate the effect of age on changes in MDA levels in the nucleus, cytosol and mitochondria from rat kidney cortex and medulla.

Methods: Young (3 months of age) and old (22 months of age) female Lewis rats were used. The kidneys were harvested from anaesthetized rats after perfusing with isotonic saline via a catheter in the abdominal aorta. The kidneys were separated into cortical and medullary sections and homogenized in isotonic saline. Differential centrifugation was used to isolate the nuclear, cytosolic and mitochondrial fractions. MDA levels were measured in the fractions using a spectrophotometric assay and expressed as nmol/kg wet weight. Differences were evaluated using a Student’s t-Test.

Results: There was a significant increase in MDA levels in age with the nucleus, cytosol and mitochondria from rat kidney cortex. There was not a significant increase in MDA levels with age in the nucleus, cytosol and mitochondria from rat kidney medulla. MDA levels of nuclei and mitochondria from kidney medulla were higher than MDA levels from kidney cortex in both Young and Old rats.

Conclusions: The findings suggest that there is increased oxidative stress in the nucleus, cytosol and mitochondria from rat kidney cortex but not rat kidney medulla with age.

SA-PO195

Angioplasty Combined with Intra-Renal Administration of a Biopolymer-Delivered VEGF Construct to Improve Renal Recovery: A New Therapeutic Strategy


Background: Renal angioplasty and stenting (PTRAS) can resolve renal artery stenosis (RAS) but not always improve renal function, possibly due to persistent parenchymal damage. We recently designed a novel biocompatible fusion vector for drug delivery (Vector EXE) capable of delivering a drug (elastin-like polypeptides, ELP) with VEGF, and showed that ELP-VEGF therapy improved stenotic-kidney function and damage. We aim to increase the therapeutic efficacy of PTRAS and hypothesize that co-adjuvant ELP-VEGF following PTRAS will enhance renal recovery to both the incised renal juxtamedullary cortex and medulla. To test this hypothesis, we undertook an in vivo study using multi-detector CT, and then pigs were randomly divided in RAS+PTRAS or RAS+PTRAS+VEGF. RAS was followed by both incised renal artery stenosis (STZ), Pigs were observed for 4 additional weeks in vivo CT studies repeated, and then euthanized for micro-CT quantification of the renal microvasculature and plasma creatinine.

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

Underline represents presenting author.

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Results: Pre-PTRA renal hemodynamics was reduced in all pigs. PTRAS similarly resolved RVH and improved basal GFR. However, RBF, cortical perfusion, responses to endothelium-dependent challenge (acetylcholine, intra-renal infusion), and creatinine showed greater improvements in RAS+PTRAS/ELP-VEGF compared to PTRAS alone, accompanied by marked recovery in renal microvascular density.

Methods: We performed real-time PCR, immunoblot, immunohistochemistry, in situ hybridization, and flow assay from aSMA and C3A knock out mice subjected to unilateral ureteral obstruction and folic acid injury.

Results: We show that pericytes/myofibroblasts (PDGFRβ+ cells) cultured from UOU or mice treated with folic acid secrete C1q without increased C1r/C1s, with increased C1q expression. Extracellular matrix (ECM) production and Wnt signaling that are hallmarks of myofibroblast activation. Increased expression of C1q protein in tubulointerstitial space and mRNA expression of C1r/C1s in PDGFRβ+ cells were observed. Alternative pathway components C3b and C5 were also increased. Flow studies localized C14 to pericytes/myofibroblasts as well as CDS and F4/80+ cells and C1q to PDGFRβ+ cells. Global deletion of C14 prevented C1q secretion, but did not reduce fibrosis or prevent increased expression of C1r/C1s or C3b in whole kidney tissue. In contrast, global deletion of C3 reduced expression of C1r/C1s, resulting in reduced fibrosis. Claudronated-mediated depletion of CD11bhi F4/80hi macrophages in UOU mice resulted in reduced expression of C1r/C1s, C3, C5 and reduced fibrosis.

Conclusions: Our study determined the effectiveness of a novel co-adjuvant intervention for PTRAS. A single intra-renal administration of ELP-VEGF improved stenotic kidney outcomes after PTRAS by protecting the renal microvascular architecture and function, supporting the potential of a new strategy to enhance renal recovery in RAS.

Funding: Other NIH Support - NHLBI, Private Foundation Support

SA-PO196
Renal Tubular-Specific Jagged1 Deletion Ameliorates Kidney Fibrosis
Shizheng Huang, Chengxiong Qiu, Jiuhwan Park, Katulina Susztak. Renal Electrolyte and Hypertension Div, Univ of Pennsylvania, Philadelphia, PA.

Background: Fibrosis is the histological manifestation of chronic kidney disease (CKD). Recent studies highlighted the reemergence of developmental pathways in fibrosis including Notch, Wnt, and Hedgehog. Notch is a basic cell-cell communication pathway where expression of the ligand, Jagged1,2 or Delta1,3,4 or signal-sending cells induces an intramembrane proteolysis of the receptor, Notch1-4 on the signal-receiving cell. Our group previously established that tubular epithelial cell (TEC) Notch signaling plays a key role in fibrosis by using models with global Notch deletion. However, the precise ligand and receptor pairs that contributes to kidney fibrosis still remains unknown. Here we performed a systematic analysis to define the specific ligand of Notch-induced fibrosis development.

Methods: Genome wide gene expression analysis of microdissected human kidney tubule samples (59 control and 36 CKD) was performed using Affymetrix microarrays. For in vivo study, Jagged1 flox/flox mice were crossed to transgenic mice expressing Cre under the cadherin 16 to generate animals with TEC deletion of Jagged1 (Ksp cre/Jagged1 flox/flox mice). Kidney injury was induced by administering folic acid intraperitoneally. Histological and gene expression changes were analyzed in mouse kidneys. In vitro studies were performed using a co-culture system of rat fibroblasts and mouse stromal cells that expressed Jagged1.

Results: In human tissue samples, Jagged1 showed the best correlation with the degree of interstitial fibrosis (p<0.005). Ksp cre/Jagged1 flox/flox mice showed no kidney specific alteration. In the other hand, following folic acid injection kidney histology was markedly protected in the ksp cre/Jagged1 flox/flox mice. There was marked reduction in inflammatory and profibrotic gene expression in the Jagged1 knock-out mice when compared to littermate controls. In vitro co-culture studies indicated that Jagged1 expression induces proliferation and myofibroblastic transdifferentiation of resting fibroblasts.

Conclusions: Excessive Jagged1 activation in tubular epithelial cells stimulates myofibroblast proliferation and activation and leads to kidney fibrosis.

Funding: NIDDK Support

SA-PO197
Pericyte C1q and Complement Activation in Tubulointerstitial Fibrosis
Sandhya Xavi,1 Ranjit K. Sahu,2 Susan G. Landes,3 Jing Yu,2 Srinivas Ayadevara,4 Judith Meyges,5 Jeremy Stuart Duffield,6 Ronald P. Taylor,4 Edinara S. Reis,1 John Lambis,3 Didier Portilla.1 1Dept of Medicine, Center for Immunity, Inflammation and Regenerative Medicine, Univ of Virginia; 2Dept of Cell Biology, Child Health Research Center, Univ of Virginia; 3Dept of Biochemistry, Univ of Virginia; 4Nephrology Div, Univ of Arkansas for Medical Sciences; 5Research and Development, Biogen Idec; 6Dept of Pathology and Laboratory Medicine, Univ of Pennsylvania; 7Salem Veterans Affair Medical Center.

Background: Increased complement expression and activation occurs in kidney cells during acute kidney injury but little is known about its potential pathogenic role during progressive kidney disease.

Methods: We investigated the renal effects of bortezomib in aristolochic acid nephropathy (AAN) mice as a renal fibrosis model. Mice were administered aristolochic acid-I (aA) with or without bortezomib twice a week for 10 weeks. After the treatment periods, we examined renal fibrosis, expression of renal injury marker proteins, and pathological changes in the kidneys.

Results: In the AAN model, renal fibrosis accompanied with renal dysfunction occurred during the 10-week administration period. Treatment with bortezomib significantly attenuated AAN-induced renal dysfunction (Cr 0.482mg/dl vs 0.275mg/dl), albuminuria, and reduced protein expression of renal fibrosis and kidney injury markers such as ASMA, KIM1 and Ngal. Furthermore, bortezomib prevented renal fibrosis pathologically assessed by Masson’s trichrome stain. TGF-β1 mRNA expression in the kidney was also reduced in the bortezomib-treatment group.

Conclusions: Bortezomib may have great potential as a drug directly inhibiting renal fibrosis in CKD possibly via reducing TGF-β1 expression.

Funding: Government Support - Non-U.S.
**SA-PO200**

**Critical Role of Histone Deacetylase 3 in the Regulation of Inflammation and Renal Fibrosis**

Yung Yu Wanga, Yanlin Wand, Medicine, Baylor College of Medicine, Houston, TX; 2Center for Translational Research on Inflammation Diseases, Michael E. DeBakey VAMC, Houston, TX.

**Background:** Inflammation and fibrosis are common features of chronic kidney disease. However, the mechanisms underlying the development of inflammation and fibrosis are not fully understood. In this study, we examined the role of histone deacetylase 3 (HDAC3) in the regulation of inflammation and fibrosis.

**Methods:** To examine the role of HDAC3 in vivo, we generated mice with inducible deletion of HDAC3 using Cre-LoxP strategy, and we treated wild-type mice with RGFP966, a selective HDAC3 inhibitor. Unilateral ureteral obstruction (UUO) and ischemia-reperfusion injury (IRI) were used to model renal fibrosis. Cultured cells were used to examine the role of HDAC3 in the regulation of inflammation and fibrosis activation in vitro.

**Results:** HDAC3 expression was increased in the kidneys during the development of renal fibrosis. RGFP966 reduced the number of myofibroblasts and total collagen deposition in the kidney and inhibited production of extracellular matrix (ECM) proteins following UUO. Mice with tamoxifen-inducible deletion of HDAC3 (Cag-Cre, floxed HDAC3) were born normal and had no obvious morphological abnormality in the kidney. Compared with Cre negative, floxed HDAC3 mice, mice with tamoxifen-induced deletion of HDAC3 exhibited fewer myofibroblasts and expressed less α-SMA protein in the kidneys following UUO or IRI. Furthermore, inducible deletion of HDAC3 significantly reduced total collagen deposition and ECM protein production in the kidneys in response to UUO or IRI. Real-time RT-PCR showed that pro-inflammatory cytokines were significantly increased after UUO or IRI, which were significantly diminished in HDAC3 deficient mice. In cultured macrophages, HDAC3 deficiency reduced pro-inflammatory cytokine expression after stimulation with LPS or TNF-α. In cultured fibroblasts, deletion of HDAC3 or treatment with RGFP966 attenuated α-SMA and ECM protein expression in response to TGF-β1.

**Conclusions:** Our study identifies HDAC3 as a critical regulator of inflammation and fibrosis. Therefore, HDAC3 may represent a novel therapeutic target for chronic kidney disease.

**Funding:** NIDDK Support, VA Support

**SA-PO201**

**Uromodulin Deficiency Modifies Tubular and Intertitial Cell Responses to Chronic Kidney Injury while Fibrosis Severity Is Not Altered**

Saifee Syed,1 Olena Maydan,2 1University of Pittsburgh School of Medicine, Pittsburgh, PA.

**Background:** Tubular epithelial cells and interstitial cells in the kidney are believed to have different roles in the pathogenesis and progression of chronic kidney disease (CKD). As the principal mediator of canonical Wnt signaling, β-catenin controls the expression of a host of fibrosis-related genes. However, tubule-specific knockout of β-catenin does not affect kidney function and outcomes after unilateral ureteral obstruction (UUO), suggesting β-catenin signaling in other cell types may play a predominant role. In this study, we examined the potential role of β-catenin signaling in interstitial fibroblasts in the pathogenesis of kidney fibrosis.

**Methods:** Mice with fibroblast-specific deletion of β-catenin were generated by mating Gli2 floxed mice and α-SMA-cre mice. Biopsies of kidneys fibrosis were established by UUO or ischemia/reperfusion injury (IRI). Kidneys were analyzed by Masson’s trichrome staining, immunostaining, Western blotting.

**Results:** Fibroblast-specific ablation of β-catenin markedly reduced renal fibrosis, which was accompanied by reduced epithelial-mesenchymal transition (EMT), characterized by an increased E-cadherin and decreased vimentin, fibroblast specific protein 1 (FSP-1), Snail 1 and N-Smooth muscle actin. In addition, fibroblast-specific deletion of β-catenin in mice induced tubular epithelial cell cycle arrest at G2/M with reduced phospho-Histone H3 and no increase in apoptosis compared to the controls. Furthermore, less renal infiltration of inflammatory cells such as CD3 positive T cells and F4/80 positive macrophages was found in conditional knockout mice, comparing to controls. We found an increased hepatocyte growth factor (HGF) expression in mice with fibroblast-specific deletion of β-catenin. Similar results were observed in the kidney at 10 days after IRI in vitro, with ligands inhibited HGF expression in culture normal rat kidney interstitial fibroblasts (NRK-49F).

**Conclusions:** These results demonstrate that loss of fibroblast β-catenin attenuates renal fibrosis by inhibiting partial EMT and tubular cell cycle arrest at G2/M, which is likely to be mediated by an increased HGF expression and secretion by interstitial fibroblasts.

**Funding:** NIDDK Support

**SA-PO202**

**Activation of Fibroblast β-Catenin Signaling Contributes to Kidney Fibrosis by Promoting Tubular EMT and Cell Cycle Arrest**

Dong-Ru Fu, Youhua Zhao,1 Olena Maydan,2 Dong-Ru Fu, Yan Liu,3 Xue-Ru Wu.2 1Pediatrics, Univ of British Columbia; 2Urology, New York Univ.

**Background:** Human GWAS and Mendelian genetic studies have linked polymorphic variants and mutations with UMOD, the gene for uromodulin (UMOD). The primary function of this unique kidney-specific and secreted protein remains elusive. This study investigated whether the response to unilateral ureteral obstruction (UUO)-induced kidney injury was altered by genetic UMOD deficiency.

**Methods:** Kidneys harvested from mice of groups of 129EVE males wild-type (WT) and knockout (KO) mice (n=7-10 each) were studied. 14 and 21 days after UUO.

**Results:** Compared to sham kidneys, UMOD deficient kidneys showed increased protein levels of 9-13x after UUO in the WT mice and were associated with increased urinary protein and fibrosis levels. TUBULAR RESPONSE: KIM-1 protein levels were higher* in the KO group at all time-points (4-13x), while NGAL protein levels were increased similar on days 7 and 14, and were 66% lower* on day 21 in the KO group. Ksp-cadherin protein levels were 40-57% lower* in the KO groups. ROMK2, NKCC2 and AQP2 mRNA levels decreased* while TRPV4 levels were increased* after UUO; only TRPV4 levels were higher* in the UMOD knockout (KO) group. Levels of pro-apoptotic genes (TNFα, FasL) and the epithelial cell apoptotic protein marker M30 (cleaved cytokeratin 18) (day 14 only) were significantly lower in the KO groups. INFLAMMATION: MCP-1 and RANTES mRNA levels and macrophage F4/80 protein levels were all lower* in the KO groups. FIBROSIS. Kidney eSMA levels showed biphasic differences between the genotypes: higher* on day 7, similar on day 14 and lower* on day 21 in the KO groups. Total kidney collagen levels were similar on days 7 (1.4x and 1.6x sham kidney levels), 14 (3.0x and 2.6x) and 21 (3.5x and 3.8x); WT vs KO, *P<0.05.

**Conclusions:** UMOD protein accumulates in the kidney with marked intraluminal precipitation after UUO. In the absence of UMOD, tubular apoptosis and interstitial inflammation are attenuated, yet overall kidney fibrosis severity is unchanged. Elevated protein levels of 9-13x after UUO in the WT mice were associated with increased urinary protein and fibrosis levels. These changes were comparable in the KO and WT groups. However, the mechanisms underlying the development of inflammation and fibrosis are not fully understood. In this study, we examined the role of histone deacetylase 3 (HDAC3) in the regulation of inflammation and fibrosis.

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

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

Underline represents presenting author.

767A
SA-PO205
MAD2B Promotes Tubular Epithelial-to-Mesenchymal Transition and Renal Tubulointerstitial Fibrosis via Skp2
Chen Ye, Hui Tang, Hua Su, Chun Zhang. Nephrology, Union Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.

**Background:** The mitotic arrest deficient protein MAD2B is a well-defined anaphase-promoting complex/cyclosome (APC/C) inhibitor and a small subunit of DNA polymerase zeta. It is critical for mitotic control and DNA repair. However, the pathological role of MAD2B in renal fibrosis has not been fully elucidated.

**Methods:** The objects of this study included patients with renal tubulointerstitial fibrosis (TIF) (secondary glomerulonephritis and interstitial nephritis were excluded), unilateral ureteral obstruction (UUO) mice and in vitro cultured rat proximal tubular epithelial cell line (NRK-52E). In vivo gene silence of MAD2B was carried out by intrarenal lentiviral gene delivery.

**Results:** By immunofluorescence and immunohistochemistry, we found an obvious MAD2B enhancement in tubular area of TIF patients and UUO mice. In vitro, transforming growth factor-β1 (TGF-β1) induced a time-dependent MAD2B accumulation prior to tubular epithelial-to-mesenchymal transition (EMT) in NRK-52E. Knocking down MAD2B with siRNA dramatically inhibited TGF-β1-induced tubular EMT process and subsequent extracellular matrix (ECM) production. We also found that the expression of Skp2, an APC/C-CDH1 substrate and E-cadherin destroyer, was increased in TGF-β1-treated NRK-52E, which could be suppressed by MAD2B depletion. Consistently, Skp2 expression was increased in renal tubular area of UUO mice. Locally knocking down MAD2B in renal cortex by using lentiviral transfection inhibited Skp2 expression, tubular EMT and subsequent ECM accumulation.

**Conclusions:** Our data suggests a pro-fibrotic role of MAD2B in the pathogenesis of tubular EMT and TIF by inhibiting Skp2 expression. MAD2B-Skp2 axis might be a promising target for renal TIF interventions.

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

SA-PO206
The Role of Galectin-3 in the Renal Tubular Epithelial-Mesenchymal Transition
Yuchen He, Linlin Qu, Wenbin Tang, Hui Li, Ping Xiao, Qiaoling Zhou. Dept of Nephrology, Kidney Inst, Changsha, Hunan, China.

**Background:** Galectin-3 is a pleiotropic lectin that plays an important role in cell proliferation, apoptosis, adhesion and inflammatory responses. Recent evidence suggest that Galectin-3 may play a key role in the development of fibrosis, but the pathogenesis is still unclear. The Objective of this study is to observe the role of Galectin-3 in the renal tubular epithelial-mesenchymal transition and renal fibrosis.

**Methods:** In vivo, the model of renal fibrosis was induced by unilateral ureteral obstruction in Sprague Dawley rats. HE and Masson staining was used to evaluate the level of renal tissue fibrosis. The location and expression of Galectin-3, E-cadherin and α-SMA were measured with immunochemistry and immuno-fluorescent double staining experiments. In vitro, expressions of Galectin-3 and α-SMA were increased remarkably in NRK-52E cell stimulated by TGF-β1 or high glucose for different time. Furthermore, Galectin-3 was inhibited by modified citrus pectin (MCP). The expressions of Galectin-3, E-cadherin, α-SMA were detected by Real-time-PCR and Western blot. In vivo, compared with the sham group rats, more severe tubular dilation, interstitial fibrosis and inflammatory cells infiltration were noted in UUO model rats. E-cadherin and α-SMA were upregulated significantly especially in renal tubular cells. Meanwhile, the expression of Galectin-3 was upregulated in UUO model rats. In vitro, expressions of Galectin-3 and α-SMA were increased remarkably in NRK-52E cells induced by angiotensin II or high glucose in a time-dependent manner compare with the control, however expression of E-cadherin reduced remarkably. The expressions of Galectin-3 were negatively correlated with E-cadherin, but positively correlated with α-SMA. When Galectin-3 inhibitor MCP were used in NRK-52E cell stimulated by high glucose, α-SMA expression was significantly increased, E-cadherin expression was significantly decreased.

**Conclusions:** Galectin-3 is upregulated during the process of renal tubular EMT. Galectin-3 inhibitor MCP can promote EMT in renal tubular epithelial cells induced by high glucose. In view of these findings it is conceivable that Galectin-3 may play as a novel protein target in pre-EMT states for the amelioration renal fibrosis seen in CKD.

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

SA-PO207
Apoptosis Signal-Regulating Kinase 1 (ASK1) Inhibitor GS-4997 Decreases Tubulointerstitial Fibrosis in a Rat Model of Ureteral Obstruction

**Background:** GS-4997 is a potent and selective ASK1 inhibitor that is currently in clinical development for the treatment of Diabetic Kidney Disease (DKD). ASK1 is a critical signaling node through which oxidative stress promotes inflammation, apoptosis, and fibrosis via downstream activation of the MAPK kinases p38 and c-Jun N terminal kinase (JNK). This study describes the pharmacodynamics and efficacy of GS-4997 in a rodent model of renal tubulointerstitial fibrosis, which is a final common pathway for progressive kidney diseases such as DKD.

**Methods:** Male Sprague-Dawley rats were subjected to unilateral ureteral obstruction (UUO) surgery (n=10/group) or sham surgery (n=6) and were orally administered GS-4997 (1, 3, 10 or 30 mg/kg, BD) or vehicle for 7 days. Fibrosis was assessed by immunohistochemistry for collagen IV and alpha-smooth muscle actin (a-SMA) quantified using ImageScope software (Aperio). Collagen IV protein was also quantified in kidney cortex lysates by ELISA. ASK1 pathway activation was assessed by western blot and/or ELISA for phosphorylated ASK1 (p-ASK1), p38 (p-p38) and JNK (p-JNK).

**Results:** ASK1 pathway activation was significantly increased in UUO kidneys compared to sham (15 ± 4 vs 1 ± 0.66, p-ASK1/IP90; 6 ± 2 vs 1 ± 0.01, p38/IP90; and 2 ± 0.2 vs 1 ± 0.02 p-JNK/IP90; p<0.01 for all groups), and was decreased by GS-4997 in a dose-dependent manner back to sham control levels. Increased immunostaining for interstitial collagen IV and α-SMA positive myofibroblasts detected in UUO kidneys was reduced by GS-4997. In addition, collagen IV protein levels in kidney lysates was increased in UUO compared to sham (2.68 ± 0.9 vs 0.9 ± 0.1 mg/mg, p<0.05), and treatment with the ASK1 inhibitor GS-4997 significantly decreased renal collagen IV protein levels (2 ± 0.3, 1.4 ± 0.07, and 1.6 ± 0.09 mg/g for the 3, 10, 30 mg/kg doses, respectively, p<0.05 for all groups).

**Conclusions:** GS-4997 inhibits ASK1 pathway activation and ameliorates renal fibrosis in the obstructed kidney. These data support the investigation of GS-4997 as a therapy to reduce renal fibrosis and halt progression in kidney diseases such as DKD.

**Funding:** Pharmaceutical Company Support - Gilead Sciences, Inc.

SA-PO208
Tight Junction Dysfunction in Proximal Tubular Cells Is Prohibited by Activation of the HSP72-Klotho Axis
Jen Xu,1 Frank Xu,1 Li-Lun Ho,1 Huixia Cao,1 Kenneth Lim,2 Tianqiang Kong,1 Tzongshi Lu.1 1Renal Div, Brigham and Women’s Hospital, Boston, MA; 2Nephrology Div, Massachusetts General Hospital, Boston, MA.

**Background:** Tight junctions (TJ) are specialized membrane domains that play multiple functions in kidney epithelial cells, including the maintenance of cellular polarity and work as a barrier to the regulatory barrier. Studies indicate emerging links between TJ dysfunction and the development of kidney disease, particularly in autosomal dominant polycystic kidney disease (ADPKD) and ischemic acute renal failure. Klotho is a transmembrane protein that has been shown to exert anti-aging properties and its deficiency is involved in the development of renal failure. Heat shock proteins (HSP) are universally expressed and their induction by a variety of stressors in organisms and cultured cells has been shown to be involved in the maintenance of cellular integrity and normal physiological functions. In this study, we describe a HSP72-Klotho axis and its role in preventing renal fibrosis and cystogenesis in ADPKD, through the regulation of TJs.

**Methods:** Madin-Darby canine kidney (MDCK) Tet-off inducible Git2 and Git2Q1 cell lines, HK2 cells were used to generate a ADPKD and fibrosis in vitro model, respectively. Sprague Dawley rats were used in an ischemia-reperfusion animal model. Heat shock proteins were induced by heat shock treatment (HST) at 43 °C for 30 minutes.

**Results:** Klotho expression was decreased in ADPKD and HK2 cells, however was preserved by HST. This was associated with the preservation of TJ proteins Occludin and Claudin-5. We also found that matrix metalloproteinase-2 (MMP2) and A Disintegrin and metalloproteinase-10 (ADAM10) were significantly increased in ADPKD cells and fibrotic kidney tissues. This was associated with significantly decreased Klotho expression. However, HSP72 was induced by HST and this resulted in partial reversal of ADAM10 and MMP2 changes with an increase in Klotho expression and forms a HSP72-Klotho complex.

**Conclusions:** Our data describes a potential HSP72-Klotho axis in the stabilization of TJ proteins. Further investigation into the molecular mechanisms and clinical application are needed.

**Funding:** Private Foundation Support

SA-PO209
Trimethylamine-N-Oxide (TMAO) Plasma Accumulates in Uremic Mice and Promotes the Progression of Kidney Fibrosis
Caroline C. Pelletier,1,2 Maud Rabeyrin,1 Mikael Croyal,1 Michel Krempf,1 Laurent Jaillaud,2 Christophe O. Soulage.2 Nephrology, Hospices Civils de Lyon, France; 1Univ Lyon, INSA-Lyon, INSERM U1060, CarMeN Lab, France; 2InRA, UMR 1280, CRNH, Mass Spectrometry Area, Nantes, France.

**Background:** TMAO was recently associated with poor cardiovascular outcomes in the general population and was described to accumulate in patients with chronic kidney disease (CKD). Some recent studies have suggested that the accumulation of TMAO could contribute to renal function.

**Methods:** TMAO was assayed in 18 control and 18 CKD mice, induced by 3 weeks of an adenin rich diet (0.25%/sw). In each group, half of the mice were then fed for 3 additional weeks with a 1% (w/w) choline-enriched diet to promote the production of TMAO.

**Results:** TMAO level is significantly increased in control mice after a choline-supplemented, to the TMAO level of the CKD mice. TMAO concentration is 10-folds higher in CKD mice fed with choline-enriched diet.

**Conclusions:** Our data describes a potential HSP72-Klotho axis in the stabilization of TJ proteins. Further investigation into the molecular mechanisms and clinical application are needed.
Characteristics of control and CKD mice, with or without enriched choline food  

<table>
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<th>Control (Standard food)</th>
<th>Enriched Choline food</th>
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<td>Kidneys, mg</td>
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<tr>
<td>Proteinuria, mg/24h</td>
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<td>TMAO μM</td>
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<td>39.1±12.1</td>
<td>31.8±5.6</td>
<td>428.4±71.0</td>
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</table>

Means were compared with ANOVA test and significant p was <0.05.

Supplementation decreased the survival of CKD mice (-33%, P<0.05) and promotes renal fibrosis assessed by 2 different histopathology techniques (HES and picro sinus red stainings).

**Conclusions:** Plasma TMAO accumulates in CKD mice. Higher plasma TMAO level in mice triggers an expansion of renal parenchyma fibrosis.  
**Funding:** Clinical Revenue Support

SA-PO210

The Role of Flavin Monooxygenase 3 in Renal Fibrosis  

**Jing Xu, Lei Jiang, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.**

**Background:** Renal proximal tubular cells (PTCs) have been recognized as one of the important contributors to renal fibrosis. Prior studies reported that trimethylamine-N-oxide (TMAO) is elevated in subjects with impaired renal function, and it contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Since flavin monooxygenase (FMO) family members, especially FMO3 exhibit the highest activity in TMAO metabolism, deciphering the role and mechanisms for FMO3 in renal fibrosis are very necessary.

**Methods:** In this study, we employed mice with unilateral ureteral obstruction (UUO) and TGFβ1-treated NRK-52E cells/primary PTCs as two model systems. FMO3 plasmid was injected one day before UUO surgery. Cells were transfected with FMO3 plasmid or siRNA to downregulate FMO3 expression and FMO3 activity was decreased by using methimazole.

**Results:** Here, western blot analysis and immunofluorescence staining confirmed that FMO3 expression was decreased in kidney from UUO and folic acid induced renal fibrosis mouse model. Then, we observed that both NRK-52E and primary PTCs exhibit higher expression of fibronectin (FN), α-smooth muscle actin (α-SMA), Type1 collagen (COL I) compared with control. In line with this, cells transfected with plasmid or siRNA exhibit higher expression of fibronectin (FN), α-smooth muscle actin (α-SMA), Type1 collagen (COL I) compared with control. In line with this, cells transfected with plasmid or siRNA exhibit higher expression of fibronectin (FN), α-smooth muscle actin (α-SMA), Type1 collagen (COL I) compared with control. In line with this, cells transfected with plasmid or siRNA exhibit higher expression of fibronectin (FN), α-smooth muscle actin (α-SMA), Type1 collagen (COL I) compared with control.

**Conclusions:** These results demonstrated that decreased expression or activity of FMO3 is critical for the development of renal fibrosis. Drugs that could specifically target FMO3 may attenuate renal fibrosis and need further research.  
**Funding:** Government Support - Non-U.S.

SA-PO211

The MRTF/TAZ Pathway Is a Critical Inducer of the Profibrotic Epithelial Phenotype  

**Andras Speight,1 Qinghong Dan,2 Stine Falsig Pedersen,2 Katalin Szasz,1 Keenan Research Centre, St. Michael Hospital, Toronto, ON, Canada; 1Cell Biology, Univ of Copenhagen, Copenhagen, ON, Canada.**

**Background:** The Hippo effector TAZ and the Rho/actin-regulated myocardin-related transcription factor (MRTF) are TGFβ- and siRNA-mediated MRTF inhibition prevented the TGFβ-induced rise in TAZ, while MRTF overexpression induced TAZ expression and promoter activation. UUO concomitantly increased tubular TAZ mRNA and tubular TGFβ1, PDGF, CTGF and Indian Hedgehog (IHH) mRNA levels. Stretch increased mRNAs for TGFβ1, CTGF, IHH, and PDGF in LLC-PK1 cells, and these effects were suppressed by pharmacological (verteporfin for TAZ, CCG1423 for MRTF) or siRNA-mediated inhibition of TAZ or MRTF.

**Conclusions:** MRTF controls TAZ expression both in fibroblasts and epithelial cells, and both MRTF and TAZ are essential mediators of PEP.

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

SA-PO212

PP242 Inhibits Fibroblast Activation and Kidney Fibrosis in Mice with Unilateral Ureter Obstructive Nephropathy  

**Jianzhong Li, Chunsun Dai. Nanjing Medical Univ.**

**Background:** PP242, an mTOR kinase inhibitor, can inhibit both mTORC1 and mTORC2 signaling pathways in many types of cell. Regarding the profibrotic role for mTORC1 and mTORC2 in kidney diseases, it is highly possible that blockade of mTOR signaling with PP242 may diminish fibroblast activation and kidney fibrosis.

**Methods:** In this study, NRK-49F cells, a rat kidney interstitial fibroblast cell line, were stimulated with TGFβ1. Unilateral ureter obstruction (UUO) was used to induce kidney fibrosis in mice.

**Results:** In cultured NRK-49F cells, TGFβ1 treatment could activate both mTORC1 and mTORC2 signaling in cultured NRK-49F cells at a time dependent manner, while administration of PP242 could dose dependently inhibit TGFβ1-induced mTORC1 and mTORC2 signaling activation. Additionally, PP242 could also dose dependently reduce TGFβ1-induced α-SMA and fibronectin expression in NRK-49F cells. In mice with UUO nephropathy, PP242 administration could markedly diminish total collagen deposition, fibronectin and α-SMA expression in the fibrotic kidneys with UUO nephropathy compared to those treated with vehicle.

**Conclusions:** In summary, these results suggest that PP242 may act as a new therapeutic reagent for fibrootic kidneys through inhibiting both mTORC1 and mTORC2 signaling pathways.

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

SA-PO213

Wnts Promote Fibroblast Activation and Kidney Fibrosis Involving Smad Signaling  

**Lei Jiang, Qi Sun. Nanjing Medical Univ.**

**Background:** Wnts are divided into canonical and non-canonical subgroups relying on whether it can activate β-catenin or not.

**Results:** In this study, we found that several Wnt family members including Wnt3a, Wnt5a and Wnt5b but not Wnt4, Wnt9b or Wnt11 could markedly induce smad3 phosphorylation in many types of kidney cell including podocyte, NRK-49F cell and HKC. In addition, Wnt3a, Wnt5a and Wnt5b but not Wnt4, Wnt9b or Wnt11 could stimulate α-SMA and fibroblastin expression in NRK-49F cells. Blockade of smad3 signaling with smad3 siRNA or SIS could largely abolish Wnt3a, Wnt5a and Wnt5b induced α-SMA expression, suggesting an indispensable role for smad3 signaling activation in Wnts-induced fibroblast activation. Co-immunoprecipitation as well as co-immunostaining analysis demonstrated the co-localization of Wnt3a and type 1 receptor of TGFβ1 in NRK-49F cells. Blockade of type 1 receptor of TGFβ1 with siRNA or SB43152 could almost completely abolish Wnt-induced α-SMA and fibroblastin expression. In mouse model with kidney fibrosis after UUO or IRI, Wnt5b expression was induced in kidney tissue and ectopic expression of exogenous Wnt5b could induce smad3 phosphorylation and mild kidney interstitial fibrosis in mice.

**Conclusions:** Together, this study indicates that smad3 phosphorylation mediates Wnt5a, Wnt5b and Wnt5b stimulated extracellular matrix production in kidney cells, which may be a novel mechanism for Wnts in promoting kidney fibrosis.

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

SA-PO214

Omega-3 Polyunsaturated Fatty Acids Ameliorate Fibroblast Activation and Kidney Fibrosis Involving Suppression of mTOR Signaling Pathway  

**Zhiqiong Zeng, Chunsun Dai. Nanjing Medical Univ.**

**Background:** Epidemiologic studies have shown the correlation between the deficiency of omega-3 polyunsaturated fatty acids (PUFAs) and the progression of chronic kidney diseases (CKD), however, the role for omega-3 PUFAs in protecting against kidney fibrosis in CKD and the underlying mechanisms TAZ remains obscure.

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

**Underline represents presenting author.**

678A
Results: Here, NRK-49F cells, a rat kidney interstitial fibroblast cell line, were stimulated with TGFβ1. DHβA, one member of omega-3 PUFA family, could remarkably suppress TGFβ1-induced fibroblast activation at a dose dependent manner. In addition, DHβA could markedly reduce TGFβ1 up-regulated p-Akt (Ser473), p-Akt (Thr308) but not p-S6 or p-smad3 abundance in NRK-49F cells. To further decipher the role for omega-3 PUFAs against kidney fibrosis, we deployed transgenic mouse model capable of endogenously producing omega-3 PUFAs while reducing omega-6 PUFAs owing to the expression of a Caenorhabditis elegans fat-1 gene encoding an omega-3 fatty acid desaturase. The mice were operated with unilateral ureteral obstruction (UUO) to induce kidney fibrosis. Compared with wild type mice, fat-1 transgenes developed much less kidney fibrosis and inflammatory cell accumulation accompanied by less p-Akt (Ser473), p-Akt (Thr308), p-S6 or p-smad3 in kidney tissue at day 7 after UUO.

Conclusions: Thus, omega-3 PUFAs strongly attenuate fibroblast activation and kidney fibrosis and may provide a therapeutic strategy for retarding the progression of chronic kidney diseases.

Funding: Government Support - Non-U.S.

SA-PO215

Dznep Ameliorates Tubulointerstitial Fibrosis via Reduction of TIMP2

Imari Mimura,1 Yusuke Hirakawa,2 Yasuhiro Kanki,3 Yutaka Suzuki,3 Hiroyuki Aburata,4 Masaomi Nangaku.1

1Department of Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan; 2Isotope Science Center, The Univ of Tokyo, Tokyo, Japan; 3Graduate School of Frontier Sciences, The Univ of Tokyo, Tokyo, Japan; 4Division of Genome Science, Research Center for Advanced Science and Technology, The Univ of Tokyo, Tokyo, Japan.

Background: Tubulointerstitial fibrosis has been recently reported to be caused by the collapse of epigenetic regulations for kidney diseases. We examined whether any of inhibitors for histone modifications is effective against renal fibrosis. Dznep (3-deazaneplanocin A) is originally developed as an anti-cancer drug to delete repressive histone mark, H3K27me3. We found that Dznep contributes to the reduction of tubulointerstitial fibrosis. The aim of our study is clarifying the epigenetic mechanisms of ameliorating renal fibrosis using genome-wide analysis of mRNA and microRNA.

Methods: Although ischemia reperfusion injury model is well known to cause acute kidney injury, we have found that the unilateral ischemia reperfusion model also leads to chronic tubulointerstitial fibrosis after two months. We administered Dznep to these model mice for 8 weeks intravenously. Because epigenetic regulation is specific to the cell species, we need to focus only on the tubular cells. Therefore we picked up only tubular cells from in vivo samples using laser captured microdissection. We examined the level of mRNA and microRNA in tubular cells using high throughput sequencers (RNA-seq) to identify novel epigenetic factors associated with renal fibrosis. We also performed RNA-seq using in vitro samples of renal proximal tubular cell lines with the stimuli of hypoxia and Dznep.

Results: We analysed the results of RNA-seq and found that TIMP2 (tissue inhibitor of metalloproteinase 2) is suppressed with Dznep both in vivo and in vitro samples. TIMP2 is reported to be associated with promoting fibrosis. In addition, we identified the novel microRNAs which target TIMP2. The novel microRNAs have possibility of inhibiting the gene expression of TIMP2, leading to reduce renal fibrosis.

Conclusions: We found the novel epigenetic molecular mechanisms showing the inhibition of TIMP2 via microRNAs might contribute to reducing renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO216

Angiopoietin-1 Deficiency Increases Tubulointerstitial Fibrosis

Krishnapriva Loganathan,1 Ebtsam Salem,1 Susan E. Quaggin,2 Marie Jeansson.1

1Innate Immunology, Genetics and Pathology, Uppsala Univ, Uppsala, Sweden; 2Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago, IL; 3Div of Nephropathy and Hypertension, Northwestern Univ, Chicago, IL.

Background: Renal tubulointerstitial fibrosis is progressive of predictive decline in kidney function, independent of underlying disease. It is characterized by an increase in aSMA+ fibroblasts, myofibroblasts, that produce collagen. Identification of factors that regulate the fibrotic response are excellent candidate targets for treatment of kidney diseases. We previously showed that loss of Angiopoietin-1 (Angpt1) in adult mice predisposes to fibrosis in wound healing and diabetic nephropathy. Angpt1 acts through the Tie2 tyrosine-kinase receptor expressed on endothelial cells. Here, we test the hypothesis that loss of Angpt1-Tie2 signaling results in an increased fibrotic response in kidney fibrosis.

Methods: We first performed lineage tagging experiments using Tie2-Cre to better understand if cells using Angpt1-Tie2 signaling could contribute to the myofibroblast population in kidney fibrosis. FACs was used to isolate the tagged cells and to study gene regulation of myofibroblast markers. To study the role of Angpt1 in renal fibrosis we utilized Angpt1 conditional knockout mice in the unilateral ureteral obstruction (UUO) model of kidney fibrosis.

Results: The Tie2-lineage contributed to almost 20% of myofibroblasts 10 days after UUO. 1addition, there was a significant (p=0.001) upregulation of Tgfβ and Fibronectin-1 gene expression in FACS sorted lineage tagged cells after UUO, suggesting that part of this population have become myofibroblasts. Angpt1 deficient mice showed a significant (p<0.05) increase in Smaa area 3 days after UUO as well as an increase in the expression of Fibronectin-1 (p=0.01), Tgfb (p=0.023) and Kim-1 (p=0.06).

Conclusions: Our results suggest that loss of Angpt1-Tie2 signaling increases tubulointerstitial fibrosis as seen by the increased expression of fibrosis markers in Angpt1 deficient mice. Ongoing work is designed to use other models of fibrosis and to elucidate the mechanism(s).

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

SA-PO217

MicroRNA Fine-Tuning of Endothelial Dysfunction and Prevention of Fibrosis by miR127-Complementary Locked Nucleic Acid Oligonucleotides

Sina Dadfarin, Jun Chen, Yujiro Kida, Michael S. Goligorsky. New York Medical College, Valhalla, NY.

Background: Endothelial cells (EC), especially SIRT1−/−, deficient, subjected to TGFB develop premature senescence. It has been demonstrated previously that microRNAs (miR) are causally involved in induction of cell senescence and dysfunction, which in turn generates pro-fibrogenic secretome.

Methods: For this reason we performed profiling miRs in EC isolated from control and SIRT1−/− mice renal microvasculature. The samples were labeled using the miRCURY LNA™Hy3-Hy5 Power Labeling Kit, Hy3™/Hy5™ and hybridized on the miRCURY LNA™ microRNA Array (7th Gen, Exiqon), following a dual-color experimental design. The microRNA profiling performed on the miRCURY™LNA array identified microRNAs that have a log fold change > than 1. We have contrasted miR profile of wild-type and endothelial SIRT1−/− EC under basal and TGFB-stimulated conditions.

Results: Notably, the known TGFB-induced miRs-145A, -579 and -143 were present in both screens of EC, a proof of technical validity. Among differentially displayed (at least a log-difference) signatures of control and endothelial SIRT1−/− EC stimulated by TGFB, miR-127 was down-regulated by 1.6 log FC. miR-127 target is p16(INK4a) pathway (induced in cell senescence) and shown to reduce expression of VEGF, was also upregulated. To gain insight into the in vivo role of elevated miR-127 and miR-410, complementary locked nucleic acid (LNA) oligonucleotides and respective scrambled controls were synthesized. Experiments were performed in 10-12 week-old o-SMA-GFP mice subjected to UUO. We treated UUO mice with LNA complementary to miR-127 and miR-410 3p. We observed no deleterious effects of LNA in FVB mice. The degree of fibrosis of UO kidneys was significantly reduced in mice that received supplemental LNA to miR-127 compared to scrambled LNA-treated mice. Mice receiving LNA to miR-410 showed a moderate reduction in fibrosis.

Conclusions: These studies demonstrate that complementary 127 3p LNA- induced amelioration of endothelial dysfunction leads to the concomitant reduction of renal fibrosis, thus establishing it as a valid therapeutic target.

Funding: NIDDK Support

SA-PO218

Galunisertib Is a Promising Drug Candidate for the Treatment of Renal Fibrosis in Ex Vivo Tissue Slice Cultures

Emilia Bigiyan1, Emilia Gore1, Miren Garmendia,2 Henricus A.M. Mutsaers,3 Detlef Schupp0,2 Peter Olinga.1

1Pharmaceutical Technology and Biopharmacy, Univ of Groningen, Groningen, Netherlands; 2Boehringer Ingelheim, Biberach, Germany; 3Inst of Translational Immunology and Research Center for Immunotherapy, Univ of Mainz Medical Center, Mainz, Germany.

Background: Galunisertib (Galu) is an inhibitor of the TGFβR1 kinase and is currently tested in clinical trials as an anticaner drug. Galu could be a potential candidate for the treatment of fibrosis. Our objective was to investigate the effects of Galu on the early and end stage of fibrosis using precision-cut mouse and human kidney slices (PKCS).

Methods: PKCS were prepared from healthy and diseased mouse and human kidneys and incubated for 48 hours in the presence of 10 µM Galu, a non-toxic concentration. Unilateral ureteral obstruction (UUO) for 7 days was used to induce renal fibrosis in mice. Gene expression of key fibrosis markers, such as procollagen α1(I) (Col1a1), a-smooth muscle actin (α-SMA), heat shock protein 47 (Hsp47) and fibronectin (Fn), was determined by qPCR.

Results: Incubation of healthy PKCS resulted in the early onset of fibrosis, as demonstrated by an up-regulation of the fibrosis markers in mouse (Col1a1 8.6 fold; Hsp47 5.0 fold; Fn 176.7 fold) and human (Col1a1 2.8 fold). The fibrosis markers were even further increased in fibrotic PCTS prepared from UUO vs control mouse (Col1a1 1.4 fold; Hsp47 1.5 fold and Fn 4.7 fold). Galu inhibited gene expression of fibrosis markers in healthy mouse PKCS (Col1a1 by 97%; α-SMA by 89%; Hsp47 by 53%; Fn by 99%) and in PKCS prepared from UUO mice (Col1a1 by 87%; α-SMA by 63%; Hsp47 by 48%; Fn by 83%). In healthy human PKCS Galu inhibited gene expression of Col1a1 (by 70%) and Fn (62%). The pilot experiment with fibrotic human PKCS indicated a similar trend (Col1a1 was inhibited by 90%; Hsp47 by 58%; Fn by 76%).

Conclusions: Galu exhibits strong antifibrotic activity in the early and end stage of fibrosis in mouse and human PKCS. The PKCS technique is a promising model to test antifibrotic agents both in rodent and human tissues, considering the latter as a bridge to clinical studies.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim, Government Support - Non-U.S.
The epithelial-to-mesenchymal transition (EMT) of renal tubules is one of the main pathogenesis of renal interstitial fibrosis. In this study, we investigated the effects of metanephric mesenchymal cells (MMCs) on the EMT of renal tubular epithelial cells in order to provide new therapeutic strategies for renal interstitial fibrosis.

Methods: MMCs were extracted from the renal cortex of fetal pig 70 days after pregnancy. Transferring transforming growth factor-β (TGF-β) was used to induce EMT of a pig proximal tubular epithelial cell line (LLC-PK1). Transwell chambers were applied to co-culture MMCs with LLC-PK1. Light microscope, immunofluorescence confocal microscopy and western blotting were used to identify the MMCs and detect the phenotypic changes of LLC-PK1.

Results: Heterozygosity was associated with a reduction in PT BRCA1 mRNA by in situ hybridization. There was reduced kidney interstitial fibrosis in mice heterozygous for PT BRCA1 deletion compared to WT littermate controls by MT and PS staining after I/R and AA. PCR analysis of whole kidney cortex revealed reduction in fibrogenic factors such as CTGF, COL4A1, fibronectin and ACTA2. There was also a reduction in markers of G2 cell cycle arrest and senescence although markers of apoptosis were increased in heterozygous mice compared to WT. These murine data are supported by in vitro experiments with AA damage and adminstration of nintedanib in a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO).

Conclusions: BRCA1 facilitates interstitial fibrosis following kidney tubular injury in mice through its role in DNA damage response.

Nintedanib, a Triple Tyrosine Kinase Inhibitor, Inhibits Fibroblast Activation and Ameliorates Renal Fibrosis in Chronic Kidney Disease Feng Liu, Li Wang, Yi Wang, Shouguang Zhang. Dept of Nephrology, Shanghai East Hospital Tongji Univ, Shanghai, China.

Background: Nintedanib (BIBF1120) is a triple kinase inhibitor of platelet derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR) that has recently been approved by FDA to treat idiopathic pulmonary fibrosis. However, its efficacy in renal fibrosis remains unknown.

Methods: In this study, we evaluated the anti-fibrotic effect of nintedanib in a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO).

Results: Administration of nintedanib immediately or 3 days after UUO injury attenuated renal fibrosis and inhibited activation of renal interstitial fibroblasts and epithelial-to-mesenchymal transition (EMT). Female and type 2 collagen matrix molecules, fibronectin and type 3 collagen were examined by immunofluorescence. PT cells were isolated from mice and treated with AA to explore the relationship between injury and cell cycle stage, apoptosis and senescence.

Conclusions: Nintedanib showed a potential anti-fibrotic agent in the kidney and may hold therapeutic potential as a treatment of chronic fibrotic kidney disease.
Post Translational Modifications to H3K9 during Renal Myofibroblast Differentiation

Timothy D. Hewitson, 1 Chrisman S. Samuel, 2 Stephen G. Holt, 1 Edward R. Smith. 1 Nephrology, Royal Melbourne Hospital, Melbourne, VIC, Australia; 2 Pharmacology, Monash Univ, Melbourne, VIC, Australia.

Background: Epigenetic regulation of histones is a key determinant of progression in renal disease. Although DNA methylation and miRNA regulation of histoblasts are reported, the pattern of post-translational histone modifications (marks) and their significance are largely unknown. Staining for H3K9 has particular interest as it can be both methylated and acetylated. In this study we examined the distribution and acquisition of H3K9 modifications in fibrogenesis.

Methods: Confocal microscopy with histone mark specific antisera was used to examine global H3K9 acetylation (H3K9Ac) and tri-methylation (H3K9Me3) after 3 and 10 days of unilateral ureteral obstruction (UUO). Cell culture studies using confocal/super-resolution microscopy and flow cytometry examined the effect of TGF-β1 on structural arrangement of these marks, and their relationship with kinetins and differentiation.

Results: H3K9Ac was diffuse and did not change after UUO, while H3K9Me3 was more intense in both proximal tubules (LTL lectin-positive cells) and myofibroblasts (a smooth muscle actin-positive cells). Sub-nuclear localisation in cultured primary rat renal fibroblasts and a proximal tubule cell line (NRK52e) showed that H3K9Ac was co-localised with phosphorylated Ser2 RNA polymerase II (pRNApol II), while H3K9Me3 was not, consistent with permissive and repressive effects on gene expression, respectively. H3K9Ac was diffusely distributed throughout the nucleus while H3K9Me3 was tethered to the nuclear membrane. Exogenous TGF-β1 had no effect on co-localisation with pRNApol II, but resulted in a redistribution of H3K9Me3 within the fibroblast nucleus. This was unrelated to any change in mitogenesis. Flow cytometry showed that H3K9Me3 but not H3K9Ac was acquired in myofibroblast differentiation.

Conclusions: Myofibroblast differentiation is accompanied by changes in both histone marks, and repression of the acquisition of the distinctive H3K9Me3 mark. Future studies will need to identify the genes involved and their ramifications.

Funding: Government Support - Non-U.S.

SA-P0225

Fibrosis and Altered Wnt10b Expression Occurs with Aging in the Kidney

Priyanka Sumudhu Katalilake, Helen Williams, Gavin Iain Welsh, Sarah J. George. School of Clinical Sciences, Univ of Bristol, Bristol, England, United Kingdom.

Background: Kidney fibrosis occurs with ageing, however little is known about the involvement of Wnt/β-catenin signalling in this process. Here we examined whether Wnt10b was altered with ageing and coincided with age-related renal fibrosis.

Methods: C57Bl/6 mice were aged to 18 months (old) and compared to mice aged 8 weeks (young). We excised the kidneys and processed them for RNA, protein and histological analysis.

Results: Initially, western blotting showed increased β-galactosidase protein in the old (n = 3 p = 0.05) mice and microtubulin staining of histology sections demonstrated increased fibrosis (n = 15 p = 0.05), confirming ageing and fibrosis, respectively. We observed a significant decrease in Wnt10b (n = 5 p = 0.05) protein with age and active β-catenin protein (n = 7 p = 0.05). Interestingly, the mRNA levels of Wnt10b however increased with age (n = 11 p < 0.01), suggesting suppressed mRNA translation of this protein. We scanned online databases for potential microRNA targets (miRs) that could target Wnt10b mRNA. Predicted miRs that target Wnt10b included miR-22 and miR-29a, which we found to be increased with age, (n = 7 p < 0.01 and n = 7 p = 0.05, respectively). As miR-22 and miR-29a are not validated targets of Wnt10b our next step is to validate them as targets against Wnt10b with a luciferase assay.

Conclusions: These results suggest that decreased Wnt10b protein and resultant β-catenin activity may occur in the kidney due to an increase in interfering microRNA preventing Wnt10b translation into protein and this may be associated with kidney fibrosis.

SA-P0226

Shikonin and 2-Deoxyglucose Attenuate Renal Fibrosis via Inhibiting Aerobic Glycolysis in Renal Interstitial Fibroblast

Hao Ding, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Almost all chronic kidney diseases lead to renal fibrosis, however, the mechanism that governs renal fibrosis remains unclear. Recently energy metabolism of the kidney, especially aerobic glycolysis, became as particularly interesting topic in kidney disease research, the questions whether aerobic glycolysis is required for renal myofibroblast activation and whether modulation of renal fibroblast aerobic glycolysis can affect the occurrence and progression of renal fibrosis are not fully elucidated.

Methods: In this study, we employed mice with unilateral ureter obstruction (UUO) and TGFβ1-treated kidney interstitial fibroblast cells as two model systems. We profiled the gene expression involved in glucose metabolism by using RT2 Profiler PCR arrays. In addition, we examined the gene expression of large number of genes correlated with fibrosis severity in mouse patient samples. To narrow target genes we identified 761 conserved expression regulators of fibrosis development. Genes differentially expressed in mouse models allowed proper clustering of control and diseased human kidney samples. Genes involved in immune response showed positive correlation with fibrosis development while genes with metabolism and oxidative reduction showed negative correlation both in mouse and human samples. Some of the known therapeutic target genes such as II1a, Aoc3 and Il6 showed distinct patterns between mouse models. We are performing functional studies to identify key transcriptional regulators of fibrosis development.

Conclusions: Comparative analysis of human and mouse kidney fibrosis have identified conserved genes and pathways in kidney fibrosis. These genes can serve as potential biomarkers or therapeutic targets for kidney fibrosis development.

Funding: NIDDK Support

SA-P0228

PBI-4425, a Novel Anti-Inflammatory/Fibrotic Compound, Improves Kidney Function in 5/6-Nephrectomized Rats


Background: Chronic kidney disease (CKD) represents an important health problem worldwide, and affects approximately one-seventh of adults in the US. PBI-4425, a novel first-in-class treatment for fibrotic diseases, possesses a pleiotropic mechanism of action with anti-inflammatory, antioxidant and anti-fibrotic properties. The aim of this study was to investigate the protective effect of PBI-4425 on kidney function and structure in the 5/6-nephrectomized (NX) rat model of CKD.

Methods: Sprague-Dawley rats were partially nephrectomized (2/3 of the left kidney) on day 0. On day 7 the right kidney was removed. Oral treatment with PBI-4425 (100 mg/kg, once a day) or vehicle was initiated at day 21, following randomization based on glomerular filtration rate (GFR) and body weight. Treatment was continued for 21 days and assessed every 5 weeks up to day 128 at which time the animals were sacrificed.

Results: Treatment with PBI-4425 resulted in a significant improvement in GFR as well as a significant reduction of urinary albumin to creatinine ratio (ACR). Histological kidney lesions scores were also significantly (p < 0.05) decreased in PBI-4425-treated rats (2.51 ± 0.9) compared to control (4.47 ± 0.9), as determined by H&E, PAS and Masson’s trichrome staining. PBI-4425 reduced the overexpression of inflammatory and fibrotic markers such as IL-6, MCP-1, TGF-β1, CTGF, collagen I, α-SMA, PAI-1, and MMP2 in both the kidneys and serum. Furthermore, a significant reduction of renal cell were observed in PBI-4425-treated 5/6 nephrectomized rats.

Conclusions: Taken together, these results suggest that PBI-4425 offers the potential as a novel therapy for chronic kidney disease by reduction of fibrosis and can potentially improve residual kidney function in patients with end stage renal failure.
SA-PO229
Gremlin 1 Neutralization Does Not Attenuate Markers of Fibrosis in the Unilateral Ureteral Obstruction Model
Philippe Costes,1 Yingqin Kan,1 Liyang Wang,2 Sheena Mumick,3 Kashmira Shah,1 Tian-Quan Cai,2 Michael Judo,3 Brian E. Hawes,2 Xiaoda Ni,4 Kenny K. Wong,2 Mashahida Handa,4 Mohammad Tabrizifard,4 Shirly Pinto.1 Cardiometabolic Diseases, Merck, Kenilworth, NJ; Discovery Operations, Merck, Palo Alto, CA; Discovery Operations, Merck, Kenilworth, NJ;1 Discovery Operations, Merck, Palo Alto, CA.

Background: Gremlin 1 (Grem1) is a secreted antagonist of the anti-proliferative bone morphogenic protein (BMP) signaling pathway, present in the extracellular space in rodents and in plasma in humans. Grem1 also promotes pro-fibrotic TGFβ signaling. Grem1 expression is increased in fibrotic organs in patients with idiopathic pulmonary fibrosis, diabetes, and nephropathy. In mice, grem1 overexpression worsens kidney fibrosis in the unilateral ureteral obstruction (UUO) model. Grem1+/− mice rendered diabetic with streptozotocin have improved kidney function compared with STZ WT mice. Our goal was to verify whether an antibody raised against grem1 can attenuate fibrosis in the kidney.

Methods: We synthesized two antibodies raised against grem1 and characterized their binding affinities for human and mouse grem1 using biacore, and their activity toward BMPs using functional assays. Next we evaluated the effect of a preventive treatment in the unilateral ureteral obstruction model.

Results: We determined the EC50 for mAb1 and mAb2 to be 1 and 5 nM by measuring BMP4-stimulated smad1/5/9 accumulation in mouse ST3 cells. UUO mice exhibited increased expression of grem1 mRNA, decreased BMP signaling and increased TGFβ signaling compared to sham-operated mice. In an experiment with a total duration of 10 days post-surgery, Grem1 antibodies decreased TGFβ activity marker psmad2 protein but there was only a trend in the increase of BMP target engagement marker psmad2/3. Some markers of fibrosis were improved, in particular collagen 1 and PAI-1 mRNAs (−33% and −66% respectively, P<0.01) and asma protein (−44%, P=0.05). These findings were not reproduced in an experiment with an extended duration of 14 days despite similar level of cell exposure.

Conclusions: Gremlin 1 neutralization did not confer robust protection against kidney fibrosis in the UUO model.

Funding: Pharmaceutical Company Support - Merck

SA-PO230
Treatment Efficacy of PBI-4050, an Orally Active Anti-Fibrotic Agent, Can Be Monitored by Measuring Urinary Biomarkers in 5/6-Nephrectomized Rats

Background: PBI-4050, a novel first-in-class orally active compound which is currently in clinical phase Ib/II in chronic kidney disease (CKD) patients, displays anti-fibrotic activities via a novel mechanism of action. In the present study, we examined the anti-fibrotic effect of PBI-4050 by evaluating urinary biomarkers in 5/6 nephrectomized (NX) rats.

Methods: Sprague-Dawley rats were partially nephrectomized (2/3 of the left kidney) on day 0. On day 7 the right kidney was removed. Oral treatment with PBI-4050 (200 mg/kg, once a day) or vehicle was initiated at day 21, following randomization based on their glomerular filtration rate (GFR) results. GFR was measured at day 21 and assessed every 3 weeks up to day 190. Urinary protein biomarker levels were determined by Multiplex analysis.

Results: We determined the EC50 for mAb1 and mAb2 to be 1 and 5 nM by measuring BMP4-stimulated smad1/5/9 accumulation in mouse ST3 cells. UUO mice exhibited increased expression of grem1 mRNA, decreased BMP signaling and increased TGFβ signaling compared to sham-operated mice. In an experiment with a total duration of 10 days post-surgery, Grem1 antibodies decreased TGFβ activity marker psmad2 protein but there was only a trend in the increase of BMP target engagement marker psmad2/3. Some markers of fibrosis were improved, in particular collagen 1 and PAI-1 mRNAs (−33% and −66% respectively, P<0.01) and asma protein (−44%, P=0.05). These findings were not reproduced in an experiment with an extended duration of 14 days despite similar level of cell exposure.

Conclusions: Gremlin 1 neutralization did not confer robust protection against kidney fibrosis in the UUO model.

Funding: Pharmaceutical Company Support - Merck

SA-PO232
The Assessment of CD80 Expression and Urinary CD80 Excretion in Childhood Nephrotic Syndrome
Rozan Topaloglu,1 Fehime Kara Erogul,1 Mihriban Inozu,2 Ali Duzova,3 Fatih Ozaltin,1 Dilecanh Orhan.1 Pediatric Nephropathy, Hacettepe Univ Faculty of Medicine, Ankara, Turkey; 1Pediatric Pathology, Hacettepe Univ Faculty of Medicine, Ankara, Turkey.

Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are the most common causes idiopathic nephrotic syndrome (INS) in children and pathogenesis is still unknown. Persistent CD80 expression was attributed in pathogenesis which may be caused by failure of regulatory T cells (Treg). But recent studies, which included mostly adult patients, questioned the reliability of immunohistochemistry (IHC) assays. Here we aimed to investigate CD80 podocyte expression and urinary CD80 excretion in a large cohort of pediatric patients and delineate the possible role of Tregs in pathogenesis.

Methods: IHC analyses of CD80, FOXP3 and CD4 were performed to 67 archival biopsies from 59 INS patients. CD80 expression was repeated with a different primary antibody by immunohistochemistry (IF). Urine CD80 excretion was also measured by ELISA.

Results: All but four biopsies showed negative expression for CD80 with IHC staining. But 23 (%57) biopsies were stained positive for CD80 in IF staining. CD80 expression was significantly higher in steroid responsive patients (p=0.041) but did not differ significantly between MCD and FSGS (p=0.169) nor presence of proteinuria at the time of biopsy (p=0.153). Urine CD80 level was significantly higher in MCD patients with relapse compared to controls (p<0.001) and MCD patients in remission (p=0.014) but showed no significant difference with FSGS patients (p=0.402). FOXP3+ CD4 T cells were observed in 20 (%36) samples (18 FSGS, 2 MCD). FSGS had significantly high interstitial FOXP3+ cells/mm2 than MCD and controls (p<0.001 and 0.001). MCD had similar FOXP3+ cells compared to controls (p=0.843).

Conclusions: Although we cannot exclude that CD80 expression may vary in different stages of disease, it seems not a solid marker of disease activity in terms of proteinuria and for differentiating MCD and FSGS. FOXP3+ Treg cells seem to play role in MCD not in a paracrine manner but increased infiltration seem to correlate with inflammation and chronicity in FSGS.
SA-PO233

Urinary Metabolomics in Clinical Hypertensive Nephrosclerosis – Is It a Real Disease or Normal Age-Related Kidney Function Decline with High Blood Pressure? 1,2 Marius Aalén Øvrehus,1,2 Manjula Darshi,3 Per Bruheim,4 Kumar Sharma,3 Stein I. Hallan.1,2 1 Inst of Cancer Research and Molecular Medicine, Norwegian Univ of Science and Technology, Trondheim, Norway; 2 Dept of Nephrology, St. Olavs Hospital Trondheim Univ Hospital, Trondheim, Norway; 3 Inst of Metabolomic Medicine, Univ of California San Diego, San Diego, CA; 4 Dept of Nephrology, Norwegian Univ of Science and Technology, Trondheim, Norway.

Background: The clinical diagnosis of hypertensive nephrosclerosis (HN) is debated and not well studied. Some argue that these patients only reflect normal aging. We therefore compared metabolic characteristics in HN cases to age- and sex-matched relevant groups.

Methods: Urine samples from HN (n=126), diabetic nephropathy (DN, n=41), hypertension (HTN, n=60) and healthy controls (CTR, n=60) from the HUNT 3 study (2006-08, Norway) were analyzed. Nephrosclerosis was defined as eGFR <60mL/min/1.73m² with ≥10 years of hypertension, and no diabetes, hematuria or proteinuria. Samples were analyzed with gas chromatography coupled to tandem mass spectrometry (GC-MS/MS).

Results: Of 75 organic acids, 31 displayed significant differences between groups. Principal component analysis (PCA) components 1, 2 and 3 explained 68% of the total variance. PLS-DA analysis showed that HTN and CTR overlapped strongly. HN and DN had substantial overlap and a large proportion of these patients were outside the 95% CI. Random forest analysis selected phenylactic, butyric, and methylcyclic acids as most important for classification. The top-25 list also included several medium-chain fatty acids, TCA-cycle metabolites, and gut microbial end products.

Conclusions: Hypertensive nephrosclerosis patients have metabolic disturbances which make them cluster together with diabetes nephropathy rather than with hypertensive patients or healthy controls.

Figure 1. Discriminant analysis (PLS-DA) showing separation of measured metabolites.

SA-PO236

Urinary Periostin Excretion Predicts Renal Outcome in IgA Nephropathy: A Prospective, Cohort Study 1,2 Jun Ho Hawng,1 Chae Rim Kim,1 Jung Nam An,1 Haejung Lee,1 Yun Kyu Oh,2 Kwon Wook Joo,2 Dong Ki Kim,1 Yun Soo Kim,1 Chun Soo Lim.1 1 Internal Medicine, Chung-Ang University School of Medicine, Seoul, Republic of Korea; 2 Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Republic of Korea.

Background: The degree of tubular atrophy and interstitial fibrosis (IFTA) is a prognostic indicator in glomerular diseases. Urinary periostin excretion may be a potential biomarker for IFTA severity in IgA nephropathy (IgAN). In the present study, we aimed to evaluate the predictive value of urinary periostin excretion on moderate to severe IFTA.

Methods: Of 399 patients from a glomerulonephritis cohort recruited between Jan. 2009 and Dec. 2014, 314 were enrolled. Serum and urine periostin were measured using ELISA. We divided the patients into 3 groups by periostin/creatinine (uPOSTN/Cr): group 1 (uPOSTN/Cr<0.3), group 2 (0.3-0.9), group 3 (≥1.0). Serum creatinine and eGFR (MDRD) were measured at initial and final visits. The initial and final IDMS-MDRD eGFRs (both <0.001). Histologically, group 3 patients had the highest IFTA severity.

Conclusions: IgA nephropathy patients with high urinary periostin excretion may be at risk for moderate to severe IFTA in the future.

SA-PO235

Urine EPIDERMAL GROWTH FACTOR, MONOCYTE CHEMOTACTIC PROTEIN-1 OR THEIR RATIO AS BIOMARKERS FOR INTERSTITIAL FIBROSIS AND TUBULAR ATROPHY IN PRIMARY GLomerulonePHRitis Surpanat Worawitchawong,1 Chagiya Kityakara,1 Suchin Worawitchawong.2 1 Dept of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand; 2 Dept of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand.

Background: The degree of tubular atrophy and interstitial fibrosis (IFTA) is an important prognostic factor in glomerulonephritis. Urine epidermal growth factor (EGF) and monocyte chemoattractant protein-1 (MCP-1) and their ratio, EGF/MCP-1, are known as potential biomarkers for IFTA in patients with IgA nephropathy. Although EGF and MCP-1 are known to be increased in patients with IFTA, the ability of EGF/MCP-1 ratio to discriminate moderate to severe IFTA has not been demonstrated. In separate studies, elevated MCP-1 and decreased EGF have been associated with IFTA severity, but the correlation of the two biomarkers in primary glomerulonephritis (GN) is unknown.

Methods: Urine samples were collected from healthy controls (n=18) and primary GN patients (n=58) at biopsy. MCP-1 and EGF were analyzed by enzyme-linked immunosorbent assay.

Results: Of 399 patients from a glomerulonephritis cohort recruited between Jan. 2009 and Dec. 2014, 314 were enrolled. Serum and urine POSTN were measured using ELISA. We divided the patients into 3 groups by urine periostin/creatinine (uPOSTN/Cr): group 1 (uPOSTN/Cr<0.3), group 2 (0.3-0.9), group 3 (≥1.0). Serum creatinine and eGFR (MDRD) were measured at initial and final visits. The initial and final IDMS-MDRD eGFRs (both <0.001). Histologically, group 3 patients had the highest IFTA severity.

Conclusions: IgA nephropathy patients with high urinary periostin excretion may be at risk for moderate to severe IFTA in the future.

Funding: Other NIH Support - Mailory University
were correlated with severe interstitial fibrosis/tubular atrophy (P = 0.004, interstitial inflammation (P = 0.007), cellular arteriolar hyalinosis (P = 0.001), and glomerular hypercellularity (P = 0.001). A higher initial uPOSTN/Cre level was associated with a greater decline in eGFR during follow-up (P = 0.043 when initial eGFR > 60, P = 0.025 when eGFR < 60 mL/min/1.73 m²), and the renal outcomes with ESRD (P = 0.03), death, and or eGFR decrease of >30% (P = 0.03) and ESRD or or eGFR decrease of >50% (P = 0.046) occurred more frequently in group 3. In multivariate analysis, uPOSTN group 3 (HR, 2.839 vs group 1 + 2; CI, 1.013-7.957; P = 0.047) was independently associated with ESRD in IgAN patients.

**Conclusions:** Urine POSTN/Cre value at initial diagnosis correlated with renal fibrosis and predicted the renal outcomes in patients with IgAN. It could be a promising urinary biomarker for renal fibrosis.

**Funding:** Pharmaceutical Company Support - This study was supported by research grant from Pfizer Inc., NY, USA

**SA-PO237**

**Urinary Exosomal Cerulposaminidase - A Potential Early Marker of Kidney Damage That Precedes Proteinuria**  

**Krishnamurthy P. Gudehithebi,1**  

Peter D. Hart, 1,2,3  

Amir J. Joshi,1,3  

George Dunce, 2,3  

Jose A.L. Arruda,1,4  

Ashok K. Singh, 1,2,4  

1 Div of Nephrology, H Stroger, Jr. Hospital of Cook County, Chicago, IL; 2The Hektoen Inst of Medicine, Chicago, IL; 3Internal Medicine and Pathology, Rush Medical College, Chicago, IL; 4Section of Nephrology, Univ of Illinois at Chicago, Chicago, IL.

**Background:** Pilot studies showed increased cerulposaminidase (CP) in urine exosomes of membranous nephropathy (n=9), lupus nephritis (n=8), FSGS (n=8), and IgA nephropathy (n=7) patients, suggesting that it could be a general marker of kidney damage. In this study we tested whether urinary exosomal CP could serve as an early biomarker of kidney damage preceding proteinuria.

**Methods:** Experiments were performed in the rat model of passive Heymann nephritis (PHN), which mimics human membranous nephropathy. PHN induced by injecting rats with anti-gp600 antibodies. At times 0, week 1, 2 and 3, urine exosomes were isolated by differential centrifugation. Exosomal pellets were extracted for measurement of CP by ELISA and protein by Bio-Rad method. PHN was confirmed by histology (trichrome staining) and glomerular IgG deposits using immunofluorescence. Histochemical staining for CP was performed to validate the ELISA results. Control rats were injected with saline instead of antibody.

**Results:** Injected with antibody showed typical intramembranous IgG deposits by week 1, and loss of brush border suggestive of proteinuria by week 2. Accordingly, PHN rats were non-proteinuric (<20 mg/day) at week 1, but presented with proteinuria (≥ 400 mg/day) at weeks 2 and 3 (n = 6). Urine exosomal CP levels (mg/mg of exosomal protein) at time 0 were 64±1.5, which increased by 3.5 fold at week 1 (228±39) and 6 fold by week 2 (409±17) and 3 (399±36) after the induction of PHN, suggesting that exosomal CP increased significantly even before proteinuria. These results were confirmed by enhanced immunofluorescent staining for CP observed in the interstitial area of proximal tubules of PHN rats compared to controls.

**Conclusions:** In conclusion, increase in urine exosomal CP could serve as a potential early biomarker of kidney damage that precedes the onset of proteinuria.

**Funding:** Private Foundation Support

**SA-PO238**

**Dysmorphic Urinary Red Blood Cells: Clinical Utility in Glomerular Disease**  


**Background:** Dysmorphic red blood cells (dRBCs) assessment on urine microscopy has been used to differentiate glomerular vs. non-glomerular disease. However, large studies to establish its usefulness are lacking. In this study, we assess the prevalence of dRBCs in a large group of biopsy proven kidney disease, and evaluate dRBCs ability to differentiate glomerular from non-glomerular kidney disease.

**Methods:** This is a retrospective study of adult patients with biopsy proven diagnoses and concurrent urine microscopy between 2012 and 2015 at our institution. The prevalence of dRBCs in glomerular vs. non-glomerular disease was assessed. dRBCs cutoff values of < 25% and ≥ 25% were compared using sensitivity, specificity, positive and negative predictive values (PPV and NPV). Variables potentially associated with glomerulonephritis (GN) (proteinuria, level of hematuria, dRBCs; 25% creatinine, and serum albumin) were assessed through univariable and multivariable logistic regression.

**Results:** We identified 482 patients who had native kidney biopsy with concurrent urinalysis. Mean age was 55 years, 47.7% were female, and 87.3% were white. Based on kidney biopsy findings, 372 (77.2%) had glomerular disease (GD) (GN 46% and non-GN 54%), 67 (13.8%) had non-glomerular disease. Significant dRBCs (≥ 25%) was seen in 28% of GN, in 12.4% of non-GN glomerular disease, and in 3.6% of non-GD. Dysmorphic RBCs level ≥ 25% showed a sensitivity of 28.5%, specificity 90.6%, PPV 63.5%, and NPV 68.7% for the diagnosis of GN. The logistic regression model showed that both dRBCs ≥ 25% (p = 0.003) and urine RBC level (11-50 vs < 11 (p = 0.003) or > 50 vs ≤ 11 (p =0.01) RBCs/µl) were associated with presence of GN on univariable analysis, however, only urine RBC level (11-50 vs < 11 (OR 6.9, 95% CI (3.8-12.7), p = 0.003) or > 50 vs ≤ 11 (OR 6.6, 95% CI (2.9-15.4), p = 0.003) RBCs/µl) was predictive of GN in multivariable analysis.

**Conclusions:** Based on a large group of biopsy-proven diverse renal disease entities, the finding of ≥ 25% dRBCs on urine microscopy, despite being specific for GN, did not add to the ability of hematuria (> 10 RBCs/µl) to predict presence of GN on kidney biopsy, and may not have a significant diagnostic yield in this setting.

**Funding:** NIDDK Support, VA Support, Private Foundation Support

**SA-PO241**

**Proteomics of Diabetic Nephropathy Glomerulus for Understanding Pathophysiology**  

Tadashi Yamamoto,1 Keiko Yamamoto,1 Hidehiko Fujinaka,2 Shigeru Miyazaki,1 1Biological Fluid Biomarker Center (BBC), Nigata Univ, Nigata, Japan; 2Pediatrics, Nigata National Hospital, Kashiwazaki, Nigata, Japan; 3Internal Medicine, Shinkaku Hospital, Nigata, Japan.

**Background:** Diabetic nephropathy (DN) is a crucial complication of diabetes mellitus, progressing to the end-stage of chronic kidney disease (CKD) in a large group of patients. Early identification of the rate and extent of tubulointerstitial fibrosis, regardless of the initiating lesion, has failed to account for this unpredictable rate of progression. We now propose that the rate and extent of tubulointerstitial fibrosis, regardless of the initiating lesion, are determined by molecular signatures specific to individual tubulointerstitial lesions and the immune make-up of the interstitium.

**Methods:** We interrogated routine human kidney biopsies with broad “omics” readouts conducted on tubular subsegments obtained by laser microdissection. We also developed a novel 3D microscopy quantitative approach to quantify the immune cell make-up in the same biopsies.

**Results:** We show that tubular subsegmental transcriptomics and proteomics can be reliably obtained from a routine human kidney biopsy. The same biopsy can also be analyzed quantitatively with 3D fluorescence microscopy to reveal the type and distribution of immune cells in relation to renal tubular segments. Using this approach we examined urine exosomes from diabetic nephropathy patients who exhibited different rates of progression despite similar traditional biopsy readings. Our studies revealed unique signatures specific to each patient that correlated well with disease progression.

**Conclusions:** Our studies support the hypothesis that at a subsegmental level, a unique molecular and cellular signature exists which determines the progression of most kidney diseases. This signature will guide our ability to determine best therapy and prognosis for individual patients, validate animal models and identify novel therapeutic targets.

**Funding:** NIDDK Support, VA Support, Private Foundation Support

**SA-PO239**

**The Association of Cardio-Metabolic Index with Microalbuminuria in General Population**  

Joon-Sung Park,1 Jong Wook Choi.2 1Internal Medicine, Hanyang Univ College of Medicine, Seoul, Korea; 2Internal Medicine, Hanyang Univ College of Medicine, Seoul, Korea.

**Background:** Cardio-metabolic index (CMI) is novel indicator of metabolic disturbance and it can discriminate diabetes and predict risk atherosclerosis progression. Here, we investigated whether CMI is related with development of microalbuminuria in general population.

**Methods:** We analyzed anthropometric and biochemical data from a nation-wide, population-based, case-control study (the Korean National Health and Nutrition Examination Surveys KNHANES VI). Eligible cases were all native Korean who were aged 20 years or more and had no any medical illness.

**Results:** A total of 5398 participants were divided into five CMI quintiles. Participants in highest CMI quintile were more hypertensive and had greater glycemic exposure, increased urinary protein/creatinine ratio (UACR) and decreased kidney function as compared with other quintiles. Our Cochran-Armitage test showed that CMI had dose-response relationship with prehypertension, diabetes, microalbuminuria, and early impaired kidney function. Adjusted multiple logistic regression analysis revealed that increased CMI was independently associated with prehypertension (adjusted OR = 1.161, 95% CI = 1.092-1.234), prediabetes (adjusted OR = 1.081, 95% CI = 1.021-1.142) and microalbuminuria (adjusted OR = 1.075, 95% CI = 1.001-1.154) although early impaired kidney function was not.

**Conclusions:** In this study, we demonstrated that mild increase of CMI is associated with slightly elevated blood pressure, mild hyperglycemia, and increased urinary excretion of albumin in the healthy population and may be a reliable predictor of with harmful effect of metabolic disturbance on kidney before appearance hypertension and diabetes mellitus. To confirm these findings, large population-based prospective clinical should be needed.
each) by histological examination. The glomerular sections were directly digested with trypsin and trypsin peptides were collected by using C18 column for liquid chromatography (LC)-MS. Proteins were identified by Mascot search engine and semi-quantified by the normalized spectrum index. The glomerular proteomes were compared between the three DN lesions and non-disease kidneys. The glomerular proteomes, which increased or decreased more than 2 fold, were subjected for IPA pathway analysis.

**Results:** Approximately more than one thousand proteins (by gene names) were identified in each glomerular sample semi-quantitatively by MS. Cellular localization was predicted for the proteins of more than 2-fold change in DN glomeruli at plasma membrane (10-15%) and cytoplasm (50-60%). Pathways related to Cell Death & Survival, Cell Mobility, Immunity & Inflammation and others were enhanced in the DN glomeruli and also upstream proteins, such as TGFβ1 were depicted.

**Conclusions:** Proteomic analysis of DN glomeruli successfully demonstrated acoustics of several molecular pathways in the site, providing new insight to the pathophysiology and making possible to select crucial molecules for drug discovery.

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

SA-PO242

**KidneySeq™, A Comprehensive Inherited Kidney Disease Panel**

M. Adela Mansilla, 1 Ramakrishna Sompallae, 1 Sara Mason, 2 Carla Nishimura, 1 Anne E. Kwikic, 1 Colleen Ann Campbell, 1,2 Christie P. Thomas, 1 Richard J. Smith, 1,3 1 Inst of Human Genetics, Univ of Iowa, Iowa City, IA; 2Internal Medicine, Univ of Iowa, Iowa City, IA; 3Kidney Disease, Univ of Iowa, Iowa City, IA.

**Background:** KidneySeq™ is a comprehensive inherited kidney disease panel using next generation sequencing developed by the Iowa Institute of Human Genetics (IIHG) and the Division of Nephrology at the University of Iowa.

**Methods:** This clinical genetic test simultaneously interrogates 179 renal genes implicated in 75 renal diseases, facilitating the diagnosis of genetic renal diseases as well for the observed phenotype has been identified.

**Results:** Since launching KidneySeq™6 months ago, we have tested 21 clinical samples that include disorders of tubular ion transport, glomerulopathies, congenital anomalies of kidney and urinary tract (CAKUT) and ciliopathies. A genetic diagnosis was identified in 10 cases (48%). By disease type, the solve rate was: disorders of tubular ion transport, 33% (3 of 9 cases); glomerulopathies, 50% (3 of 6 cases); CAKUT, 67% (2 of 3 cases); and ciliopathies, 67% (2 of 3 cases).

**Conclusions:** In 7 cases, the genetic diagnosis differed from the clinically suspected diagnosis, emphasizing the overlapping phenotypic spectrum that characterizes several renal diseases and highlighting the value of comprehensive genetic testing. KidneySeq™ provides a rapid, cost-effective method to improve the care of patients with renal disease.

**Funding:** Private Foundation Support

SA-PO243

**Assessment of the IRIDICA Technique for Rapid Detection of Acute Infection in Renal Patients Recently Treated with Antimicrobials**

Anamika Advaney, 1 Sevada Hassan, 1 Arinka Massiah, 2 Mark Wilks, 1 Raj Thurasingham. 1 Renal, Barts Health Trust, London, London, United Kingdom; 2Microbiology, Barts Health Trust, London, United Kingdom.

**Background:** The IRIDICA bacterial bloodstream (BAC BSI) assay is a semi-quantitative diagnostic test that uses polymerase chain reaction (PCR) and electrospray ionization-mass spectrometry (ESI-MS) to detect and identify bacterial, viral and fungal nucleic acids from a blood sample within 6 hours. Prompt management of sepsis is essential. Detection of pathogens with the current gold standard blood culture is challenging in the context of recent antimicrobial therapy. We compared the IRIDICA assay against blood culture technique in pyrexial renal patients.

**Methods:** We included renal patients who presented with a fever of >38°C from January 2015 to April 2016. This included immunosuppressed transplant recipients and dialysis patients. Blood cultures were taken with blood culture for retrospective IRIDICA analysis. The IRIDICA technician was blinded. We used our renal database to establish if patients had received antimicrobial therapy in the preceding 30 days. We excluded the patients who did not have a blood culture analysis at the time of fever.

**Results:** We analysed 182 samples from January 2015 – April 2016. Mean age of patients was 57.6 years. This included patients who had more than one presentation during this period. Compared to blood culture the IRIDICA assay demonstrated a sensitivity and specificity of 70%. The positive predictive value was 26% and the negative predictive value was 94%, 39% (21%) samples were positive for IRIDICA but negative for blood culture. Of these 72% had received antimicrobials in the preceding 30 days. 14 samples had both positive blood culture and IRIDICA samples. None of these patients had antimicrobial therapy in the preceding 30 days.

**Conclusions:** The IRIDICA assay is superior to blood cultures when detecting a pathogen in a renal patient who has been treated with antimicrobials in the preceding 30 days. IRIDICA is also effective in excluding infection. Without preceding antibiotic use, blood cultures are just as effective as the IRIDICA assay. However, the IRIDICA assay allows faster identification of pathogens compared blood culture, which can take 5 days.

SA-PO244

**Decreased Expression of the Gut-Homing CCR9 Chemokine Receptor on Memory B-Cell Subsets in IgA Nephropathy**

Marten Segelmak, 1 Camilla Skoglund, 1 Daniel Soderberg, 1 Per Eriksson. 2 Medical and Health Sciences, Linköping Univ, Linköping, Östergötland, Sweden; 2Clinical and Experimental Medicine, Linköping Univ, Linköping, Östergötland, Sweden.

**Background:** IgA nephropathy and IgA vasculitis are characterized by the deposition of polymeric undergalactosylated IgA1 (GdIgA1) in the renal mesangium. GdIgA1 should normally be secreted into the respiratory and gastrointestinal tract, but is in IgAN often elevated in the systemic circulation. Defective homing of lymphocytes could contribute to ectopic production of GdIgA1.

**Methods:** The putative human counterparts to the three B-cells lineages defined in mice B1-, B2- and MZ-B-cells were characterized by multi-channel flow cytometry and the percentage of each subset expressing IgA as well as the chemokine receptor CCR9 was determined.

**Results:** There were no differences between IgAN and IgAV patients. IgAN/V patients tended to have more lymphocytes and a larger percentage of B-lymphocytes, but differences were not significant. There were no differences in the proportion of naïve, B1-, MZ- and B2-like populations between patients and controls. Similarly the proportion of IgA+ cells was similar in all subsets. However, patients exhibited a significantly lower proportion of CCR9+ B1-like cells. When comparing the CCR9+ on IgA positive cells, the proportion was lower in patients for all types of memory B-cells, the most pronounced difference was found among the MZ-like cells.

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

SA-PO245

**Identification of CD146 as a Novel Biomarker to Evaluate the Disease Progression and Prognosis in Early Diabetic Nephropathy**

Yang Fei, 1 Ying Fan, 1 Li Zheng, 1 Jemin Wang, 2 Jiejun Wen, 1 Zhenzheng Jiang, 1 Li He, 1 John C. He, 1 Niansong Wang, 1 Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People’s Hospital, Shanghai, China; 2Project and Portfolio Management Team, Asia & Emerging Market iMED, AstraZeneca R&D, Shanghai, China; 3Medicine, Icahn School of Medicine at Mount Sinai, New York.

**Background:** Glomerular endothelial cell injury plays a crucial role in the development and progression of diabetic nephropathy (DN). CD146, an endothelial marker, was reported to increase in chronic renal failure reflecting endothelial dysfunction. However, the role of CD146 in DN remains largely unknown.

**Methods:** 159 non-diabetes type 2 DN patients from 2008 to 2015 were enrolled to measure the serum concentration of soluble CD146 (sCD146). 94 pure diabetes mellitus type 2 and 100 healthy participants were taken as controls. The subjects were categorized by their CKD stages and CKD-1-3 was defined as early eGFR loss. Another independent cohort of 49 patients with definite diagnosis of DN by kidney biopsy were eligible for the immunohistochemistry study of CD146.

**Results:** Our data showed that serum concentration of sCD146 was upregulated in patients with DN (648.2±292.6 ng/ml) as compared to DM (434.8±150.0 ng/ml) and healthy control (358.3±121.4 ng/ml). As compared to DM (434.8±150.0 ng/ml) and healthy control (358.3±121.4 ng/ml) < 0.001 . Elevated serum sCD146 was inversely associated with renal function (r = -0.01) and proved to be a more optimal marker(AUC=0.803) than urine albumin creatinine ratio (UACR) (AUC=0.574, p<0.01) to evaluate disease progression of DN at early GFR loss. In kidney tissues, CD146 was co-localized with endothelial marker CD31 and increased in DN when compared with MCD and normal controls. The intensity of CD146 in kidney was associated with disease progression and with severity of pathological findings in DN patients at early GFR loss. We further evaluated Cox regression suggested that both serum concentration of sCD146 and kidney in situ expression of CD146 were associated with the renal outcomes.

**Conclusions:** Our findings demonstrate that CD146 could be a practical biomarker to evaluate disease progression and predict renal outcomes in patients with early to moderate stages of DN. The aberrant expression of CD146 may reflect endothelial dysfunction and vascular angiogenesis in DN.
SA-PO246

Background: The aim is to study isolated segmental sclerosis (IS) seen in transplant (Tx) biopsies (Bx) from patients (pt) who do not have proteinuria.

Methods: Tx Bx from 01/2000-12/2015 were included. IS was defined as segmental sclerosis seen within 12 months of Tx from a pt without significant proteinuria (<750 mg/day) at time of Bx. Histology data, pt demographics and follow-up (FU) data ranging from 6-72 months were analyzed.

Results: IS was seen in 21/6366 (0.33%) of all Bx in the study period. 7/21 (33%) resulted in eventual graft loss, 1/21 (4.7%) of which progressed to focal segmental glomerulosclerosis (FSGS) with nephrotic range proteinuria (NRP). 14/21 (67%) had stable creatinine levels and no proteinuria in the 72 month FU period. 20/21 (95%) had FSGS-like histology. 5/21 (24%) had concurrent acute cellular rejection. Electron microscopy in 12 Bx showed: 5 with intact podocytes; 7 with focal effacement; and 0 with diffuse effacement.

Conclusions: IS in the early post-Tx period is rare. 1 case (4.7%) progressed to NRP, consistent with FSGS. Our study did not reveal sex, age or race predilection for IS. IS had no correlation with acute rejection. Histology could not predict which IS lesions would progress to FSGS. Awareness of IS and avoidance of usage of the term “FSGS” may help to prevent unnecessary treatment. Further studies are needed.

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SA-PO247
Validation of Whole Slide Digital Imaging in the Renal Biopsy Service at a Large Academic Medical Center  Vighnesh Walavlalkar, Kuang-Yu Jen, Zoltan G. Laszik. UCSF Medical Center, San Francisco, CA.

Background: The aim of the study was to validate the use of whole slide digital imaging (WSDI) and the renal biopsy (RBx) service at our institution. Patient care, efficiency, education and quality control (QC) were emphasized.

Methods: From 11/1/2015 to 4/30/2016 three slides (2H&E and 1 PAS) from all TxBx from 01/2000-12/2015 were included. IS was defined as segmental glomerulosclerosis (FGS) with nephrotic range proteinuria (NRP). 1 case (4.7%) progressed to NRP, consistent with FSGS. Our study did not reveal sex, age or race predilection for IS. IS had no correlation with acute rejection. Histology could not predict which IS lesions would progress to FSGS. Awareness of IS and avoidance of usage of the term “FSGS” may help to prevent unnecessary treatment. Further studies are needed.

Conclusions: Standardized history and scanning operational protocols were crucial for validating the use of WSaD for RBx interpretation. There were no false positive results attributed to WSDI and the TAT decreased significantly for a pDx. WSDI also contributed to improved education and allowed for remote on-line RBx review with nephrologists at other sites. Overall use of WSaD was met with great enthusiasm by technologists, trainees and referring nephrologists.

SA-PO248
Glomerulonephritis Associated with Allogeneic Bone Marrow Transplantation  Yu Tatsuki,1 Eiji Ishimura,2 Mari Sakura,2 Mitsuru Ichii,2 Yoshiiteru Ohno,2 Shin'ya Nakatani,1 Akihiko Tsuda,1 Masayuki Hino,1 Masashi Inaba.1 1Osaka City Univ Graduate School of Medicine, Japan; 2Ishikiri Seiki Hospital, Japan.

Background: Clinicopathological characteristics of glomerulonephritis (GN) associated with allologeneic bone marrow transplantation (BMT) are still insufficient. Previous reports on these cases have mainly referred to glomerular immunological changes; while tubulointerstitial and vascular lesions are known to be major findings of graft rejection in cases with renal transplantation.

Methods: Out of 129 BMT cases in Osaka City University Hospital from 2008 to 2011, nephrotic syndrome (NS) was seen in 4 patients (50.8 ± 9.3 year-old, 3 males and 1 female) after BMT. Their primary hematologic diseases consisted of 2 cases with acute lymphocytic leukemia, 1 with adult T-cell leukemia, and 1 with aplastic anemia. We analyzed these 4 cases with BMT associated GN clinicopathologically.

Results: Mean duration (± SD) between BMT and the onset of NS was 29.5 ± 9.8 months. One case received immunosuppressive therapy (cyclosporine (CsA) 10mg/day) at the onset. Urinary protein level was 7.4 ± 4.2 g/day. Renal histological diagnosis of membranous GN (MGN) and proliferative GN (PGN) was made in 3 cases and in 1 case, respectively. Moderate to severe interstitial infiltration of mononuclear cells accompanied by tubulitis, approximately 20-50% of parenchyma, was observed in 2 cases with MGN. In a case with PGN, several glomerular segmental double contours with segmental endocapillary proliferations were seen in light microscopy. The lesions were not accompanied with epithelial cell increase nor mesangial proliferation, suggesting the presence of acute endothelial cell injury. Mild interstitial infiltration of mononuclear cells was also observed in this case. All 4 cases were treated with prednisolone 40-50 mg/day and/or CsA 40-100 mg/day. Complete or partial remission was achieved after the treatment (urinary protein levels: 1.1 ± 0.9 g/day) within 3 months.

Conclusions: This study indicates that MGN is main lesion and acute tubulointerstitial and vascular lesions accompany BMT-associated GN, which may not be so rare complication of BMT. Clinically, favorable response to immunosuppressive therapy can be expected.

SA-PO249
Improvement of Clinical Outcome in Kidney Diseases via Online – Thai Glomerular Disease Registry: The First Year Report Ratana Chawanasuntorapoj,1 Thai Glomerular Disease Collaborative Network, Bangkok.

Background: End stage renal disease (ESRD) cause the high morbidity, mortality, and cost in health care system. The prevention of ESRD is the early recognition and appropriate treatment. Glomerulonephritis is the third most common cause of ESRD in Thailand comparable to the Western country. In 2013, Thailand Renal Replacement Therapy (TRT) reported Lupus nephritis (LN) was the most common cause of ESRD followed by IgA nephropathy (IgAN), and focal segmental glomerulosclerosis (FSGS). The quality registry and network can provide the prompt management in these patients.

Methods: Thai Glomerular Disease Collaborative Network (TGDCN) originally consists of 9 tertiary care centers, We developed the Web-based Online registry to collect the data from GN patients with aged>18 years. We recorded the demographic data including gender, age, education, native habitat, the laboratory tests, and the pathological findings.

Results: We recruited666 patients performed native kidney biopsy during Jul 1, 2014 to Jun 30, 2015. The female to male ratio was 2.16:1. The mean age, creatinine, albumin, and cholesterol were 42 (18-82) years, 1.4 (0.4-13) mg/dL, 2.9±0.8 g/dL, and 296±118 mg/dL in respectively. The median proteinuria was 3.2 (0-22) g/day. The patients presented with 34% of nephrotic syndrome, 22% of nephritis, 21.7% of nephrotic nephritis, 52% of renal impairment (creatinine>1.2 mg/dL), and 54.4% of new or aggravated hypertension. The renal pathological findings showed 38% of LN, 17.6% of IgAN, and 9% of FSGS with the initial renal impairment at kidney biopsy. This study was not able to show significant difference in proteinuria, gender, age, education, native habitat, the laboratory tests, and the pathological findings.

Conclusions: This study described the first three common renal pathological findings including LN, IgAN, and FSGS with the initial renal impairment at kidney biopsy. This might be the severity of the disease or the delay in performing biopsy due to failure of kidney biopsy and referring system. All three diseases were the most common GN causing the ESRD in Thailand. The development of qualified registry and GN network may improve the health care service and support the further study in both clinical and translational research.

Funding: Private Foundation Support
SA-PO250

Serum Cholesterol in Predicting Nephrotic Syndrome Diseases
Wonnagarm Kittanmongkolchai,1 Samih H. Nasr,2 1Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Anatomic Pathology, Mayo Clinic, Rochester, MN.

Background: Hypercholesterolemia is one of the criteria for nephrotic syndrome. However, the cut-off level of serum cholesterol for nephrotic syndrome has not been well defined.

Methods: The pathologic reports of native kidney biopsies of patients ≥18 years of age with proteinuria ≥3 g/day performed at Mayo Clinic, Rochester, MN between 1/2000 and 8/2014 were reviewed. Patients who had liver disease, malnutrition, urinary dysmorphologic RBC or RBC cast, paraproteinemia with urine albumin ≥3 g/day, inconclusive diagnosis, no electron microscopy report or received immunosuppression within 6 months prior to renal biopsy were excluded. Patients were divided into group 1: nephrotic syndrome diseases (MCD, primary FSGS, membranoproliferative and amyloidosis) and group 2: other diseases presented with nephrotic range proteinuria (secondary FSGS, diabetic nephropathy, glomerulonephritis, TMA, advanced kidney disease and other diseases). Receiver operating characteristic (ROC) curve was used to determine sensitivity and specificity of serum cholesterol for prediction of nephrotic syndrome diseases.

Results: From total of 6,707 native renal biopsy reports, 251 patients fulfilled the above criteria and were included in the study. 137 patients were classified into group 1 and 114 were in group 2. The average serum cholesterol was significantly higher in group 1 (303±105 vs 266±68 mg/dL, P=0.0001). The ROC area under the curve for serum cholesterol to predict nephrotic syndrome diseases was 0.79 (P<0.001). Serum cholesterol 300 and 350 mg/dl were highly specific for nephrotic syndrome diseases (specificity 89% and 99%, respectively).

Conclusions: Total cholesterol ≥300 mg/dL is highly specific to nephrotic syndrome diseases and may help differentiate with other diseases that also contribute to nephrotic-range proteinuria. Renal biopsy should be considered in patients with nephrotic-range proteinuria and serum cholesterol more than 300 mg/dL.

SA-PO251

Bedside Real-Time Ultrasound-Guided Kidney Biopsy Service Fully Run by Nephrology: Safety and Procedure Adequacy
Mohammed Alzubaidi, Jalal E. Hakmei, N’Da Abouhasan, Juan Carlos V. Velez. Internal Medicine, Div of Nephrology, Medical Univ of South Carolina, Charleston, SC.

Background: Percutaneous kidney biopsy (PKB) is routinely performed by a nephrologist under ultrasound (US) guidance from a radiologist, or solely by interventional radiology (IR). There is paucity of data regarding safety and feasibility of PKBs performed by a nephrology (NEPH) team without participation of a radiologist. We hypothesized that PKBs independently performed by a NEPH team are as safe and optimal in yield of kidney tissue as those performed by IR.

Methods: We established a NEPH clinical service to independently perform bedside real-time US-guided PKBs. Records were reviewed to compare complication rate [minor: hematoma, major: blood transfusion (ordered at the discretion of the radiologist)] of PKBs performed by NEPH team vs. those performed by IR (electronic microscopy) of PKBs performed by the NEPH team vs. those performed by IR by a nephrology (NEPH) team without participation of a radiologist. We hypothesized that PKBs independently performed by a NEPH team are as safe and optimal in yield of kidney tissue as those performed by IR.

Results: We identified 109 PKBs performed by NEPH (16g needle) and 103 by IR (18g needle) and 103 by IR (18g needle) and 103 by IR (18g needle). P<0.05), and small artery vitreous degeneration(53.4% vs. 36.2%, p<0.05), are higher than in NEPH patients. The patients with the reduced RPT showed more glomerular sclerosis >50% (40.7% vs. 15.9%, p<0.05),renal tubular atrophy (83.1% vs. 35.8%, p<0.05),interstitial fibrosis(67.6% vs. 45.8%, p<0.05). There is no significant difference in age, blood pressure, hemoglobin, serum creatinine and lipids. In the reduced RPT group, the ratio of total renal parenchymal thickness of the reduced RPT group vs. those performed by IR under computer tomography (CT) guidance.

Results: We identified 109 PKBs performed by NEPH (16g needle) and 103 by IR (16g needle), and 103 by IR (18g needle) and 103 by IR (18g needle). P<0.05), and small artery vitreous degeneration(53.4% vs. 36.2%, p<0.05), are higher than in NEPH patients. The patients with the reduced RPT showed more glomerular sclerosis >50% (40.7% vs. 15.9%, p<0.05),renal tubular atrophy (83.1% vs. 35.8%, p<0.05),interstitial fibrosis(67.6% vs. 45.8%, p<0.05). There is no significant difference in age, blood pressure, hemoglobin, serum creatinine and lipids. In the reduced RPT group, the ratio of total renal parenchymal thickness of the reduced RPT group vs. those performed by IR under computer tomography (CT) guidance.

Conclusions: Total cholesterol ≥300 mg/dL is highly specific to nephrotic syndrome diseases and may help differentiate with other diseases that also contribute to nephrotic-range proteinuria. Renal biopsy should be considered in patients with nephrotic-range proteinuria and serum cholesterol more than 300 mg/dL.

SA-PO252

The Characteristics of Class II MHC+ Mononuclear Cells within Native Kidney Are Distinct from Peripheral Blood and Transplant Kidney
Bairbre McNicholas1, Susan K. Anderson,1 Matthew D. Griffin,2 Kimberly A. Maczynski,1 1Div of Nephrology, Univ of Washington, Seattle, WA; 2REMEI, National Univ of Ireland, Galway, Ireland.

Background: Mononuclear phagocytes (MPs) are a heterogeneous population of cells that resides in the kidney. Little is known of their phenotype in normal human kidney and of their contribution to injury compared to influx of circulating monocytes from blood.

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

687A
Results: The mean age was 38 years and the mean creatinine clearance using 24-hour urine collection was 138 ml/min. Overall 6 of 15 markers had FE > 100 (range 218 –1019%), 5 of which had been reported in prior studies using 24-hour urine samples. The FE of these 6 candidate secretion markers was relatively stable, with diurnal variation in secretion described as maximum to minimum FE ratios as high as 3.2:1 for cinnamoylglycine to a low of 1.9:1 for phenylacetylglutamine.

Conclusions: Several endogenous markers of tubular secretion are relatively stable over the day, making spot urine specimens feasible for assessing tubular secretion. Studies evaluating these markers in older persons and across a wide range of eGFR are needed.

SA-PO255
Stretching and Exposure to Protein Synergistically Activate Innate Immunity and Inflammation in Proximal Tubular Cells
Simone C. A. Arias,1 Viviane D. Faustino,1 Luciene dos Reis,2 Flavia G. Machado,2 Niels O. S. Camara,1 Clarice K. Fujihara,1 Roberto Zatz.1 1Univ of Sao Paulo; 2Washington Univ.

Background: Cell cyclic stretching (ST) stimulates inflammation in glomerular cells, but it is unclear whether tubular cells respond to ST in the same manner. Moreover, a conceivable effect of ST on innate immunity activity has not been examined. In addition, the effect of ST has been studied in the absence of protein, a condition not seen in vivo. We investigated whether: 1) ST alone activates innate immunity in proximal tubular cells (PTC); 2) Simultaneous PTC exposure to ST and protein results in more intense inflammation and innate immunity activation than ST alone.

Methods: Rat PTC (NRK52E) were cultured and subjected to ST (20% maximum elongation) (ST, N=4) or ST plus bovine serum albumin (BSA), 1 mg/ml (ST+BSA, N=4). Control cultures (C, N=4) were exposed to no ST or BSA. After 24 h, MCP-1 (pg/ML), IL-6 (pg/ml) and IL-1β (pg/ml) were evaluated by ELISA, while TGF-β, Collagen-1 (COL-1), TLR4 and Caspase-1 contents were assessed by WB (x C).

Results: Exposure of PTC to ST or ST+BSA resulted in no limitation of cell viability or proliferative capacity (not shown). ST alone significantly increased TGF-β. Exposure to both ST+BSA increased MCP-1, IL-6 and COL-1 protein expression. In addition, ST+BSA activated innate immunity, as indicated by increased expression of TLR4, caspase-1 and IL-1β.

Conclusions: ST and BSA synergistically activate innate immunity and enhance inflammation and COLl production. Since both abnormalities can be present in both ST+BSA increased MCP1, IL-6 and COL1 protein expression. In addition, ST+BSA activated innate immunity, as indicated by increased expression of TLR4, caspase-1 and IL-1β.

SA-PO258
Risk of Percutaneous Renal Biopsy of Native Kidneys in the Evaluation of Acute Renal Failure
Stephen M. Korbet, William Luke Whittier. Internal Medicine, Rush Univ Medical Center, Chicago, IL.

Background: The purpose of this study is to assess the risk of bleeding complications in pts undergoing percutaneous renal biopsy (PRB) of native kidneys for the evaluation of acute renal failure (ARF).

Methods: PRB of native kidneys was performed in 958 adult pts from 1991 through 2015 at Rush Medical Center with real-time ultrasound and an automated biopsy needle. Baseline demographic, clinical and laboratory information was collected along with the indication for PRB and pts were followed prospectively for complications. PRB for evaluation of ARF was performed in 160 pts (17%). The remaining 798 pts were biopsied for hematurnia, and/or proteinuria, and/or chronic kidney disease. Complication rates were compared between these 2 groups. A complication was defined by the need for an intervention (transfusion of packed red blood cells, an interventional radiologic (IR) or surgical procedure) or the need for re-admission or death. Statistical analysis was performed using Fischer exact test for categorical data and Mann-Whitney test for continuous data. Results are reported as means ± standard deviation and a p-value of <0.05 was considered significant.

Results: Pts biopsied for ARF were older (58±17 vs. 44±16 yrs, P<0.01), had a higher level of serum creatinine (SCr) (4.5±2.7 vs. 1.8±1.6 mg/dl, P<0.01 and <1.5 mg/dl in 94% vs. 37%, P<0.001), a lower hemoglobin (10.4±1.7 vs. 12.1±2.1, P<0.01 and <10.0 g/dl in 43% vs. 17%, P<0.01), and a greater proportion with an abnormal bleeding time (>9 min: 1% vs. 7%, P<0.05) and an abnormal PTT (>33 seconds: 15% vs. 5%, P<0.01), all risk factors for complications. The diagnostic adequacy of the biopsy was similar in both groups (ARF-98% vs. 99%). Complications post-PRB were significantly greater in pts biopsied for ARF (11.3% vs. 6.6%, P<0.05; OR 1.78) with pts biopsied for ARF requiring more transfusions (10% vs. 5.1%, P=0.03) and twice as many IR procedures (1.9% vs. 1.0%, P=0.4). There were no deaths in pts biopsied for ARF.

Conclusions: We conclude that pts biopsied for evaluation of ARF have increased risk factors for a complication and a greater rate of complication requiring intervention post-PRB compared to pts biopsied for other reasons.

SA-PO256
Proteomic Analysis of Micro-Dissected Neprhon Segments and Urine Selected PLA2R1 and GGT5 as New Urinary Biomarker Candidates for Chronic Kidney Disease
Hitoshi Fujinaka,1 Shigeru Miyazaki,2 Yuya Eriguchi,3 Yoshio Konishi,1 Tadashi Yamamoto.1 1Inst of Research Collaboration and Promotion, Biofluid Biomarker Center, Inst of Research Collaboration and Promotion, Niigata Univ, Niigata, Japan; 2Shirakawa Hospital, Niigata, Japan; 3Osaka City General Hospital, Osaka, Japan; 4COJ Biofluid Biomarker Center, Inst of Research Collaboration and Promotion, Niigata Univ, Niigata, Japan.

Background: New biomarkers have been searched for the early diagnosis of chronic kidney disease (CKD), mostly in patients with overt proteinuria. The trials have not been so successful since most of the urinary proteins are derived from plasma in the patients. About 20% to 30% of the proteins in our previous microdissected kidney segments or urine samples were derived from plasma proteins. These observe the urine samples from healthy volunteers and subjects with chronic kidney disease (CKD). We have generated 2 datasets of nephron segment and of urine samples. Each of these datasets was used for urinary protein discovery. The datasets were compared by mass spectrometry followed by semi-quantitative analysis. By comparing these proteome datasets, nephron-segment-unique urinary proteins were selected as urinary biomarker candidates. The site-uniqueness in the kidney was confirmed by IHC using specific antibodies. Amounts of the selected proteins in urine were measured by Surface Plasmon Resonance System in IgA nephropathy (IgAN) patients and healthy volunteers.

Results: Nephron-segment-unique urinary proteins were selected: glomerulus; 89, proximal tubule; 68, distal tubule; 8, collecting duct; 5, others. Amongst them, PLA2R1 expression was confirmed in glomerular podocytes, and GGT5 in the interstitial and peritubular cell layer. Expression of these proteins in urine were measured by Surface Plasmon Resonance System in IgA nephropathy (IgAN) patients and healthy volunteers.

Conclusions: PLA2R1 and GGT5 might be new urinary biomarkers for chronic kidney disease.
Conclusions: Proteomic analysis of the micro-dissected nephron segments and urine with antibody-based validation revealed a highly polarized and interstitial-matrix derived GGT5 are proposed as a urinary biomarker for glomerular injury and interstitial events.

SA-PO259

The Clinicopathological Characteristics of Central Fibrosis Nodule in Glomerular Vascular Pole

Satoshi Harai,1 Yutaka Yamagami,2 Mitsuhiro Kawano.1 1Internal Medicine, Kanazawa Univ Graduate School of Medicine, Kanazawa, Ishikawa, Japan; 2Yamaguchi’s Pathology Laboratory, Chiba, Japan.

Background: Central fibrous nodule in glomerular vascular pole (CFN) is histologically characterized by periodic acid Schiff-negative small nodular lesion located in glomerular vascular pole. Although this pathological finding is observed in various disease entity, the clinicopathological characteristic remains fully undetermined. The present study was conducted to clarify the epidemiology and clinicopathological characteristics of CFN.

Methods: 103 kidney biopsy specimens diagnosed in Kanazawa University Hospital during 2013 were used. First, the components of CFN were analyzed by immunostaining and electron microscopy. Second, patients were divided into 2 groups [CFN (+) or CFN (-) group], according to the presence of CFN. Clinical and histological features were compared between 2 groups.

Results: CFN was observed in 57 of 103 cases (55.3%). Immunostaining revealed that CFN consisted of fibrillar collagens (collagens I and III) in addition to collagen IV. Congo red staining was negative in all cases. Electron microscopy confirmed fibril-rich lesions of CFN. Clinically, CFN (+) group were older age (62.3±20.4 vs. 49.8±3.0 years; p<0.01) and had significant increase of hypertension (66.9 vs. 41.3%; p=0.01) and hyperlipidemia (58.9 vs. 34.9%; p=0.05) compared with CFN (-) group. Histologically, elastofibrosis of interlobular artery (72.5 vs. 44.2%; p=0.01) and arteriolar hyalinosis (66.7 vs. 41.3%; p=0.01) were significantly evident in CFN (+) group compared with CFN (-) group. There were no significance in regard to gender, body mass index, diabetes mellitus, hyperuricemia, proteinuria, hematuria, kidney dysfunction, and background kidney disease.

Conclusions: CFN is a fibril-rich nodule and the formation is associated with aging, hypertension and hyalinopelically clinically. CFN is also associated with arteriolosclerosis and arteriolar hyalinosis histologically, suggesting that the pathophysiology of CFN resembles that of atherosclerosis in the kidney.

SA-PO260

A Novel Transgenic Mouse Model to Study Renal Tumorigenesis

Anna Julie Peiró,1 Alessandro Sisti,2 Giulia Antonelli,2 Paola Romagnani.1,2

1Excellence Centre Nephrology - Immunology, Univ of Florence, Florence, Italy; 2Nephrology Unit, Meyer Children’s Univ Hospital, Florence, Italy.

Background: Kidney cancer accounts for about 2% of all cancers, with about 190,000 new cases per year worldwide, with a higher incidence in developed countries. Recent studies suggest that chronic kidney disease (CKD) is a crucial risk factor for the development of kidney cancer. As other studies hint that the Notch pathway may be critical for CKD progression to end stage kidney disease, we created a transgenic mouse model that chronically expresses Notch1 in the tubular compartment, in order to study the mechanisms of kidney regeneration.

Methods: To this aim, we developed Pax8-rtTA/tetO-Cre/Rosa26-Confetti/Rosa26-Notch1 mice, in which the constitutive expression of cleaved Notch1 is limited to Pax8+ tubular cells, and is controlled by the inducible Tet-On system, allowing us to activate Notch1 expression only in adult animals. The Confetti reporter activated together with Notch1 led to the stochastic expression of one out of four fluorescent proteins, allowing us to verify the eventual presence of clonal cell proliferation.

Results: Analysis of kidneys showed numerous, multicentric and progressive pretumoral and tumoral lesions. Indeed, persistent Notch1 expression in tubular cells led to the formation of a broad spectrum of lesions of proliferative and non-proliferative nature.

Conclusions: This mouse model represents a useful new tool for the study of tumor development mechanisms in the kidney and provides the first experimental demonstration of the role of Notch1 in the development of renal pre-neoplastic and neoplastic lesions up to cancer.

Funding: Government Support - Non-U.S.

SA-PO261

Influence of Physical Preconditioning in Renal Damage Induced by Adriamycin in Rats and Its Relationship with Endothelial Lesions and Angiogenesis in the Renal Cortex

Camila M. Faletros, Heloisa Della Coletta Francescato, Cleonice Silva, Terezila Machado Coimbra. Univ de Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil.

Background: A single dose of adriamycin (ADR) in rats induces a progressive and irreversible proteinuria that progresses to focal segmental glomerulosclerosis and tubulointerstitial lesions. Recent studies, suggest that physical activity can be a preventive and therapeutic intervention in clinical and experimental conditions. Physical training has beneficial effects on endothelial function. This study evaluated the influence of physical preconditioning in renal damage induced by ADR in rats and its relationship with endothelial lesions and angiogenesis.

Methods: Male Wistar rats were submitted or not to treadmill running for 4 weeks and injected (i.x) with ADR (2.5 mg/kg) or saline. The animals were divided in: sedentary + saline (SED+SAL), physical training + saline (PT+SAL), sedentary + adriamycin (SED+ADR), physical training + adriamycin (PT+ADR). Two ADR groups. Twenty rats were injected and housed 7, 30, and 60 days after injections to quantify albuminuria. The kidneys were removed 60 days after treatment for morphometric and immunohistochemical analysis.

Results: SED+ADR group presented progressive increase in albuminuria from the 7th to 60th day, which was less intense in PT+ADR group. Those animals also presented higher desmin expression (marker of podocyte lesion) at the glomerular edge (1.3±1.0), enlargement of tubular interstitial area (33.7±2.12%), as well as higher macrophage numbers in the renal cortex (10.5±1.77) compared to control. These alterations were smaller in PT+ADR group (0.65±0.09, 21.23±1.71, 6.37±0.58, respectively). The SED+ADR group also presented reduction in vascular endothelial growth factor (0.95±0.1), endothelial cells (0.74±0.15) and endothelial nitric oxide synthase (3.41±0.36) expressions in the renal cortex, which were attenuated in the PT+ADR group (1.2±0.06, 1.07±0.08, 5.61±0.48, respectively).

Conclusions: Physical training prior to ADR injection reduced the renal damage induced by this drug. This effect was related to angiogenesis, reduction in the endothelial lesions and inflammatory processes in the renal cortex of these animals. Grants: CAPES, FAPESP (12/50180-2).

Funding: Government Support - Non-U.S.

Funding: Government Support - Non-U.S.

SA-PO262

Primary Endothelial Lesions in Mouse Kidneys Induce a Platelet Mediated Inflammatory Response

Sophie Jungering, Jan Sradnic, Anika Luedemann, Bernd Hohenstein, Christian Hugo. Div of Nephrology, Dept of Internal Medicine III, Univ Hospital CGC, Dresden, Germany.

Background: We have recently shown that platelets (PLT) directly mediate endothelial lesions in a murine model of site-selective endothelial cell (EC) injury. With respect to indirect, pro-inflammatory effects, PLT’s status remains unclear. To further investigate their potential role for the inflammatory response we here induced EC lesions and depleted PLT 24 hours later.

Methods: The induction of EC injury was performed by renal-arterial perfusion of Concanavalin (ConA) anti-clone in 51 C57Bl/6 mice. On day 1, PLT were depleted using anti-GBP alpha antibodies (n=13), mice perfused with NaCl solution (n=23) or polynuclear macrophage. IgG (IgG) (15) served as controls (CTRL). Mice were sacrificed on days 2 and 5. FACS analysis was used to verify PLT depletion (morphological and CD41+), and recruitment of neutrophils (CD11b+ GR1+), macrophages (F4/80+ CD11c+ CD11c+ GR1+), B-cells (ImgB20 positivity) and T-cells (CD4+ or CD8+). Harvested kidneys were also partly fixed for immunohistochemical staining with MAC2, F4/80 and CD31 antibodies.

Results: Platelet depletion was successfully established (CD41+ CTRL: 92.99%; PLT depleted: 2.42%). FACS analysis detected a significant reduction of T-Cells, CD4+ (day 2: 2.02% vs. 1.01% and day 5: 1.96% vs 1.14% in CTRL vs. PLT depleted mice), as well as CD8+ (day 2: 2.64% vs. 1.08%, day 5: 3.77% vs. 1.87%). B-Cells were not different. Monocytes and their subpopulation of macrophages were reduced in PLT depleted mice (day 2: 0.29%, day 5: 0.48%) compared to CTRL (day 2: 0.53%, day 5: 0.84%). This finding was approved by periglomerular cell count of F4/80 positive cells and glomerular cell count of MAC2 positive cells. Systemic measurements did not reveal differences in cell counts.

Conclusions: The present study emphasizes the relevance of activated platelets after EC injury. It directly links the presence of platelets with the recruitment of various inflammatory cells in injured kidneys, representing an additional therapeutic aspect of platelet inhibition.

SA-PO263

Compound K Inhibits NF-κB/NLRP3 Inflammasome Activation and Ameliorates Renal Inflammation in Unilateral Ureteral Obstruction

M. Shuk-Ma Ka,1 Ann Chen.2 1Graduate Inst of Aerospace and Undersea Medicine, National Defense Medical Center, Taipei, Taiwan; 2Dept of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Background: Compound K (CK), a major absorbable intestinal bacterial metabolite of ginsenosides, has been shown to be anti-inflammatory, but its effect on renal inflammation and fibrosis remains largely unknown.

Methods: The present study, we verified both the nonprotective and therapeutic effects on renal inflammation and fibrosis in a mouse unilateral ureteral obstruction (UUO) model and investigated the mechanisms of action, including the use of urine samples removed from the isolated pelvic kidney. The diseased kidney, renal draining lymph nodes, renal tubular epithelial cells (TECs) under mechanical-induced pressure, and macrophages.

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

Underline represents presenting author.
Results: The results show that administration of CK decreased: [1] parenchymal loss, inflammation and fibrosis; [2] infiltration of macrophages and T cells; and [3] production of proinflammatory cytokines (renal tissues and in urine samples, the latter of which was collected from dilated pelvic cavity), in the kidney of the treated UUO mice. Notably, while given three days after the induction of UUO, CK clearly improved the tubulointerstitial lesions in the UUO mice. These beneficial effects from CK treatment correlated well with the inhibition of NF-kB/NLRP3 inflammasome in the kidney; [2] NLRP3 inflammasome in cultured renal TECs under a mechanical-induced pressure; [3] NF-κB/NLRP3 inflammasome and mitochondrial damage in cultured macrophages; and [4] CD4 T cells activation in renal draining lymph nodes. These mechanistic investigations were also partly confirmed by a quantitative proteomics analysis.

Conclusions: We concluded that CK conferred its favorable effects on the renal tubulointerstitial lesions of UUO mice mainly by negatively regulating the NF-κB/NLRP3 inflammasome-mediated inflammatory pathway in the kidney.

Funding: Government Support - Non-U.S.

SA-PO264

Retrospective Review of a Kidney Biopsy Series in an Urban Teaching Hospital among a Predominantly African-American Cohort

Background: Kidney biopsy can aid in confirming a diagnosis, anticipating disease recurrence, and prognostication. It may alter the pre-biopsy proposed management.

Methods: Epidemiological retrospective analysis, single-center, urban hospital with a predominant demographic of African Americans. All kidney biopsies from February, 1st 2011 till June, 6th 2016. All biopsies were done using ultrasound guidance by either the nephrology service or interventional radiology.

Results: There were total of 561 biopsies in this time period. All pediatric, transplant, and surgical biopsies were excluded. The final 143 biopsies were analyzed with the following indications: nephrotic/nephritic syndrome, and unexplained acute kidney injury.

Funding: Government Support - Non-U.S.

SA-PO266

Serum (pro)Renin Receptor Is Associated with the Index of Glomerular Lesion in Mesangioproliferative Glomerulonephritis

Among African Americans, FSGS diagnosis was incorrectly presumed in 53% of the cases and was not suspected in 65% of the cases. There was a weak correlation between creatinine values and different extents of fibrosis.

SA-PO265

Plasma Soluble Coagulation Receptor Levels Are Not Associated with Venous Thromboembolism in Systemic Vasculitis

Among African Americans, FSGS diagnosis was incorrectly presumed in 53% of the cases and was not suspected in 65% of the cases. There was a weak correlation between creatinine values and different extents of fibrosis.
Methods: Here we initially described the case of a 56-year-old woman with normal renal function who developed unexplained very acute renal failure after administration of vancomycin.

Results: The renal biopsy, despite performed 2 weeks after vancomycin withdrawal, showed acute tubular necrosis with atypical granular tubular casts formation. These casts were surrounded by macrophagic infiltration and exhibited the infrared spectroscopy vancomycin signature. The location of vancomycin deposits was also confirmed by immunohistochemistry that we developed in-house. Scanning electron microscopy showed that the vancomycin-associated casts were made of non-crystal vancomycin nanospheres. To our knowledge, this is the first report analyzing C3 deposition from 1999 to 2016 seven additional cases of unexplained ATN associated with high vancomycin trough levels. We found similar tubular vancomycin deposits in these patients. Genuine control (that is ATN with concomitant vancomycin injection at time of the renal biopsy) did not express the staining of vancomycin. Finally, similar vancomycin nephrotoxicity mechanism was replicated experimentally in mice following vancomycin infusion. Intravital microscopy using fluorescent-tagged vancomycin dye showed vancomycin deposits formation in tubular lumens, starting 40 minutes after drug injection.

Conclusions: Taken together, these data confirm the yet unsuspected mechanism of acute tubular injury associated with vancomycin toxicity and the deleterious effect of non-crystal vancomycin intra-tubular deposits.

SA-PO268

Autoantigen Determinants of Complement Activation by Goodpasture and Anti-PLA2R Autoantibodies Dörin-Bogdan Borza,1 Tanu Rana,2 Joshua M. Thurman,2 Stephen Tomlinson,3 Paul E. Brenchley,4 Rachel Lennon,4 1Dept of Microbiology, Meharry Medical College, Nashville, TN; 2Univ of Colorado School of Medicine, Denver, CO; 3Medical Univ of South Carolina, Charleston, SC; 4Manchester Royal Infirmary, Manchester, United Kingdom; 5Univ of Manchester, Manchester, United Kingdom.

Background: Complement activation is a prominent effector mechanisms of IgG autoantibodies (autoAbs) binding to glomerular autoantigens. Major epitopes targeted by Goodpasture (GP) and PLA2R autoAbs in membranous nephropathy (MN) have been identified, but their role in complement activation is not known.

Methods: We assayed in vitro complement activation by GP autoAbs bound to αIV collagen NC1 domain (αIVNC1) or MN autoAbs bound to PLA2R. Recombinant autoantigen fragments containing select epitopes as well as competing mouse IgG mAbs were used to modulate the subsets of autoAbs forming immune complexes.

Results: GP sera containing predominantly IgG1 autoAbs activated complement, requiring a functional classical pathway (AP) up-regulation of complement C3aR. gp R(1) antibodies targeting these αIVNC1 epitopes competitively inhibited complement activation by human GP autoAbs. For MN autoAbs, complement activation (C3 deposition) was inhibited by the PLA2R N-C3 domain or a peptide from the Cry2 domain, encompassing a major epitope, and also by mAbs raised against the N-C3 domain.

Conclusions: These results provide proof of concept that complement activation by autoAbs mediating glomerular disease can be inhibited in antigen-specific manner. Thus, detailed knowledge of the pathogenic epitopes may translate into disease-specific therapies.

Funding: Other NIH Support - NIMHD, Private Foundation Support

SA-PO269

Proteomic Analysis of Complement Expression in Kidneys of Patients with Membranous Nephropathy Isabelle Avouh1, Michael Merchant,2 John P. Shapiro,1 Daniel J. Birmingham,1 Sergey V. Brodsky,2 Jon B. Klein,2 Tibor Nadasy,3 Brad H. Rovin.1 1Medicine, The Ohio State Univ, Columbus, OH; 2Pathology, The Ohio State Univ, Columbus, OH; 3Medicine, The Univ of Louisville, Louisville, KY.

Background: Membranous nephropathy (MN) is a common cause of adult nephrotic syndrome. It is an autoimmune disease characterized by glomerular sub-epithelial deposits containing IgG. In experimental MN these deposits activate complement and cause kidney damage. The role of complement in human MN is less clearly defined. To further our understanding of this role, we performed a proteomic study of kidney biopsy tissue of MN, and focused the analysis on complement proteins.

Methods: Samples of normal kidney (n=5) were compared to 3 types of MN defined as: PLA2R+ (by glomerular staining or serum anti-PLA2R levels, n=3); PLA2R- (n=5); PLA2R- with electron dense spheres in the GBM (EDS, n=4). Glomeruli were isolated by laser capture microdissection, and analyzed by mass spectrometry. The levels of each complement protein among the four groups were analyzed by ANOVA or by Kuskal-Wallis for non-parametric data, and those showing significant differences were further analyzed by appropriate post-hoc tests. The alpha level for significance was set at 0.05.

Results: Seven complement activation proteins (C3, C4, C5, C6, C7, C8, C9) and two complement regulators (complement receptor type 1 (CR1), and FH-related protein 2 (FHR2)) were differentially present. Of the activation proteins, compared to normal controls, C3 and C4 levels were higher in all three MN groups, while C5, C6, C7, C8, and C9 were significantly higher only in MN with EDS. Of the regulators, compared to normal controls, CR1 levels were lower in EDS and PLA2R-, and FHR2 levels were greater in EDS.

Conclusions: Elevated levels of C3 and C4 in all MN groups, and decreased CR1 levels in at least two MN groups, support the involvement of complement activation in the pathogenesis of MN. Finding components of the membrane attack complex (C5-C9) that are unique to MN suggests complement’s effect may be more severe, and direct, in this type of MN. These data raise the possibility that anti-complement therapies may be effective in some forms of MN.

Funding: NIDDK Support

SA-PO270

Synthesis of Complement Protein C3 in Podocytes Is an Important Mediator of Renal Injury in Glomerular Diseases Xuejuan Li,1 Jie Ding, Fangrui Ding. Peking Univ First Hospital, Beijing, China.

Background: We previously studied demonstrated complement C3 was increased after podocyte injury by puromycin in vivo and in vitro. Podocytes are one of the major intrinsic glomerular cells, the foot processes of the neighboring podocytes form slit diaphragm, which is considered to be one of the most important structures for the glomerular filtration barrier, plays an important role in preventing the initiation and development of proteinuria. However, whether the increased podocyte-derived C3 is involved in glomerular podocyte injury are important questions that remain unclear. Therefore, the role of podocyte-derived C3 involving podocyte injury, as well as in proteinuric kidney diseases, further investigation is needed.

Methods: We generated transgenic mice that overexpress C3 in podocytes using the podocin promoter. The genotyping of these transgenic mice were performed by conventional PCR. The gene and protein expression of C3 was detected by Real-time PCR and confocal microscopy in isolated renal glomerular mouse. C3 transgenic mice were treated with PAN or saline solution. Excision of albumin was expressed as the albumin-to-creatinine ratio. Transmission electron microscopy was used to evaluate the ultrastructural changes of glomeruli. The confocal and western blot were used to detect the podocyte injury marker proteins expression changes.

Results: We successfully constructed the podocyte specific overexpression C3 transgenic mice. The albumin-to-creatinine ratio and podocytes damage in PAN induced wild type mice were aggravated in the Podocyte specific overexpression of C3 (Podo-C3) transgenic mice. Moreover, the expression of podocyte injury marker protein nephrin, synaptopodin, podocin decreased in PAN induced Podo-C3 transgenic mice. Moreover, the expression and distribution of the activated C3 cleavage fragment C3a and the C3aR were significantly increased in Podo-C3 PAN nephropathy model.

Conclusions: We demonstrated for first time that the podocyte-derived C3 aggravated podocyte damage in PAN nephropathy model. The possible mechanism might be through up-regulation of complement C3aR.

Funding: Other NIH Support - NIMHD, Private Foundation Support

SA-PO271

Complement Activation in Diabetic Nephropathy Pascal Bus, Jamie S. Chua, Celine Klessens, Malu Zandenbergen, Jan A. Brujin, Ingeborg M. Bajerna, Hans J. Baedle. Pathology, LUMC, Leiden, Zuid-Holland, Netherlands.

Background: Complement activation plays a role in various renal diseases. Experimental models suggest a role for complement activation in diabetic nephropathy. Therefore, the aim of this study was to investigate the prevalence and significance of complement deposits in a large cohort of renal tissue from patients with diabetes and diabetic nephropathy.

Methods: We investigated the presence of glomerular C4d, C1q, MBL, C5b-9 depositions on 163 renal autopsies with both type 1 and type 2 diabetes mellitus. Diabetic patients were divided into 2 groups: patients with and without histologically proven diabetic nephropathy; confirmed by light- and electron microscopy. Autopsies were re-evaluated histologically. Complement deposition patterns were scored blinded to the clinical and histological data.

Complement C4d was present in 63% of patients. Complement activation marker C4d was significantly more prevalent in patients with DN (45%), compared to patients without DN (26%) (p<0.05). Glomerular C4d was associated with the presence of C1q (p<0.01) and C5b-9 (p<0.01). MBL was infrequently observed (6% of all diabetic patients). C4d and C5b-9 deposits were significantly more prevalent in patients with interstitial fibrosis and tubular atrophy, than patients without these deposits (p<0.05). Patients with C4d also had more arteriosclerosis, and glomerular and arteriolar hyalinosis, than patients without C4d. No difference was seen between patients with type 1 DM and type 2 DM.

Conclusions: Complement activation is present in a selected number of patients with diabetic nephropathy, and seems to be associated with chronic lesions. Classic pathway complement activation was the route most frequently found. In our study, there were no differences between complement deposits in type 1 and type 2 diabetes.

Funding: Other NIH Support - NLM, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-PO272
Clinically Available Janus Kinase (JAK) Inhibitors May Offer Treatment for Recurrent Focal Segmental Glomerulosclerosis (rFSGS)
Virginia J. Savin, 1,2 Mukut Sharma, 1,2 Ellen T. McCarthy, 1 Tarak Srivistava, 1 Ram Sharma, 1 Jean-Francois Gauchat, 1 Jianping Zhou. 1 Nephrology, 2VA Medical Center, Kansas City, MO; 3Research, MBRF, 2VA Medical Center, Kansas City, MO; 4Kidney Institute, 2VA Medical Center, Kansas City, KS; 5Pharmacology, Univ of Montreal, Montreal, QC, Canada; 6Nephrology, Children’s Mercy Hospital, Kansas City, MO.
Background: Patients with rFSGS alters glomerular barrier function. We have identified CLCF1 in rFSGS plasma and proposed that its signaling via the JAK-STAT pathway is essential to injury induced by rFSGS plasma. Podocytes express primarily JAK2 and STAT3 and specific JAK2 or STAT3 inhibition prevents the effects of CLCF1 or rFSGS plasma. We studied 3 clinically available JAK inhibitors (Ruxolitinib, Incyte, Rux) in immunized mice podocytes was analyzed using Western blotting at 5-60min.
Results: The JAK2-specific inhibitor BMS915453 prevented increases in pSTAT3 and glomerular P in rFSGS plasma (p<0.001) (Transl Res 2016, 166:384-98). Rux, Tofa and Bari each decreased basal podocyte pSTAT3 in a dose- and time-dependent manner. At 60min, Rux (6nM), Tofa (6nM) or Bari (5nM) prevented CLCF1-induced increase in pSTAT3 (P<0.001).
Conclusions: JAK inhibition is sufficient to prevent STAT3 and P in rFSGS responses to CLCF1; JAK1 and JAK3 inhibition do not appear to be required. Repurposing available JAK inhibitor(s) may offer effective and specific treatment of rFSGS. Since Rux and Bari have relative specificity for JAK1 and JAK2 they may provide favorable toxicity profiles compared to Tofa. A clinical trial based on JAK2 inhibition in rFSGS may be warranted.
Funding: VA Support

SA-PO273
An Endothelin Receptor Antagonist as a Promising Drug for Minimal Change Nephrotic Syndrome: Its Anti-Proteinuric Effect in Puromycin Nephrosis in Rats
Change Nephrotic Syndrome: Its Anti-Proteinuric Effect in Puromycin An Endothelin Receptor Antagonist as a Promising Drug for Minimal
Wesseling, 1,2 Sohsaku Aminonucleoside-Induced Nephrosis in Rats
Background: Studies examining the etiology of minimal change nephrotic syndrome (MCNS) have suggested a role for cytokine(s) in its pathogenesis. The results of these studies have been mixed. This study aimed to reconcile the cytokine profile in MCNS patients using high throughput multiplexed Luminex® assay.
Methods: Forty MCNS patients (median age 12 years, range 3-25 years), of whom 12 had had samples in relapse and remission, were analyzed. Paired blood samples were obtained from these patients when they were: i) Not on any treatment during blood sampling, or ii) On prednisone only during relapse and remission for steroid-dependent patients. Forty aged-matched controls and seven pediatric focal segmental glomerulosclerosis (FSGS) patients were included in the analysis. Plasma samples were obtained from these patients when they were: i) Not on any treatment during blood sampling, or ii) On prednisone only during relapse and remission for steroid-dependent patients. Forty aged-matched controls and seven pediatric focal segmental glomerulosclerosis (FSGS) patients were included in the analysis. Plasma samples were performed using multiplexed Luminex® Cytokine Human 27-plex assay. Statistical analysis was performed using Wilcoxon signed-rank test and Mann-Whitney U with a p-value of less than 0.05 considered as statistically significant.
Results: Of the 27 cytokines analyzed, there was no significant difference in each measured plasma cytokine level between controls and MCNS patients in remission. There were significantly higher plasma levels of IL-1b, IL-1RA, TNF-α, IL-6, IL-2, IL-5, IL-9, IL-13, IL-10, PDGF-BB, IL-8 and a significantly lower plasma level of RANTES in MCNS patients in relapse compared to controls (p<0.05). Patients with MCNS patients in relapse had significantly higher plasma levels of IL-1RA, IL-10 and PDGF-BB compared to controls (p<0.05). In the paired analysis, there were significantly higher plasma levels of IL-6, IL-15, IL-4, IL-5, IL-17, IL-10, and VEGF in MCNS patients in relapse compared to remission. Cytokine levels in MCNS patients in remission were consistently significantly different from levels in FSGS patients in remission. MCNS patients in relapse and remission/controls in both paired and unpaired analyses were IL-5, IL-6, IL-10, and IL-13, majority of which were Th2-related cytokines.
Conclusions: Cytokine profiling of pediatric MCNS patients in relapse demonstrated a cytokine bias, distinct from those found from FSGS pathophysiological conditions. Further mechanistic studies are required to ascertain the roles of these cytokines in the pathogenesis of MCNS.
Funding: Government Support - Non-U.S.

SA-PO274
B-Cell Signature in FSGS Rituximab Responders Chang-Yien Chan, Isaac Liu, Kar Hui Ng, Wee Song Yeow, Hui Kim Yap. Pediatrics, National Univ of Singapore, NUHS, Singapore.
Background: A pathogenic role of B cells in non-genetic nephrotic syndrome (NS) has been suggested by the efficacy of rituximab, a B cell–depleting antibody, in inducing a prolonged remission. However, little or no information is available on B cell homeostasis in NS patients using high throughput multiplexed Luminex® assay. We retrospectively evaluated by flow cytometry levels of B cell subsets in 19 healthy age-matched children (HCs) and in 66 NS pediatric patients in different states of disease (37 in active disease and 29 in remission) and treated with differently combined immunosuppressive agents. 20 patients were at disease onset (active disease before any treatment). 17 were at relapse (12 treated with prednisone (PDN), 1 with cyclosporine (CSA), and 2 with PDN+CSA), and among the patients in remission, 7 were treated with PDN/mycophenolate mofetil (MMF), 13 with PDN+CSA/tacrolimus, and 9 with PDN+MMF+CSA/tacrolimus (triple immunosuppression).
Results: At onset, patients presented comparable levels of CD19+, transitional, and total memory B cells respect to HCs, whereas mature B cells were reduced (p<0.01) and switched memory B cells were increased (p<0.05). Levels of B cell subsets did not significantly differ between patients at onset and in relapse, despite PDN and CSA treatment. Prednisone alone did not seem to have any effect on B cell subpopulations. CD19+ levels were significantly reduced only in patients undergoing triple immunosuppression when

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Enhanced Monocyte Responses to Toll-Like Receptor (TLR) and Inflammasome Stimuli in Chronic Kidney Disease
Sav P. Naicker,1 Magali M. Petit,2 John D. Naicker3
1Nephrology Services, Galway Univ Hospital, Saolta Univ Health Care Group, Galway, Ireland; 2Nephrology Services, Galway Univ Hospital, Saolta Univ Health Care Group, Galway, Ireland.

Background: CKD is associated with systemic inflammation but the stimuli and pathways responsible remain poorly understood. We compared the profiles and responses of blood monocytes to TLR ligands ± the inflammasome activator extracellular (e)ATP in healthy adults and subjects with CKD.

Methods: Peripheral blood mononuclear cells (PBMCs) from healthy adults (Ctrl, n=23) and adults with CKD stages 2-5 (n=90) were analyzed by 8-color flow cytometry to quantitely monocyte subsets and their expression of TLRs and the ATP-binding sensor P2RX7. PBMCs were stimulated with TLR4 (LPS, 0.5µg/ml) or TLR7/8 (R848, 50ng/ml) for 2hrs followed by eATP (5mM) for 45mins ± P2RX7 blocker. Additionally, healthy adult PBMCs were cultured with 5%Ctrl or CKD serum during activation. Cytokines were quantified by ELISA. Assay results were correlated with clinical and laboratory indices. Statistical analyses were performed using GraphPad Prism software.

Results: Surface P2RX7 (but not TLR2,4,7,8) was increased on classical (CD14+CD16-) monocytes of CKD compared to Ctrl and correlated with serum uric acid and total cholesterol. Monocyte release of IL-1β following TLR4 or TLR7/8 + eATP was greater for CKD3/4 compared to Ctrl and was partially suppressed by P2X7R blockade. LPS/eATP-activated monocytes released classical monocyte cytokine count and eGFR. R848/eATP-triggered IL-1β release correlated with intermediate(CD14+CD16+) monocyte count, serum creatinine and with eGFR. LPS and R848-triggered release of TNFα and IL-6 was greater for CKD3/4 compared to Ctrl irrespective of eATP presence. Culture of healthy PBMCs with serum from CKD compared to Ctrl resulted in greater TNFα (but not IL-1β or IL-6) release following LPS+eATP.

Conclusions: Our results indicate that CKD is associated with altered inflammation response profiles of classical and intermediate monocytes involving multiple TLR pathways and the inflammasome. The mechanism underlying monocyte inflammatory profiles in CKD is likely to be multi-factorial.

Funding: Government Support - Non-U.S.

Increased Neutrophil Extracellular Trap (NET) Formation Is Associated with Chronic Inflammation and Coronary Artery Disease in Uremic Patients
Jwa-Kyung Kim,1 Sun Ryong Choi,2 Jae-Won Lee,3 Sung Gyun Kim.
1Internal Medicine, Kidney Research Inst, Hallym Univ Sacred Heart Hospital, Anyang, Korea; 2Internal Medicine, Sahmyook Medical Center, Seoul, Korea; 3Internal Medicine, G sam Hospital, Anyang, Korea.

Background: Neutrophils are involved in the pathogenesis of atherosclerosis by neutrophil extracellular traps (NETs) formation. End-stage renal disease (ESRD) patients have extremely higher mortality rate because of uremic toxins-associated inflammation and advanced atherosclerosis. We hypothesized that the NETs formation of neutrophils might be changed in ESRD patients, leading to the higher prevalence of cardiovascular diseases.

Methods: A cross-sectional study was performed in 60 maintenance hemodialysis patients and compared with 60 healthy controls. Neutrophil count, serum creatinine and eGFR were measured. Neutrophil extracellular trap (NET) formation was measured by flow cytometry and histology. NET formations were compared with clinical, laboratory and dialysis variables.

Results: Compared with healthy patients, neutrophils extracted from MHD individuals displayed significantly higher levels of basal NET formation as well as ROS production, indicating that they were activated. The median levels of NET fluorescence were 5187.3, 7767.6, and 9784.2 in the HV, MHD, and positive control groups, respectively. And neutrophils from HV patients were normal CD16a+CD62L+ cells, however neutrophils from MHD patients were CD16a+CD62L-, similar to those from patients with acute infections. Baseline NET formation was positively correlated with the prevalent coronary artery disease (CAD), peripheral neutrophil count, and inflammatory markers such as neutrophil/lymphocyte ratio, and hs-CRP levels. Multivariate analyses identified the prevalent CAD and neutrophil counts as independent predictors of baseline NET formation (β=0.323, p=0.016 and β=0.369, p=0.006, respectively).

Conclusions: In ESRD, NET formation is significantly increased at basal state, and it has a close relationship with inflammatory conditions and prevalent CAD. Baseline neutrophil activation may be a sign of the presence of atherosclerotic vascular complications.

Funding: Private Foundation Support

Increased Tubulointerstitial Recruitment of Human Natural Killer Cells in Renal Fibrosis and Chronic Kidney Disease
Helen G. Healy,1,2 Becker Meng-Lo Po,1,2 Xiaojing Wang,2 Andrew J. Kassanos,1,3,4 Ray Wilkinson,1,3,4 1Conjoint Kidney Laboratory, Pathology Queensland, Brisbane, Queensland, Australia; 2Kidney Health Service, Royal Brisbane and Women’s Hospital, Brisbane, Queensland, Australia; 3School of Medicine, University of Queensland, Brisbane, Queensland, Australia; 4School of Medicine, Univ of Queensland, Brisbane, Queensland, Australia.

Background: Natural killer (NK) cells are innate lymphoid cells that play a significant role in immune surveillance of stressed autologous cells. Mouse studies suggest a pathological role for NK cells in immune-mediated models of kidney disease. This study evaluates the NK cell profile in human fibrotic chronic kidney disease (CKD).

Methods: We extracted peripheral blood from healthy tissue and diseased biopsies with and without fibrosis. NK cell subsets were identified, enumerated and phenotyped by twelve-colour flow cytometry. Localization of NK cell subsets was examined by multi-colour immunofluorescence microscopy.

Results: We detected significantly elevated numbers of total NK cells (CD3+CD56+) in diseased biopsies with interstitial fibrosis compared with diseased biopsies without fibrosis and healthy kidney tissue. Numbers of both the CD56dim NK cell subset and, in particular, the CD56bright NK cell subset, were also significantly elevated in fibrotic kidney tissue. The increased numbers of CD56dim NK cells correlated significantly with loss of kidney function (eGFR). Furthermore, expression of the activation molecule CD69 on CD56dim NK cells was significantly increased in fibrotic biopsies compared with non-fibrotic kidney tissue, indicative of a pathogenic phenotype. Chemokine receptor analysis showed CXCR3 and CCR5 expression on CD56dim NK cells. Immunofluorescent staining of fibrotic kidney tissue localised the accumulation of NK cells within the tubulointerstitial compartment.

Conclusions: The correlation of activated CD56dim NK cells with functionally more severe CKD suggests a pathological role. Further functional dissection of this NK cell subset is necessary for the development of therapeutics capable of blocking this previously untargeted immune cell population.

Funding: Government Support - Non-U.S.

Leukemia Inhibitory Factor Attenuates Tubulointerstitial Fibrosis by Suppression of Pro-Inflammatory Cytokines
Sebastian Alexander Potthoff, Fabian Strugess, Lara C. Rump, Ivo Quack.
Nephrology, Medical Faculty - Heinrich-Heine Univ, Duesseldorf, Germany.

Background: Tubulointerstitial fibrosis is common in chronic kidney disease which is often sustained by chronic inflammation. CD4+ T-cells play an important role in immune response in kidney disease. Leukemia inhibitory factor (LIF), a member of the Interleukin 6 family, and Interleukin 6 (IL-6) play a crucial role in regulating the balance between Th1- and regulatory T-cells (Treg). LIF augments expression of forkhead-box-P3 (Foxp3) leading to Treg, IL-6 induces RAR-related orphan receptor gamma (RORY) driving Th17 lineage development. Dysregulation or overproduction of Th17 cells result in sustained inflammation. Here, we showed that LIF influences inflammatory response in a UO model.

Methods: 6-week old male C57BL/6 mice were treated intraperitoneally daily either with LIF (10µg/kgBW; n=6 day 3–7 day 10) or PBS (control; n=8 day 3-8 day 10). 3 and 10 days after UO, kidneys, spleen and paraaortal lymphnodes were extracted.

Results: LIF treatment significantly reduced tubulointerstitial fibrosis in obstructed kidneys. qPCR from tissue lysates of obstructed kidneys day 3 (OB) revealed that IL-1β, MCP-1, RANTES, IL-6, TNFα, Colla1, TGFB and PAI-1 were upregulated in LIF treated mice. In contrast, qPCR from tissue lysates of obstructed kidneys day 10 (OB) revealed that NFκB and RANTES as well as collagen I and TGF-β were significantly downregulated in LIF treated mice. There was no significant difference between IL-1α, IL-1β, MCP-1, IL-6, TNFα, PAI1 and PDGFR1. Accordingly, expression of MCP1, NFκB, RANTES and TNFα in paraaortal lymphnodes were reduced by LIF. IL-1β and IL-6 expression were reduced by LIF but failed to reach each statistical significance. CD3+ cells accumulated in obstructed kidneys. IFNγ significantly reduced CD3+ cells at day 10 (OBvs.OB+LIF: 144±16s vs 15.8±3.8; p<0.01) but not day 3. LIF treatment lead to a significant increase of the anti-inflammatory cytokine IL-10 (p=0.001) and downregulated pro-inflammatory IL-6, RANTES and G-CSF in plasma.

Conclusions: These data confirm the critical role of inflammation in UO. LIF treatment suppresses a prolonged inflammatory response after UO and therefore protects against tissue injury and fibrosis.

Funding: Clinical Revenue Support

T-Cell Depletion Improves Diastolic Dysfunction in Mice with Uremic Cardiomyopathy
Pamela D. Winterberg,1 Mandy L. Ford,2 1Pediatric Nephrology, Emory Univ; 2Dept of Surgery, Emory Univ, Atlanta, GA.

Background: Uremic cardiomyopathy, characterized by left ventricular hypertrophy (LVH) and diastolic dysfunction, is a significant cause of morbidity and mortality among patients with chronic kidney disease (CKD), but the underlying mechanisms are incompletely understood. We aimed to determine whether T cells are involved in cardiac remodeling during CKD.

Methods: CKD was established in male 129X1/SvJ mice via two-stage partial nephrectomy with sham-operated mice serving as controls. CKD mice were further randomized to receive isotype antibody (Ab) or anti-CD3 Ab to deplete T cells. LVH Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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and diastolic dysfunction were assessed via echocardiograms at 6 weeks of CKD. Flow cytometry was used to verify depletion of T cell populations in spleen, blood, and mediastinal lymph nodes and to characterize memory (CD44) and activation (CD69) status of T cells. Blood pressures were measured using the tail-cuff method. Kidney function was assessed via measurement of plasma urea and cystatin C concentrations.

Results: Mice with CDK developed diastolic dysfunction as previously described, and displayed enlarged mediastinal lymph nodes (mLN) and accumulation of T cells bearing markers of activation (CD44) in spleen and mLN. Anti–CD3 Ab resulted in 100-fold reduction of T cell counts in blood and 50-75% in spleen (at 48 hours) compared to sham controls. Measures of diastolic function including isovolumic relaxation time (IVRT: isotype 22.3 ± 2.28 vs anti-CD3 16.9 ± 2.25 ms; p<0.01), myocardial performance index (0.63 ± 0.05 vs 0.48 ± 0.08; p<0.001) and trans-mitral flow index (E/A ratio: 0.9 ± 0.14 vs 1.2 ± 0.23; p<0.01) improved in CDK mice receiving T cell depletion, however, LVH, systolic blood pressure and measures of renal function were unaltered.

Conclusions: Mice with uremic cardiomyopathy have profound alterations in T cell differentiation and activation status including mediastinal lymphadenopathy. Depletion of T cells improved diastolic function in mice with CKD independent of blood pressure and kidney dysfunction. We are pursuing further work into the mechanisms by which T cells mediate diastolic dysfunction during uremic cardiomyopathy.

SA-PO282
Sulfatide-Selective NKT Cells Mediate M2 to M1 Polarization Resulting in Amelioration of Kidney Fibrosis

Suzhao Li,1 Seung Hee Yang,1 Yong Chul Kim,2 Mi-Yeon Yu,1 Seung Seok Han,1 Hajeong Lee,3 Jung Pyo Lee,3 Ran-Hui Cha,4 Dong Kim Ki,5 Yong Su Kim.6 1Biomedical Research Inst, Seoul National Univ; 2Seoul National Univ Hospital; 3Seoul National Univ Boramae Medical Center; 4National Medical Center.

Background: Kidney fibrosis is the major pathological features of chronic kidney disease, and currently efficient treatment for kidney fibrosis is absent. Macrophage subtype polarization has been suggested as a key player related to kidney fibrosis. However, the immunomodulatory role of natural killer T (NKT) cell in macrophage transdifferentiation has not been elucidated.

Methods: Sulfatide-selective NKT II cells from unilateral ureteral obstruction (UUO) B6.Jα281 mice lacking the invariant type I NKTs were used to elucidate its impact on phenotypic switch of bone marrow derived M1/M2 macrophages and interstitial fibrosis. A co-culture system, primary cultured proximal epithelial cells with sulfatide-selective type II NKT cells, was designed. In addition, macrophages stimulated by Sulfatide-selective NKT cells were adoptively transferred to the kidney capsule of WT and B6.Jα281 on the 7th day of UUO, followed by isolation of total cellular RNAs from minced kidney tissue for microarray.

Results: Severity of renal fibrosis of B6.Jα281 was attenuated compared to WT. Subsequently, adoptive transfer of sulfatide-selective NKT cells stimulated transdifferentiation from M2 to M1 accompanied by increased iNOS, STAT1, SOCS3 and decreased arginase, fibronectin and TGFβ, decreased by adding sulfatide-selective NKT induced M2 to M1 accompanying by increased iNOS, STAT1, SOCS3 and decreased arginase, fibronectin and TGFβ, decreased by adding sulfatide-selective NKT induced M2 to M1 accompanying by increased iNOS, STAT1, SOCS3 and decreased arginase.

Conclusions: Sulfatide-selective NKT cell mediate transdifferentiation from M2 to M1 macrophage via switching in vitro resulting in ameliorating renal fibrosis. Inducing the polarization of macrophages by modulation of NKT cells can be suggested as therapeutic target for curing fibrosis.

SA-PO283
Reparative Renal Macrophages Contribute to Curtailing Fibrosis in the Stenotic Murine Kidney

Kyra L. Jordan,1 John R. Woollard,1 Luke Barron,3 Kyra L. Jordan,1 Hui Tang,1 Stephen C. Te xt o r,1 Jeremy Stuart Duffield,1 Lilach O. Lerman.2 1Divis of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Biogen, Cambridge, MA.

Background: We have previously demonstrated that chronic renal artery stenosis (RAS) induces increase in CD64+/80+/CDS11+/CD11c+ macrophages (Mφ3s) and that this effect precedes the development of renal fibrosis in RAS. This study tested the hypothesis that renal Mφ3s are partly derived from bone marrow (BM), but the replenished Mφ3s might not abolish fibrosis effect.

Methods: Wild type C57 CD45.2 mice underwent whole-body irradiation. Within 6 hours, BM cells obtained from donor CD45.1 mice were transplanted (BMT) retro-orbitally. After a reconstitution period of 60 days, unilateral RAS was induced and systemic kidney injuries were harvested 28 days later to study Mφ3s populations (polychromatic flow cytometry) and assess fibrosis (trichrome). Wild type mice 28 days after RAS or sham served as controls. We also transplanted the ability of BM cells in vitro to exhibit TGFβ-induced induction of fibrotic genes (aPC) and protein (FlowSight, Millipore) in murine embryonic fibroblast (MEF) obtained from Cola1-gfp mice.

Results: Flow cytometry data showed that in BMT Sham Mφ3s repopulate from donor-derived (CD45.1) BM (Figure). However, upon induction of RAS in BMT mice the donor-derived Mφ3s decreased significantly in RAS+BMT compared to untreated RAS and Sham kidneys, and mice with BM-derived Mφ3s experienced enhanced fibrosis.

In vitro, Mφ3s blunted expression of TGFβ-induced profibrotic genes in MEF.

Conclusions: BM can regenerate Mφ3s in healthy kidneys following radioablation, but are incapable of sustaining their Mφ3 phenotype and anti-fibrotic properties in response to kidney injury. Hence, endogenous renal Mφ3s protect the stenotic kidney against injury more effectively than BM-derived Mφ3.

Funding: NIDDK Support

SA-PO284
The Immunoglobulin Heavy Chain Locus Enhances Susceptibility to Renal Injury in Hypertensive Rats

Jinming Zhou,1 2Yaming Zhu,2 Manuel Leonardo Gonzalez-Garay,3 Scott E. Wenderfer,2 Michael C. Braun,2 Peter A. Doris.1 1Inst of Molecular Medicine, Univ of Texas Health Science Center at Houston, Houston, TX; 2Dept of Pediatrics, Baylor College of Medicine, Houston, TX.

Background: Hypertensive renal injury involves an immune component, though the specific molecular pathways are incompletely understood. We have demonstrated that high hypertensive renal injury diverges from the immunoglobulin heavy chain (IgH) locus across the renal injury-provoked spontaneously hypertensive rat SHR-A3 strain and the closely related SHR-B2 strain that resists renal injury. This divergence affects the complement of VDJ genes and creates functional variation in Fe encoding genes in the IgH locus. Additionally, serum IgG levels are genetically determined by sequence variation in the IgH locus across these two lines. We hypothesized that congenic substitution of the IgH locus from SHR-B2 into the SHR-A3 genetic background to create SHR-A3(chr6-IgH-SHR-B2) will reduce renal injury without affecting BP in this model.

Methods: We generated a congenic rat line in which the SHR-B2 IgH locus was transferred by backcrossing onto the SHR-A3 genetic background. The congenic status of the line was confirmed by genome-wide SNP genotyping and by examining serum IgG levels. BP was measured in conscious, unrestrained rats by telemetry at 7 weeks starting at age 18 weeks of age, when renal injury begins to emerge in SHR-A3 rats. Urine and kidneys were collected at 40 weeks of age to assess albuminuria and renal injury.

Results: Measurements of BP by telemetry indicated no difference between SHR-A3 and the congenic line both before and during the emergence of renal damage and proteinuria. Glomerular and tubulointerstitial injury, but not albuminuria, were significantly reduced in the congenic compared to SHR-A3 rats at 40 weeks of age. Our findings provide evidence that genetic variation in the IgH locus contributes to susceptibility to glomerular and tubular injury, independently of hypertension in SHR-A3 rats. However, differences distinct from the IgH variation possibly contribute to the complex phenotype of urinary albumin excretion.

Funding: NIDDK Support, Private Foundation Support

SA-PO285
Hemoglobin Levels Increased by ESA Suppress the Progression of Renal Injury in Chronic Glomerulonephritis Rats


Background: It has been reported that erythropoiesis-stimulating agents (ESAs) confer renoprotection in several kidney disease models. We previously reported that a single injection of epoetin beta pegol (continuous erythropoietin receptor activator; C.E.R.A) blunted more effective renoprotection than a single injection of epoetin beta (EPO) in chronic glomerulonephritis (cGN) rats. At that time, hemoglobin levels were higher in the C.E.R.A-treated group than in the EPO-treated group in the early phase of the disease. Therefore, we evaluated whether hemoglobin levels increased by ESA affect the amelioration of renal injury in cGN rats.

Methods: To increase hemoglobin levels, EPO, 1(000 IU/kg) was intravenously injected into rats (F344, 6 wks old, male) once on Days 0 (EPO first injection), and 2, 4, 8, 12, and 16 weeks. cGN was induced by injection of anti-Thy-1.1-antibody (OX-7, 0.6 mg/kg, i.v.) to unphenotypedized rats (7 wks old) 5 days after the last EPO injection (Day 9) in order for EPO rat to affect the amelioration of renal injury directly. To evaluate renal function, 24-hr urinary total protein (uTP) and 24-hr liver-fatty acid-binding protein (L-FABP) were measured at Day 67. Hemoglobin levels and EPO levels in blood were measured at cGN induction (Day 9).

Conclusions: Our findings provide evidence that genetic variation in the IgH locus contributes to susceptibility to glomerular and tubular injury, independently of hypertension in SHR-A3 rats. However, differences distinct from the IgH variation possibly contribute to the complex phenotype of urinary albumin excretion.

Funding: NIDDK Support, Private Foundation Support
levels (287.7 ± 28.6 ng/day, n=10) were high at Day 67. In the EPO-treated cGN group, uTP levels (287.7 ± 28.6 ng/day, n=10) were significantly lower than those in the untreated cGN group at Day 67.

Conclusions: This study suggested that hemoglobin levels themselves increased by ESA could suppress the progression of renal injury in cGN rats.

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

SA-PO287
NaCl - Hypertonicity Inhibits the Cross-Priming Capacity of Dendritic Cells
Zoran Popovic, Federica Chessa, Mahnaz Bonrouhi, Viola Nordström, Hermann-Josef Groene. Dept of Cellular and Molecular Pathology, German Cancer Research Center, Heidelberg, Germany.

Background: Biophysical microenvironmental signals may modulate gene expression pattern and functional signature of infiltrating and resident monocytic phagocytes. Tissue hyperosmolality may be associated with physiologic and pathologic conditions, including both inflammation and neoplasia. Cross-priming is crucial for initiation of a specific cytotoxic immune response.

Methods: Here, we examined how a hyperosmotic microenvironment (340 mOsm - 450 mOsm) affects cross-priming capacity of dendritic cells. We applied ex vivo antigen uptake, processing, and presentation as assays involving murine bone marrow-derived dendritic cells; and stimulated emission depletion (STED) imaging as well as proximity ligation assay to analyze surface receptor cluster formation.

Results: Exposure of dendritic cells to hyperosmotic micromelii inhibited the cross-priming in a NFAT5-independent manner. A significant inhibition of cross-priming has been achieved by application of nonionic osmolyte mannitol as well. We have observed TRIF as a key mediator of this phenomenon. Moreover, we have identified a hypertonicity-triggered, TRIF-dependent clustering of MHC class I - SINFEKL complexes, but not of single MHCI molecules, associated with reduced dendritic cell - T cell contact. Our in vivo data using a renal allotransplantation approach has shown a similar distribution of T lymphocytes across kidney compartments of normotonic cortex and hyperosmolar medulla, upon transplantation to TRIF deficient recipients.

Conclusions: Collectively, this study provides evidence that high salt reduces cross-priming and suggests a novel mechanism of antigen-specific immune response inhibition in hyperosmolar microenvironments.

SA-PO288
Renal Sodium Gradient Orchestrates a Dynamic Antibacterial Defence Zone
Miriam Berry, Rebecca J. Mathews, Chenzhi Jing, Menna R. Clatworthy. Dept of Medicine, Univ of Cambridge, United Kingdom.

Background: Urinary tract infections are one of the commonest bacterial infections in humans yet infection of the renal parenchyma (pyelonephritis) is relatively rare. This protection is often attributed to the anterograde flow of urine which limits the ascent of bladder microbes. The medulla is the region of the kidney most vulnerable to infection, and also presents a novel environmental challenge to bacteria and resident immune cells due to the regional hyperosmolality generated in order to concentrate urine. Little is known about mechanisms of innate immunity that protect the human kidney from infection, nor the modulating role played by the specialised micro-environment.

Methods: We characterised human kidney macrophages and DCs (mononuclear phagocytes, MNPs) using entire human kidneys, and evaluated the effect of the renal micro-environment on their role in defence against infection.

Results: We show that to counter the threat of bacterial infection, the mammalian immune system uses the renal sodium gradient to position functionally specialised MNPs in the region of the kidney most susceptible to infection. In human renal medulla, we identified an enrichment of MHC II+ CD11c+ CD14+ MNPs that avidly phagocytosed UPEC and promoted neutrophil recruitment and activation via the production of interleukin-8. MNPs also identified an enrichment of MHC II+ CD11c+ CD14+ MNPs that avidly phagocytosed UPEC and promoted neutrophil recruitment and activation via the production of interleukin-8. MNPs also presented a novel environmental challenge to bacteria and resident immune cells and also presents a new environmental challenge to bacteria and resident immune cells.

Conclusions: We show that urinary concentrating mechanisms essential for homeostasis in terrestrial mammals also act as a cue to optimise local immune defense in the kidney.
effect is blocked by antibodies to CD40, CD55 and HLA-DR and enhanced by antibodies to PD-L1 (B7-H1, CD274) and anti-CD55. We hypothesized that IL-33 effect on T-cells is dependent on T-cells and IL-33 production was reduced in the presence of ILCs for protection from progressive CKD. The tissue-protective mechanisms deployed by IL-5- and IL-13-producing ILCs included enhanced activation of alternatively activated macrophages, recruitment of eosinophils and limitation of neutrophil influx by downregulation of neutrophil-attracting chemokines.

Conclusions: In summary, we show that kidney-residing ILCs2 can be effectively expanded by IL-33 in the mouse kidney and are central regulators of renal repair mechanisms. The presence of ILCs in the human kidney tissue, identifies ILCs as attractive therapeutic targets for chronic kidney disease in humans.

Funding: Government Support - Non-U.S.

SA-PO294
Renal Insufficiency and Impaired T-cell Differentiation
Florian Kajbeka,1 Angèle Leick,1 Martin G. Zeier,1 Andrea Steinborn,2 Matthias Schaier,1
1Nierenzentrum Heidelberg, Univ of Heidelberg, Heidelberg, Deutschland, Germany; 2Obstetrics and Gynaecology, Univ of Heidelberg, Heidelberg, Deutschland, Germany.

Background: Regulatory T cells (Tregs) play a key role in maintaining immune homeostasis. The influence of renal insufficiency on Treg differentiation has not been elucidated. However patients with end-stage renal disease (ESRD) often present with an impairment of their immune system functions. The underlying mechanisms are not yet understood. Moreover the influence of a renal replacement therapy on a possible recovery of T-cell function needs further investigation.

Methods: Six-color flow cytometric analysis was used to determine the percentages of different subsets of naïve and memory T-cells within total ICOS- and ICOS-Tregs. Hence, the differentiation of both ICOS- and ICOS-IRE-Tregs in healthy patients (N=131), in patients with ESRD (N=49) and dialysis treatment (N=61) and in patients after kidney transplantation (N=190) could be analyzed.

Results: Patients with ESRD show significantly reduced amounts of naïve Tregs compared to healthy control patients, possibly induced by uremia toxins. Hence the share of highly differentiated CD31- memory Treg cells is increased reducing the adaptability of immune system functions.

Healthy controls & End Stage Renal Failure without dialysis

ICOS-Tregs

ICOS-Tregs

However, after initiation of a hemodialysis treatment Treg cell function recovers as the percentage of naïve Tregs increased compared to ESRD patients without renal replacement therapy having started. This effect is even clearer after kidney transplantation.

Conclusions: Present data elucidate for the first time possible mechanisms underlying an impaired immune system of ESRD patients. The share of naïve Treg cells is significantly reduced compared to healthy control patients. Moreover evidence is given for a remarkable improvement after initiation of a renal replacement therapy.

SA-PO295
NET-Inducing Capacity Is a Potential Biomarker in MPA and GPA
Independent of ANCA Antibodies
Tineke Krajìli,1 Sylvia Kamerling,1 Jaap A. Bakker,1 Francesca Brunini,1 Charles D. Pusey,2 Rene Toes,1 Hans Ulrich Scherer,1 Ton J. Rabelink,1 Coes van Kooten,1 Yoe Kie Onno Teng1
1Nephrology, Clinical Chemistry, Rheumatology, Leiden Univ Medical Center, Netherlands; 2Imperial College, London, United Kingdom.

Background: Neutrophil extracellular traps (NETs) play an important role in the pathogenesis of ANCA-associated vasculitides (AAV). Sera of MPO-ANCA or PR3-ANCA positive patients can induce NETs in vitro. This study investigates whether NET induction could serve as a biomarker in MPO- and PR3-ANCA positive AAV patients.

Methods: Healthy neutrophils were stimulated with 10% serum from 62 GPA patients, 37 MPA patients and 18 healthy subjects. NETs were imaged by automated 3D confocal microscopy. NET-inducing capacity was defined as fold increase of quantified NETs relative to healthy controls. To investigate NET induction by ANCA autoantibodies, IgG was isolated using protein G-agarose beads. IgG depletion in the flow through was confirmed with ELISA.

Results: Both GPA and MPA samples showed significantly higher NET-inducing capacity (fold change mean=SEM for GPA 40±7.4, p<0.0001 and for MPA 153±44.9, p<0.01). MPA sera had a significantly higher NET-inducing capacity than GPA (p<0.0001).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
In 14 AA patients who had seroconverted, we observed that the NET-inducing capacity was similar to patients with non-renal disease (1.40±0.42) genes implication innate immunity pathways (e.g. LPS, IFNG, TNF). The top predicted upstream regulators associated with the glomerular gene set (88 anti-PLA2R, 140.42 genes implicated innate immunity pathways (e.g. LPS, IFNG, TNF). In contrast, there was a relative enrichment of adaptive immunity upstream regulators (e.g. TCR, BCR) in the tubulointerstitial gene set (109 correlated genes).

**Conclusions:** The titer of circulating anti-PLA2.R correlated with the expression level of a number of glomerular and tubulointerstitial genes. Such an approach offers a means by which to explore novel pathogenetic mechanisms in human MN.

**Funding:** NIDDK Support, Other NIH Support - Office of Rare Diseases Research / National Center for Advancing Translational Sciences

**SA-PO298**

Identification of Components of the Canonical Wnt Signalling Pathway in the Developing Kidney

**Kyle Dickinson,1 Thomas J. Carroll,2 Paul R. Goodyer,1,3 1Dept of Experimental Medicine, McGill Univ, Montreal, QC, Canada; 2Dept of Molecular Biology, UT Southwestern, Dallas, TX; 3Dept of Human Genetics, McGill Univ, Montreal, QC, Canada.

**Background:** The Wnt-signalling pathway has been shown to be essential for kidney development and exhibits a very specific and tightly regulated expression pattern, however, the specific signal transduction components have yet to be identified. Wnt specificity is determined by a co-receptor complex, consisting of one Frizzled (Fzd) and one Lipoprotein related receptor protein (Lrp). More recently, R-spondin1 (Rspo1), expressed in the developing kidney, has been shown to associate with this complex and also act as a Wnt agonist, increasing the signal transduction capacity of the signalling complex.

**Methods:** We investigated the role of a specific Wnt receptor complex responsible for potentiation response to Wnt9b exposure in M15 cells, a cell model representative of an early renal progenitor cell (RPC). To measure activation of the canonical Wnt pathway, we transfected our cells with reporter plasmid X1 TOPFlash and measured luciferase activity. RT-qPCR was also performed to determine mRNA expression levels.

**Results:** We took a systematic approach to test the effect of the addition of Fxds, Lrps and Rspo1 on Wnt response to determine the components involved in priming a RPC to complete a normal differentiation program. Exposure to exogenous Wnt9b resulted in no luciferase activity suggesting a signalling component is absent in our cell line. Signal activation was only observed in Wnt9b+Rspo1 conditions, indicating Rspo1 is a potent activator of Wnt signalling in our cells. Next, knockdown of Lrpf using siRNA resulted in a 50% reduction in luciferase and mRNA levels. Lastly, we tested the effect of ectopic Fxds (Fzd1-10). A significant increase in luciferase activity was only observed in the Fzd5 condition in addition to Wnt9b and Rspo1 suggesting it is involved in potentiating a Wnt9b signal.

**Conclusions:** These data suggest that early RPCs require a specific receptor complex consisting of Fzd5, Lrpf and Rspo1 to become responsive to a Wnt9b stimulus and to activate canonical Wnt-signalling during kidney development.

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

**SA-PO299**

Development of Multipotent Adult Kidney Stem Cells

**Hiroki Nomura,1 Deborah P. Hyink,2 Tomoko Obara,1 1Cell Biology, Univ of Oklahoma Health Sciences Center; Oklahoma City, OK; 2Medicine, Baylor College of Medicine, Houston, TX.

**Background:** Nephrons are formed prenatally, and loss of nephrons leads to chronic kidney disease (CKD). In the past few years, it has been possible to use adult tissues to “reprogram” cells into adult stem cells that can be used to make variety of cell types, though the kidney remains a major challenge because of its complexity both in structure and function. To date, no one has been able to regenerate or model functional mammalian nephrons from normal or diseased kidneys. Recently, we identified a member of the ARID transcription factor family that regulates plasticity in renal cells. When knocked out, ARID3a allowed the generation of developmentally plastic cell lines from adult kidney that exhibited increased expression of multiple pluripotency-associated genes.

**Methods:** In this study, we explored the utility of an adult mouse ARID3a-knockout kidney cell line (KPK55) for generating nephron structures in both in vitro and in vivo model systems. Furthermore, we determined the effect of ARID3a knockdown at the adult stage of kidneys using both mice and medaka.

**Results:** We showed that an adult mouse ARID3a-knockout kidney cell line (KPK55) contains adult renal progenitors, and that these cells spontaneously developed into different kidney cell types in 3D matrigel cultures. Importantly, ARID3a elimination increased the number of renal adult stem cells in mice and in medaka kidneys. We are unaware of the existence of this unique multipotent property.

**Conclusions:** These data indicate that KPK55 cells provide a unique advantage for exploring kidney development. Moreover, we predict that further studies based on our findings will provide renal tissue available for transplantation for CKD treatment.

**Funding:** Private Foundation Support
SA-PO300

Lineage Tracing Identifies c-Kit as a Marker of a Progenitor Cell Population with Regenerative Potential in Adult Kidney

Erika B. Rangel,1,2 Samirah A. Gomes,1,3 Janaina Paulini Aguier,1 Mathew Van Schaik,1 Garrett Goss,4 Bradley J. Goldstein,4 Barbara Seidler,4 Dieter Sauer,4 Joshua M. Hare,4 Erika B. Rangel,1,2 Albert Einstein Hospital, Sao Paulo, SP, Brazil; 1Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; 2Univ of Sao Paulo, Sao Paulo, Sao Paulo, Brazil; 3Interdisciplinary Stem Cells Inst, Univ of Miami, Miami, FL, 4Medizinische Klinik, Technische Univ München, Munich, Germany.

Background: We recently reported that c-Kit cells isolated from developing kidneys exhibit progenitor cell properties. We hypothesize therefore that c-Kit cells represent a tissue-specific progenitor population that is involved in development, is maintained during adult life, and contributes to kidney regeneration.

Methods: We crossed the inducible c-Kit Cre reporter mice with IRG, mTmG, LacZ, and multicolored Confetti mice. By varying the timing of tamoxifen treatment, c-Kit+ cells and their descendants were specifically labelled with enhanced green fluorescent protein (EGFP), LacZ or multicolor fluorescence, and their spatiotemporal distribution was followed during kidney development and acute kidney injury {ischemia-reperfusion and rhabdomyolysis}.

Results: c-Kit expression was more abundant in early postnatal (P) period (7.91 in P0-5.3-5; 10.6 in P7-14 vs 3.13 in embryonic [E]7.5-18.5, P<0.0001), and was maintained in adult life, although at lower levels (5.7 in P30 and 2.2 in P90-180). When tamoxifen was administered during E7.5-9.5, a few EGFP/LacZ+ cells were observed in tubular segments from cortex to medulla, and at E10.5-12.5, when metanephos development initiates, ribbons of c-KitEGFP/LacZ+ cells expanded to form tubular structures and were detected in structures resembling the S-shaped bodies. In postnatal period, the number of c-Kit-EGFP/LacZclonal multicolored cells increased in the cortex, medulla, and papilla. In adult mice, c-Kit-EGFP/LacZclonal multicolored cells were found in distinct renal segments (macula densa, distal tubules and collecting ducts). After acute kidney injury, the number of c-Kit clones increased from 10±3 to 36.5±8 (P<0.0001) in the outer medulla.

Conclusions: c-Kit is a unique kidney progenitor population that is maintained in adult life and may have therapeutic application.

Funding: Government Support - Non-U.S.

SA-PO301

A Novel Method to Differentiate Human ES Cells into Renal Tubule-Like Cells by a Combination of Transcription Factors Administration

Ken Hiratsuka,1 Toshiaki Monkawa,1 Shintaro Yamaguchi,1 Ryuji Morizane,1 Shigeru B.H. Ko,1 Hiroshi Itoh,1 Minoru S.H. Ko.1 1Dept of Internal Medicine, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan; 2Dept of Systems Medicine, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan.

Background: Various protocols to differentiate human pluripotent stem cells (hPSCs) into kidney organoids have been developed recently. In a previous study, we have reported a method to differentiate human Embryonic Stem Cells (hESCs) to the cells which are positive for proximal tubule markers in kidney by an administration of single transcription factor (TF) into hESCs.

Methods: To identify TFs which promote differentiation towards a renal lineage, we utilized the comprehensive date set, and represents correlation of gene expression response to the induction of human TFs (~350 genes) under doxycycline (Dox) control in hESCs with tissue-specific gene expression. Modified mRNAs for TFs were synthesized by in vitro transcription. hESCs were transfected with several combinations of synthetic mRNAs for TFs by lipofection and cultured for up to 9days. Morphological changes of these cells were microscopically observed. Marker gene expression were examined by qPCR analysis and protein expression by immunohistochemistry.

Results: By analyzing the data in silico, three candidate TFs which show highest correlation scores to the gene expression profiles of human kidney at 48 hours after Dox induction of each human TF were identified. Two days after the transfection of 3 TFs together into hESCs, intermediate mesoderm cell populations (PAX2, LHX1) were induced. On day 9, differentiated, epithelial cell-like morphological changes were clearly observed. mRNA expressions of proximal tubule cell markers such as AQP1, KSP or MEGALIN and distal tubule cell marker SLC12A3 were detected. We successfully isolated and characterized for the first time human renal diseases correlate with nephron endowment deficit, identifying factors affecting nephron number like self-renewal/differentiation balance can potentially advance our understanding of renal disease initiation and progression.

Conclusions: We successfully isolated and characterized for the first time human kidney derived iPS cells (F-IPS) and kidney epithelial-derived iPS cells (K-IPS). We have analyzed the exhaustive 60,000 genes, OSR1 and T (brachyury) as the kidney development key gene by DNA microarray. As two kinds of induction methods using F-IPS and K-IPS cells, one is an intermediate mesoderm cell lines system (induction 1) (Nature Commu,), another is body axis stem cell lines system (induction 2) (Cell Stem Cells).

Results: In microarray cluster analysis, the whole gene expression of kidney induction using K-IPS cells was consistent with the renal epithelial cells, moreover was stronger expressed the kidney development gene than F-IPS cells. Also we confirmed the expression change (IPS cells/origin cells) in 73 epigenetic memory genes. In high methylation 56 genes, some gene expressions were downregulated in F-IPS cells as compared with K-IPS cells, such as GPR137B (F-IPS/K-IPS=0.39), HSBB1(0.49), and MAP3K5 (0.35). In low methylation 17 genes, some gene expressions were upregulated in F-IPS cells, such as GRR10 (2.27) and SOX8 (5.41). Further the expression of OSR1 (0.16) and T (0.45) was downregulation in F-IPS cells. Especially by kidney induction, the expression of OSR1 did not show strong expression, but T showed markedly strong expression by kidney induction 2 using K-IPS cells.

Conclusions: Interestingly, the expression of HSBB1 and SOX8 which regulates cell development and differentiation, showed high expression with kidney induction using K-IPS cells as compared with F-IPS cells. Transcription factor T which regulates mesoderm formation and notochord differentiation, may be newly involved in HSBB1 and SOX8.

Our results demonstrate the functional role of epigenetic memory genes in human kidney derived IPS cells, and the mechanical role of these genes, including OSR1 and T, in kidney lineage specific induction will be discussed.

SA-PO302

Functional Role of Epigenetic Memory Genes in Human Kidney Derived iPS Cells

Osamu Takase, Taro Tsujimura, Masaoi Nangaku, Keichi Hishikawa.

Dept of Advanced Nephrology and Regenerative Medicine, Graduate School of Medicine, the Univ of Tokyo, Tokyo, Japan.

Background: Kidney specific differentiation induction method using iPS cells is not still established. Last year, we reported 73 epigenetic memory genes for advantage of kidney specific induction by genome-wide methylation analysis between fibroblast-derived iPS cells (F-IPS) and kidney epithelial-derived iPS cells (K-IPS).

Methods: We have analyzed the exhaustive 60,000 genes, OSR1 and T (brachyury) as the kidney development key gene by DNA microarray. As two kinds of induction methods using F-IPS and K-IPS cells, one is an intermediate mesoderm cell lines system (induction 1) (Nature Commu), another is body axis stem cell lines system (induction 2) (Cell Stem Cells).

Results: In microarray cluster analysis, the whole gene expression of kidney induction using K-IPS cells was consistent with the renal epithelial cells, moreover was stronger expressed the kidney development gene than F-IPS cells. Also we confirmed the expression change (IPS cells/origin cells) in 73 epigenetic memory genes. In high methylation 56 genes, some gene expressions were downregulated in F-IPS cells as compared with K-IPS cells, such as GPR137B (F-IPS/K-IPS=0.39), HSBB1(0.49), and MAP3K5 (0.35). In low methylation 17 genes, some gene expressions were upregulated in F-IPS cells, such as GRR10 (2.27) and SOX8 (5.41). Further the expression of OSR1 (0.16) and T (0.45) was downregulation in F-IPS cells. Especially by kidney induction, the expression of OSR1 did not show strong expression, but T showed markedly strong expression by kidney induction 2 using K-IPS cells.

Conclusions: Interestingly, the expression of HSBB1 and SOX8 which regulates cell development and differentiation, showed high expression with kidney induction using K-IPS cells as compared with F-IPS cells. Transcription factor T which regulates mesoderm formation and notochord differentiation, may be newly involved in HSBB1 and SOX8.

Our results demonstrate the functional role of epigenetic memory genes in human kidney derived iPscs, and the mechanical role of these genes, including OSR1 and T, in kidney lineage specific induction will be discussed.

SA-PO303

Should I Stay or Should I Go? Influence of Cell Cycle on Self-Renewal and Differentiation in Human Nephrogenic Progenitors

Stefano Da Sacco, Matthew Edward Thornton, Astigik Petrozayan, Ursula Kreuser, Sinem Kargin, Brendan Grubbs, Roger E. De Filippo, Laura Perin.

Children’s Hospital Los Angeles.

Background: Nephron progenitors (NP), co-expressing SIX2 and CITED1, control nephron endowment through proliferation and differentiation. The mechanisms involved in maintaining this balance are still poorly understood. Recent studies have linked lineage commitment and cell cycle progression; self-renewing cells present a short cell cycle and spend most of their time in replicative phase. In this work, we have investigated the relationship between cell cycle and renal differentiation in NP isolated from human fetal kidneys (hFK).

Methods: NP were isolated using RNA SmartFlare probes. Nephrogenic characteristics were confirmed by RNA-seq and nephrogenic potential by in vitro differentiation and dissociation/reaggregation assays. Expression of cell cycle markers was confirmed by RNA-seq and by immunofluorescence on hFK. Cell cycle was studied using FUCCI (Fluorescent Ubiquitination-based Cell Cycle Indicator) in isolated NP under self-renewing or differentiating conditions.

Results: RNA-seq confirmed elevated expression of renal developmental genes including SIX2, SIX1, CITED1, WT1, EYA1 within NP and they differentiated into functional podocytes and tubules. RNA-seq analysis also revealed high levels of CDK1/ cyclin B, CDK1/cyclin A, E2F2/E2F1 and low levels of retinoblastoma protein and cyclin E possibly suggesting that NP are in M or S phase. Immunofluorescence analysis on hFK confirmed expression of CDK4 and cyclin B in NP but lack of terminally differentiated cell markers like p21 or p27. We also found that increased G1 phase length leads to higher rates of NP differentiation, suggesting a key role of G1 in determining cell fate in NP.

Conclusions: We successfully isolated and characterized for the first time human NP based on SIX2 and CITED1 expression, confirming their nephrogenic identity. Our preliminary data indicate a strong link between cell cycle progression and induction. Since renal diseases correlate with nephron endowment deficit, identifying factors affecting nephron number like self-renewal/differentiation balance can potentially advance our understanding of renal disease initiation and progression.

Funding: Private Foundation Support
Hemodialysis Patients-Derived Induced Pluripotent Stem Cells Can Be Powerful Tool for Kidney Regeneration

Susumu Tajiri,1 Toshinari Fujimoto,1 Shuichiro Yamanaka,1 Kei Matsumoto,1 Makoto Ogura,1 Takashi Yokoo,1 "Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan; 2Div of Regenerative Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.

Background: We could generate neokidneys using human-derived mesenchymal stem cells (hMSCs). However, we previously reported that hemodialysis (HD) patients derived- hMSC might not be appropriate for kidney regeneration due to their long-term uremic condition. Therefore, we hypothesized that induced pluripotent stem cells (iPsc) derived from HD patients could reset the uremic condition and could be useful cell source for kidney regeneration.

Methods: Three patients with end stage renal disease attending our institution for HD were enrolled. Of the three, one had diabetes mellitus and the other 2 had chronic glomerulonephritis. We generated and characterized iPsc from all patients and differentiated iPsc into nephron progenitor cells (NPC) following published protocol. Gene expression markers were compared between healthy control-derived NPC (HC-NPC) and HD patients-derived NPC (HD-NPC) using quantitative RT-PCR. To investigate whether NPC could undergo mesenchymal-to-epithelial transition (MET), we co-cultured them with spinal cords and conducted a histological analysis and gene expression of the structures.

Results: Established iPsc lines showed typical human embryonic stem cell-like morphology and expressed pluripotency markers. Moreover, they exhibited the ability to give rise to teratomas that contained derivatives of all three germ layers and a G-band analysis confirmed normal karyotype. We could differentiate them into HD-NPC that expressed several markers including WT1, PAX2 and SIX2 at the same level as HC-NPC. In addition, HD-NPC exhibited the ability to undergo MET and exhibited robust tubulogenesis. Moreover, clustered podocytes were formed and they expressed podocyte specific markers, such as nephrin and podocin.

Conclusions: To the best of our knowledge, this is the first instance of generating NPC, which were derived from HD patients and then differentiated them into renal tubules and podocyte. Our study demonstrated that HD patient-derived iPsc can be useful cell source for kidney regeneration.

Identification of a microRNA Signature in Renal Cancer Stem Cells: A New Regulatory Mechanism

Grazia Serino,1 Fabio Sallustio,1 Vanessa Galleggiante, Monica Rutigliano,2 Claudia Curci,2 G. Lucarelli,2 P. Ditommaso,3 M. Battaglia,3 Francesco Paolo Schena.1 IRCCS, Castellana Grotte, Bari, Italy; 2Univ of Bari, Bari, Italy.

Background: Clear cell renal cell carcinoma (ccRCC) is the most common form of kidney cancer in adults. Recent evidences show that in several human cancers a small subset of tumors cells called cancer stem cells (CSCs) is present. These cells can be responsible for tumor initiation, growth, metastasis, drug resistance and recurrence. CSCs have been found and characterized also in ccRCC tissue. To date, the role of microRNAs (miRNAs) in ccRCC have been extensively studied, but their function in renal CSCs has not yet been reported.

Methods: We isolated CD133+/CD24+ cells from healthy and tumor renal tissue of 28 patients who underwent nephrectomy for ccRCC. Cells were characterized for their mesenchymal phenotype and stemness proteomic profile. The global miRNA profile was identified using small RNA-Seq (llumina). Target gene prediction was performed using Miranda software. Results obtained from sequencing.

We identified 120 miRNAs differentially expressed in renal CSCs compared to healthy counterpart, of which 12 were downregulated and 108 were upregulated. Then, we studied the genomic distribution of the differentially expressed miRNAs. Interestingly, we found that 48 upregulated miRNAs were codified all together in a cluster on chr14:103143170-103533138, near the region 14q LOH that is associated with tumor progression of ccRCC. Moreover, some of these miRNAs putatively regulated the VHL gene on chr14:101341370-101533138, near the region 14q LOH that is associated with tumor progression of ccRCC. To date, the role of microRNAs in ccRCC have been extensively studied, but their function in renal CSCs has not yet been reported.

Conclusions: Our data support a new role of miRNAs in renal CSCs and these new molecules could provide a potential pharmacological target for new therapeutic approaches in ccRCC. Funding: Government Support - Non-U.S.
SA-PO309
Urine of Cystinosis Patients as Source of Undifferentiated Renal Cells for Disease Modelling and Therapy
Background: Cystinosis is characterized by the pathological accumulation and crystallization of cystine in the lysosomes. If not treated, end stage renal disease invariably develops within the first decade of life. We have shown that cystinosis patients who have been treated for their disease show an absence of renal cystinotic cells which might indicate a fast turnover of cells and the attempt of tissue regeneration to compensate epithelial cell loss. Urinary undifferentiated cystinotic cells might have a therapeutic application in regenerative medicine once the correction of the genetic defect and consequent correction of the phenotype are successful.

Conclusions: We demonstrate the presence of kidney-undifferentiated cells in urine of cystinotic patients, which might indicate a fast turnover of cells and the attempt of tissue regeneration to compensate epithelial cell loss. Urinary undifferentiated cystinotic cells might have a therapeutic application in regenerative medicine once the correction of the genetic defect and consequent correction of the phenotype are successful.

SA-PO310
Direct Reprogramming of Fibroblasts into Renal Tubular Epithelial Cells by Defined Factors
Michael Kaminiski,1 Jelena Tosis,2 Catena Krebsbach,1 Roman Pichler,1 Florian Gramhammer,1 Tobias B. Huber,1 Gerd Walz,2 Sebastian Arnold,3 Soeren S. Lienkamp,1,3 1Dept of Medicine, Renal Div; Univ of Freiburg Medical Center, Freiburg, Germany; 2Dept of Clinical Pharmacology, Inst of Experimental and Clinical Pharmacology, Freiburg, Germany; 3Center for Biological Signaling Studies (BIOSS), Univ of Freiburg, Freiburg, Germany.
Background: Over-expression of transcription factors can convert one cell type into another. This process, referred to as direct reprogramming, is fast and bypasses pluripotency. However, conversion of fibroblasts towards renal cell types has not been achieved yet.

Methods: Based on in silico analysis and whole-mount in-situ screens we identified candidate reprogramming factors. These transcription factors were tested for their potential to convert cells towards a renal fate using fibroblasts from tubule specific reporter mice. Induced cells were analyzed for their transcriptomic profile, renal marker expression and function.

Results: We identified four transcription factors whose combined expression induced cells with high similarity to native renal epithelial cells. They displayed typical epithelial markers, a global expression profile resembling their native counterparts, functional properties of renal tubular epithelial cells and sensitivity to nephrotoxic drugs. Further, they formed tubules along the extracellular matrix of decellularized kidneys and integrated into renal organoids.

Conclusions: Candidate reprogramming factors can be predicted based on their expression characteristics. Directly reprogrammed renal epithelial cells could facilitate nephrotoxicity and drug testing, serve as a platform for disease modeling and may pave the way for regenerative approaches.

Funding: Government Support - Non-U.S.

SA-PO311
Differentiation of Human iPSC into Functional Renal Proximal Tubular Cells and Functional Podocytes with the Application for Drug Toxicity Screening
Ania Wilmes, Caroline Rauch, Georg Kern, Elisabeth Feifel, Clemens Kogut, Arnold Grau, Sebastian Gruenwald, Paul Jennings, Medical Univ of Innsbruck, Dept Physiology and Medical Physics, Physiology, Innsbruck, Tirol, Austria.
Background: Cystinosis is characterized by the pathological accumulation and crystallization of cystine in the lysosomes. If not treated, end stage renal disease invariably develops within the first decade of life. We have shown that cystinosis patients who have been treated for their disease show an absence of renal cystinotic cells which might indicate a fast turnover of cells and the attempt of tissue regeneration to compensate epithelial cell loss. Urinary undifferentiated cystinotic cells might have a therapeutic application in regenerative medicine once the correction of the genetic defect and consequent correction of the phenotype are successful.

Conclusions: We demonstrate the presence of kidney-undifferentiated cells in urine of cystinotic patients, which might indicate a fast turnover of cells and the attempt of tissue regeneration to compensate epithelial cell loss. Urinary undifferentiated cystinotic cells might have a therapeutic application in regenerative medicine once the correction of the genetic defect and consequent correction of the phenotype are successful.

Funding: Government Support - Non-U.S.
Results: Toxicity studies require relatively pure cultures of single cell types. Both, podocyte-like and PT-like cells are derived in a relative pure culture after 10 and 16 days, respectively. Characterization of these cells show expression of specific podocyte marker, including synaptopodin and podocin, as well as specific PT markers including, claudin 2, AQP1, megalin and CD13. Functional analysis showed secretion of VEGR by podocyte-like cells and uptake of albumin and fluorescently labeled cations by PT-like cells. Preliminary toxicity experiments have been carried out with Doxorubicin (aka Adriamycin), a gold standard compound for glomerular toxicity, and with Bboxodolone methyl (aka CDDO) an activator of the Nrf2 oxidative stress response pathway.

Conclusions: While we have made some gains in the development of renal target cells, more efforts need to be invested to increase the differentiation status, purity and stability of the derived cells.

Funding: Government Support - Non-U.S.

SA-PO312
Urinary Renal Progenitors as a Novel Predictor of Graft Outcome

Anna Mananelles, Roser Gutierrez, Oriol Bestard, Paola Romagnani, Josep M. Cruzado.1 Nephrology and Transplant Unit, Hospital Unive de Bellvitge, Barcelona, Catalunya, Spain; 2Nephrology, Meyer’s Children Hospital, Florence, Italy; 3Nephrology and Transplant Unit, IDIBELL, L’Hospitalet de Llobregat, Spain.

Background: Long-term improvement of kidney allograft (KA) survival remains as unmet need. Most studies focus on environmental mechanisms of graft injury, whereas kidney reparative mechanisms were neglected. Isolation of Renal Progenitors from urine (uRP) may be a potential tool to evaluate the intrinsic regenerative capacity of the graft.

Methods: We have transplanted patients at the time of 6 month protocol biopsy. After cell culture, uRP were FACs cells-sorted (CD24/CD133). Cells were differentiated into podocyte and tubular cells. Clinical (demographic parameters, type of KA treatment), analytical (GFR, proteinuria) and immunological data (donor specific antibodies, ELISPOT, urinary biomarkers) were assessed. Kidney biopsy was evaluated according to Banff classification and CD133/CD44 staining performed. We followed this cohort for 2 yrs.

Results: uRP were isolated in 62.1% patients at the time of 6-m protocol biopsy. Therefore we divided patients in two groups: Group A having uRP and Group B without uRP. Groups were comparable regarding baseline characteristics, proteinuria, immunosuppression, DGF, acute rejection, GFR and proteinuria. Protocol biopsy evaluation was similar between groups, without differences for particular Banff items. Glomerular CD44 staining was higher in patients without uRP. T-cell IFN-γ ELISPOT assay and donor specific antibody detection was comparable. We determined the variation of GFR between months 6 and months 12 and 24. Interestingly, patients with uRP at 6m showed a significant increase of GFR at 12m in comparison with stabilization of renal function in patients without uRP (+10±2 vs -3±1%; P=0.003), finding maintained at 2 years.

Conclusions: Development of similar effective protocols of damage, renal function and 6-month kidney histology to patients without uRP, the presence of renal progenitors on urine of kidney recipients at 6 months identifies a subgroup of patients with significant improvement of GFR at 1 year. This finding raises new possibilities as novel predictors of better graft outcomes.

Funding: Government Support - Non-U.S.

SA-PO313
Dedifferentiation-Reprogrammed Mesenchymal Stem Cells with Improved Therapeutic Potential in Diabetic Nephropathy

Yan Lu, Alice Zou, Wai Han Yiu, Dickson W.L. Wong, Kam Wa Chan, Loretta Y.Y. Chan, Joseph C.K. Leung, Kar Neng Lai, Sydney C.W. Tang. Dept of Medicine, The Univ of Hong Kong, Queen Mary Hospital, Hong Kong.

Background: Podocyte loss is a hallmark of diabetic nephropathy (DN). Stem cell therapy has shown rescue effects on podocytes in animal models of DN, but low efficiency and poor survival of transplanted cells still are the major obstacles. We previously reported that dedifferentiation-reprogrammed mesenchymal stem cells (De-MSCs) derived from bone marrow mesenchymal stem cells (BM-MSCs) had therapeutic advantages over unmanipulated BM-MSCs in a brain hypoxic-ischemic animal model (Liu Y, et al. Stem Cells, 2016). However, the clinical application of these cells might be limited due to their dedifferentiation-reprogramming ability, and poor survival of transplanted cells still are the major obstacles. We previously reported that De-MSCs achieved improved therapeutic potential in DN both in vivo and in vitro in a model of DN both in vivo and in vitro in a model of DN both in vivo and in vitro in a model of DN both in vivo and in vitro in a model of DN both in vivo and in vitro in a model of DN both in vivo and in vitro in a model of DN both in vivo and in vitro in a model of DN both in vivo and in vitro in a model of DN both in vivo and in vitro.

Methods: De-MSCs were generated by inducing human BM-MSCs to go through renal lineage reprogramming. BM-MSCs were isolated from Sprague-Dawley (SD) rats and were injected into the left kidney of SD rats to study their therapeutic potential in the rat model of DN.

Results: Compared to BM-MSCs, De-MSCs retained stem cell properties with similar morphology but enhanced survival ability under normal condition or H2O2 stress. Co-culture with De-MSCs significantly prevented apoptosis in podocytes exposed to AGEs via rescuing expression of Bcl-2 and survivin, and cytoketone-related genes synaptopodin, CD24A and tight junction protein ZO-1. Compared with BM- and BM-MSCs-treated groups, BTBR ob/ob mice injected with BM- or BM-MSCs had significantly lower urinary albumin-to-creatinine ratio and BUN. Mechanistically, De-MSC treatment in animals remarkably restored podocin expression and reduced renal cortical HIF1 and p44/42 phosphorylation.

Conclusions: De-MSCs achieved improved therapeutic potential in DN both in vivo and in vitro, and deserve further investigation as a potentially important source of cell-based therapy for DN.

Funding: Health and Medical Research Fund of Hong Kong (02132586), HKU Seed Funding (201411159105) and HKSN Research Grant 2014.

Funding: Government Support - Non-U.S.

SA-PO314
Pharmacological Proof-of-Concept of Extracorporeal Mesenchymal Stromal Cell Immunotherapy in Large Animals

Biiju Pareekadan, Surgery (Bioengineering), Harvard Medical School, Boston, MA.

Background: Human mesenchymal stromal cells (MSCs) metabolize and secrete molecular mediators that can globally shift a wound healing response. Controlled exposure to this cell therapy has been challenging with intravenous infusion of MSCs due to limits in the cell dose and the chemotactic and effector cell-mediated responses to injury. We have developed an extracorporeal MSC technology that maintains MSC viability and enables the continuous, controlled delivery of MSC molecules into the blood stream in a clinical setting. A human scale prototype of the technology will be presented showing sustained cell viability and functionality throughout cGMP manufacturing.

Methods: MSCs were integrated into hollow-fiber bioreactor devices whereby the cells, separated by a permeable membrane, can directly and dynamically supply systemic immunotherapy without entering the body. Pharmacological analysis of this bioreactor technology in a large animal model of kidney and efficient stability of the extracorporeal MSC technology in maintaining kidney injury (AKI) followed for an unprecedented look at AKI therapy during product use.

Results: The study verified a pharmacokinetic and pharmacodynamic response to extracorporeal MSCs that is consistent with a potent immunomodulatory mechanism of action in large animals. The presentation will also report encouraging in vivo survival results of extracorporeal MSCs in a canine model of ischemic AKI.

Conclusions: We expect that a combined strategy to optimize MSC therapy that employs pharmacology principles and cell delivery strategies will be essential to translating this stem cell product to AKI in humans and many other clinical applications of immunotherapy.

Funding: NIDDK Support, Pharmaceutical Company Support - Sentien Biotechnologies, Inc.

SA-PO315
Late Stage Therapy of Chronic Kidney Disease with Multiple Doses of Mesenchymal Stem Cells Improves Renal Function in a Rat Model

Jon D. Ahlstrom,1 Huihui Shi,2 Jorge Isaac,2 Anna Gooch,1 Christof Westenfelder. 1Dept of Medicine, Div of Nephrology, Univ of Utah and Salt Lake City VA Medical Center, Salt Lake City, UT; 2Pathology, UPSI Mountain Healthcare, Murray, UT; 3Dept of Physiology, Univ of Utah, Salt Lake City, UT.

Background: Advanced stages of Chronic Kidney Disease (CKD) are difficult to treat and even required to die or a kidney transplant. We developed and clinically tested a Mesenchymal Stem Cell (MSC)-based therapy for cardiac surgery patients at high risk for post-operative AKI (NCT00733876). This intervention was shown to be safe and it prevented post-operative AKI, mortality and development of CKD long term. These observations prompted us to test in the present preclinical studies whether MSC therapy might also be of benefit to patients at later stages of CKD.

Methods: MSCs were derived from Sprague-Dawley (SD) rat bone marrow and used for therapy at passage 3 (~10 population doublings). After late-phase CKD was established in male SD rats as indicated by reduced renal function, elevated albuminuria and blood pressure (10-16 weeks post 5/6th nephrectomy), MSC therapy was given i.v. (2 million cells/kg b.wt.) 1 x per week for 4 weeks. Therapy was maintained and then the progression of CKD was further monitored for 10 additional weeks.

Results: Our CKD model of 5/6th nephrectomy led to a progressive decline in renal function, elevated systolic blood pressures and albuminuria. MSC therapy given at this late-phase CKD significantly improved renal function (reduced Scr and BUN, increased GFR) and reduced albuminuria and blood pressures compared to vehicle controls. Improvements in albuminuria and hypertension with MSC therapy were sustained for 10 weeks after cessation of MSC therapy, while renal function again declined to baseline.

Conclusions: These data suggest that MSC therapy for CKD may be clinically feasible, even at later stages of CKD, a time when most pharmacological interventions become less or are no longer effective in the prevention of progression to end stage renal disease. Optimal long-term treatment protocols and investigation of the underlying mediator mechanisms of administered MSCs are in progress.

Funding: VA Support

SA-PO316
SGLT2 Inhibitor Attenuates Ischemia Reperfusion Renal Injury via HIF1 Activation

Jin Young Jeong,1,2 Hyunso Choi,1 Yoon-Kyung Chang,1,3 Hong Jin Bac,1 Young Rok Ham,1 Dae Eun Choi,1 Ki Ryang Na,3 Kang Wook Lee.1 Nephrology, Chungnam National Univ, Daejeon, Korea; 2Medical Science, Chungnam National Univ, Daejeon, Korea; 3Clinical Research Inst, Daejeon Saint Mary Hospital, Daejeon, Korea; 4Nephrology, Catholic Univ, Seoul, Korea; 5Nephrology, Daejeon Saint Mary Hospital, Daejeon, Korea.

Background: SGLT2 inhibitor, dapagliflozin were developed for diabetes control. it wastes the glucose to urine. Some studies showed SGLT2 inhibition have renal protection(reduction of hyperfiltration and tubular oxidative stress) in Type1 DM. We evaluate whether SGLT2 inhibitor reduces the renal damage via ischemia reperfusion (IR). Also we investigate the associated mechanism.

Methods: In vitro, hypoxia was simulated by mineral oil in HK-2 cells. Cell survival, apoptosis signal pathway, reactive oxygen species (ROS) generation, HIF1, ERK, and AMPK were evaluated in control and hypoxic HK-2 cell with or without SGLT2 inhibitor.

Conclusions:
In vivo 10 weeks C57BL/6 mice were divided into 4 groups; vehicle (n=5) and dapagliflozin (100 mg/kg). On day 15, a shunt group (n=5), vehicle (n=5) and dapagliflozin (n=5) with ischemia-reperfusion renal injury. Kidneys and blood were harvested 24hr after IR injury. We performed real time RT-PCR, western blot and immunohistochemistry for molecular study and H&E stain and PAS stain for histologic examination.

Results: Dapagliflozin treatment significantly increased the survival of hypoxic HK-2 cells. Dapagliflozin treatment increased the level of HIF1 in hypoxic HK-2 cells. Also it decreased the Bax/Bcl2 ratio and 8-OH deoxyguanosine generation. In vivo, Dapagliflozin treatment significantly reduced the levels of BUN and serum creatinine in IR mice (p<0.05). In microcopy, dapagliflozin significantly reduced renal tubular epithelial cell necrosis and detachment in IR mice kidney. Dapagliflozin significantly increased the expression of HIF1 in IR kidney. Dapagliflozin significantly reduced the level of Bax/Bcl2 ratio and cleaved caspase-3, 8-OH deoxyguanosine positive and TUNEL positive cells in IR kidney.

Conclusions: dapagliflozin significantly increases HIF1 in IR injured kidney. Also it attenuates ischemia reperfusion renal injury.

SA-PO317
Extra Domain A Fibronectin Is An Acute Marker in AKI and A Novel Therapeutic Target in a Murine Model of Aristolochic Acid Nephropathy
Prithipal Singh Virdie,1 Sujit Kumar Saha,2 Subash Somalakna,1 Claire C. Sharpe,2 Mark E. Dockrell,1 Myrose Keshavmurthy Phanish,1 1South West Thames Inst for Renal Research, Epsom and St. Heliers NHS Trust, Carshalton, Surrey, United Kingdom; 2Div of Transplantation Immunology and Mucosal Biology, Kings College Foundation Trust, London, United Kingdom.

Background: In models of tissue injury in animals and in vitro in human cells, proximal tubular cells express an isoform of fibronectin (EDA-FN). We have previously shown that this fibronectin (EDA-FN) is differentially regulated by alternative splicing. We explored the potential of EDA + FN as a target for RNAse H Independent antisense oligonucleotide (ASO) therapy with a view to attenuating fibrosis in a murine model of acute kidney injury induced by aristolochic acid (AA). We have previously shown effective knockdown of EDA + FN in human proximal tubule cells

Methods: We compared expression of EDA + FN in 2 murine models. CD1 mice were injected with Intraperitoneal AA at 3mg/kg at D1 and D5. RNA from whole kidney lysate was extracted at D0, 12, 20 and 100 and qPCR performed using primers targeted to EDA + FN, EDA - FN and CTGF. Folic acid (FA) model involved IV injection of Folic acid at D0 and D21 at 125mg/kg and whole kidney lysate retrieval at D0 and D84.

Results: In the AA model of kidney injury at D0 there was negligible detection of EDA + FN RNA by qPCR, at D12 there was a 250 fold increase in its expression compared to its normal saline control (p<0.005). at D20 there was <900 fold (p<0.005) which was reduced to 13 fold (p<0.05) compared to control. EDA - FN RNA expression was also increased at D12, 20 and 100 (p<0.05) but to a lesser degree (40-70 fold increase) compared to normal saline control. CTGF expression followed a similar pattern with peak at D12 and subsequent fall. By comparison in FA model there was a 15 fold (p<0.005) increase in EDA + FN RNA expression at D84.

Conclusions: EDA-FN expression is significantly increased in the acute phase of kidney injury by AA. This isoform appears to be preferentially expressed by alternative splicing. We explored the potential of EDA + FN as a target for RNAse H Independent antisense oligonucleotide (ASO) therapy with a view to attenuating fibrosis in a murine model of acute kidney injury induced by aristolochic acid (AA). We have previously shown effective knockdown of EDA + FN in human proximal tubule cells

SA-PO318
Ameliorating Effect of Gemigliptin on Renal Injury in Murine Adriamycin-Induced Nephropathy
Da Ra Kim,1 Shin Yeong Lee,2 Jin Sug Kim,1 Tae Won Lee,1 Chun-Gyoo Ihm,1 Kyung-Hwan Jeong,1 1Div of Nephrology, Dept of Internal Medicine, Kyung Hee Univ Hospital, Seoul, Republic of Korea; 2Artificial Kidney Unit, Iss Clinic, Seoul, Republic of Korea.

Background: Previous studies demonstrated anti-apoptotic and anti-inflammatory potential of DPP-IV in experimental models of renal injury. We assumed that renoprotective effect of gemigliptin in adriamycin-induced nephropathy might be mediated by suppression of apoptosis, inflammation and oxidative stress.

Methods: The mice were randomly separated into four groups and received a single tail-vein injection of normal saline(control), gemigliptin(GM), adriamycin(ADR) and adriamycin combined with gemigliptin(ADR+GM). Body weight change, urine albumin and creatinine ratio(UACR) and serum glucose level between four groups were compared. Apoptosis, inflammation and oxidative stress-related molecules were analyzed by western blotting and real-time PCR. Glomerulosclerosis index(GSI) and tubulointerstitial index(TII) were examined using light microscope. WT-1 and nephrin were evaluated by immunofluorescence microscopy.

Results: In ADR+GM group, UACR significantly decreased compared with ADR group on day 15(ADR: 2016±231.20 mg/g vs. ADR+GM: 623.40±134.23 mg/g, p<0.015). Serum DPP-IV activity and adriamycin level was increased in ADR+GM group compared with ADR group. GSI and TII in mice of adriamycin-induced nephropathy was decreased with treatment of gemigliptin[GM] (ADR: 62.79% vs. GM: 21.93%, p<0.05). [TII] ADR: 16.25% vs. GM: 5.74%, p<0.0012. Mice of adriamycin-induced nephropathy expressed higher levels of apoptosis marker (Bax:Bcl2 ratio: 1.91 vs. 0.80, p<0.01). Increased Bax/Bcl2 ratio of AA-I treated cells was restored by gemigliptin. Increased Bax/Bcl2 ratio of AA-I treated cells was restored by gemigliptin. Increased Bax/Bcl2 ratio of AA-I treated cells was restored by gemigliptin. Increased Bax/Bcl2 ratio of AA-I treated cells was restored by gemigliptin. Increased Bax/Bcl2 ratio of AA-I treated cells was restored by gemigliptin. Increased Bax/Bcl2 ratio of AA-I treated cells was restored by gemigliptin.

Conclusions: We demonstrated that gemigliptin ameliorated renal injury in adriamycin-induced nephropathy. These effect may be attributable to decreased inflammation, apoptosis and oxidative stress.

SA-PO319
Estrogen-Related Receptor (ERR)-γ Protects against Pururoycin Aminonucleoside-Induced Podocyte Apoptosis by Targeting PI3K/Akt Signaling
Wei Gong,2 Guixia Ding,1 Jing Yu,1 Shuzhen Li,2 Zhanjun Jia,2 Songming Huang,1 Aihua Zhang,1 1Dept of Nephrology, Nanjing Children’s Hospital affiliated to Nanjing Medical Univ, Nanjing, China; 2Nanjing Key Lab of Pediatrics, Nanjing, China.

Background: Accumulating evidence has shown that podocyte apoptosis is of vital importance for the development of glomerulosclerosis and progressive loss of renal function. However, the molecular mechanisms leading to podocyte apoptosis are still elusive. In this study, we investigated the role of estrogen-related receptor (ERR)-γ in modulating podocyte apoptosis, as well as the underlying mechanisms.

Methods: Pururoycin Aminonucleoside (PAN) was administered to the cultured podocytes or rats to induce podocyte injury. ERRγ siRNA and PI3K inhibitor were used to determine their roles in this experimental setting.

Results: Application of PAN caused a dose- and time-dependent podocyte apoptosis in line with a significant reduction of ERRγ by about 50%. Interestingly, the occurrence of ERRγ downregulation appeared earlier than the onset of cell apoptosis, suggesting a potential that ERRγ reduction triggers apoptotic response in podocyte. To test this hypothesis, ERRγ siRNA was subjected to the podocytes. Strikingly, ERRγ silencing resulted in a significant cell apoptosis accompanied with increased injury markers of B7-1 and cathepsin L, and decreased podocyte protein nphrin. In contrast, overexpression of ERRγ remarkably attenuated PAN-induced cell apoptosis. More importantly, ERRγ overexpression stimulated PI3K/Akt signaling pathway evidenced by increased expression of PI3K subunits p85α (+3.2 folds) and p110ε (+88%) and phosphorylated Akt (+1.27 folds). Application of LY294002, a specific PI3K inhibitor, entirely reversed the anti-apoptotic effect of ERRγ following PAN treatment. Finally, we observed a remarkable reduction of ERRγ (66%) in PAN-treated rat kidneys in line with an apoptotic response, suggesting that this cell model could replicate the in vivo condition.

Conclusions: These data highly suggested that ERRγ played a novel role in regulating apoptotic process in podocytes by targeting PI3K/Akt signaling pathway.

SA-PO320
Relaxin Attenuates the Aristolochic Acid Induced Human Tubular Epithelial Cell Apoptosis In Vitro by Activation of PI3K/Akt Signaling Pathway
Xiaocheng Xie,1 Ming Wang, Xiao Fei, Dept of Nephrology, Hangzhou First People’s Hospital, Hangzhou, Zhejiang, China.

Background: Aristolochic acid nephropathy (AAN) has long been known as a rapidly progressive renal fibrosis associated with the intake of Chinese herbs containing aristolochic acids (AAs). The treatment strategies remain limited. Emerging evidence has shown that H2 relaxin possesses powerful antifibrosis and anti-apoptotic properties, therefore, we aimed to investigate whether H2 relaxin can be employed to reduce AA-induced cell apoptosis.

Methods: Human proximal tubular epithelial (HK-2) cells exposed to AA-I were treated with or without H2 relaxin. Cell viability was examined using the WST-1 assay. Apoptotic morphologic alterations were observed using Hoechst 33342 staining method. Apoptosis was detected using flow cytometry. The expression of Caspase3, Bax, Bcl-2, and Akt proteins were determined by Western blot.

Results: Increased apoptosis was observed in AA-I treated group, which was reversed by relaxin co-treatment.

Conclusions: The present study demonstrated H2 relaxin can decrease AA-I induced cell apoptosis by activating PI3K/Akt signaling pathway.
Background: The glomerulosclerosis induced by podocyte injury is most evident in the pathological change mechanisms. However, loss and apoptosis of podocyte in human renal biopsy is a rare case, podocyte injury mechanism has not been definitively elucidated. BMP4 is an important cytokine that cause mesangial expansion, we examined the mechanism of podocyte injury by BMP4-TAK1 pathway in this study. 

Methods: We focused on the BMP4-TAK1 signaling and BMP4-Smad1 signaling in the development of podocyte injury. In cultured podocyte cells, apoptosis-related molecules (cleaved caspase3 and PARP) and tight junction molecule (occludin, connxin 43) were analyzed under BMP4 stimulation. As inhibition experiments were analyzed using SB203580 treatment (Dorsomorphin) and p38 suppression molecule (SB203580) for the analysis of apoptosis induction. The podocyte specificity induction Bmpm transgenic mice were generated by CAG-CAT-Bmp4 (Bmp4 Tg) mice and Podocin Cre (PodCre) mice. These mice were induced diabetes by streptozotocin injection. From these experiments, we clarified the detailed mechanism of the BMP4 signal, which induce podocyte apoptosis. 

Results: The expression of pSmad1, pTAK1, pp38 and cleaved caspase3 was increased by BMP4 stimulation in the cultured podocytes. The expression of nephrin and connxin 43 decreased was increased by BMP4 treatment. The activated of pp38 and cleaved caspase3 was inhibited by SB203580 under BMP4 treatment. Dorsomorphin inhibited the phosphorylation of Smad1, but did not affect the activation of p38 and caspase 3. Bmp4 Tg x PodCre mice increased the expression of BMPM in the kidney as age advances. Diabetic Bmp4 Tg x PodCre mice showed significantly increased expression of mesangial matrix as compared to the control group in early stage. 

Conclusions: We made clear that podocyte apoptosis was induced by BMP4-TAK1 signal pathway. Bmp4 Tg x PodCre mice caused the development of glomerulosclerosis. These results suggested that BMP4 acted on the podocyte apoptosis in the early stage of diabetes and induces glomerulosclerosis. 

Funding: Government Support - Non-U.S.

SA-PO322
Protective Effect of Epigallocatechin-3-Gallate (EGCG) against Oxalate-Induced Epithelial-Mesenchymal Transition (EMT) of Renal Tubular Cells
Visith Marashi Shoshtari, Judith Fujita, Akihiko Taniguchi, Tatsuya Fujita, Hideharu Nagai, Tominaga, Taichi K. Nephrology, Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan.

Background: Oxalate can induce oxidative stress, cellular injury, calcium oxalate kidney stone formation, and chronic kidney disease (CKD). However, the underlying mechanisms of oxalate induced CKD remain largely unknown. In this study, screening and study evaluation of effects of oxalate on epithelial-mesenchymal transition (EMT), one of the prominent phenomena preceding CKD. Moreover, epigallocatechin-3-gallate (EGCG), the most abundant polyphenol found in Camellia Sinensis (green tea), was also assessed for its potential anti-fibrotic property. 

Methods: MDCK renal tubular cells were incubated with 0.5 mM sodium oxalate for 24-h with/without 1-h pretreatment with 25 µM EGCG. The cells were then subjected to morphological analysis, immunofluorescence staining and Western blot analyses of markers and epithelial-mesenchymal, flow cytometric analysis of intracellular reactive oxygen species (ROS) production using dichlorofluoresceindiacetate (DCFH-DA) assay, immunofluorescence staining of NFκB, and Western blot analysis of an anti-oxidant, catalase. 

Results: Microscopic examination, immunofluorescence and immunoblotting results revealed that oxalate induced EMT and increased expression of vimentin and fibronectin, while levels of epithelial markers (E-cadherin, occludin, cytokeratin and ZO-1) were decreased. EGCG pretreatment could prevent all these changes and molecular mechanisms underlying the prevention by EGCG were most likely due to reduced production of intracellular ROS through activation of NFκB signaling and increased catalase anti-oxidant enzyme. 

Conclusions: Taken together, our data indicate that oxalate turned on EMT of renal tubular cells that could be prevented by EGCG. These findings also shed light onto development of novel therapeutics or preventive strategies of renal fibrosis in the future. 

Funding: Government Support - Non-U.S.

SA-PO323
HIV Promotes SNAIL Expression and Proliferative Molecular Phenotype in Glomerular Epithelial Cells via Down Regulation of Micro-RNA193a
Abheepsa Mishra, Vinod Sharma, Manoj K. Tembhare, Waqar Khanwar, Seyedeh Shadafarin Marashi Shoshtari, Judith Eng, Ashwani Malhotra, Pravin C. Singhal. Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North West Medical School, Great Neck, NY.

Background: Micro-RNA (miR) 193a has been considered to be a tumor suppressor by inhibiting down regulation of miR193a and prevented enhanced SNAIL expression in parietal epithelial cell (PECs) lineage. However, the involved mechanism of PECs's proliferation is not clear. Since HIV promotes pyroptosis in podocytes (Am J Pathol, 2016), we hypothesized that IL-1β production by HIV-infected podocytes leads to PEC proliferation in HIVAN. 

Methods: Vector-transduced and transfected podocytes (NL4-3) transduced podocytes in media for 48 hours. Incubation media (conditioned media, C. media) of vector –transduced podocytes (Control C. media) and HIV-transduced podocytes (HIV C. media) were collected (stored at -80°C). Equal numbers of PECs were plated in Petri dishes. PECs were serum starved for 24 hours, followed by incubation in serum-free media containing vector conditioned media (Control C. media, 10%), HIV conditioned media (HIV C. media, 10%), HIV conditioned media + IL-1β neutralizing antibody (HIV C. media + IL-1βab, 20 µg/ml), IL-1β antibody alone or human IgG (20 µg/ml) for 48 hours at 33°C (n=4). To determine the dose response effect of IL-1β, equal number of PECs were plated in Petri dishes and serum starved for 24 hours, followed by incubation in serum-free media containing variable concentrations of IL-1β (0, 100, 200, 400 ng/ml) for 48 hours at 33°C (n=4). At the end of experimental periods, the cells were counted. Renal tissue and serum levels of IL-1β in control and HIVAN (Tg 26) mice were analyzed. 

Results: HIV conditioned media enhanced proliferation of PECs (P<0.05) and this effect of HIV conditioned media was inhibited by IL-1β neutralizing antibodies. IL-1β enhanced PEC proliferation in a dose dependent manner (IL-1β 0 vs 100 ng/ml, P<0.01; IL-1β 200 and 400 ng/ml vs 100 ng/ml, P<0.05). Renal tissue as well as serum levels IL-1β in HIVAN mice were several fold higher (P<0.01) than in control mice. 

Conclusions: HIV infection of podocytes may be contributing to parietal cell proliferation in HIVAN via generation of IL-1β. 

Funding: NIDDK Support

SA-PO325
The Role of Chemerin/ChemR23 in the Regulation of Inflammation and Endothelial-Mesenchymal Transition of Glomerular Endothelial Cells in Diabetic Kidney Disease
Yuanyuan Wang, JuGuo, Yanna Dou, Zhanzheng Zhao. The Nephrology Center, The First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China; Inst of Nephrology, Zhengzhou Univ, Zhengzhou, Henan, China.

Background: DKD has become the leading cause of end-stage kidney disease, there is no effective treatments so far. Chemerin, a novel adipocyte-derived factor, plays multiple roles by combining with its main ligand chemR23. Chemerin and its ligand chemR23 are closely associated with inflammation and Endothelial-to-mesenchymal transition (EndMT) of glomerular endothelial cells (GECs), which play important roles in the process of DKD. GECs injury could lead to an increased filtration of albumin in DKD. However, the role of Chemerin/ChemR23 in the pathogenesis of DKD is still not clear. 

Methods: GECs were incubated with normal condition, 10ng/ml Chemerin, 50ng/ml Chemerin, 100ng/ml Chemerin, 200ng/ml Chemerin respectively for 24 hours. Cell morphology was studied by light microscopy. The protein expressions of Chemerin, ChemR23, CD31, α-SMA, TGF-β1, AKT, phosphorylated AKT (p-AKT) were measured by Western Blot. The protein expressions of Chemerin, ChemR23, IL-6, TNF-α were measured by ELISA. The cells co-expression of α-SMA and CD31 were determined by immunofluorescence double labeling. 

Results: The expressions of Chemerin, IL-6, TNF-α, ChemR23, α-SMA, TGF-β1, AKT, phosphorylated AKT were upregulated in GECs treated with 200ng/ml Chemerin, 100ng/ml Chemerin, 50ng/ml Chemerin respectively for 24 hours. Cell morphology was studied by light microscopy. The protein expressions of Chemerin, ChemR23, CD31, α-SMA, TGF-β1, AKT, phosphorylated AKT were upregulated in GECs treated with 200ng/ml Chemerin, 100ng/ml Chemerin, 50ng/ml Chemerin respectively for 24 hours. 

Conclusions: The expression of Chemerin/ChemR23 in the regulation of inflammation and EndMT of GECs in DKD remains unclear. 

Funding: Government Support - Non-U.S.
SA-PO326

The Phosphodiesterase 5 Inhibitor Can Alleviate the Epileptiform Mesenchymal Transition in Kidney via Klotho Modulation Independent of Nitric Oxide System

Jae Won Yang, Jae Seok Kim, Min Keun Kim, Minseob Eom, Byoung Geun Han, Seung-Ok Choi. Internal Medicine, Yonsei Univ Wonju College of Medicine, Wonju, Republic of Korea; *Pathology, Yonsei Univ Wonju College of Medicine, Wonju, Republic of Korea.

Background: The phosphodiesterase-5 inhibitor can vasodilate through blocking of cyclic GMP degradation. However, there are many controversies in whether it has another action in case of blocked nitric oxide system. The renal klotho level decreased in animals treated with L-NAME, suggesting that decreased NO result in down-regulation of klotho gene, but the inter-relationship between these two proteins is still obscure. We investigated PDE-5i can preserve epileptiform mesenchymal transition and whether relationship existed between the NO pathway and the klotho expression in kidney.

Methods: The 10th weeks male SD rats were divided four groups. We supplied low salt diet to the control group (N=6), L-NAME 1 mg/ml in drinking water to the L-NAME group (N=6), udenafil 5 mg/kg SO to udenafil group, and L-NAME and udenafil to the L-NAME and udenafil group (N=6) for 4 weeks. After the collection of blood and urine on day 28, serum creatinine was measured and urine nitrite/nitrate, NAD+, and cGMP were measured by ELISA, respectively. Kidney tissues were investigated by IHC stainings or western blot of PCNA, α-SMA, E-cadherin, and klotho expression.

Results: The urine cGMP level showed 2.59±0.88, 1.79±0.99, 1.20±0.22, 0.69±0.59 mmol/ml (p<0.05, control vs udenafil and L-NAME with udenafil). The klotho protein expression was increased in L-NAME with udenafil group compared with L-NAME group. The urine NGAL showed 279.8±126.8, 651.0±195.3, 473.7±114.9, 326.5±279.4 ng/ml (p<0.05 control vs LNAME and LNAME with udenafil), and PCNA expression showed 0.11±0.08, 0.31±0.14, 0.17±0.02, 0.19±0.08 cells/ml (p<0.05, control vs L-NAME, and L-NAME vs L-NAME with udenafil). α-SMA showed increased density in L-NAME group compared with L-NAME and udenafil group (p<0.05) and E-cadherin protein density was decreased in L-NAME group compared with other groups (p<0.05).

Conclusions: The phosphodiesterase 5 inhibitor can alleviate the epileptiform mesenchymal transition in kidney via klotho modulation independent of nitric oxide system.

SA-PO327

PGC1α Regulates NAD+ Biosynthesis, Mitochondrial Function, and Injury-Related Cellular Metabolism

Kenneth M. Rahn, Vinod Raman, Samir M. Parikh. Div of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.

Background: PPAR-γ coactivator 1 alpha (PGC1α) is a transcriptional coactivator which regulates mitochondrial biogenesis. This protein has been shown to be protective against neurodegenerative diseases, ischemia-reperfusion injury, and toxicant exposure. NAD+ regulates mitochondrial biogenesis. This protein has been shown to be protective against neurodegenerative diseases, ischemia-reperfusion injury, and toxicant exposure. NAD+ is a coenzyme involved in cellular redox reactions and is a transporter of electrons for use in oxidative phosphorylation. Both PGC1α and PDX-1 play key roles in cells with high energy requirements, such as those found in the renal tubular epithelium.

Methods: A stable PGC1α-overexpressing mIMCD3 cell line was created with lentiviral transduction. A PGC1α knockout mIMCD3 cell line was developed using the CRISPR-Cas9 system. RNA isolation was performed, followed by quantitative PCR to analyze NAD+ biosynthesis. Molecules preventing podocytes from apoptosis are now at the center of new efforts in kidney therapeutics. The objective of this study is to establish and validate a high throughput screening assay to identify small molecules preventing podocytes from ER stress –dependent and –independent death, which may lead to new potential therapeutic strategies.


Results: The urine cGMP level showed 2.59±0.88, 1.79±0.99, 1.20±0.22, 0.69±0.59 mmol/ml (p<0.05, control vs udenafil and L-NAME with udenafil). The klotho protein expression was increased in L-NAME with udenafil group compared with L-NAME group. The urine NGAL showed 279.8±126.8, 651.0±195.3, 473.7±114.9, 326.5±279.4 ng/ml (p<0.05 control vs LNAME and LNAME with udenafil), and PCNA expression showed 0.11±0.08, 0.31±0.14, 0.17±0.02, 0.19±0.08 cells/ml (p<0.05, control vs L-NAME, and L-NAME vs L-NAME with udenafil). α-SMA showed increased density in L-NAME group compared with L-NAME and udenafil group (p<0.05) and E-cadherin protein density was decreased in L-NAME group compared with other groups (p<0.05).

Conclusions: The phosphodiesterase 5 inhibitor can alleviate the epileptiform mesenchymal transition in kidney via klotho modulation independent of nitric oxide system.

SA-PO328

High-Throughput Microfluidic Platform for Culture of 3D-Kidney Tissue Models


Background: Drug toxicity remains a major issue in drug discovery and stresses the need for better predictive models. Here, we describe the development of a perfused renal proximal tubule cell (RTC) model in Mitenmas’ OrganPlate®[1] to predict kidney toxicity. The OrganPlate® is a microfluidic platform, which enables high-throughput culture of kidney tissues in miniaturized organ models. In OrganPlates®, extracellular matrix (ECM) gels can be freely patterned in microchannels through the use of PhaseGuide technology. PhaseGuides (capillary pressure barriers) define channels within microchannels that can be used to modulate the microenvironment. The microfluidic channel dimensions not only allow solid tissue and barrier formation, but also perfused tubular epithelial vessel structures can be grown. The goal of developing a perfused RTC model is to reconstruct viable and leak-tight boundaries for cytotoxicity, as well as transport and efficacy studies.

Methods: Human RTC (SA7K clone, Sigma) were grown against an ECM in a 3channel OrganPlate®, yielding access to both the apical and basal side.

Results: Confocal imaging revealed that the cells formed a tubular structure. Staining showed tight junction formation (ZO-1), cilia pointing into the lumen (acetylated tubulin) and in cell energy metabolism. PGC1α overexpressing and knockout transgenic cell lines will allow for research to further elucidate the role of PGC1α underlining represents presenting author.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: A case-control study which included 35 male patients with CKD between ages 3 and 70 years as the cases, an equal number of age matched healthy male controls and an equal number of elderly healthy male controls in age group 61-70 years, was conducted. Telomere length was measured by Real Time PCR (RT-PCR) for which telomere specific primer was used. Number of copies of mtDNA was estimated by RT-PCR using specific primers.

Results: The median (Inter-quartile range) values of relative telomere length in CKD patients was found to be 15 (6.25-27); whereas in elderly healthy controls it was 19 (10-35) and in age matched healthy controls it was 103 (70-202). On comparing CKD patients with elderly healthy controls, the difference in telomere length was significant (p < 0.001) while on comparing CKD patients with elderly healthy controls there was no significant difference. The median (Inter-quartile range) values of mitochondrial DNA copy number in CKD patients was found to be 123 (73.75-282.25), and that in elderly healthy controls to be 139 (76.82-185) and that in age matched healthy controls it was found to be 289 (214-541). There was significant difference in number of copies of mtDNA between CKD and age matched healthy controls but comparable results between CKD group and elderly healthy control group.

Conclusions: In our study it was found that telomere length and number of copies of mitochondrial DNA, a marker of mtDNA damage, were markedly reduced in CKD patients when compared with healthy controls of same age group but were comparable with that of elderly healthy controls.

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

Underline represents presenting author.

SA-P0331
Increased Cellular Senescence in the Murine Stenotic Kidney: Effect of Mesenchymal Stem Cells
Seo Rin Kim,1 Xiangyu Zou,1 Xiaong-Yang Zhu,1 Hui Tang,1 Kyra L. Jordan,1 LaTonya J. Hickson,1 Tamara Tchkonia,2 James L. Kirkland,1 Lilach O. Lerman,3 ‘Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, MN.

Background: Cellular senescence is a proliferation arrest evoked in response to stress and is often associated with irreversible growth arrest. Renal artery stenosis (RAS) induce stenotic kidney (STK) ischemia and injury, but it is unclear whether these are associated with cellular senescence. Furthermore, while mesenchymal stem cells (MSC) decrease some forms of STK injury, it remains unknown if they can reverse cellular senescence in RAS. We hypothesized that murine RAS evokes STK cellular senescence, which would be ameliorated by MSC.

Methods: Three groups (n=6 each) of 129-mice were studied after 4 weeks of RAS, RAS treated with a tail-vein injection of MSC (5 x 106 cells) 2 weeks after induction, or sham. β-galactosidase activity (fluorometric) and H2AX (western blot), P16, P21, P53, Activin-A and HIP-1a gene expression were used to assess senescence in STK, CLK, or sham homogenates.

Results: After 4 weeks of RAS, the STK was smaller than the sham and contralateral kidney (CLK) (both P<0.033), and blood pressure was higher than sham (P<0.049). MSC had no effect on either kidney weight (P=0.59 vs. RAS) or blood pressure (P=0.83 vs. RAS). β-galactosidase activity was significantly increased in RAS (P=0.009 vs. sham) and normalized in MSC treated mice (P=0.009 vs. RAS). Renal P16, P21, P53, Activin-A and HIP-1a gene expression was markedly (up to 1,000-fold) elevated in the STK compared to sham and CLK (all p<0.007), but showed no change after MSC delivery (p>0.4 for all vs. RAS).

Conclusions: This study shows that murine RAS triggers cellular senescence, implicating this process in STK injury. MSC therapy partly mitigates renal senescence activity, supporting exploration of a targeted senolytic therapy in RAS.

Funding: Private Foundation Support

SA-P0332
Oligomerization of Fnu14-TRAIL to Endogenous TWEAK Leads to Robust, TRAIL-Mediated, Apoptosis of Renal Cell Carcinoma
Michal Dranitzki Elhahil,1 Kobi Tzdaka,2 Prigozina Tatyana,1 Oral Avramov,1 Fanny Shked,1 Shirra Amalsi,2 Nomi Shimoni,2 ‘Nephrology and Hypertension, Hadassah-Hebrew Univ Medical Center, Jerusalem, Israel; 1KAHE Medical LTD, Israel.

Background: Renal Cell Carcinoma (RCC), the most abundant kidney tumor has no current treatments available for disseminated disease. TNF-Related Apoptosis-Inducing Ligand (TRAIL) was shown to induce selective apoptosis of malignant cells and spares normal ones. TNF-Related Weak Apoptogen of TWEAK (TWEAK) with its receptor, Fnu14, was shown to contribute to tumor growth and metastasis. Treatments designed to activate TRAIL signaling or block TWEAK were not effective enough in clinical trials and ways to potentiate TRAIL activity specifically at tumor microenvironment are needed. The novel dual signaling fusion protein Fnu14-TRAIL (FT) is comprised of Fnu14 domain that can bind and block endogenous TWEAK and of TRAIL domain that can direct apoptotic signals to TRAIL receptor bearing cells.

Methods: Potentiation of apoptosis inducing agent of RCC was tested in vitro (by flow-cytometry, MTS and WB), and in a xenograft model.

Results: 1) FT induces apoptosis in different RCC cell lines, while sparing non-malignant renal cells; 2) FT is more effective than sTRAIL, Fnu14-Fc or their combination; 3) TRAIL decoy receptors expression was negatively correlated with sensitivity to FT; 4) FT activity can be blocked by anti-TRAIL or Faf1 Abs; 5) TWEAK KO cells lost sensitivity to FT effect and this could be reversed by TWEAK addition. 6) Interestingly, adding TWEAK to FT results in the formation of large Fnu14-TRAIL-TWEAK complex which shows pro-apoptotic activity specifically in RCC cells and not in non-malignant renal cells, and 7) FT effectively inhibits the growth of RCC tumors in a xenograft model.

Conclusions: These findings suggest that FT specifically in TWEAK’s presence becomes super-active inducer of apoptosis of malignant cells, probably because of the larger amount of TRAIL receptors available in a cluster form that is known to trigger the TRAIL receptors better than the trimmer form. Taken together, these results propose Fnu14-TRAIL as a potential treatment for TWEAK expressing RCC.

Funding: Pharmaceutical Company Support - KAHR Medical LTD

SA-P0333
Interleukin-15-Receptor-a Contributes to Podocyte Anti-Apoptotic Signaling Through Activation of the PI-3K/AKT and JAK/STAT Pathways
Gentzon Hall,1,2,3 Gina E. Kovalik,1,2 Robert F. Spurney,1,2,3 Guanghong Wu,1,4 Brandon M. Lane,1,4 Megan Chryst-Ladd,1 Eugene C. Kovalik,1,3 Rasheed A. Gbadegesin,1,2 ‘Dept of Medicine, Duke Univ Medical Center; 2Div of Nephrology, Duke Univ Medical Center; ‘Div of Nephrology, Duke Univ Medical Center; ‘Duke Molecular Physiology Inst, Duke Univ Medical Center.

Background: We recently identified a rare heterogeneous missense variant (K47R) in the Interleukin-15 Receptorα (IL-15Rα) as a contributor to autosomal dominant FSGS in an African American kindred. The K47R variant occurs within the high-affinity “sushi” ligand binding domain of IL-15Rα and exerts a loss-of-function effect on the receptor, which impairs podocyte anti-apoptotic signaling. To further characterize the role of IL-15Rα in podocyte anti-apoptotic signaling, we examined the effects of IL-15Rα overexpression and gene knockdown (KD) on its two known downstream effector pathways, PI-3K/AKT and JAK/STAT.

Methods: We used immunoblotting and immunofluorescence imaging to evaluate PI3K/ AKT and JAK/STAT signaling in IL-15Rα knockdown, IL-15Rα WT-overexpressing, and IL-15Rα KD-overexpressing podocytes.

Results: In response to IL-15 stimulation, podocytes overexpressing IL-15Rα exhibited reduced Akt and STAT3 activation relative to IL-15Rα−/− overexpressing podocytes. Nuclear localization of activated STAT3 was also examined by examining the effect of IL-15Rα overexpression and gene knockdown (KD) on its two known downstream effector pathways, PI-3K/AKT and JAK/STAT.

Conclusions: IL-15Rα is a key component of the podocyte anti-apoptotic signaling repertoire and the PI-3K/AKT and JAK/STAT pathways are important mediators of IL-15/ IL-15Rα-induced anti-apoptosis.

Funding: NIDDK Support, Private Foundation Support

SA-P0334
mTORC1 Regulates TCA Cycle in Renal Cyst Formation and Transformation
Luca Drusian,1,2 Monika Pema,1,2 Valeria Mannella,1 Marco Chiaravalli,1 Ana Sofia Henriques da Costa,1 Christian Frezza,1 Giovanna Musco,1 Alessandra Boletta,1 ‘DGCBR, San Raffaele Scientific Inst, Milano, Italy; 2PhD Program in BBC, Univ San Raffaele, Milano, Italy; ‘MRC Cancer Unit, Cambridge Biomedical Campus, Cambridge, United Kingdom.

Background: In many syndromes the kidney is affected by cyst formation, benign lesions of renal tubules. These lesions can evolve into cystadenomas and then renal cell carcinomas (RCC). Molecular causes of these manifestations are largely unknown. The TGFβ pathway has been well studied in RCC.

Methods: To investigate the role of selective upregulation of mTORC1 in the kidney, we developed a mouse model carrying kidney-specific inactivation of the Tsc1 gene. These mice develop renal cysts due to downregulation of PC-1, the product of the PKD1 gene. In Autosomal Dominant Polycystic Kidney Disease (Pena et al, NatComm 2016). In Tsc1 mutants cortical lesions progressively transform with complete penetrance within a short window of time (3 months). Biochemical analysis performed on kidneys displaying cysts (P20), cystadenomas (P50) and carcinomas (P90) showed the expected upregulation of mTORC1.

Results: We performed metabolic profiling by NMR and LCMS on kidneys from Tsc1 mutants and control mice. The analysis revealed unexpected increased levels of TCA cycle metabolites in the mutants. Fumarate was virtually exclusively detected in the mutant kidneys. These mice develop renal cysts due to downregulation of PC-1, the product of the PKD1 gene. In Autosomal Dominant Polycystic Kidney Disease (Pena et al, NatComm 2016). In Tsc1 mutants cortical lesions progressively transform with complete penetrance within a short window of time (3 months). Biochemical analysis performed on kidneys displaying cysts (P20), cystadenomas (P50) and carcinomas (P90) showed the expected upregulation of mTORC1.

Conclusions: To our knowledge this is the first animal model recapitulating a progressive RCC in kidney cortex. Our data suggest a previously unreported link between renal cyst formation and TCA cycle alterations. Most importantly we show that mTORC1 can directly regulate the storage of fumarate in this mouse model, likely leading to progressive transformation.
SA-PO335

Intrinsic APOL1 Toxicity Requires Acidification along the Secretory Pathway
Biological Sciences, Hunter College, New York, NY.

Background: Apolipoprotein L-1 (APOL1) is an innate immunity protein that forms pores in trypanosomes. Variants in APOL1 have been linked to kidney disease, yet the mechanism responsible remains controversial. Here we tested the hypothesis that APOL1 toxicity is cell intrinsic and dependent upon secretion via the Golgi, and thereby acidification, followed by neutralization upon delivery to the plasma membrane, wherein the cation selective pore initiates plasma membrane wound repair.

Methods: HEK293 cells were transfected with APOL1 and its variants, including deletion of the signal peptide. After 48h, cell cytotoxicity and viability were measured. Treatment with ammonia chloride was performed 2h prior to transfection to screen for prerequisite acidification. Recombinant APOL1 was purified from E. coli and reconstituted in planar lipid bilayers, where ion channel conductivity and selectivity were measured. 24 and 48h after transfection with APOL1, lysosomal enzyme activity of acid sphingomyelinase (ASM) and β-hexosaminidase were assayed in the supernatant, to probe for plasma membrane repair.

Results: Toxicity of APOL1 required the signal peptide, with complete ablation of toxicity across all variants. Pretreatment of cells with ammonia chloride prior to transfection reduced the toxicity of all APOL1 variants. In planar lipid bilayers, rAPOL1 allowed the passage of Ca2+. Influx of Ca2+ activates the cell wound repair pathway by causing lysosomal migration and fusion with the plasma membrane, releasing lysosome contents to initialize repair. Expression of APOL1 indeed activates the cell wound healing process, assayed by an increase in ASM and β-hexosaminidase activity in the supernatant.

Continued delivery of pores to the membrane ultimately causes cell lysis.

Conclusions: These results support a model of APOL1 cell death, which mirrors that in trypanosomes. Herein, endogenous APOL1 inserts into membranes due to acidification along the secretory pathway, and forms pores upon neutralization at the plasma membrane. Prior to cell lysis, the lysosomal contents are released into the supernatant in an attempt to repair the APOL1-mediated damage at the cell surface.

Funding: Other NIH Support - National Science Foundation Bread Award 10S-1249166

SA-PO336

Comparison of Gene Expression Profiles in Podocyte Caused by APOL1 Wild Type and Risk Variants
Guolan Wang, Ming Shi, Guohua Ding.
Dept of Nephrology, Renmin Hospital of Wuhan Univ.

Background: Apolipoprotein L-1 (APOL1) is an innate immunity protein that forms pores in the cell membrane, and activation of these pores is associated with kidney disease.

Methods: Polyclonal anti-wild type APOL1 antibodies were used to knockdown APOL1 expression in human podocytes. Gene expression analysis was performed using Affymetrix U133plus2 microarray.

Results: Our study demonstrated the different gene expression profiles caused by APOL1 wild type and its variants, and will help to reveal the underlying molecular mechanisms.

Conclusions: We conclude that overexpression of APOL1 G0/G1 in fly nephrocytes, first increases the function of nephrocytes, causing hypertrophy rather than direct cell death. This new Drosophila model suggest a novel mechanism through which overexpression of APOL1 could precipitate renal diseases in humans, and may enable the identification of APOL1 interacting molecules that could serve as new targets for treatments against APOL1-associated renal diseases.

Funding: NIDDK Support

SA-PO337

Expression of APOL1 Risk Allele in Drosophila Nephrocytes Induces Hypertrophy and Leads to an Accelerated Cell Death
Children’s National Health System, Washington, DC.

Background: Apolipoprotein L-1 (APOL1) risk alleles are strongly associated with an increased risk of developing renal diseases among persons of African ancestry. However, the mechanisms underlying APOL1 associated renal diseases are unknown. Because the APOL1 gene is unique to humans and some primates, new experimental models are needed to understand the function of the APOL1 risk alleles in vivo.

Methods: We generated transgenic Drosophila lines expressing the human APOL1 wild type (G0) and the predominant APOL1 risk allele (G1) in different tissues, including the nephrocytes, which share striking similarities to human podocytes. Various functional and activity assays were performed to access the role APOL1-R-A effects in different tissues with focus on the nephrocytes.

Results: Ubiquitous expression of either G0 or G1 Apol1 in Drosophila induced lethal phenotypes, with G1 being more toxic than G0. When G0 and G1 were expressed specifically in Drosophila nephrocytes, the structurally and functionally homologous to mammalian podocytes, these cells showed first an upregulated endocytic activity and increased accumulation of hemolymph proteins, dextran particles, and silver nitrate, leading to increase nephrocyte size and function. As these flies aged, the function of nephrocytes decreased, and showed a reduced endocytic activity associated with progressive cell swelling, and cell death, mimicking the changes seen in cultured podocytes overexpressing APOL1. Furthermore, G0 and G1 impaired the acidification of organelles in nephrocytes.

Conclusions: We conclude that overexpression of APOL1 G0/G1 in fly nephrocytes, first increases the function of nephrocytes, causing hypertrophy rather than direct cell death. This new Drosophila model suggest a novel mechanism through which overexpression of APOL1 could precipitate renal diseases in humans, and may enable the identification of APOL1 interacting molecules that could serve as new targets for treatments against APOL1-associated renal diseases.

Funding: Pharmaceutical Company Support - Biogen

SA-PO338

Scaffolding Protein JLP Modules Kidney Fibrosis Induced by Unilateral Ureteral Obstruction via Mediation of Autophagy Activation
Qi Yan, Huiiming Wang, Ming Shi, Guohua Ding.
Dept of Nephrology, Renmin Hospital of Wuhan Univ.

Background: Scaffolding protein JNK-associated leucine (JLP) plays a crucial role in signal transduction and molecular trafficking. Our previous study found that JLP deficiency deteriorated kidney fibrosis in mice model of unilateral ureteral obstruction (UUO), but the precise contribution of JLP in kidney fibrosis remains unknown. In the present study, we investigate the effect of JLP on the activation of autophagy in kidney fibrosis of UUO model. We hypothesized that JLP deficient mice would be more susceptible to kidney fibrosis than wild type mice.

Methods: 6-week-old male C57BL/6 mice were divided into six groups: jlp+/+ - UUO - Rapa group, jlp−/− - UUO - Rapa group, jlp−/− - UUO group, jlp−/− - UUO - Rapa group, jlp−/− - UUO - Rapa group and jlp−/− - UUO - Rapa group. Mice were sacrificed at the days of 7 to evaluate the fibrosis by Masson and H&E staining. The expression of α-smooth muscle actin (α-SMA) was assayed by immunohistochemistry staining. The activity of autophagy was measured by expression of LC3 and p62.

Results: 1) One week after the surgery, more collagen deposition and expression of α-SMA was observed in the renal interstitial area in jlp−/− - UUO group compared with jlp+/+ - UUO group. Moreover, the collagen deposition and α-SMA expression was also increased in jlp−/− - UUO - Rapa group rather than in jlp−/− - UUO group. 2) Expression of LC3 was significantly increased in jlp−/− - UUO-operated groups compared with jlp−/− - UUO group, whereas expression of p62 showed opposite trend. 3) Expression of LC3 was also significantly higher in jlp−/− - UUO-operated - Rapa group than in jlp−/− - UUO - Rapa group. 2) Expression of LC3 was significantly increased in jlp−/− - UUO-operated groups compared with jlp−/− - UUO group, whereas expression of p62 were decreased in jlp−/− - UUO-operated - Rapa group compared with jlp−/− - UUO - Rapa group.

Conclusions: Scaffolding protein JLP deficiency activates autophagy, which aggravates kidney fibrosis in UUO model.

Funding: Government Support - Non-U.S.

SA-PO339

Human Point Mutation in Umod Causes Progressive Interstitial Kidney Disease and Organ Failure in Mice

Background: An estimated 10% of adults in the U.S. (~20 million individuals) are living with Chronic Kidney Disease (CKD), and kidney failure is a leading cause of death. UAKD accounts for ~1% of CKD cases. The hallmarks of UAKD are hyperpericinemia, poluria, cortico-medullary cysts, and progressive tubulo-interstitial fibrosis leading to kidney failure by 30-70y. UAKD is caused by mutations in the UMOD gene that result in misfolding of the protein, and accumulation in the ER. This aggregation of misfolded protein sets off cascades of ER stress response.

Methods: We designed a CRISPR/Cas9 system to generate the Umod c.257G>A - point mutation knock-in mouse model with Crisp/Cas9 technology. Whole kidney tissue prep and individual cell populations were isolated from mutant mice and analyzed compared to wild type littermates. Immortalized human UMOD+ cell lines were generated harboring both WT and CI47W mutant alleles.

Results: Heterozygous mice develop spontaneous and progressive kidney disease with organ failure, highly similar to humans, over 24 wks. There is activation of the PERK/ATF4 and IRE1a/XBP1 ER stress pathways in the cells expressing misfolded protein. Surprisingly, mTOR is inhibited in this setting, potentially by putative inhibitors of ATF4/ Chop in the mTOR pathway, which antagonizes autophagy, is highly active in the kidney of diseased animals. Diseased cells express increased amounts of pro-apoptotic factors, and are more susceptible to TNFα and Trai induced apoptosis in vitro.

Conclusions: We conclude that this new mouse model provides an excellent means for studying progressive human renal disease, as well as other human disease characterized by insult to prototestan by mutant protein accumulation, leading to organ failure.

Funding: Pharmaceutical Company Support - Biogen
SA-PO340

D-Serine, a Novel Emerging Uremic Toxic Candidate, Induces Cell Cycle Arrest and Apoptosis Through Up-Regulation of ER Stress and Oxidative Stress in Proximal Tubular Cells

Takao Akira,1,2 Chae Hoon In,1,2 Yu Ikyubok Han,1,2 Eun Hui Okada,1,2 Yu-Tzu Ming Jao,1 Hiroshi Maekawa,1 Yu Ishimoto,1 Masao Nangaku,1 Reiko Inagaki,2 1 Division of Nephrology and Endocrinology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan, 2 Department of Pathophysiology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background: Elevated D-serine concentration in plasma has been reported to be a poor prognosis marker of patients with chronic kidney disease (CKD), indicating the pathophysiological significance of D-serine in the kidney. However, the molecular mechanisms underlying D-serine induced toxicity in the kidney remain largely unknown. In the present study, we aimed to explore D-serine-mediated signaling pathways in the proximal tubular cells.

Methods: Human proximal tubular cell line, HK-2, was treated with D- or L-serine for 48 hr and evaluated the cell damages by cell proliferation (MTS assay and cell count), cell cycle status (PI staining, p53, apoptosis (Annexin V staining and caspase 3/7 activity). To find out the molecular mechanism of the cell damage by D-serine, we assessed the status of endoplasmic reticulum (ER) stress (real time RT-PCR and Western blotting for GRP78 and CHOP), oxidative stress (NADPH oxidase activity, mitochondrial ROS), pro-inflammatory cytokine expression (IL-1β, and IL-6) known as senescence-associated secretory phenotype (SASP). CHOP siRNA was also used.

Results: D-serine, but not L-serine, induced ER stress signal and oxidative stress associated with increased intracellular ROS, and thereby caused G2/M cell cycle arrest. Importantly, the cell arrest by D-serine was associated with the upregulation of p53 and SAPK/JNK. Downstream of pro-inflammatory cytokines in HK-2, D-serine also induced apoptosis mediated by CHOP, namely apoptotic ER stress axis. It was supported by the results showing that CHOP siRNA ameliorated the apoptosis.

Conclusions: D-serine causes tubular cell damage via both premature senescence and apoptotic signals, both of which are mediated by ER stress or oxidative stress, suggesting a novel renal pathogenesis of D-serine as a potential uremic toxic entity in CKD patients. Our study sheds a new light on CKD pathophysiology from the point of view of vicious cycle of tubular damage by uremic toxins including D-serine. Funding: Government Support - Non-U.S.

SA-PO341

Effect of Cyanate on the p-AMP Kinase, Isocitrate Dehydrogenase, and Apoptosis in Huh7 Cells

Ye-Jin Lim,1,2 Sang Mok Yeo,1,2 Seong Sik Kang,1,2 Yu-Hyun Kwak,1,2 Hyun Jung Park,1,2 Kyo Yoo,1,2 Hye-In Han,1,2 Seungyup Han,1,2 1 Dept of Internal Medicine, Keimyung Univ School of Medicine, Daegu, Republic of Korea, 2 Keimyung Univ Kidney Inst, Daegu, Republic of Korea, 1 Dept of Biochemistry, Keimyung Univ School of Medicine, Daegu, Republic of Korea.

Background: Urea is a major factor of uremic syndrome which is accumulated by decreased kidney function. It can be degraded by ammonia and cyanate. We studied alteration of major enzyme for energy metabolism and effectiveness of apoptosis to confirm the effect of cyanate on energy metabolism in a patient of chronic kidney disease.

Methods: We checked pAMP kinase and isocitrate dehydrogenase which are major enzymes of energy metabolism. It was performed by using Huh7, liver cell carcinoma cell strain which is key cell in creation of energy. After cyanoate processing to Huh7 cell, we analyzed a viability of cell, performed western blot analysis about pAMP kinase and apoptotic factors like PARP, p53, cytochrome C, clp and xIAP. And we checked activity of isocitrate dehydrogenase and took reverse transcriptional polymerase chain reaction.

Results: The viability of Huh7 cell was decreased in proportion to time of cyanate processing. After cyanoate processing to Huh7 cell, pAMP kinase which mainly works in energy metabolism was decreased as time passes in Western blot analysis. Although isocitrate dehydrogenase activity was increased compared with control, expression of mRNA of isocitrate dehydrogenase was decreased after cyanoate processing.

Conclusions: In our study, cyanoate as uremic toxic induced apoptosis in Huh7 cells, activated TCA cycle, and inhibited energy metabolism. As a result, it leads to decline of energy generation, which makes CKD patients meet with fatigue, musculoskeletal problem and hypothermia.

SA-PO342

a-Lipoic Acid Attenuates p-Cresol Sulfate-Induced Renal Tubular Injury Through Suppression of Apoptosis and Autophagy in Human Proximal Tubular HK-2 Cells

Jong Un Kyubok Park, Hoon In Choi, Eun Hui Bae, Seong Kwon Ma, Jong Un Lee, Soo Wan Kim. 1Internal Medicine and Physiology, Chonnam National Univer Medical School, Kwang Ju, Korea.

Background: The protein bound solute p-cresol sulfate accumulates in chronic kidney disease, and may play significant roles in the progression of renal injury. a-lipoic acid (ALA) is biologically active as an antioxidant. In tubular cells, we investigated the effects of a-lipoic acid treatment on p-cresol sulfate-induced renal tubular injury.

Methods: The effects ofa-lipoic acid by p-cresol sulfate-induced cell death were determined using human proximal tubular cell line (HK-2) cells. Apoptosis was determined by flowcytometry using annexin-V-FITC/PI assay and levels of lactate dehydrogenase (LDH). The protein expression of apoptosis- and autophagy-related proteins (Bax, Bcl-2, cytochrome C, and LC3B, Beclin-1) was determined by semiquantitative immunoblotting. Mitochondria membrane potential (MMP/ΔΨm) was evaluated using fluorescence microscopy and flow cytometry analysis with Rhod2 as the fluorescent probe.

Results: p-Cresol sulfate treatment significantly increased levels of lactate dehydrogenase (LDH) and induced time-, dose-dependent cell death in HK-2 cells. p-Cresol sulfate treatment increased the expression of apoptosis-related protein Bax/Bcl-2, cytochrome C, as well as autophagy-related protein Beclin-1 and LC3B in HK-2 cells. In contrast, a-lipoic acid significantly reduced p-cresol sulfate-induced the expression of Bax/Bcl-2, cytochrome C, and loss of mitochondria membrane potential. Apoptosis of p-cresol sulfate-induced HK-2 cells was significantly reduced by specific autophagy inhibitor 3-methyladenine. Additionally, in the presence of the specific apoptosis inhibitor Z-VAD-FMK, p-cresol sulfate-induced autophagy was significantly reduced.

Conclusions: a-lipoic acid attenuated p-cresol sulfate-induced cell death through suppression of apoptosis and autophagy in HK-2 cells. Funding: Government Support - Non-U.S.

SA-PO343

R428 as a Novel Therapeutic Agent for the Treatment of Experimental Immune-Mediated Nephritis

Wenhai Zhang, Medicine, Temple Univ, Lewis Katz School of Medicine, Philadelphia, PA.

Background: Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease. Glomerulonephritis is a major cause of morbidity in SLE. Nephrotic serum-mediated anti-glomerular basement membrane (anti-GBM) disease is a well-studied mouse model of immune-mediated glomerulonephritis. Glomerular proliferation is essential for the pathogenesis and progression of glomerular diseases. Axl receptor tyrosine kinase mediates glomerular cell survival signaling, resulting in proliferative responses. R428 is a recently described selective small molecule inhibitor of Axl.

Methods: R428 was administered through oral gavage two day before nephrotic serum injection and continued for 12 days. Control mice were administered with the vehicle bufler. Blood samples were collected. Kidney samples were prepared for RNA and Western analysis.

Results: Our results show R428 effectively prevents disease progression and exacerbation with significantly reduced blood urea nitrogen levels and enhance survival rates as compared to the vehicle-treated nephritic mice. Mechanistic studies revealed that R428 suppresses the expression of pro-inflammatory cytokines and reduces Akt phosphorylation in the kidney.

Conclusions: In summary, these results indicate that R428, currently under clinical trial in cancer patients, may have clinical therapeutic application in lupus nephritis patients.

Funding: NIDDK Support

SA-PO344

Nicotine Induces Podocyte Apoptosis Through Increasing Oxidative Stress

Yuan Lan, Judith Eng, Seyedeh Shadafarin Masrati Shoshhtari, Ashwani Malhotra, Pravin C. Singhal. Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY, USA.

Background: Cigarette smoking plays an important role in the progression of chronic kidney disease (CKD). Nicotine, one of the major components of cigarette smoking, has been demonstrated to increase proliferation of renal proximal tubular and mesangial cells. In this study, we examined the effect of nicotine on podocyte injury.

Methods: To determine the effect of nicotine on podocyte apoptosis, we performed western blot analysis to detect apoptosis in cultured human podocytes and mouse kidney, protein blots and cDNAs of renal tissues were probed for nAChR. We studied the effect of nicotine on podocyte ROS generation (DCFDA loading followed by fluorometric analysis), cell proliferation, and cellular lysates were probed for nAChR. We studied the effect of nicotine on podocyte downstream signaling (phosphorylation of AKT, ERK1/2, JNK, and p38) and established causal relationships by using specific inhibitors.

Results: Human podocytes displayed robust mRNA and protein expression of nAChR. Immunofluorescence studies in renal cortical sections of mice revealed co-localization of nAChR along with synaptopodin. NAC, an ROS scavenger, inhibited ROS generation; however, antioxidants such as N-acetyl cysteine and TEMPOL (speroxido dismutase mimetic agent) inhibited this effect of nicotine. Nicotine did not modulate proliferation but promoted apoptosis in podocytes. Nicotine enhanced podocyte phosphorylation of AKT, ERK1/2, JNK, and p38 and their respective inhibitors.

Conclusions: Nicotine induces podocyte apoptosis through ROS generation and associated downstream signaling. The present study provides insight into molecular mechanisms involved in smoking associated progression of chronic kidney disease.

Funding: NIH Support

Poster/Saturday

Funding: Government Support - Non-U.S.

J Am Soc Nephrol 2027: 16

Apoptosis, Proliferation, Autophagy, Cell Senescence, Cell Transformation

Underline represents presenting author.

707A
Podocyte Damage Is Mitigated by Normal High Density Lipoprotein (HDL) by Wolfgang Neuhofer,1,2 Franz Xaver Beck,1 Wolfgang Neuhofer,1,2 Kon.1

Methods: Our findings indicate that expression of MARCKS in RCC can serve as a therapeutic target. Methods: The clinical relevance of MARCKS and its phosphorylation was first confirmed. Next, we used genetic and pharmacologic approaches to verify the functionality and molecular mechanisms of MARCKS in RCC. Results: In a screen of 56 patients with RCC, we found that MARCKS expression and its phosphorylation are increased in RCC specimens and positively correlated with tumor grade. Genetic and pharmacologic suppression of MARCKS in high grade RCC cells led to a decrease in cell proliferation and migration. We further demonstrated that higher MARCKS expression promotes xenograft tumor growth and angiogenesis. Mechanistically, MARCKS acted upstream of the AKT/mTOR pathway, we identified the major protein kinase C substrate MARCKS as a potential target molecule in kidney cancer. In this study, we aim to determine if MARCKS can serve as a therapeutic target. Results: In a screen of 56 patients with RCC, we found that MARCKS expression and its phosphorylation are increased in RCC specimens and positively correlated with tumor grade.

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SA-PO349 Genetic Variation at the 8q24.21 Renal Cancer Susceptibility Locus Affects HIF-Binding to an Enhancer of Oncogenic MYC and PVT1 Expression Steffen Gramp,1 James L. Platt,2 Victoria Lauer,1 Rafik Salama,2 Kai-Uwe Eckardt,3 Peter J. Ratcliffe,4 David Robert Mole,2 Johannes Schödell,5 1Dept of Medicine & Nephrology and Hypertension, Univ Erlangen-Nürnberg, Erlangen, Germany; 2Henry Wellcome Building for Molecular Physiology, Univ Oxford, Oxford, United Kingdom.

Background: Clear cell renal cell carcinoma (ccRCC) origin from tubular cells. ccRCC is characterized by loss of von Hippel-Lindau protein (VHL) and uncontrolled expression of hypoxia inducible transcription factors (HIF). A genome-wide association study (GWAS) identified single nucleotide polymorphisms (SNP) on chromosome 8q24.21 interposed between MYC and PVT1. The SNPs are associated with increased susceptibility for ccRCC. MYC is upregulated in ccRCC, but compared to other tumors amplification of the MYC locus is rare. Hence, dysregulation of MYC in ccRCC must be caused by other mechanisms.

Methods: Using RNA analysis, chromatin immunoprecipitation (Chip), analysis of open Chromatin, allele specific assays and genome editing (CRISPR/Cas9) we have investigated the 8q24.21 locus in primary human tubular cells and RCC cell lines.

Results: Hypoxia led to induction of MYC and PVT1 in primary tubular cells and VHL re-expressing ccRCC cell lines in a HIF-dependent manner. Strikingly, HIF-Chip-Seq experiments identified HIF-binding events in a distal regulatory DNA element which encompasses the ccRCC associated SNPs identified in GWAS. Hypoxic regulation of MYC and PVT1 RNA, HIF-binding and open chromatin at the 8q24.21 locus are highly cell type specific and restricted to cells of renal tubular origin. Physical and functional interaction of the distal enhancer with the MYC promoter was verified by capture-c-assy and genome editing. In cell lines heterozygous for the SNP, allele specific assays showed an increased activity of chromatin and HIF-binding for the risk haplotype.

Conclusions: In cells of tubular origin HIF are capable of regulating MYC and PVT1 expression through binding to a distal enhancer. Therefore, in VHL-defective ccRCC unrestrained expression of HIF leads to overexpression of the oncoproteins MYC and PVT1. We conclude that the ccRCC associated SNP on 8q24.21 promotes these effects by modifying accessibility and activity of this site.

SA-PO350 Erythrocyte Sodium Sensitivity: Distribution in Hemodialysis Patients and Correlation with Eryptosis Anna Meyring-Wosten, Viktoria Kutnyschvili, Isreal Campos,1 Jie Ma,2 Samir D. Patel,1 Schantel Williams,1 Stephan Thijsen,1 Peter Kotanko.1 1Renal Research Institute, New York, NY.

Background: The glycocalyx of the vascular endothelium and erythrocytes selectively buffers sodium. Hence, damage of the glycocalyx leads to increased erythrocyte sodium sensitivity (ESS), which can be quantified by the ‘salt blood test’ (SBT) [Obereiter and Wilhelmi, Pflugers Arch 2013]. Eryptosis, suicidal death of red blood cells (RBCs), is accelerated in hemodialysis (HD) patients and is characterized by phosphatidylserine (PS) exposure on the RBC surface. While both ESS and eryptosis relate to RBC surface properties, their relationship has not yet been explored. Also, the acute impact of HD on eryptosis and ESS warrants investigation.

Methods: We enrolled 20 chronic HD patients. Blood samples were collected pre- and post-dialysis. SBT was performed in triplicates. PS exposure, a measure of eryptosis, was determined in duplicates from Annexin-V-FLOUS (ROCHE, Germany) binding by BD FACSCalibur™ System.

Results: The age of the subjects ranged from 28 to 75 years, 55% were white, 45% male, and 50% diabetic. ESS ranged from 2.4 to 8.0 with a median of 3.4 before HD and from 1.9 to 7.7 with a median at 3.5 after HD. The ESS dropped on average by 0.2 (95% confidence interval, 0.5 to 0.1; p = 0.64). PS exposure decreased from 0.60±0.42% to 0.40±0.13% (p = 0.02) during HD. There was no correlation between ESS and % eryptotic RBCs (R² = 0.005).

Conclusions: Glycocalyx integrity estimated by ESS did not correlate with suicidal death of erythrocytes. Kliche et al. [Cell Physiol Biochem 2015] observed a decrease of the ESS after dialysis in patients with high ESS. This could not be confirmed in our population, possibly due to a different dialysis modality (hemodialysis vs. postdilutional hemodiafiltration). The decrease of eryptosis after the hemodialysis treatment is contrary to findings by Aker et al. [J Mol Med, 2014] which might be the result of using ultrapure dialysate, a different type of erythropoiesis-stimulating agent used or uric acid removal.

Funding: Pharmaceutical Company Support - Renal Research Institute

SA-PO351 Lipophagy Maintains Energy Homeostasis during Prolonged Starvation in the Kidney Proximal Tubule Satoshi Minami,1 Takeshi Yamamoto,1 Yoshitsugu Takahatake,1 Atsushi Takahashi,1 Tomoko Namba,1 Jun Matsuda,1 Fuji Matsuoka,1 Fumio Niimura,1 Yoshitaka Isaka,1 1Dept of Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 2Inst of Medical Science and Dept of Molecular Life Science, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.

Background: Autophagy is a self-degradation process and combats starvation. Lipids are main energy source in the kidney proximal tubular cells (PTCs). Under starvation, PTCs increase fatty acids (FAs) uptake, form intracellular lipid droplets (LDs), and hydrolyze them for use. The involvement of autophagy in lipid metabolism in the kidney remains largely unknown.

Methods: We investigated the autophagy-mediated regulation of renal lipid metabolism under prolonged starvation using PTC-specific Atg5-deficient (Atg5-/-) KAP mice and in vitro serum starvation model.

Results: Twenty-four hours of starvation comparably induced LDs formation in the PTCs of control and Atg5-/- KAP mice; however, additional 24 hours of starvation lead to the reduction of the number of LDs in control mice, whereas they rather increased in Atg5-/- KAP mice. Autophagic degradation of LDs (lipophagy) in the PTCs was demonstrated by electron microscopic observation and biochemical analysis. In vitro pulse-chase assay elucidated that lipophagy mobilizes FAs from LDs to mitochondria during starvation, whereas impaired LDs degradation in autophagy-deficient PTCs lead to decreased ATP production and subsequent cell death. In contrast to the in vitro assay, despite impairment of autophagy induction, ATP content was preserved in 48 hour starved Atg5-/- KAP mice probably due to increased utilization of ketone bodies. This compensatory mechanism was accompanied by higher plasma fibroblast growth factor (FGF) 21 level and its expression in the PTCs; however, which is not essential for production of ketone bodies in the liver under prolonged starvation.

Conclusions: Autophagy combats prolonged starvation by promoting lipophagy in the PTCs to avoid cellular energy depletion.

SA-PO352 Endothelial Autophagy Is Essential for the Integrity of Glomerular Capillaries Jun Matsuda,1 Tomoko Namba,1 Yoshitsugu Takahatake,1 Atsushi Takahashi,1 Takeshi Yamamoto,1 Satoshi Minami,1 Tomonori Kimura,1 Jun-Ya Kaimori,1 Isao Matsui,1 Yoshitaka Isaka,1 1Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 2Advanced Technology for Transplantation, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.

Background: Autophagy is a lysosomal degradation system by which cytotoxic materials and damaged organelles are broken down into basic components. Although some previous studies have suggested endothelial autophagy contributes to maintaining vascular homeostasis, the physiological role of glomerular endothelial autophagy remains poorly understood.

Methods: We generated endothelial cell-specific Atg5-deficient mice (Tie2-Cre Atg5-/-; KAP mice). As Tie2 is expressed in some hematopoietic lineages as well as the endothelial cells, KO mice are dead by 3 months of age due to pancytopenia. Therefore, we subjected 1-month-old KO mice and controls to irradiation followed by bone marrow transplantation from Tie2-Cre negative littermates (WT/Atg5+ and WT/Atg5- mice, respectively).

Results: Although 1-month-old KO mice had no obvious changes except for splenomegaly, their glomeruli exhibited slightly distended capillary loops. Furthermore, electron microscopic analysis revealed segmental loss of glomerular endothelial fenestra accompanied with foot process effacement of podocytes adjacent to the transformed endothelial cells. The accumulation of reactive oxygen species and the number of apoptotic endothelial cells were increased in the glomerular capillaries of KO mice. Glomeruli of 2-month-old KO mice demonstrated lobular pattern with thickening of capillary loops and mesangial matrix expansion. WT/Atg5+ mice exhibited similar glomerular phenotypes of KO mice, while no obvious histological changes were detected in other organs. In addition, mesangiolysis and glomerulosclerosis were observed in 12-month-old WT/Atg5+ and WT/Atg5- mice, and they developed significant increase in serum urea nitrogen and albuminuria compared with WT/WT mice.

Conclusions: These data suggest that endothelial autophagy protects glomeruli from oxidative stress and maintains the integrity of glomerular capillaries. Enhancing endothelial autophagy may provide a novel therapeutic approach to minimize glomerular diseases.

SA-PO353 Autophagy in Primary Renal Tubular Epithelial Cells Mediates Cellular Senescence Arpita Baisantry,1,2 Sagar Bhayana,2 Christoph Wrede,3 Jan Hegermann,1 Hermann G. Haller,1 Anette Melk,1 Roland Schmitz,1 1Kidney, Liver and Metabolic Diseases, Children’s Hospital, Hannover Medical School (MIH), Hannover, Germany; 2Nephrology, MHII, Hannover, Germany; 3Functional and Applied Anatomy, MHII, Hannover, Germany.

Background: Autophagy and senescence are two discrete pathways triggered during acute kidney injury and during renal repair especially in tubular epithelial cells. Although autophagy is considered renoprotective, it’s a proven mediator of oncogene induced senescence and its specific role in promoting or exacerbating senescence is still debatable.

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

709A Underline represents presenting author.
SA-PO354

Autophagy in Kidney Allografts of Rapamycin Treated Patients

Arpita Baisanyu,1,2 Sagar Bhayana,3 Thomas D. Kraemer,2 Christoph Wrede,2 Clemens L. Bockmeyer,1 Jan U. Becker,1 Jan Hegermann,2 Wilfried Gwinner,2 Hannelore G. Heine,2 Heike Merk,3 Roland Schmitt,2 Suzanne L. Bockmeyer,1

Results: Our results indicate that ex vivo PTEC culturing is associated with development of senescence and is preceded by a strong induction of baseline autophagy. Speculative attribution of this autophagic activity by Atg5 silencing counteracts senescence development under baseline and stress conditions and preserved the epithelial phenotype. Interestingly, while autophagy induction by chloroquine mildly enhanced senescence induction, rapamycin treatment bypassed senescence in PTEC.

Conclusions: Our results highlight a complex interaction between cell culture induced stress, autophagy and renal senescence. While chemical modulators of autophagy such as chloroquine and rapamycin might have off-target effects, specifically silencing Atg5 attenuates the pro-senescent pathway of stress induced autophagy in vitro.

Funding: Government Support - Non-U.S.

SA-PO356

Role of TGF-β1 in the Abrupt Autophagy of Podocyte Induced by Mesangial Cell Proliferation

Xiao Mao,1 Xilian Xu,2 Zhigang Zhang,2 Huijuan Wu,1,2 Department of Pathology, Fudan Uni., Shanghai, China; 2Shanghai Inst for Kidneys and Dialysis, Shanghai, China; 1Dept of Nephrology, Zhongshan Hospital, Fudan Uni., Shanghai, China.

Background: Proteinuria is a common clinical manifestation of IgAN and an indicator of a chronic filtration membrane of which IgAN is an indispensable component. Under physiological condition, autophagy plays a pivotal role in podocyte homeostasis. During mesangial cells (MCs) proliferation, the activated MCs release various cytokines which influence other glomerular cells. Among those cytokines, it remains unknown whether and how TGF-β1 excreted by MCs interfered the autophagy of podocytes and what role decorin (DCN), a natural inhibitor of TGF-β1, acted.

Methods: In IgAN and rat anti-Thy-1.1 nephritis, proteinuria was examined by gel electrophoresis, and podocyte autophagy was observed by electron microscope and LC3 staining. The level of TGF-β1 and TGF-β1/Smad3 was quantified by ELISA and TGF-β1/Smad3/mTORC1 signaling was examined by western blot. Then in vitro, we firstly examined autophagy and TGF-β1/Smad/mTORC1 signaling in the cultured podocytes treated by TGF-β1 with/without Chloroquine. We next quantified TGF-β1 in the supernatant of MCs treated by TGF-β1 with/without SB431542 and TGF-β1 with/without soluble DCN, autophagy and TGF-β1/Smad/mTORC1 signaling were detected by western blot and IF.

Results: In IgAN and anti-Thy-1.1 nephritis, we observed a presence of proteinuria, accumulations of phospholipids in the lysosomes were observed, and LC3II/LC3I ratio elevated and DCN declined. In the glomeruli of anti-Thy-1.1 nephritis and the cultured podocytes treated by TGF-β1, TGF-β1/Smad/mTORC1 signaling was activated with LC3II/LC3I ratio declined. When activated, the cultured MCs excreted a bulk of TGF-β1. Inhibition of autophagy by TGF-β1 with/without SB431542 and TGF-β1 with/without soluble DCN, autophagy and TGF-β1/Smad/mTORC1 signaling were detected by western blot and IF.

Results: In IgAN and anti-Thy-1.1 nephritis, we observed a presence of proteinuria, accumulations of phospholipids in the lysosomes were observed, and LC3II/LC3I ratio elevated and DCN declined. In the glomeruli of anti-Thy-1.1 nephritis and the cultured podocytes treated by TGF-β1, TGF-β1/Smad/mTORC1 signaling was activated with LC3II/LC3I ratio declined. When activated, the cultured MCs excreted a bulk of TGF-β1. Inhibition of autophagy by TGF-β1 with/without SB431542 and TGF-β1 with/without soluble DCN, autophagy and TGF-β1/Smad/mTORC1 signaling were detected by western blot and IF.

Conclusions: Activated MC excreted excessive TGF-β1 which mediated the abortion of macroautophagy in podocyte by activating mTORC1 in a TGF-β1/smad2-dependent way. The deficiency of DCN in serum failed to neutralize TGF-β1 activity, making DCN and TGF-β1 the potential clinical indicators of IgAN.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

SA-PO357

High Fat Diet-Induced Lysosomal Dysfunction and Impaired Autophagy Flux Contribute to the Lipotoxicity in the Kidney

Takeshi Yamamoto,1,2 Yoshitsugu Takakatake,1 Atsushi Takahashi,1 Tomoko Namba,1 Jun Matsuda,1 Satoshi Minami,1 Tomonori Kimura,1 Taiji Matsuoka,2 Fumio Niinuma,2 Yoshitaka Isaka,1 1Dept of Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 2Inst of Medical Science and Dept of Molecular Life Science, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan; 3Dept of Pediatrics, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.

Background: Excessive fat intake contributes to the progression of metabolic diseases via cellular injury and inflammation (termed lipotoxicity).

Methods: We investigated 1) the pathophysiology of lipotoxicity in the kidney proximal tubular cells (PTCs) with a focus on lysosomes and mitochondria, 2) lipid overload-mediated alterations in autophagy activity in vivo and in vitro, and 3) the effects of autophagy-deficiency on kidney morphology and function during lipid overload.

Results: High fat diet (HFD) first induced autophagy in the PTCs, which in itself mobilized phospholipids from cellular membranes to lysosomes, resulting in an accumulation of phospholipids in the enlarged lysosomes. Autophagic degradation activity progressively stagnated due to the impaired lysosomal acidification and consequent lipid accumulation. Autophagy also suppressed HFD-induced mitochondrial dysfunction and inflammasome activation. However, HFD-fed mice had no capacity to counteract autophagic numbness resulted in severer injury on ischemia-reperfusion. Pharmacological correction of phospholipid accumulation by eicosapentaenoic acid successfully restored autophagic numbness.

Conclusions: Collectively, these observations highlight the homeostatic actions of autophagy in podocytes and the importance of TGF-β1/Smad/mTORC1 signaling in these cells. They also raise the possibility that therapeutically modulating TGF-β1 activity may improve podocyte health in glomerular disease.

Funding: Government Support - Non-U.S.
Fatty Acids Suppress Autophagy in Renal Proximal Tubule Epithelial Cells
Aala Jaberi, Ryan M. Mulhern, Angela Nolan, Steven C. Borkan, John H. Schwartz, Andrea Havasi. Renal Section, Boston Univ Medical Center; Boston, MA.

Background: Fatty acids are an important source of energy in renal tubular cells and have a key role in cellular signaling. However, under pathological conditions excess fatty acids promote lipotoxicity. In proteinuric states, large amounts of fatty acids carried by albumin enter proximal tubular epithelial cells by crossing both the basolateral and apical membranes. We hypothesize that fatty acid endocytosis with albumin results in tubular cell damage and suppresses macroautophagy including mitophagy, a process that maintains healthy organelles.

Methods: Autophagosomes, lysosomes, albumin and fatty acids were visualized in live cells using specific fluorescent markers. The effect of fatty acids on primary tubular cell autophagy was assessed by measuring autophagosome flux, LC3-II and p62 levels. Mitochondrial morphology was visualized using confocal microscopy. Mitochondrial fusion and fission proteins were assessed by western blot. Mitophagy was assessed by confocal imaging of mCherry-GFP-LC3 transfected tubular cells.

Results: Exposure of primary proximal tubular epithelial cells to albumin-bound fatty acids caused rapid endocytosis of these compounds and transport to both lysosomes and autophagosomes as well as decreased autophagic flux and mitochondrial integrity. Fatty acid treatment also altered mitochondrial morphology evidenced by increased mitochondrial fission and autophagosomes as well as decreased autophagic flux and mitophagy. Fatty acid treatment with 1µM AA significantly increased cell death (mean ± SEM, control: 100±1.8; erastin 0.1µM: 44.0±0.7, and 10µM: 53.8±1.9 %, p<0.0001, n=3/group).

Conclusions: Albumin-bound fatty acid endocytosis suppresses mitophagy in proximal tubular cells. Endocytosis of fatty acids may be related to apoptosis and programmed cell death and contribute to increased cell death and mitochondrial toxicity. Mitochondrial dysfunction might contribute to tubular damage in proteinuric states.

SA-P0359
Synchronized Regulation of mTOR and Autophagy in Podocytes
Tillmann Bork,1 Wei Jiang,1 Kosuke Yamahara,1 Pierre-Louis Tharaux,2 Tobias B. Huber.1 1Dept of Nephrology, Univ Hospital Freiburg, Freiburg, Germany; 2PARC Paris Cardiovascular Centre, INSERM, Paris, France.

Background: Autophagy emerged as a key mechanism to eliminate unwanted cytoplasmic materials, thereby preventing cellular damage and stress to safeguard long-lived podocytes. The atypical serine/threonine kinase mTOR (mammalian target of rapamycin) is a central regulator of cell growth and metabolism. Active mTOR signaling is a strong suppressor of autophagy in many tissues and cell lines. Podocytes however show highly activated mTOR-signaling in parallel with active autophagy. Aim of our experiments was to further elucidate the interplay of mTOR signaling and autophagy in podocytes.

Methods: Autophagy levels were monitored in vivo by crossing GFP-LC3 reporter mice to models of mTOR hyperactivation (Tsc1 PcKO) and mTOR loss of function (Raptor PckO). In addition, podocyte-specific Raptor and Tsc1 KO mice were crossed to a Tomato/GFP reporter line to efficiently isolate podocytes for primary cell culture studies. Treatment studies were performed to assess autophagic flux and dynamic changes in autophagy regulation in vivo and in vitro.

Results: Strikingly, podocytes did exhibit high basal autophagy rates independently of the mTOR activation status. There was no difference in LC3 conversion in vivo and no difference of the GFP-LC3 signal between Raptor and Tsc1 PcKO mice. Pharmacologic mTOR inhibition with Rapamycin increased autophagy, whereas long-term treatment showed no effect. In vitro and in vivo experiments revealed AMPK as an alternative regulator of autophagy bypassing the mTOR signaling cascade.

Conclusions: mTOR and autophagy are key regulators of podocyte function and maintenance. Our data highlight now a podocyte-specific AMPK-autophagy regulatory axis of autophagy bypassing the mTOR signaling cascade.

SA-P0360
Wnt9A Accelerates Renal Fibrosis Through Induction of Tubular Senescence
Lili Zhou, Congwei Luo. Dept of Nephrology, Nanfang Hospital, Southern Medical Univ; Guangzhou, Guangdong, China.

Background: As a key factor, Wnt is involved in pathogenesis of kidney diseases. However, the underlying mechanism is unknown. In this study, we detected the potential role of Wnt9a in tubular cell senescence and renal fibrosis.

Methods: Wnt9a expression in renal tissues, primary culture of tubular cells, and mice kidneys were tested in mouse models of ADR nephropathy, UUO, and ischemia-reperfusion. The co-localization of Wnt9a and a biomarker for senescence, p16, was checked in sequential sections. In unilateral ischemic/reperfusion injury, ectopic overexpression or knockdown of Wnt9a was respectively induced. Fibrosis and tubular senescence were detected. To further confirm the effect of Wnt9a in senescence, 24-month-old mice were performed the surgery of UIRI, and a vector encoding the secreted form of Klotho was administrated to inhibit Wnt9a. In cultured tubular epithelial cells (HK-2), cell cycle and senescence-related gene were determined by overexpression of Wnt9a.

Results: (1) Wnt9a was upregulated in UUO and ADR nephropathy, and mainly located in tubules. Wnt9a overexpression was correlated with tubular senescence and renal fibrosis, as evidenced by increased p16, Ki-67, Shh, and Ambre expression. Wnt9a dramatically promoted renal fibrosis, deteriorated renal function, and induced tubular senescence. To the contrary, knockdown of Wnt9a protected renal fibrosis and tubular senescence. Compared to young mice, Wnt9a was remarkably upregulated in aging mice. In HK-2 cell line HK-2, we found Wnt9a induced cell cycle arrest and upregulation of senescence-related gene p16/ARF and p21. However, siRNA to Wnt9a significantly inhibited AA-induced S-phase arrest and senescence-related gene expression. Wnt9a also directly induced fibroblasts proliferation, or indirectly induced secretion of matrix protein through conditioned-medium from cultured tubular cells. On the other hand, Wnt9a contributed to transition from fibroblasts promoted senescence in tubular cells.

Conclusions: These results suggest that Wnt9a accelerates renal fibrosis through induction of tubular senescence.

SA-P0361
Heme Oxygenase-1 Protects Proximal Tubule Epithelial Cells from Ferroptosis
Ooreoluwa O. Adegovin,1 Ravindra Boudlu,1 Amie Traylor,1 Jeremiah M. Lever,1 James George,2 Anupam Agarwal.1,3 1Div of Nephrology, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL; 2Div of Cardiothoracic Surgery, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL; 3Birmingham VA Medical Center, Birmingham, AL.

Background: Ferroptosis is an iron-dependent form of programmed cell death that occurs in models of acute kidney injury (AKI) in vitro and in vivo. A potential source of iron for this process is HO-1, a cytoprotective enzyme that is robustly induced in renal proximal tubules in AKI where it generates CO, biliverdin, and iron. Therefore, we tested the hypothesis that HO-1 plays a role in regulation of ferroptotic cell death in renal proximal tubular epithelial cells (PTECs).

Methods: Immortalized PTECs obtained from HO-1−/− and HO-1+/− mice were treated with erastin (ferroptosis inducer), and analyzed for morphological changes and cellular metabolic activity. Induction of HO-1 in response to erastin treatment, and following co-treatment with anti-oxidants, iron, or an iron chelator were determined using qPCR and western blotting.

Results: Treatment of HO-1−/− PTECs with erastin resulted in a dose-dependent increase in HO-1 expression, as well as significant inhibition of cellular metabolic activity compared to vehicle-treated controls (mean ± SEM, control: 100±1.8; erastin 0.1µM: 91.6±2.5; erastin 1µM: 58.3±0.9, and 10µM: 62.5±1.8%, p<0.0001, n=3/group).

Conclusions: HO-1 induction appears to attenuate erastin-induced ferroptotic cell death in renal epithelial cells; therefore, it may serve as a viable therapeutic target for intervention in AKI.

Funding: Other NIH Support - T32 - DK007545
SA-PO363

The Effects of Periostin on the Aging Process: "Seeho Park; Jung Nam Am,2,3 Eun Nim Kim,4 Sunhwa Lee,5 Jinhyuk Kim,6 Seung Hee Yang,1 Dong Ki Kim,1 Yun Kyo Oh,2 Chun Soo Lim,1 Yon Su Kim,1 Jung Pyo Lee.2 1Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea; 2Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; 3Dept of Critical Care Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; 4Dept of Internal Medicine, The Catholic Univ of Korea, Seoul, Korea.

Background: Periostin, a matricellular protein, has been reported in diverse processes and pathologies in tissue remodeling through the promotion of adhesion, cell survival, cellular dedifferentiation, and fibrogenesis. However, its role in aging process is unknown.

Methods: We investigated expressions of periostin in normal human kidney tissues classified by age (20, 40, and 60 years) and in mouse kidney tissues of wild type (WT) C57Bl/6 mice or Postn null (Postn-) mice aged 24 months. In addition, chemistry data including serum creatinine and histopathology findings of WT mice or Postn null mice classified by age (young vs. aged, 2-months old vs. 24-months old) were examined.

Results: Periostin expressions in normal human kidney tissues were significantly different according to the age. Intrarenal periostin expressions were prominent in the aged WT mice than in the young WT mice. However, all these changes were diminished in the aged Postn null mice, serum creatinine levels were also considerably lower in aged Postn null mice than in aged WT mice. Apparent tubular atrophic changes, interstitial fibrosis, and collagen fiber deposition which were prominent in the aged WT mice than in the young WT mice, were remarkably alleviated in aged Postn null mice. Moreover, the expressions of periostin were also attenuated in aged Postn null mice compared to aged WT mice.

Conclusions: Aging resulted in morphologic/physiologic changes and increased expressions of periostin. Periostin ablation could have protective effects in aging process.

SA-PO364


Background: Kidney transplantation in patients with atypical hemolytic uremic syndrome (aHUS) is frequently complicated by recurrence of aHUS, often resulting in graft loss. Eculizumab prophylaxis prevents recurrence, improving graft survival. An alternative treatment strategy has been proposed where eculizumab is administered upon recurrence. We combined available evidence and performed a cost-effectiveness analysis of these competing strategies.

Methods: We created a decision tree with treatment strategies for aHUS patients with end stage renal disease (ESRD): (ERSD: dialysis treatment; kidney transplantation; kidney transplantation with eculizumab upon recurrence of aHUS; and kidney transplantation with lifelong eculizumab prophylaxis. We assumed that transplantation was performed with a kidney from a living donor. We performed a Markov analysis to compare cost-effectiveness of the strategies.

Results: The predicted probability of recurrence in the kidney transplantation and eculizumab upon recurrence strategies was 23% and 37% after 5 and 12 months. Kidney transplantation was the least costly strategy. By comparison, dialysis was more costly and resulted in fewer Quality Adjusted Life Years (QALYs) gained, and was therefore considered inferior to kidney transplantation. Eculizumab upon recurrence was more costly than kidney transplantation without eculizumab, but resulted in more QALYs gained. The incremental cost-effectiveness ratio (ICER) was $42,961 per QALY. Lifelong eculizumab was even more costly, and gave an ICER of $63.1 million compared to eculizumab upon recurrence.

Conclusions: Kidney transplantation was more cost-effective than dialysis to treat ESRD due to aHUS. However, Eculizumab upon recurrence was more cost-effective than kidney transplantation. Gain in QALYs is in the lifelong eculizumab strategy was offset by extremely high costs. Therefore, eculizumab upon recurrence of aHUS was more acceptable.

SA-PO365

Kidney Transplant in Atypical HUS: A Single Center Experience Gianluigi Ardissoni,1 Donata Cresseri,2 Antenore Giussani,3 Stefania Salardi,4 Francesco Pernici,3 Paola Tresta,1 Michela Perrone,2 Fabio Pagliaronga,2 Mirco Belingheri,2 Martina Sgarbanti,2 Lucrezia Furlan,2 Angela Nocco,2 Silvana Tedeschii,2 Piergiorgio Messa.1 1Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico; 2Univ Hospital, Padova, Italy.

Background: For decades, atypical hemolytic uremic syndrome (aHUS) has been considered a contraindication to kidney transplantation (KTx) for the very high risk of disease recurrence. The availability of Eculizumab (EUC) has made it possible to safely perform kidney transplants (KTx) with aHUS to KTxs but the best approach to treatment (Rx) as to timing of 1st dosing, schedule, possibility of Rx discontinuation and pts’ monitoring, is not well established.

Methods: During the past decade, a total 20 pts (6 children) with aHUS were followed for KTx at our Center (in 3 KTx had been performed elsewhere). Five pts had a previous KTx(s) and the median time on RRT prior to KTx was 8.5 years. One pt has received the KTx from a living-related donor. CFI-related disease (n:13) was the most common etiology followed by mutations on CFI (n:4), C3 (n:1), MCP (n:1) and Idiopathic (n:1). Based on the strategy used to prevent disease relapse before and after KTx, 3 groups can be identified (were grafts were exposed to multiple preventive strategies): A: no prophylaxis (n:7); B: plasmaexchanger-plasmapherist (n:5); C: ECU (n:14).

Results:

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eculizumab upon recurrence</td>
<td>3/4</td>
<td>5/9</td>
</tr>
<tr>
<td>Cumulative observation period on KTx (yrs)</td>
<td>47</td>
<td>7</td>
</tr>
<tr>
<td>Relapse rate (event/patient/10 yrs)</td>
<td>0.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Graft loss due to relapse</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Graft loss for other causes</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Pts in group B were switched to ECU once available. One pt discontinued ECU as soon as AntiCFH Ab were no longer detectable. Based on complement activity targeted to <30%, out of the 12 pts currently on ECU, 4 are regularly receiving the infusion every 3 weeks and 8 every 4 weeks.

Conclusions: Our experience favours the prophylactic use of ECU in pts undergoing KTx with a history of aHUS. We recommend complete characterization (as to disease etiology) pre-KTx and that maintenance ECU is continued lifelong.

SA-PO366

Kidney Transplantation Discussion Timing and Subsequent Wait Listing in a National Cohort Nancy G. Kutner,1 Yijian Huang,2 Rebecca H. Zhang.3 1Reproductive Medicine, Emory Univ, Atlanta, GA; 3Biostatistics, Emory Univ, Atlanta, GA.

Background: Patient awareness and understanding of kidney transplantation (KT) are widely shared goals, but variables associated with timing and outcomes of KT discussion merit ongoing study.

Methods: The USRDS CDS survey of 1634 incident dialysis patients (18+, median vintage 4 mos) from 296 randomly selected clinics asked “Was kidney transplantation discussed with you before your regular treatment for kidney failure?” and, later in the interview, “Has kidney transplantation been discussed with you since your started dialysis?” Patient characteristics, early nephrology care, whether “informed of KT options,” and wait-listing (WL) events were identified in USRDS files. Excluding 60 patients with pre-dialysis WL, the adjusted association of KT discussion timing with WL (333 events, median 21.7 mos follow-up) was examined in Cox models.

Results: KT discussion was reported (a) Pre- and post-dialysis by 37.3% (b) Post-dialysis only by 25.4% (c) Pre-dialysis only by 12.5% (d) Not at all by 24.8%. Compared with no discussion, discussion post-dialysis only was associated with greater likelihood of WL (HR 3.78 [95% CI 2.28-6.25]), but patients with both pre- and post-dialysis discussion had even greater WL likelihood (HR 4.20 [95% CI 2.58-6.84]). Pre-EsrD nephrology care had highest (82.2%) in the dual exposure group. Patients with only pre-dialysis discussion had lower (6.5%) WL likelihood of WL. Overall, 75% of patients reported exposure to KT discussion at one or both time points, similar to the proportion reported by providers on CMS Form-2728 as informed of KT options (72%).

Conclusions: Consistent with other research, perceived KT discussion after dialysis was associated with greater likelihood of subsequent WL, but pre-dialysis post-dialysis exposure was associated with even greater likelihood. Patient-provider discrepancy in reported KT information exposure was minimal when patient-reported exposure included pre- and post-dialysis exposure. The content as well as timing of reported “KT discussion” and “informed of KT options” are important variables in ongoing efforts to advance the understanding of effective KT education.

Funding: NIDDK Support

SA-PO367


Background: The 2014 OPTN Kidney Allocation System (KAS) prioritizes allografts with Kidney Donor Profile Index (KDPI) ≤ 50 to pediatric recipients. Most donors < age 12 have KDPI over 35 even with ideal function. We sought to determine if transplants using such grafts differed in outcomes compared to ideal KDPI ≤ 35 grafts.

Methods: UNOS data from first deceased donor renal transplants 2000-2010 with follow-up to 3/31/2014 were used to compare graft survival among donors and recipients across the groups, using Kaplan-Meier. Public Health Service (PHS) high risk comparisons used Pearson’s chi-square. Donor height and weight median from US growth charts for age with no additional risk parameters were used to calculate KDPI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 712A
**SA-PO368**

Validation, Calibration and Model Revision of the Kidney Donor Risk Index Scoring System of a Deceased Donor Kidney for Transplantation in the Netherlands

**Background:** The prognostic Kidney Donor Risk Index (KDRI)—developed and validated at the US National Organ Sharing System (NOSs) in 2002—was created to predict graft failure in the first year.

**Methods:** We aimed to externally validate the KDRI as proposed by Rao et al. (2009), containing 10 donor and 4 transplant factors. We used the Dutch Organ Transplantation Registry to include recipients (≥18y), transplanted from 2002 to 2012 with a first brain-dead organ.

**Results:** Among 2554 transplanted kidneys, the median of the KDRI was higher compared with the US (1.05 vs. 1.21, see figure 1). Kidneys in the highest KDRI quintile (>0.79) showed 84.7% survival. At year 1, the time-dependent (t) ROC of the KDRI showed a 65% increase in total number of deceased donor cross matches performed during post-KAS (1188) and pre-KAS (715) intervals was observed, respectively. The percentage of XMs performed for sensitized patients (cPRA=0%) increased from 19% pre-KAS to 34% post-KAS (p<0.0001).

**Conclusions:** The NL-KDRI distinguished donors with low and high KDRI scores (<1 vs. >1.45) better than middle-ranged scores. We correctly validated the baseline risk and recalibrated donor factors from the KDRI into the NL-KDRI. The discriminative ability of the NL-KDRI performs at least as well as in the US, and is useful for decision-making regarding the acceptance of a kidney organ offer.

**Funding:** NIDDK Support

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**SA-PO369**

Impact of the New Kidney Allocation System on the Transplant Rate of HLA Sensitized Patients. A Single Center Experience

**Background:** Increasing access to transplantation of difficult-to-match patients was a key goal of the new kidney allocation system (KAS) implemented on Dec 4, 2014. In this study, we evaluated the impact of the new KAS on the transplantation rate of HLA sensitized candidates at our center.

**Methods:** During Jan 1 - Dec 4, 2014 (pre-KAS interval) and Jan 1 - Dec 4, 2015 (post-KAS interval), immunologic risk was assessed prior to transplantation using the same approach. Unacceptable HLA antigens were defined using the following cutoffs: 5000 MFI for HLA-A, -B and DR, and 10,000 MFI for HLA-C/DP.

**Results:** A 65% increase in total number of deceased donor cross matches performed during post-KAS (1188) and pre-KAS (715) intervals was observed, respectively. The percentage of XMs performed for sensitized patients (cPRA=0%) increased from 19% pre-KAS to 26% post-KAS (p<0.0001).

**Conclusions:** The NL-KDRI facilitated a marked increase in the transplant rate of sensitized candidates at our center.

**Funding:** DaVita Inc, Denver, CO; Apex Health Innovations, Simi Valley, CA.

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**SA-PS417**

Variation in Dialysis Facility Referral for Kidney Transplantation in the Southeastern United States

**Background:** While variability in dialysis facility kidney transplant (KTx) referral between dialysis units has been studied in one state (Georgia), regional, facility-level data for KTx referrals has not been examined.

**Methods:** We analyzed ESRD Network 6 data on KTx referrals from dialysis facilities in 2013, collected from 8 transplant centers in Georgia, North Carolina, and South Carolina. We linked with the 2012 Dialysis Facility Report data to obtain dialysis facility key.

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

Underline represents presenting author.
characteristics. Multivariable-adjusted linear regression models were used to identify characteristics associated with low KTx referral (% of prevalent dialysis patients aged 18-69 years referred in 2013).

Results: Among 604 dialysis facilities, the median facility-level percentage of adult prevalent dialysis patients referred for transplant in 2013 was 12.7% (IQR: 7.2%-19.6%; range: 0% to 78.6%); 25 facilities (4.1%) referred no dialysis patients.

Conclusions: The observed facility variability in transplant referral suggests the need to use transplant referral as a quality measure for dialysis facilities that could be tracked nationally.

Funding: Other NIH Support - National Institutes on Minority Health and Health Disparities

SA-PO372

Willfulness of Canadian ESRD Patients to Consider Transplant Tourism


Background: Transplant tourism refers to travel for transplantation that involves organ trafficking and/or transplant commercialism, and is associated with poor outcomes after transplantation. While characteristics of transplant tourists have been described, there are no data on end-stage renal disease (ESRD) patients who may be at high risk for engaging in this practice.

Methods: We surveyed Stage V chronic kidney disease (CKD) and dialysis patients in British Columbia, Canada to determine their willingness to travel outside of Canada and purchase a kidney.

Results: Of 592 patients surveyed, 342 (58%) were willing to travel for transplantation, with 149 (25%) strongly willing to travel. Figure 1 shows the willingness of patients to travel for transplantation under different circumstances. N=354 (60%) were willing to travel if they had lived in a different country or could be placed on an official transplant list in another country, while 143 (24%) were willing to pay for the kidney on top of paying the medical costs of the transplant. Thirty-three percent were willing to travel even if they knew the donor was an executed prisoner, but only 4% admitted that they were willing to break the law to obtain the transplant.

Patients that were willing to travel and purchase a kidney included a higher proportion of patients that were younger, male, of Asian ethnicity, had higher median household income, had initiated dialysis within the last year, and were less knowledgeable about the risks and legality of transplant tourism.

Conclusions: Nearly one quarter of ESRD patients surveyed were willing to purchase a kidney outside of Canada, and may be at high risk to engage in transplant tourism. Educating at-risk patients (particularly those who recently started dialysis) about the legal and medical risks of transplant tourism may help to deter this practice.

Funding: Government Support - Non-U.S.

SA-PO373

Histo-Molecular Assessment of Pre-Implantation Biopsies Demonstrates That Many Discarded Kidneys Are Similar to Successfully Transplanted Kidneys in Other Center

Konrad S. Farniols,1 Jeff Reeve,1 Silke V. Niederhaus,2 Jonathan Bromberg,2 Philip F. Halloran.3 1Univ of Alberta, Edmonton, Canada; 2Univ of Maryland, Baltimore.

Background: Increasing numbers of kidneys from older brain dead donors (DBD) are considered for transplantation. Many of these kidneys are discarded based on conventional (clinical or histologic) features. We previously observed that 50% of DBD kidneys discarded by conventional features had similarly low expression of Acute Kidney Injury (AKI) associated genes as those that were transplanted. Here, we are asking whether the combined histology and expression of AKI genes, that also are associated with transplant fibrosis, can demonstrate that kidneys discarded by conventional features are indeed similar to kidneys accepted for transplantation, using discarded and accepted kidneys from different centers.

Methods: We compared 43 discarded kidneys in one USA center to 64 accepted kidneys transplanted in one European center, all from older DBD, using Principal Component Analysis. All 64 functioned and 63 were surviving at 3 months post transplant. Following variables were used: summarized expression of AKI genes and histologic lesion scores: glomerulosclerosis, fibrous intimal thickening, fibrosis/atrophy and arterial hyalinosis.

Results: The Principal Component 1 (PC1) was associated with histologic lesions, while PC2 component (PC2) represented the summarized expression of AKI genes. Both PC1 and PC2 component scores did not show clear separation of discarded kidneys from the accepted kidneys (figure 1), also confirmed by the density plot analysis of PC1 and 2 scores.

Conclusions: Combined histo-molecular features were not able to separate discarded kidneys in one center from the kidneys accepted and functioning in another center. We conclude that the current criteria for discarding kidneys based on conventional features, particularly histology, need to be reassessed.

Funding: Other NIH Support - K24

SA-PO374

Examining the Willingness of Canadian ESRD Patients to Travel Outside Canada for Kidney Transplantation

Gill, Adeera; Rose, John; Bromberg, Jonathan; Halloran, Philip. Medicine-Nephrology, Univ of British Columbia, Vancouver.

Background: According to U.S. Organ Procurement and Transplantation Network policies, “measured... calculated glomerular filtration rate (Cockcroft-Gault or other reliable formula) less than or equal to 20 mL/min” triggers start of time-accrual on the kidney transplant waitlist. Since only a single CrCl or eGFR ≤20 is needed, the policy implicitly assumes that decline in renal function is monotonic (Mitch et al, Lancet 1976), but recent studies demonstrate that this is often not the case (Li et al, AJKD 2012).

Methods: To assess whether requiring patients to demonstrate renal function “persistently ≤20” would change waitlist qualification, we compared time to qualification as defined by 2 different rules: 1) at first eGFR ≤20, regardless of subsequent measurements (current paradigm) and 2) at second eGFR ≤20 given a prior eGFR ≤20 at least 3 months before (akin to the definition of CKD). We applied the CKD-EPI equation to serial creatinine measurements from 3 patient cohorts: 1) of waitlisted patients at a major U.S. academic center and 2 national, multicenter cohorts of CKD patients (the NIH-sponsored AASK and MDRD studies). Kaplan-Meier curves for the two rules were constructed for each cohort and used to estimate median times to qualification.

Results: Requiring patients to demonstrate eGFR ≤20 on two occurrences at least 3 months apart delays median time to qualification on the order of 0.5 to 2 years.

Conclusion: Combined histo-molecular features were not able to separate discarded kidneys in one center from the kidneys accepted and functioning in another center. We conclude that the current criteria for discarding kidneys based on conventional features, particularly histology, need to be reassessed.

Funding: Other NIH Support - K24
SA-PO375
Health Disparities Impact Transplant Referral

Background: Kidney transplantation (TXP) offers longer life expectancy and better quality of life than any dialysis modality and is the treatment of choice for ESRD patients. We postulated that racial/ethnic and demographic factors may be associated with transplant related health disparities, which significantly impact referral, refusal, wait-listing and ultimately TXP rates.

Methods: To explore this hypothesis we studied 11,950 dialysis patients under age 70, treated in 230 facilities in 2015 operated by DCl, a large not-for-profit provider. We used a MIS to abstract demographic data and TXP status. We constructed a random intercept, multinomial logistic regression model using Proc Glimmix in SAS with adjustment for clustering within facilities.

Results: Overall, 34.5% were referred but not yet listed, 19.3% refused referral, 23.8% were not referred, 18.7% were waitlisted (WL) and 3.7% received a transplant. The odds ratios for each step in the process leading to TXP by patient characteristics are shown. Females were more likely than males to refuse evaluation but if referred they just as likely to progress to being WL or TXP. African Americans were more likely than whites to be referred but were less likely to progress to WL-TXP. Asians were less likely than whites to refuse. Extremes of BMI (<22 or ≥37), in-center dialysis, and age ≥63 years were not referred, 18.7% were waitlisted (WL) and 3.7% received a transplant. The odds for each effect in the process leading to TXP by patient characteristics are shown.

Conclusions: Racial/ethnic and demographic factors are associated with significant TXP related health disparities leading to decreased referral. Dialysis facilities should have increasing roles in educating patients about TXP, referring patients and facilitating completion of evaluation and listing.

SA-PO376
Risk Factors for Preterm Birth in Kidney Transplant Recipients
Swati Rao, 1,2 Fengzheng Zhu, 3 Dawn Armenti, 1 Lisa Coscia, 1 Mythili Ghanta, 1 Iris J. Lee, 1 Avrum Gillespie, 1 Serban Constantinescu, 1 Michael J. Moritz, 1,4 Nephrology, Temple Univ; 2Fox School of Business, Temple Univ; 3Gift of Life Inst; 4Lehigh Valley Health Network.

Background: The rate of preterm birth (<37 wks) in kidney transplant (KT) recipients is 5 times higher than general population (10%), but the risk factors have not been well quantified.

Methods: We analyzed 1374 pregnancies which resulted in live birth in 948 KT recipients from the National Transplantation Pregnancy Registry using logistic regression.

Results: The mean conception age was 29.7 yrs, gestational age was 36 wks, and birth weight was 2567g. The preterm birth rate was 49%. Recipients with HTN, DM, pre-eclampsia, acute rejection during pregnancy, higher serum creatinine pre-conception, higher BMI (<22 or ≥37), in-center dialysis, and age ≥63 years were less likely to be referred and more likely to refuse referral. Extremes of BMI (<22 or ≥37), in-center dialysis, and age ≥63 years were associated with less likely to be referred and more likely to refuse referral.

Conclusions: Preterm births are more likely related to worse renal and cardiovascular outcomes such as hypertension, diabetes and obesity. Future work will investigate how changes in body composition 12-months after KT affect frailty status and clinical outcomes.

SA-PO377
Association of Body Composition with Changes in Frailty after Kidney Transplantation
Natalia Cortez, Daniel Velez, Eugenia Xiao, Sumit Mohan, Tom Nickolas. Dept of Medicine, Columbia Univ, NY, NY.

Background: Frailty is emerging as a risk factor for poor clinical outcomes in kidney transplant (KT). Preoperative frailty is associated with increased risk for early hospital readmission, delayed graft function and mortality after KT independent of age. Weight loss is a component of frailty that can occur after KT, but changes in weight and body mass index (BMI) do not fully account for changes in lean and fat mass, which have opposing associations with frailty. We hypothesized that lower lean and higher fat mass at KT would be associated with greater degree of frailty 1-month after KT.

Methods: Whole body composition was obtained by dual-energy X-ray absorptiometry (DXA) within 3-weeks of KT. The Fried Frailty Assessment was completed both pre-and 1-month post KT. Each frailty component was scored 0 or 1 (absent or present) and the aggregate frailty score was calculated. Increases in frailty after KT were defined as an increase of ≥1 in the frailty score. Associations between percent lean and fat mass with frailty and change in frailty were determined by logistic regression and expressed as the odds ratio (95% CI).

Results: Forty-seven patients were enrolled (64% men) with a mean age of 51±14 years and BMI of 28.7±5; mean percent lean mass was 67.8±8.6% and fat mass was 32.4±8.6%. At baseline 56% were frail and at 1-month post KT 47% had an increase in frailty degree of frailty after KT was associated with older age (OR 1.10, 1.03-1.17), higher BMI (OR 1.13; 1.01-1.26) and fat mass (OR 1.12, 1.02-1.22), and lower lean mass (OR 0.90; 0.82-0.98) at baseline. An increase in frailty at 1-month after KT was associated with lower frailty (OR 0.99) and decreases in BMI (OR 0.89, 0.79-0.99) after KT.

Conclusions: Frailty early after KT is associated with higher fat and lower lean mass at the time of KT, while increases in frailty after KT are associated with lesser frailty pre-KT and decreases in BMI after KT. Assessment of body composition before KT may predict frailty status early after KT. Future work will investigate how changes in body composition 12-months after KT affect frailty status and clinical outcomes.

Funding: Private Foundation Support

SA-PO378
Calcium Scores in Pre-Transplant Myocardial Percufusion Scans Are Increased by Beta-Blockers

Background: End stage kidney disease (a) is a risk factor for cardiovascular mortality. The prognostic value of myocardial perfusion scan (MPS) is reported to be 90% in renal transplants. Previous reports show a person with high calcium scores reflect coronary artery calcification and increased narrowing of the coronary arteries compared with a low calcium score. It is unclear if traditional cardiac risk factors or medications in particular beta-blockers affect the calcium score in patients with ESKD.

Methods: All pre-transplant patients in a single centre were identified. Clinical data, including investigations results, were recorded in patients who underwent MPS as part of their transplant work up between 2011-2014. Cardiac risk factors including: hypertension, previous cardiovascular incident, cardiac family history, hypercholesterolaemia, diabetes mellitus(DM), body mass index(BMI) and smoking were recorded. Calcium scores of <100 reflected moderate atherosclerotic disease with high risk of coronary artery disease and significant vessel narrowing. Logistic regression was used for statistical analysis.

Results: 172 patients had a MPS with analysis performed on 154 who had no coronary stenosis. 62.8%/55.6% 56% had DM. 85 patients on RRT. Median age was 60 ±20(8-23). There was strong evidence that the odds of having Calcium scores >100 were 5.5% higher in patients on beta-blockers than those without (OR 6.07, 95%CI 2.62-14.1, p<0.001) and increased with 9.3% for each year of age (OR 1.093, 1.04-1.14, p<0.001), independent of other factors. Weaker evidence that patients from black ethnicity had 83% lower odds of calcium scores >100 (OR 0.17, 95%CI 0.042-0.69, p=0.031), while patients who were on statins had 3.2 fold higher odds of having calcium score>100 (OR 3.17, 95%CI 1.25-8.03, p=0.015), adjusted for beta-blocker intake and age. Calcium scores were unaffected by calcium antagonists, ACE inhibitors/angiotensin receptor blockers, vitamin D, other traditional cardiac risk factors or dialysis.

Conclusions: We show beta-blockers are associated with a raised calcium score that is independent of age. The beta-blocker effect on calcium scores requires further investigation.

SA-PO379
Pre-Transplant Health Related Quality of Life Is Not Associated with Short-Term Outcomes after Kidney Transplantation
Beatrice P. Concepcion, Hassan Alhalabi, Rachel C. Forbes, Irene D. Feurer. Vanderbilt Univ Medical Center.

Background: Novel measures, such as frailty and physical functioning, which forecast post transplant outcomes are increasingly being recognized as potentially useful tools in risk stratifying kidney transplant candidates. We investigated whether pre-transplant patient-reported health-related quality of life (HRQOL) is associated with short-term adverse events after kidney transplantation.

Conclusions: Graft function and co-morbid conditions significantly influence the risk of preterm birth, and should guide management of female KT recipients contemplating pregnancy.
Methods: Pre-transplant HRQOL was measured using the 8 scales and physical and mental component summary scores of the Short Form 36 Health Survey. Continuous scores were stratified based on scale- and component-specific general population norm quartiles. Binary outcomes (present/absent) were: delayed graft function (DGF), readmission within 90 and 365 days of transplant, any acute rejection episode(s). Data were analyzed using multivariable logistic regression models that adjusted for age, donor type and cardiovascular disease.

Results: The sample included 230 adults who were referred to our center for kidney transplantation and were subsequently transplanted. Patients were 59±1 years of age, 24% with CV comorbidity. Time pre-transplant at HRQOL was 13±9 months and follow-up time 52±35 months. Figure 1 shows the proportion of patients that were in the lowest norm-based quartile for each pre-transplant measure.

Conclusions: Pre-transplant HRQOL is not a useful metric for risk stratification of kidney transplant candidates for short-term adverse events after transplantation.

SA-PO380
Effect of Pre-Transplant Dialysis Modality and Duration on Recipient's Outcome: A National Population-Based Cohort Study between 2005 and 2008 in Korea

Hyunjeong Cho, Jung Nam An, Yumi Kim, Eunjeong Kang, Dong-Ryeol Ryu, Kyong Hoon Kim, Yun Kyu Oh, Chun Soo Lim, Yon Su Kim, Jung Pyo Lee. Critical Care Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; Internal Medicine, Seoul Natinal Univ College of Medicine, Seoul, Korea; Internal Medicine, Ewha Womans Univ, Seoul, Korea; Public Health, Graduate School, Seoul Univ, Seoul, Korea.

Background: So far the effects of pre-transplant dialysis modality or duration on clinical outcomes after kidney transplantation (KT) have not been investigated.

Methods: We analyzed the clinical outcomes of 1,563 KT recipients among the 35,422 adult patients who were started hemodialysis and peritoneal dialysis from 2005 to 2008, using the Korean Health Insurance Review & Assessment Service database.

Results: During the median 6.9 years follow-up after KT, 106 (6.8%) patients were died and 28 (1.8%) patients had experienced major adverse cardiovascular events (MACE). In the multivariable-adjusted Cox proportional hazard model, pre-transplant dialysis modality was not associated with an increased risk of mortality and the development of MACE. Pre-transplant dialysis duration was not associated with the occurrence of MACE; however, the HR for mortality (comparing the group greater than 10.8 months with the group lower than 10.6 months regarding the duration of dialysis before KT) was 1.66 (95% CI 1.11-2.47) in total populations. In each group of hemodialysis and peritoneal dialysis, the duration of pre-transplant dialysis was also an independent risk factor for mortality.

Conclusions: The duration of dialysis before KT was independently associated with mortality, regardless of the dialysis modality in this national population-based cohort study. Pre-transplant dialysis duration could be useful marker in predicting mortality in KT recipients.
Factors Associated with Health-Related Quality of Life (HRQOL) in Renal Transplant Recipient (RTR) in France

Background: The factors associated with HRQOL are not well defined in renal transplant studies using extensive observations in large cohorts. A cohort of RTR was conducted in a retrospective observational study in France in order (a) to improve a disease-specific questionnaire, the ReTransQOL (RTQ) validated in French language for RTR (b) to identify factors associated with HRQOL in this population.

Methods: A 2-year longitudinal study was conducted in a representative sample of RTR. Measures included patient questionnaire (socio-demographic characteristics), medical questionnaire including kidney disease, health status, comorbidities, treatments and their side effects, and biological data. The RTQ and the generic scale (SF36) were used. Multiple linear regressions analysis were performed for RTQ and SF36.

Conclusion: The factors associated with HRQOL are important to the development of psychosocial interventions to improve HRQOL in the context of long-term transplantation.

Utility of Pre-Implantation Deceased Donor Kidney Biopsy and Scoring System in Predicting Early Graft Outcome Based on Kidney Donor Profile Index and Estimated Post-Transplant Survival

Background: Demand for kidney (K) grafts excces supply of available organs. There is increasing interests in evaluating the intrinsic donor organ quality by performing pre-transplant (tx) k biopsies (bx), especially in the older donors, is important for post-tx histologic evolution & long-term graft survival. Kidney Donor Profile Index (KDPI) characterizes deceased donors based on 10 factors, ranges from 1% to 100%. Estimated Post Transplant Survival (EPTS), assigned to tx candidates on the waiting list, is based on 4 factors (age, time on diaylsis, diabetes status, and prior solid organ tx). We are interested in assessing pre-tx donor bx characteristics and EPTS affecting early graft outcome.

Methods: This is a single center retrospective study from University of Buffalo Transplant Center from January 2012 to Sept 2015. 183 deceased kidney tx recipients who had time zero donor kidney biopsies were included. Induction immunosuppression was with Thymoglobulin 3 mg/kg, maintenance therapy was with prednisone, tacrolimus, MMF.

Results: A total of 1,424 adults RTR were included. Patient’s mean age was 56 ± 13 years and 61.4% were male. 38% had college education level, 39% had full time work, 35% were recipients of disability, and 68% lived with a partner. Clinical data were : 13% had a pretransplantation, 15% suffered from at least one rejection episode, 31% had a chronic transplant dysfunction (serum creatinine > 16mg/dl). 18% had diabetes mellitus, 82% hypertension, and 15% obesity. In both questionnaires, we identified that older age, female gender, diabetes, to receive any social support, a chronic transplant dysfunction, and a high Charlson Comorbidity index were associated with a low HRQOL scores. HRQOL increased with higher monthly incomes, employment status and high Karnofsky performance score (≥70%). Home internet connection increased significantly HRQOL for mental health dimensions.

Conclusion: We evidenced several variables related to HRQOL in RTR. A better understanding of the psychosocial factors’ roles is essential for the development of psychosocial interventions to improve HRQOL in the context of long-term transplantation.

Predictors of Survival in Deceased Kidney Transplant Using Data Mining Methods

Background: Prediction of graft survival after kidney transplantation is the most important factor in the donor/patient matching process. Several conventional statistical methods are employed to assess the effect of certain candidate variables on graft survival. However, the role of data mining using a large pool of variables in predicting survival is unknown. The objective of this study was to define predictors of renal graft survival by analyzing a large set of variables using data analytical approaches.

Methods: In this study, we used UNOS database of deceased kidney transplantation between. A comprehensive variable selection methodology was employed using medical literature search, conventional data analysis and data analytical approaches. The analytical approach included Elastic Net regression and the data-driven analytic based information fusion technique. The selected variables obtained from the medical literature and analytical methods were incorporated in the Bayesian Belief Network (BBN) to create a multi-class prediction survival model and to identify the interactions between these variables.
SA-PO388

Time Varying Proteinuria is a Strong Predictor of Mortality and Graft Loss in Patients after Kidney Transplantation

Young May,1 Davood Shams,1 Shelly Lichtenberg,1,2 Hefziba Green,1,2 Ruth Rahamimov,2 1Nephrology and Hypertension, Rabin Medical Center, Petach-Tikva, Israel; 2Sackler School of Medicine, Tel Aviv Univ, Tel Aviv, Israel.

Background: proteinuria is known to be associated with decreased graft and patient survival after kidney transplantation. Nevertheless, most of the data comes from cross sectional and cohort studies and the effect time varying proteinuria was not adequately evaluated.

Methods: we used the routine dipstick urine protein evaluation performed every three to six month for all patients at our post transplantation follow-up clinic. Urine protein concentration was allocated into ordinal scale (no proteinuria, trace, 25 ng/dl, 75 mg/dl, 150 mg/dl and 500mg/dl). The follow-up time was divided into 6 months intervals and proteinuria was evaluated using all available protein measurements during each interval. The primary outcome was graft loss defined as the combination of death from any cause and graft dysfunction requiring chronic dialysis or retransplantation. Time dependent Cox proportional hazard model was used using univariate and multivariate adjusted analysis.

Results: among the thousand two hundred and twenty patients transplanted between 1/1/2000 and 31/12/2013 had 153 events (91 graft loss and 62 death events) during median follow-up of 4 years (range 0.5 to 12.3 years). Time varying proteinuria was strongly associated with increased graft loss Hazard Ratio (HR) 1.78 per stage, 95% Confidence Interval (CI) 1.62-1.95, p<0.001). The association was not changed after adjusting for age, gender, time on dialysis, recipient heart disease, diabetes, donor type (living or deceased), donor age, HLA mismatch, panel reactive antibodies, delayed graft function, duration of hospital stay following transplantation, creatinine at six month and urine protein level at 6 months (HR 1.78, 95% CI 1.61-1.96, p<0.001). Death censored graft survival was also associated with time varying proteinuria at univariate and multivariate analysis (HR 2.1, 95% CI 1.86-2.36,p<0.001) and (HR 2.16, 95% CI 1.87-2.49,p<0.001) respectively.

Conclusions: Time varying proteinuria is strongly associated with poor graft survival even after adjustment for baseline proteinuria and renal function.

SA-PO389


Background: Myocardial perfusion scans(MPS) is used in pre-transplant workup as a minimally invasive tool to determine coronary artery disease in the potential recipient. The prognostic value of using this test has been reported with sensitivity 90%, specificity 85%. Vascular calcification is common with many renal patients taking calcium-based phosphate binders/vitamin D analogues to help regulate bone metabolism and reduce renal bone disease. It is unclear whether using calcium-based phosphate binders(CBPB) adds to vascular calcification. This retrospective study looked at whether calcium-based phosphate binders/vitamin D analogues to help regulate bone metabolism and reduce renal bone disease.

Methods: In this small cohort, phosphate binders did not affect Calcium scores in patients pre-transplant workup, irrespective of age, gender, serum calcium or PTH levels. There were no coronary complications in those who went on to have renal transplants. Further larger studies are required to confirm these findings and elucidate the mechanisms behind coronary artery vascular calcification in renal patients thereby providing novel therapeutic targets.

SA-PO390

A Single Center Experience of Kidney Transplant Recipients due to Scleroderma Kidney Disease Nishkarsh Saxena, Arjang Djamali, Brad C. Astor, Didier A. Mandelbrot, Maha A. Mohamed, Sandesh Parajuli. Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: There is limited information on renal transplant recipients with end stage renal disease (ESRD) due to scleroderma.

Methods: This was an observational study that included patients with ESRD due to scleroderma kidney disease who received renal transplant between 01/1994 and 06/2013.

Results: There were ten kidney transplant recipients during the study period. They were all Caucasian females. Mean post-transplant follow up was 76.75 ± 56.18 months. Mean age at time of transplant was 56.6 ± 11.99 years. Seven of them were living kidney transplant recipients. Mean diaylsis vintage was 46.4 ± 80.35 months, ranging from 8 to 272 months. Mean serum creatinine (Scr) at 3, 6 and 12 months were 1.31 ± 0.47 mg/dl, 1.35 ± 0.51 mg/dl and 1.34 ± 0.49 mg/dl respectively. There were five graft failures with the mean graft survival of 102.48 months. Causes of graft failure were chronic transplant glomerulopathy in three patients, thrombotic microangiopathy and antibody mediated rejection in the other two patients. In those without graft failure, Mean Scr at last follow up was 0.96 ± 0.39 mg/dl. Six patients were on angiotension converting enzyme inhibitors (ACE-I) after transplant. One patient had developed new onset diabetes after transplant.

In univariate analysis, none of the factors including, age, time at time of transplant (HR 1.10, 95% CI 0.89 to 1.36, p= 0.35), diaylsis vintage (HR 1.01, 95% CI 0.99 to 1.02, p= 0.16), use of ACE-I (HR 0.57, 95% CI 0.31 to 1.13, p= 0.49) and Scr at 1 year (HR 1.49, 95% CI 0.26 to 8.64, p= 0.66), were predictive of graft survival.

Conclusions: In this observational study we found a wide variation in outcomes after kidney transplantation in patients with scleroderma kidney disease. More studies are needed to assess the factors that may influence graft survival in this rare disease.

SA-PO391

Pre-Transplant Cardiovascular Risk Factors Affect Kidney Allograft Survival: A Multi-Center Study in Korea Jung Nam An,1 Eunjin Bae,1 Eunjong Kang,2 Yun Kyu Oh,1 Chun Soo Lim,1 Yon Si Kim,1 Young Hoon Kim,1 Jung Pyo Lee,1 1Dept of Internal Medicine, Seoul National Univ Boramee Medical Center, Seoul, Korea; 2Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea; 1Dept of Surgery, Asan Medical Center, Seoul, Korea; 2Dept of Internal Medicine, Gyeongsang National Univ Changwon Hospital, Gyeongsangnam-do, Korea.

Background: Pre-transplant cardiovascular (CV) risk factors affect the development of CV events even after successful kidney transplantation (KT). However, the impact of pre-transplant CV risk factors on allograft failure (GF) has not been reported.

Methods: We analyzed 2681 KT recipients who were enrolled in a multi-center cohort from 1997 to 2012. We calculated the pre-transplant CV risk scores based on the Framingham risk model using age, gender, total cholesterol level, smoking status, and history of hypertension. Cox proportional hazard model, CV risk scores, Diabetes (presence of ischemic heart disease, peripheral vascular disease, and cerebrovascular disease) was noted in 6.5% of the patients. During the median 6 years follow-up, 286 (9.9%) patients had developed GF. In the multivariable-adjusted Cox proportional hazard model, pre-transplant vascular disease was associated with an increased risk of GF (HR 2.5; 95% CI 1.66-3.80). The HR for GF (comparing the highest with the lowest tertile regarding the pre-transplant CV risk scores) was 1.65 (95% CI 1.22-2.23). In the competing risk model, both pre-transplant vascular disease and CV risk score were independent risk factors for GF. Moreover, the addition of the CV risk score, pre-transplant diabetes, or both had a better predictability for GF compared to the traditional GF risk factors.

Conclusions: In conclusion, both vascular disease and pre-transplant CV risk score were independently associated with GF in this multi-center study. Pre-transplant CV risk assessments could be useful in predicting GF in KT recipients.

SA-PO392

Sustained Improvement in Depression after Renal Transplantation Aditi Gupta, David K. Johnson, Jeffrey M. Burns. Univ of Kansas Medical Center.

Background: Depression is a common problem in patients with end stage renal disease (ESRD). Whether renal transplantation improves depression is unexplored.

Methods: We followed patients with ESRD prospectively till one year after their renal transplantation. We assessed depressive symptoms by administering Beck Depression Inventory (BDI) at baseline (pre-transplant), 12 weeks and one year post-transplant. We used paired t tests for analyzing the change in depression score from baseline to 12 weeks after transplant, baseline to one year after transplant and 12 weeks after transplant to one year after transplant.

Results: The participants were 56.5 ± 10.7 years old, 11 men and 2 women, 10 Caucasian and one African American. All 11 patients had successful transplantation with a creatinine concentration of 1.6 ± 0.6 mg/dl with an estimated glomerular filtration rate (eGFR) of 45.2 ± 11.2 ml/min at 12 weeks after transplantation. The mean BDI score of depressive symptoms at baseline was 11.09 ± 8.14, at 12 weeks after transplant was 4.55 ± 2.98 and at one year after transplant was 5.73 ± 6.28. Compared to baseline scores there

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO394
Utilization of Statin Medications in U.S. Veterans with Post-Transplant Chronic Kidney Disease
Aroum Senthilkumar, Talar Markossian, Kevin Streupe, Nicholas Burge, Vinod K. Bansal, David J. Leehey, Julia Schneider, Holly J. Kramer, Benjamin Ling. Hines VA Hospital, Hines, IL.

Background: KDIGO and KDOQI guidelines recommend statin medications for kidney transplant recipients due to demonstrated cardiovascular benefits of statins with graded evidence of 2A. Results from few empirical studies suggest that statins are underutilized in transplant patients.

Methods: Retrospective analysis of U.S. Department of Veterans Affairs Healthcare System (VA) national databases to determine statin use in post-transplant patients with CKD. Medications acquired within the VA system were obtained from the Managerial Cost Accounting National Data Extracts. Medications acquired outside the VA were obtained from the Corporate Data Warehouse (CDW). Statin medication utilization was ascertained from pharmacy dispensing records in 2012 and 2013.

Results: A total of 626 veterans with CKD and history of kidney transplantation were identified. The majority of patients (97.3%) were male, 74.4% were aged ≥50 years and <2% were aged ≥75 years; 52.4% were white and 37.4% were African-American. Coronary artery disease, peripheral vascular disease and diabetes were present in 26.8%, 6.4% and 54.4% respectively. In 2012, 60.4% were using statins but only 54.8% were using statins during years 2012 and 2013 with 5.6% discontinued statins in 2013 and while 7.8% initiated statins in 2013.

Conclusions: Despite KDIGO and KDOQI guidelines recommending statin use in transplant recipients, statin use is suboptimal in patients with post-transplant CKD receiving care in the VA health system. Interventions are needed to increase knowledge among treating physicians regarding the clinical importance of statin use in adults with post-transplant CKD.

Funding: VA Support

SA-PO395
Outcomes after Open Heart Surgery in Kidney Transplant Recipients and Matched Controls
Bartlomej J. Witekaz,1 Jan L. Svennevig,2 Anders Hartmann,2 Anders Aasberg,2 1Dept of Nephrology, Akershus Univ Hospital, Norway; 2Dept of Transplant Medicine, OUS, Rikshospitalet, Norway; 3Dept of Thoracic and Cardiovascular Surgery, OUS, Rikshospitalet, Norway.

Background: Cardiovascular disease is common in kidney transplant recipients. We evaluated results of open heart surgery in these recipients at our center 1989-2015.

Methods: Ninety-five kidney transplant recipients underwent open heart surgery (48 coronary artery bypass operations, 27 valve replacements and 20 combined procedures) in the period. Controls (n=95) were matched for age, sex, diabetes and type and year of surgery. Mean follow-up time was 5.6 (4.9) years. Cox regression analyses were performed in the transplant group.

Results: Included were 76 men and 19 women with mean age 60.3 (11.1) years. Demographic and comorbidity data were similar, except a lower eGFR, more hypertension and less pulmonary hypertension in transplant recipients (p<0.001). Intraoperative data did not differ between groups, except that transplant recipients had higher hemoglobin volume (p=0.009). Postoperative data were also similar, although, transplant recipients received more red cell transfusions (p=0.04). Thirty-day mortality was similar in transplant patients and controls, but long-term survival was significantly lower in the former (p<0.001). Median survival in transplants was 6.3 years and in controls 13.3 years. Univariate Cox-regression analyses revealed only age, pulmonary hypertension and dialysis as risk factors for long term mortality. In a multivariate Cox-regression model, the same risk factors were significant: age (HR 1.07 per year, p<0.001), chronic dialysis (HR 4.29, p<0.001) and pulmonary hypertension (HR 2.53, p=0.012). Excluding transplant patients on chronic dialysis at time of surgery (n=13) showed similar results.

Conclusions: Kidney transplant recipients experienced more bleeding postoperatively. Intraoperative data and other postoperative complications, including short-term survival, were similar in kidney transplant patients compared with controls. Long-term survival was significantly lower in transplant recipients. Independent preoperative risk factors for long-term mortality were age, pulmonary hypertension and chronic dialysis.

SA-PO396
Trajectory of Renal Function following Heart Transplant: Single Center, Retrospective Cohort Study

Background: Heart transplant recipients with pre-transplant renal impairment have higher rates of mortality in the years following transplantation. Identifying appropriate candidates for combined heart-kidney transplantation relies on our ability to estimate the trajectory of renal function following heart transplantation. This study assessed longitudinal creatinine trends in heart transplant recipients stratified by pre-transplant renal function.

Methods: Using the Stanford Translational Research Integrated Database Environment, we identified all adult heart transplant recipients between May 1, 2008 and December 31, 2014. A mixed model analysis was used to assess pre- and post-transplant creatinine trends in those with normal versus abnormal pre-transplant renal function (defined as creatinine ≥ 1.5 mg/dl in the week prior to transplant).

Results: Twenty-two of the 115 identified heart transplant recipients had abnormal pre-transplant renal function. Baseline demographics and co-morbidities were similar in both groups. Renal function declined in both groups over time, but the group with abnormal pre-transplant renal function demonstrated initial improvement in renal function immediately following transplant (see figure 1). For patients with normal pre-transplant renal function, creatinine values continued to climb after transplant, however, on average, these values did not exceed 1.5 mg/dl 1-year post-transplant. The likelihood of having a creatinine below 1.5 mg/dl at 1-year post-transplant was 74% and 21% in the normal and abnormal renal function groups respectively.

Conclusions: Despite KDIGO and KDOQI guidelines recommending statin use in transplant recipients, statin use is suboptimal in patients with post-transplant CKD receiving care in the VA health system. Interventions are needed to increase knowledge among treating physicians regarding the clinical importance of statin use in adults with post-transplant CKD.

Funding: VA Support
Conclusions: Many patients with pre-transplant renal dysfunction experience initial improvement in renal function following heart transplantation, however, renal function in this group gradually worsens with time at a rate that is similar to those with normal pre-transplant renal function.

Funding: Other NIH Support - T32 Grant, Diversity Supplement

SA-PO397
Can Be Relied on Estimated GFR Decline in Renal Transplantation? The Nephrologist in the Mist Sergio Luis Lima,1 Domingo Marrero,1 Ana González Rinne,1 Armando Torres,1 Natalia Negrín,1 Federico J. Gonzalez-Rinne,1 Esteban Peruñi.1 1Hospital Univ de Canarias, Spain; 2Univ de La Laguna, Spain.

Background: Renal transplant patients have a high rate of graft loss (4% per year). Thus, a reliable evaluation of graft function is crucial. Estimated GFR (eGFR) is neither accurate nor precise in the prediction of real GFR. Whether this error marks renal function loss in this population is not clear.

Methods: We measured GFR in 67 patients with the clearance of iohexol annually during 3 years. eGFR was evaluated by 52 creatinine and or cystatin C formulas. The agreement between mGFR and eGFR-based decline was analyzed with the Concordance Correlation Coefficient (CCC).

Results: The area under curve for predicting mGFR less than 45 ml/min/1.73m² was 0.784 for SCys which was better than that for SCr of 0.745. The area under curve for predicting mGFR less than 45 ml/min/1.73m² was 0.784 for SCys which was better than that for SCr of 0.745. The area under curve for predicting mGFR less than 45 ml/min/1.73m² was 0.784 for SCys which was better than that for SCr of 0.745. The area under curve for predicting mGFR less than 45 ml/min/1.73m² was 0.784 for SCys which was better than that for SCr of 0.745.

Conclusions: Cystatin C-based equations showed a better predictive performance of eGFR decline than creatinine-based equations especially for the KTRs with lower mGFR. Cystatin C might be a good alternative method to monitor allograft function after kidney transplantation.

SA-PO399
Association of Gender and Age with Delayed Graft Function after Deceased Donor Kidney Transplantation Xia Luo, Allan Massie, Dorry L. Segev, Johns Hopkins.

Background: Previous studies demonstrated that better tolerance of ischemia-reperfusion injury, and hence lower delayed graft function (DGF) rate among females were mediated by higher estrogen level. Given the decreased estrogen level among older females, we hypothesized that the protective association between female sex and DGF might be attenuated among older recipients.

Methods: We identified adult kidney-only deceased donor recipients between 2000-2013 from SRTR data. DGF was defined as dialysis needed within the first week post-transplant. Recipients with primary non-functioning graft were excluded. We modeled DGF using logistic regression, adjusting for recipient, donor and transplant characteristics, and incorporating an interaction term of age (categorized as <40y, 40-59y, and 60+) and female sex.

Results: Out Of 120,533 recipients, 47,603 (39.5%) were female. The rate of DGF was 19.8% among females and 26.1% among males. After adjustment, female sex was associated with 32% lower odds of DGF (aOR=0.68, 95% CI:0.60-0.76, p<0.001). The aOR was attenuated with greater age. Among recipient age <40, 40-59, and 60+, female sex was associated with 39% (aOR=0.64, 95% CI:0.60-0.68, p<0.001), 52% (aOR=0.48, 95% CI:0.45-0.50, p<0.001), and 26% (aOR=0.70, 95% CI:0.64-0.77, p<0.001) lower risk of DGF, respectively. Older age was associated with higher DGF rate only among female recipients (Table 1).

Conclusions: Female recipients had lower risk of DGF than male recipients. This association was attenuated among older recipients. Older age conferred higher DGF among female recipients but not male recipients. Clinical caution is warranted for older female recipients.

SA-PO400
30 Years of Kidney Transplantation in Infants (Age < 2 Years): A Single Center Experience Blanche M. Chavers,1 Michelle N. Rheault,2 Scott Jackson,2 Arthur J. Matas,3 Marie E. Cook,2 Srinath Chinnakotla,2 1Pediatrics, Univ of Minnesota, Minneapolis, MN; 2Transplant Information Services, Univ of Minnesota, Minneapolis, MN; 3Surgery, Univ of Minnesota, Minneapolis, MN.

Background: Infants (age < 2 years) with end stage renal disease (ESRD) have increased morbidity and mortality on dialysis compared to older age groups. Yet, because of technical and management issues, there are still concerns about transplanting infants. We evaluated our long-term experience with kidney transplants (KTx) in infants.

Methods: Between 1984-2014, 136 infants (mean age 1.3 ± 0.4 years) underwent KTxs (116 living donor) with cyclosporine, prednisone, azathioprine maintenance immunosuppression. We examined trends in survival rates and complications by era (1984-1993 [era 1, n=59], 1994-2003 [era 2, n=42], 2004-2014 [era 3, n=35]).

Results: Patients were 92.6% Caucasian, 70.6% male, and 61.8% with ESRD due to congenital renal anomalies. Mean follow up was 15.7 ± 7.9 years. PostTx initial length of hospital stay declined 37% over the 30-year period (24 d era 1 vs 15 d era 3, p <0.01). Five-year patient survival improved from 95% in eras 1 and 2 to 100% era 3 (not statistically significant). Ten-year death censored graft survival improved from 60% era 1 to 80% era 2 to 90% era 3 (p=0.04). The incidence of acute rejection, renal artery thrombosis, cytomegalovirus, and urine leaks did not significantly change across eras. Epstein Barr virus (EBV) infection (era 2 vs 3, p =0.01) frequency increased. PostTx lymphoproliferative disorder (PTLD) incidence was increased in era 2 vs era 3 (p=0.01). Hypertension, post Tx diabetes mellitus, and avascular necrosis frequency did not significantly change across eras. Urine leaks (p=0.01) and EBV infection (p=0.02) but not PTLD were higher in infants compared to Tx patients > 2 years of age.

Conclusions: This is the largest series on complications of KTxs in infants. Length of initial hospital stay, patient and graft survival rates after KTxs have improved in infants since 1984. Urine leaks and EBV infection remain significant postTx complications in infants. Funding: NIDDK Support
SA-PO401
Immunological Profiling after Pediatric Kidney Transplantation
Mariselis Rosa-Sanchez,1 Marissa J. Defreitas,1 Chryso P. Katsoufis,1 Carolyn L. Abitbol,1 Wacharee Seehurunyong,1 Yonique P. Petgrave,1 George William Burke,2 Aura Jeannette Arenas Morales,3 Jayanthi Chandar.1
1Pediatric Nephrology, Jackson Memorial/Holtz Children’s Hospital, Miami, FL; 2Miami Transplant Inst, Univ of Miami, Miami, FL.

Background: Induction immunosuppressive therapy with anti-thymocyte globulin (ATG) is used by 22% of centers in the US after pediatric kidney transplantation (KT). We assessed the evolution of lymphocyte subsets and Immunoglobulin G (IgG) in the first year after KT in children with our center protocol.

Methods: Data was collected by retrospective analysis of pediatric KT recipients from January 2012 to June 2015 and included demographics, lymphocyte subsets and IgG in children <21 years of age at baseline, 1 week, 1, 6 and 12 months. Induction therapy consisted of ATG (cumulative dose of 3 to 5mg/kg), 2 doses of basiliximab and high dose methylprednisolone for 5-7 days with maintenance therapy of tacrolimus and mycophenolic acid.

Results: Among 52 patients, racial distribution was predominantly Hispanic and African American and 63% were male. Mean age was 10 ±6years. There was a significant drop from baseline in CD4 (55%), CD8 (63.5%), CD25 (13.4%) and NK cells (55%) at week one and a rise at 1 month with a gradual increase to baseline levels between 6 months to 1 year and a significant decline in IgG in younger children at 1 week (see figure; p=0.0002; R² 0.55) post transplant which improved with time. One child developed bacteremia following treatment of rejection and another had BK virus nephropathy. 1 year graft and patient survival were 98% and 100% respectively.

Conclusions: Triple induction therapy facilitated a steroid sparing protocol with good 1 year graft survival. However, younger patients were prone to hypogammaglobulinemia. Therefore, it is important to exercise vigilance and avoid excessive immunosuppression in the vulnerable younger patients.

SA-PO402
Donor Specific Antibodies and Gift Function in Pediatric Kidney Transplant Recipients
Gilad Hamdan,1 Jens W. Goebel,2 Paul Brailey,3 Elizabeth Portwood,1 David K. Hooper,1 Alin L. Girma.1,4 1Div of Nephrology & Hypertension, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Nephrology Div, Children’s Hospital Colorado, Aurora, CO; 3Hoxworth Blood Center, Univ of Cincinnati Academic Health Center, Cincinnati, OH; 4Dept of Surgery, Univ of Cincinnati Medical Center, Cincinnati, OH.

Background: Anti-HLA donor specific antibodies (DSAs) are associated with antibody mediated rejection (AMR) and graft loss in kidney transplant recipients. We aimed to find an association between specific DSA IgG subclasses and graft outcomes in pediatric and young adult kidney transplant recipients (KTRs).

Methods: We performed a single center retrospective chart review of pediatric KTRs with positive anti-HLA DSAs. Data regarding number, HLA classes, MFI, and IgG subclasses of the first positive DSAs was collected. Outcomes studied included AMR (based on the 2013 Banff criteria), clinical AMR (AMR with 15% eGFR reduction), and significant graft dysfunction (graft loss/50% decrease in eGFR). Results: 35 patients (median age 15.6y, 66% white, 68% male) with DSAs detected 8 days-14 years post transplantation were included and were followed for a median time of 2.8y. Rates of IgG subclass detection were 89%, 31%, 57%, and 26% for IgG1, IgG2, IgG3, and IgG4, respectively. 76% of patients had AMR following DSA detection, 58% had clinical AMR, and 29% experienced significant graft dysfunction during follow up. No association between any IgG subclass and AMR was found. However, 91% of patients with significant graft dysfunction during follow up, all with clinical AMR, had positive IgG3 DSAs as compared with 42% with more stable graft function (p=0.01). This association remained significant in a multivariable analysis (table).

<table>
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Conclusions: Presence of IgG3 donor specific antibodies is independently associated with significant graft dysfunction in pediatric and young adult kidney transplant recipients. Funding: Private Foundation support

SA-PO403
Longitudinal Renal Function after Liver Transplantation in Pediatric Patients
Mai Sato,1 Koichi Kamei,1 Mureo Kasahara,1 Kenji Ishikura.2 1Div of Nephrology and Rheumatology, National Center for Child Health and Development, Tokyo, Japan; 2Transplantation Center, National Center for Child Health and Development, Tokyo, Japan.

Background: Adult liver transplant (LT) recipients commonly develop advanced kidney disease; however, the burden of chronic kidney disease (CKD) in children is not well described. The objective of this study was to determine the incidence of CKD after pediatric LT.

Methods: We retrospectively analyzed the data of patients aged < 20 years who underwent LT between November 2005 and March 2015 in our institute. The following potential risk factors for renal dysfunction were analyzed: sex, age, primary liver disease, pre-existing kidney disease, rejection, and immunosuppressive agents.

Results: The cohort included 314 pediatric LT recipients (135 males). The median age at LT was 3.3 years (IQR 4.5) and the median follow-up duration was 3.9 years (IQR 4.5). Thirty-one patients died after LT. We divided the patients to three groups according to the primary disease: BA (biliary atresia), non-BA (other liver disease without primary renal complication), and KD (patients with pre-existing kidney disease). There were 143 patients (47 males) in the BA group, 139 (70 males) in the non-BA group, and 32 (18 males) in the KD group. The KD group comprised autosomal recessive polycystic disease (13 cases), methylmalonic acidemia (13 cases), primary hyper-auxoluria (5 cases) and nephrotic syndrome (1 case). Five-year renal survival, which endpoint was CKD stage 3, was 0.97 in BA group, 0.91 in non-BA group and 0.61 in KD group. We performed Cox regression survival analysis to adjust renal survival for confounding risk factors. There was no independent predictor by multivariate analyses, sex, age, rejection, but male and adolescent patients were likely to develop CKD.

Conclusions: In non-pre-existing kidney disease patients, 1.9% of patients developed over CKD 3 and 0.35% developed ESKD. These rates were lower than those in previous reports. Immunosuppressant strategy, additional mycophenolate mofetil and lower calcineurin inhibitor level may be effective to prevent progressive kidney damage.

SA-PO404
Sex and Age Differences in Medication Adherence in Adolescent and Young Adult Kidney Transplant Recipients
Julie Bouquequem,1,2 Bethany J. Foster.3 The TAKE-IT Investigators.3 1Research Inst. of the McGill Univ Health Centre, Montreal, QC, Canada; 2Dept of Epidemiology, Biostatistics and Occupational Health, McGill Univ, Montreal, QC, Canada; 3The TAKE-IT Investigators.

Background: Immunosuppressive medication adherence is poorer in adolescents than younger children, but it is unknown whether adherence differs between males and females, or by age, among adolescent and young adult kidney transplant recipients. We aimed to determine whether adherence differs by sex and age in this population.

Methods: We examined data from the 3-month run-in period (no intervention) of the randomized TAKE-IT trial. Adherence was monitored using a multidose electronic pillbox in 124 patients (11-24 y, ≥3 mo. post-transplant, followed in 8 transplant centers in Canada and USA), and classified as perfect (all doses taken; all doses on time) or not for each day of observation for each patient. We used logistic regression, with a random effect to account for correlation between adherence measurements within patients, to estimate the association between sex and adherence. We adjusted for race and time since transplant, and included an age by sex interaction.

Results: Among 124 patients, 61% were male; 65% were white. Median age at baseline was 16.2y [IQR 13.6-17.5]; median time since transplant was 2.7y [IQR 0.8-7.0]. There was a significant interaction between age and sex (p=0.009). Males ≥17y had a significantly lower likelihood of perfect adherence than younger males (OR=0.26, 95% CI [0.14-0.48]). There was no significant difference by age for females. Adherence did not differ by sex among patients <17y. Among those ≥17y, females had a significantly higher likelihood of perfect adherence than males (OR=3.82, 95% CI [1.09-13.40]).

Conclusions: Male kidney transplant recipients ≥17y have poorer adherence than younger adolescent males, whereas adherence does not differ by age among females. Adherence does not differ by sex in those <17 y, but among those ≥17y, adherence may be poorer in males than females. Funding: NIDDK Support

SA-PO405
Risk Factors for Decline in eGFR Below 60 ml/min/1.73 m2 after Kidney Transplantation in Japanese Children
Kiyonobu Ishizuka, Ken-Ichiro Miura, Keichi Takizawa, Yui Tomii, Yohsei Sasada, Naoto Kaneko, Tomoo Yabuuchi, Yasuyuki Sato, Hiroko Chikamato, Yuko Akikoa, Motoshi Hattori. Dept of Pediatric Nephrology, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Maintenance of eGFR above 60 ml/min/1.73 m2 is necessary for optimal growth in children after kidney transplantation (KTx). The objective of this study was to investigate serial change in eGFR after KTx in children and identify risk factors for decline in eGFR below 60 ml/min/1.73 m2.

Logistic Regression Analysis of Factors Associated with Significant Graft Dysfunction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG3 DSA</td>
<td>72.91</td>
<td>2.50–1,000</td>
<td>0.013</td>
</tr>
<tr>
<td>Time Post Transplantation (y)</td>
<td>1.34</td>
<td>1.03–1.74</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Conclusions: Presence of IgG3 donor specific antibodies is independently associated with significant graft dysfunction in pediatric and young adult kidney transplant recipients. Funding: Private Foundation support
Methods: This study was approved by the Institutional Review Board at Tokyo Women's Medical University. Fifty-eight children aged < 20 years with congenital anomalies of kidney and urinary tract who underwent living donor KTx from 2003 to 2013 and were transplanted before 12/31/2015, were included. We compared outcomes to a non-transplanted population of Ontario residents <18 years old using provincial administrative data. The primary outcome was overall incidence of cancer. Secondary outcomes included survival and incidence of solid/non-solid cancers.

Results: A total of 951 childhood transplant recipients (kIdney n=400, liver n=283, heart n=218, lung n=36, multorgan n=14) were compared to over 5 million children from the general population of similar ages. Median age was 8 years old; 50% were male. Over a median follow-up of 10 years (range 0–24), the cumulative incidence of cancer was 20% in transplant recipients compared to 0% in the general population. Incidence of cancer, cancer-free and all-cause mortality are shown in Table 1. The incidence rate ratio of cancer in transplanted vs. non-transplanted was 33.

Conclusions: Recipients of solid organ transplants in childhood have a 30 times higher incidence of cancer compared to the general population up to 24 years after transplantation. Our data suggest that early surveillance may be warranted in this high-risk population.

Table 1: Incidence of Cancer and Mortality

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Event rate/1000 patient-years (95% CI)</th>
<th>Incidence rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cancers</td>
<td>0.52 (0.31–0.33)</td>
<td>10.6 (8.53–13.1)</td>
</tr>
<tr>
<td>Non-solid Cancers (incl TLED)</td>
<td>0.08 (0.07–0.08)</td>
<td>6.28 (4.77–8.28)</td>
</tr>
<tr>
<td>Solid Cancers</td>
<td>0.24 (0.24–0.25)</td>
<td>4.27 (3.06–5.98)</td>
</tr>
<tr>
<td>Cancer-free Mortality</td>
<td>0.26 (0.26–0.27)</td>
<td>18.5 (15.72–21.7)</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>0.29 (0.29–0.30)</td>
<td>21.2 (18.32–24.6)</td>
</tr>
</tbody>
</table>

SA-PO409

Impact of Obesity and Metabolic Syndrome on Myocardial Function and Strain in Children after Kidney Transplant


Background: In light of the major impact of cardiovascular (CV) morbidity on outcomes in children with End Stage Renal Disease (ESRD), a prospective controlled longitudinal study was conducted to investigate myocardial function and strain in children before and after kidney transplant (Tx). Impact of obesity and metabolic syndrome (MBS) on CV morbidity was investigated.

Methods: Kidney Tx recipients (3-20 yrs) had standard echo and myocardial strain by speckle tracking measured at 12 months pre-Tx, and 1, 18, and 30 months post-Tx. More negative strain signifies better cardiac contractility. Tx with MS met ≥3 criteria: glucose intolerance (HbA1c ≥5.6% or glucose ≥100), BP ≥95th %ile, central obesity (WC-95th %ile), HDL ≤5th %ile, TG ≥95th %ile. Controls were healthy, obese children. Statistical analysis by Student’s t-test used for comparison between groups (pre-Tx, post-Tx, and controls) and multivariate longitudinal GEE regression for association of variables.

Results: 39 Tx recipients (23 lean, 16 obese) were compared to 24 healthy children (age 10.2±1.1 yrs). 1 VM/H18O was included for obese children and lean post-Tx. More negative strain signifies better cardiac contractility. Tx with MS met ≥3 criteria: glucose intolerance (HbA1c ≥5.6% or glucose ≥100), BP ≥95th %ile, central obesity (WC-95th %ile), HDL ≤5th %ile, TG ≥95th %ile. Controls were healthy, obese children. Statistical analysis by Student’s t-test used for comparison between groups (pre-Tx, post-Tx, and controls) and multivariate longitudinal GEE regression for association of variables.
SA-PO410

Acute Rejection Is the Primary Determinant of Worse Kidney Allograft Outcomes in Patients with De Novo Donor-Specific Antibodies

Scott Davis,

Jane Grailla,

Alexis G. Wiseman,

James E. Cooper.

1 Medicine, Univ of Colorado, Aurora, CO; 2Pediatrics, Univ of Colorado, Aurora, CO.

Background: Although many patients develop de novo donor-specific antibodies (dnDSA), only a portion will experience associated graft impairment or loss. Clinical acute rejection (cAR) may lead to or result from the development of dnDSA and may be the primary determinant of worse graft survival among these patients. The purpose of this study was to delineate the impact of cAR and dnDSA on graft outcomes.

Methods: From 2007 to 2013, 593 consecutive kidney recipients without pre-existing DSA were screened for dnDSA at months 1, 6, 12, yearly and when indicated. Acute rejection was diagnosed by clinical suspicion and was biopsy-proven in 89% of cases. Graft survival was assessed by KM analysis and time-dependent Cox modeling with median (IQ) follow-up time of 49 (31-69) months.

Results: 204 (34.4%) patients developed dnDSA (median onset 8.3 months). 5-year death-censored graft survival was lower in patients with dnDSA (Figure 1) cAR was more common in dnDSA (+) vs. dnDSA (-) patients (27% vs. 5%, p=0.001) and its timing relative to dnDSA detection did not effect graft outcomes. When stratifying patients by cAR and dnDSA status, patients had worse eGFR (p<0.001), more proteinuria (p=0.001), and lower 5-year graft survival (p=0.001) only when combined with cAR, regardless of dnDSA status (Figure 2). In a multivariable analysis accounting for both cAR and dnDSA, cAR had a stronger association with graft loss (HR 9.1, 95% CI 4.3-19.0, p<0.001) compared to dnDSA alone (HR 2.2, 95% CI 1.1-4.5, p=0.026).

Conclusions: In this large retrospective analysis of a prospective dnDSA screening protocol, both dnDSA and cAR were associated with inferior intermediate term graft outcomes. Importantly, the deleterious impact of dnDSA on eGFR, proteinuria, and graft loss was only seen when combined with cAR.

SA-PO411

Indoleamine 2,3-Dioxygenase Is a Biomarker of Rejection in Experimental Kidney Transplantation


1Surgery, Medical College of Georgia at Augusta University, Augusta, GA; 2Medicine, Medical College of Georgia at Augusta University, Augusta, GA; 3Pathology, Medical College of Georgia at Augusta University, Augusta, GA; 4Gift of Life Michigan, Ann Arbor, MI.

Background: Indoleamine 2,3-dioxygenase (IDO) degradation of tryptophan promotes the induction of regulatory T cells (Treg), implying a role for IDO in mitigating alloimmune rejection. However, the effects of renal ischemia (RI) and alloprotein on transplantation in kidney IDO expression remain undefined. To address this question, we conducted auto and allo kidney transplants (Tx) in pigs.

Methods: Pigs underwent orthotopic allogeneic kidney Tx (Allo) (n=9) or autoTx (Auto) (n=10). For Allo, pairs of mismatched Yorkshire piglets were operated simultaneously with left kidneys exchanged. Allo and Auto had ~ 30 months of RI. All pigs had right nephrectomy (Nx) prior to closure and left Nx at sacrifice at 72hrs. No immunosuppression was used. IDO activity in kidney homogenates was assessed using HPLC. IDO mRNA was quantitated by PCR. Tissue IDO expression was assessed using IHC with specific antibodies. Activation of Tregs, dendritic cells (DC) and macrophages (MP) were identified using IHC with IDO antibody. Activation of Tregs, dendritic cells (DC) and macrophages (MP) were identified using IHC with specific antibodies.

Results: All pigs experienced increased postop creatinine with significantly higher levels in Allo vs Auto (8.12±1.50 vs 2.83±0.60 mg/dL respectively, P<0.006). Auto had mild tubular injury without significant changes in IDO mRNA nor IDO activity when compared to right Nx controls (n=16). In contrast, Allo demonstrated acute rejection, increased IDO mRNA, and a 19.5 fold increase in IDO activity vs Auto. IDO expression (IHC) came from infiltrated cells and sloughed tubular cells. Both Auto and Allo had a notable infiltration of MP. There was a substantial accumulation of Tregs and MP observed in Allo kidneys vs Autos.

Conclusions: IDO does not increase as a consequence of RI. A dramatic increase of IDO mRNA, protein, and activity occurs in rejecting allografts. These data suggest that IDO may act as a biomarker of rejection in experimental renal transplantation.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO412

The Clinical Significance of Severe Ischemia-Reperfusion Injury (IRI) in Triggering Rejection


1Columbia University, New York, NY; 2Brigham & Women’s Hospital/Harvard Medical School, Boston, MA.

Background: In non-immunosuppressed animals, IRI enhances allograft immunity and triggers rejection. In the era of potent immunosuppression, the effects of severe IRI on allograft function and alloimmunity in kidney transplant recipients need to be systematically assessed.

Methods: Acute tubular injury in post-reperfusion biopsies is a morphologic reflection of the severity of IRI. All post-reperfusion biopsies from patients who underwent deceased donor kidney transplantation at Columbia University Medical Center from 2006 through 2009 (n=382) were assessed for the presence of diffuse acute tubular injury (ATN) as a reflection of severe IRI. The samples were classified as “ATN” (n=134) and “no ATN” (n=248).

Results: Compared to patients without ATN, patients with ATN had a trend toward worse allograft survival (P=0.08) and a higher incidence of primary non-function [10/134 (8%) vs. 7/248 (3%), P=0.07]. However, even when primary non-function were excluded, patients with ATN had a mean lower eGFR at 1-year (P=0.04), 2-years (P<0.005), and 3-years (P=0.001) post-transplantation and showed increased number of rejection episodes during 1st year after transplantation [44/124 (35%) vs. 61/241 (25%), P=0.05], and higher frequency of rejection episodes/year [0.46 +/- 0.99 vs. 0.30 +/- 0.85, P=0.03] compared with patients without ATN. To provide a better understanding of the potential role of graft dendritic cells (DCs) in triggering rejection, DCs were assessed in a pilot cohort of post-reperfusion biopsies with (n=15) or without (n=12) subsequent rejection using the BDCA-1 marker. Patients who developed subsequent rejection had lower DC density compared to these without rejection (0.4 +/- 0.5 vs 0.8 +/- 0.6 cells/high power field, P=0.007).

Conclusions: ATN in post-reperfusion biopsies is associated with subsequent inferior allograft function and increased rejection episodes in later biopsies. Low DC density in post-reperfusion biopsies may be associated with increased allograft immunogenicity.

Funding: Clinical Revenue Support

SA-PO413

Urine Fibrosin Markers and Risk of Kidney Allograft Failure: The FAVORIT Trial


1UCSD, 2UB, 3Tufts, 4UCSF, 5Roosevelt Island.

Background: Tubulo-interstitial fibrosis marks risk of allograft failure in kidney transplant recipients (KTRs) but is poorly captured by eGFR or urine ACR. Urine alpha 1 macroglubulin (α1M), monocytic chemotactant protein-a (MCP1), procollagen type III (PIIINP) and type 1 (PINP) N-terminal propeptide are correlated with tubulo-interstitial fibrosis on biopsy. Whether these markers can noninvasively identify risk of allograft failure independent of eGFR and ACR is unknown.

Methods: In this case-cohort study in KTRs participating in the FAVORIT trial, we measured urine α1M, MCP1, PIIINP, and PINP in random sub-cohort of 491 participants and 257 allograft failure cases. We used weighted Cox models adjusted for demographics, CKD risk factors, eGFR, ACR, and urine creatinine (to account for toxicity). Each biomarker was evaluated on the log2 scale (“per doubling”) and by quartiles.

Results: In the random sub-cohort, mean age was 51±9 years, median graft vintage was 3.7 years, 42% had live donors, and mean baseline eGFR was 46±18 ml/min/1.73m2. During 3.5 years mean follow-up, there were 257 kidney allograft failure events. Higher α1M (HR per doubling 1.71 [1.45, 2.08]) and MCP1 (HR 1.60 [1.32, 1.93]) were associated with allograft failure, independent of eGFR, ACR and other risk factors. Evaluating high vs. low quartiles, associations were similar in strength to extreme eGFR and ACR quartiles, despite adjusting for eGFR and ACR. Urine PIIINP and PINP were not independently associated with allograft failure.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: Measurement of s1m1 and MCP1 in urine of KTRs may serve as a non-invasive biomarker of tubulointerstitial fibrosis severity and risk of allograft failure independent of eGFR and ACR.

Funding: NIDDK Support, Private Foundation Support

SA-PO414
Outcomes of Severe Tubulitis Are as Poor as Vascular Rejections Shefali Patel, Hilda E. Fernandez, Ibrahim Batal, Russell J. Crew. Columbia Univ. NY.

Background: The continuum of renal transplant acute cellular rejection(ACR) progresses in severity from borderline changes to tubulitis to vasculitis. Optimal treatment of severe tubulitis (grade 1B) is poorly defined with some centers given steroids and others immediately using lymphocyte depletion.

Methods: We identified transplant rejection and collected the following: demographics, induction therapy, rejection grade, other pathologies findings, therapy response and infections complications. Rejecters were compared to a control group without rejection.

Results: From 1/2012-12/2014, we transplanted 681 pts using lymphocyte depletion (antithymocyte globulin[ATG] or campath1B), tacrolimus, mycophenolate, and rapid steroid withdrawal. 169 patients had ACR: 91 Borderline, 42 ACR1A, 39 ACR1B, 14 ACR2A and 1 ACR2B. There were no differences in age, sex, race, induction, or donor type between pts w/ ACR1B or ACR2. Creat at time of rejection was similar (2.83 vs 2.77, p-NS) as time to rejection. ATG was used in 64.3% of ACR1B and 78.5% of ACR2. Creat remained higher in the ACR1 group during follow up (2.55 vs 1.73, approaching statistical significance (p = 0.064)), despite no initial difference in the distribution of chronic pathologic findings. Persistent (59%) and recurrent (79%) rejections were common in ACR2B, but similar to ACR2 group (33% and 20%). Allograft failure occurred in 14.2% in ACR1B vs 1 ACR2. There were no differences in creat, persistent or recurrent rejections among ACR1B pts who received ATG vs steroids alone. Viremic complications after treatment were similar between groups (1B rejectors= 3 BK, 5 CMV, 1 EBV, grade 2-3 BK). IFTA > 25% on initial ACR1B biopsy was associated with a higher creat at last follow-up 2.8 mg/dL vs 1.69 mg/dL (p = 0.019) but not failure or recurrent rejections. A control group of 40 pts w/o rejection had a median serum Cr 1.38 mg/dl at last follow-up 2.8 mg/dL vs 1.69 mg/dL (p = 0.019) but not failure or recurrent rejections. A control group of 40 pts w/o rejection had a median serum Cr 1.38 mg/dl at last follow-up 2.8 mg/dL vs 1.69 mg/dL (p = 0.019) but not failure or recurrent rejections.

Conclusions: Acute cellular rejection with endarteritis showed better outcomes after treatment. Endarteritis with CD20+ cell infiltration implies lower graft loss and better graft survival.

Funding: Government Support - Non-U.S.

SA-PO417

Background: Immunity is traditionally dichotomized as innate immunity and adaptive immunity. We and others have identified intragraft expression of mRNA encoding T and B cell proteins, cytokines and chemokines central to adaptive immunity. We now report that innate immunity is a strong feature of human allograft rejection following RNA-sequencing (RNA-Seq) of human kidney allograft biopsies.

Methods: We did RNA-Seq of of 5 clinically indicated acute cellular rejection (ACR) biopsies from 5 patients and 5 surveillance normal biopsies from 5 patients. Total RNA isolated from the biopsies were sequenced using the Illumina HiSeq platform. Differential gene expression analysis was done using edgeR. We used KEGG and NCBI databases for molecular gene grouping, gene family or gene pathway.

Results: As predicted, there was overexpression of adaptive immunity related transcripts in ACR biopsy. In addition, innate immunity related transcripts were overexpressed in ACR biopsy. In the ACR biopsy, 9 complement genes, 9 inflammasome-related genes, 5 damage associated molecular pattern (DAMP) genes and 11 pathogen associated molecular pattern (PAMP) genes were significantly differentially expressed. In the figure, genes belonging to overlapping categories are shown once only.

Funding: Government Support - Non-U.S.

SA-PO416

Background: Acute rejection, especially the irreversible episodes, has definite impact on renal allograft. However, it is controversial whether lymphocytes infiltration exhibited in biopsy specimen is important for transplant outcomes. This study focused on the effect of CD20+ B cell infiltration in the biopsy specimens from the allografts with acute cellular rejection in Chinese population.

Methods: Totally 217 cases of biopsy-proved acute cellular rejection were documented in our renal transplantation system from Sep. 2001 to Dec. 2014. There was only 1 case lost-to-follow. According to the presence of CD20+ cell infiltration and its degree, all 216 cases were divided into CD20-group (n=83), mild CD20+ group (n=76), moderate CD20+ group (n=36), and severe CD20+ group (n=21). Baseline information, serum creatinine and GFR before and after treatment, steroid resistance, reversal rate, graft loss and survival were analyzed.

Results: There was no significant difference between groups in baseline information. Steroid and antibodies combination treatment in CD20+ group (39.1%, 52/133) and CD20- group (59.0%, 49/83) didn't show significant difference (p=0.004). CD20+ group showed better serum creatinine and GFR before treatment. After treatment, however, groups showed similar graft function. CD20+ group had fewer graft loss (18.8% vs 32.5%, p=0.022) and better survival rate. Further exploration in infiltration degree suggested that it was positively related with graft survival with no statistical significance.

Conclusions: Acute cellular rejection with CD20+ B cell infiltration showed better outcomes after treatment. The presence of CD20+ B cells is protective for renal allografts.

Funding: Government Support - Non-U.S.

SA-PO415

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Funding: Government Support - Non-U.S.

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

724A
SA-PO418
Impact of HLA Mismatch on the Renal Allograft Survival among ABO Incompatible Renal Transplant

Background: Given the advances in immunosuppressive regimens and medical care, ABO incompatible kidney transplantation has become an acceptable option for highly sensitized patients. Data on the influence of HLA matching among ABO incompatible renal transplant outcomes are sparse.

Methods: We performed a retrospective analysis of ABO incompatible transplant recipients over 18 years of age at the time of transplantation from the Organ Procurement and Transplantation Network (OPTN) Database between 2000 and 2013. Patients were categorized into 4 groups according to the level of HLA mismatch: 0, 1-3, 4-5 and 6 HLA mismatches (HLA MM). Associations between HLA MM and post-transplant graft failure and patient death were examined by Cox regression.

Results: There were 1266 ABO incompatible living transplant recipients. Out of these, 7.3% had 0 HLA MM, 37.2% had 1-3 HLA MM, 43.2% had 4-5 HLA MM, and 12.32% had 6 HLA MM.

Conclusions: 0 antigen mismatched ABO incompatible transplants had a better kidney allograft survival compared to other HLA mismatches. No significant differences existed between 1-6 antigens mismatched ABO incompatible recipients.

SA-PO419
The Effect of Regulatory T Cells on the Interaction of T Follicular Helper Cells and Memory B Cells during Plasmablast Formation
Paul Fadakar, Kevin Hadi, Camila Macedo, Diana Metes. Starzl Transplantation Inst, UPMC, Pittsburgh, PA.

Background: Donor-specific antibodies (DSA) are an important biomarker for acute rejection, transplant glomerulopathy and late allograft failure in kidney transplantation. However, few studies have looked at the immunologic events that occur prior to DSA formation. T follicular helper (Thf) cells provide B cells with critical cognate help necessary for differentiation into plasmablasts that secrete antibodies in response to antigen stimulation. Our previous results obtained in a cohort of KTx recipients receiving Thymoglobulin induction showed an imbalance between circulating Th cells and regulatory T cells (Tregs), which correlated with development of DSA. Here, we inquired whether Tregs can temper Tfh cell function to interfere with B cell responses, or if they directly modulate B cells’ ability to differentiate into plasmablasts (PBs).

Methods: We isolated peripheral blood mononuclear cells from 5 healthy controls and 5 DSA positive KTx patients. PBs were generated from healthy controls and DSA positive KTx patients with or without stimulation with Tfh cell-priming cytokines. The PBs were then co-cultured with or without Tfh cells in the presence or absence of SEB to mimic antigen-specific interactions, with or without Tregs. In parallel, CD3/CD28-stimulated CFSE-labeled Tfh cells or mB cells exposed to a cytokine cocktail mimicking T cell help were incubated with or without Tregs at increasing ratios for 6 days.

Results: Co-culture of mB cells with Tfh cells induced 30-50% of mB cells to differentiate into plasmablasts (PBs). Inhibition of Tfh cell proliferation measured by CFSE dilution and PB formation (CD19-CD27+CD38+) were measured to assess Tfh function. Tregs suppress PB formation via direct effect on mB cells and indirectly by tempering Tfh cell function. These results provide valuable mechanistic understanding of the role of Tfh cells and Tregs during antibody responses with implications for monitoring for early detection of patients at risk for DSA formation.

Funding: NIDDK Support

SA-PO420
Protective Effect of 1α,25-Dihydroxyvitamin D3 on Effector CD4+ T Cell Induced Injury in Human Renal Proximal Tubular Epithelial Cells
Jie-You Chen,1 Kyoung Chan Do,2 Byung Ha Chung,2 Chul Woo Yang,1,2 Div of Nephrology, Dept of Internal Medicine, Seoul St. Mary’s Hospital, The Catholic Univ of Korea, Seoul, Korea; 3Transplant Research Center, Seoul St. Mary’s Hospital, The Catholic Univ of Korea, Seoul, Korea.

Background: The aim of this study was to investigate the effects of Vitamin D pretreatment on inflammatory response in human proximal renal tubular epithelial cells (HRPTEpCs) induced by effector T cells or inflammatory cytokines.

Methods: First, we investigated the effect of 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3) on CD4+ T cell proliferation by FACs analysis and ELISA. Second, we investigated the effect of 1,25(OH)2D3 on IL-6, IL-8, KIM-1 and fibronectin-1 expression in HRPTEpCs, co-cultured with without activated CD4+ T cells using ELISA and real-time PCR, and we analyzed mTOR/STAT3 signaling. Lastly, we divided 90 kidney transplant recipients (KTR) according to serum 25-hydroxyvitamin D [25(OH)D] level (<20 ng/ml) and compared the level of urine IL-6, IL-8, and KIM-1 between the groups.

Results: Pre-incubation with 1,25(OH)2D3 significantly reduced the percentage of Th1 and Th17 cells compared to Th0 condition (P = 0.05 for each). In contrast, 1,25(OH)2D3 increased the proportion of Th2 and Treg cells in a dose dependent manner (P = 0.05 for each).

Conclusions: In conclusion, we suggest that treatment with 1α,25-dihydroxyvitamin D3 could be a new therapeutic strategy to reduce allograft tubule cell injury by effector T cells in kidney transplantation.

Funding: Government Support - Non-U.S.

SA-PO421
Late Antibody Mediated Rejection in Renal Transplant: Retrospective Review of Outcomes and prognostic Indicators
Jirina Ruderman,1 Matthew Sypec,2 Moira J. Finlay,3 Rosemary Masterson,1 Peter D. Hughes,1 1Dept of Nephrology, Royal Melbourne Hospital, Melbourne, Victoria, Australia; 2Dept of Anatomical Pathology, Royal Melbourne Hospital, Melbourne, Victoria, Australia.

Background: Late antibody mediated rejection (AMR) is recognised as a major contributing cause to late allograft failure. Our aim was to identify predictors of renal allograft outcomes in late AMR in the context of a previously normal three-month protocol biopsy in a single centre transplantation population.

Methods: We conducted a retrospective review and identified 106 transplant patients with late AMR. We went on to analyse the impact of histological, antibody and clinical factors on graft survival and compared the characteristics of this cohort with 968 patients without late AMR transplanted during the same period.

Results: Median time to diagnosis of rejection was 58 months post-transplantation (range 26-97 months). Thirty three percent of the cohort with late AMR was ABO incompatible (ABOi). Compared with the control group the late AMR group were younger (p < 0.001) and had higher rates of ABOi. Late AMR was associated with a 2.8 times increased risk of graft loss compared to non-AMR controls. In the late AMR group, high chronicity scores on diagnostic biopsy and high serum creatinine at the time of diagnosis but not the degree of micro-vascular inflammation, C4d positivity or DNA were associated with worse graft outcomes. Graft survival was poor in the late AMR group with 50% graft loss 29 months post late AMR diagnosis.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO422 Absolute Measurements of Plasma Draft-Derived Cell-Free DNA Are Higher in Kidney Transplant Antibody Mediated Rejection John B. Whitlam,1 Ling Ling,2 Francesco L. Ierino,1 Damien Luis Bruno,2 Howard Slater,2 David A. Power.1 1Nephrology Dept, Austin Health, Heidelberg, Australia; 2Mardoch Childrens Research Inst, Royal Children’s Hospital, Parkville, Australia.

Background: Cell-free DNA is an emerging biomarker of graft injury. We have developed a novel strategic approach that exploits ubiquitous copy number variation (specifically skeleton), to create a “negative background” against which multiple independent informative markers can be used to measure absolute draft-derived ctDNA (gdcfDNA) using digital droplet PCR without prior donor or recipient genotyping.

Methods: A panel of 31 copy number variation assays was run on ctDNA extracted from plasma of 38 adult kidney transplant recipients undergoing biopsy for acute graft dysfunction. GdcfDNA and total ctDNA (tcfDNA) concentrations were measured and graft fraction (GF) calculated. The results were correlated with diagnostic biopsy histopathology.

Results: Biopsy results included 18 normal, 8 acute antibody mediated rejection (aAMR), 7 other rejection (OR) and 5 other non-rejection pathologies (“Other”). GdcfDNA was significantly elevated in aAMR compared with all other groups (p<0.01)(Figure 1, left panel). GF was higher in aAMR (p<0.01) compared to all groups except “Other” (p=0.1)(Figure 1, right panel). For aAMR diagnosis, there is an indication that gdcfDNA is a better measure than GF.

Conclusions: Unlike other methods which rely upon GF, this novel approach permits absolute quantification of both gdcfDNA and tcfDNA. Both gdcfDNA and GF appear to be better primarily in aAMR. Further study is warranted to confirm this pattern and establish whether dependence on GF by other approaches is subject to confounding by coincident rises in tcfDNA.

Funding: Private Foundation Support

SA-PO424 Evaluation of Soluble Urokinase Receptor as a Biomarker in Plasmapheresis Managed Focal Segmental Glomerulosclerosis David Changji Wei,1 Jing Li,1 Jochen Reiser,2 Nada Alachkar.1 1Dept of Medicine, Rush Univ Medical Center, Chicago, IL; 2Dept of Medicine, Johns Hopkins Univ School of Medicine, Baltimore, MD.

Background: Plasmapheresis is the standard therapy in the management of recurrent focal segmental glomerulosclerosis (FSGS) post kidney transplantation. However, an effective biomarker justifying its application is still lacking. Elevated soluble urokinase receptor (suPAR) level was found independently associated with chronic kidney disease incidence and could contribute to the development of FSGS. In this study, we evaluated the applicability of suPAR as a biomarker in plasmapheresis managed post-transplant FSGS.

Methods: A retrospective cohort of post-transplant FSGS (n=19) managed at Johns Hopkins Hospital was analyzed for serum suPAR levels pre and post-transplantation, post-transplant FSGS diagnosis, before and after plasmapheresis. suPAR was then correlated with the clinical course. A prospective cohort of recurrent FSGS (n=14) was used for validation. suPAR downstream effect factor β3 integrin activity was indicated by podocyte APS immunofluorescence intensity.

Results: In the retrospective cohort, post-transplant suPAR was significantly lower than that at pre-transplant, but not distinct from that at the diagnosis of post-transplant FSGS. Plasmapheresis therapy alone or with Rituximab effectively reduced serum uPAR. The decrease in suPAR after treatment was correlated with the decrease in proteinuria (r=0.59, p<0.05). In the prospective cohort of recurrent FSGS, single course of plasmapheresis lowered serum suPAR by (37.0±2.85%). The combined treatment significantly decreased proteinuria and proteinuria. For patients resistant to therapy, a high podocyte APS activity was persisted after treatment; 2 of 3 had increased in serum suPAR as well. When the two cohorts analyzed together, the results remained unchanged in that the combined therapy lowered suPAR and proteinuria significantly in 16 out of 26 patients, and that the changes of the both were significantly correlated.

Conclusions: In this study of post-transplant FSGS, our data suggests that serum suPAR is an effective biomarker in the monitoring of plasmapheresis therapy.

Funding: Pharmaceutical Company Support - Terumo BCT

SA-PO425 Diffuse Extent of Peritubular Capillaritis in Late Antibody Mediated Rejection - Association with Transplant Glomerulopathy and More Severe Chronic Allograft Damage Zeliko Kikic,1 Farsad Alexander Eskandary,2 Harald Herkner,3 Georg Bohmig,4 Nicolas Kozakowski.1 1Nephrology and Dialysis, Medical Univ Innsbruck, Austria; 2Emergency Medicine, Medical Univ Vienna; 3Inst of Clinical Pathology, Medical Univ Vienna.

Background: Peritubular capillaritis (ptc) is a diagnostic criterion of antibody-mediated rejection (ABMR). Recently diffuse ptc extent (>50% of the cortical renal tissue) has been identified as an independent risk factor for inferior outcomes.

Methods: This study assesses the clinical relevance of ptc subcharacterization (ptc score, extent and leukocyte subpopulation) in recipients with donor-specific antibody (DSA) and is a secondary analysis of a large prospective trial (BORTJECT; NCT01873157). It included 85 out of 741 stable transplant recipients subjected to cross-sectional antibody screening (≥6 months post transplantation). Based on DSA detection [mean fluorescence intensity (MFI) threshold >1000], patients underwent protocol biopsy (scoring according Banff 2013 scheme). Outcomes were the presence of transplant glomerulopathy (TG) and the chronic lesion score (CLS), scoring was performed by one pathologist blinded for the outcome.

Results: Ptc (n=42) scores 1, 2 and 3 were present in 36%, 55% and 9 % while focal and diffuse extent were found in 36% vs. 64% respectively. Monocytes were the most prevalent leukocyte subpopulation (76%). Recipients with diffuse ptc were more frequently pre-sensitized, and presented with significantly higher post transplant DSA MFI sum (5172 (IQR: 3007-13783) vs. 2444 (IQR: 1335-7873), p=0.019). TG and CLS scores were significantly higher in recipients with diffuse ptc extent (1.1±1.1, p<0.002 and 6.8±2.2, p=0.01, respectively) vs. no ptc (0.3±0.6 and 5.2±3.3). Ptc score 2 was only associated to TG (1.2±1.0, p<0.001) but not to CLS. In cox regression analysis diffuse ptc remained an independent risk factor for TG (OR: 4.22 (95%CI: 1.47-12.14, p=0.007) and higher CLS (recession coefficient: 1.63 (95%CI: 0.18-3.07, p=0.03) while ptc score 2 lost its significant association.

Conclusions: Our results suggest diagnostic and prognostic relevance of reporting diffuse ptc extent and further emphasize its role as a risk factor for chronic damage in kidney allografts.


Background: Although the risk for morbidity and mortality is studied in subjects with renal transplantation, there are limited data to access the long-term renal survival effects of non-classical HLA class I (HLA-G) in Japanese.

Methods: We investigated the alteration of estimated glomerulat filtration rate (eGFR) based on the 3-variable GFR-estimating equation for Japanese (95 ± age x 0.876 x 0.793, if female), and factors affecting the eGFR in 156 adult patients, and that the changes of the both were significantly correlated.

Conclusions: Unlike other methods which rely upon GF, this novel approach permits absolute quantification of both gdcfDNA and tcfDNA. Both gdcfDNA and GF appear to be better primarily in aAMR. Further study is warranted to confirm this pattern and establish whether dependence on GF by other approaches is subject to confounding by coincident rises in tcfDNA.

Funding: Private Foundation Support

SA-PO423 Urinary 1-Methylhistidine and 3-Methylhistidine Excretion as Biomarkers for Meat Intake and Long-Term Outcomes in Renal Transplant Recipients Mohammad Yousof Saadi,1 Joelle Catharina Schutter,1,2 Lynanne M. Kienecker,1,2 Else van den Berg,1 Gerjan Navis,1,3 M. Rebecca Heiner-Fokkema,1 Stephan J.L. Bakker,1,4 Univ Medical Center Groningen,1 Kidney Center, Groningen, Netherlands.

Background: Mild protein restriction is recommended for chronic kidney disease (CKD) patients. It is unknown whether this also holds true for renal transplant recipients (RTR). Studies in CKD subjects did not take variation in nutritional value into account. Questionnaire-derived information may be biased, while information derived from biomarkers is more objective. We therefore aimed to study the associations of 24h urinary 1-methylhistidine and 3-methylhistidine excretion (UMH and UMH respectively) with meat intake and with the risk of mortality and graft failure (retransplantation or return to dialysis) in RTR.

Methods: We used food frequency questionnaires to assess total and specific protein intake, such as fish and processed meat intake. We measured 24h urinary acyl acid excretion by the colorimetric ninhydrin method. Linear and Cox regression analyses were applied to analyse associations with outcome.

Results: We included 342 RTR, with mean age 53±13 years, 188(55%) males and mean eGFR 45±19 ml/min. Median UMH and UMH were 343 mmol/24h [IQR: 162-716] and 199 mmol/24h [IQR: 151-264], respectively. UMH was associated with intake of white meat (R²=0.072, St. β=0.181, P=0.002) and UMH with intake of processed red meat (R²=0.137, St. β=0.131, P=0.002), both independent of adjustment for age, sex, and eGFR. During median follow-up of 3.9 years [IQR: 3.5-4.1], 52 RTR died and 24 developed graft failure. UMH was neither associated with mortality nor graft failure. UMH was associated with decreased risk of mortality, independent of adjustment for age, sex, eGFR, and urinary albumin excretion (HR 0.38, 95%CI 0.20-0.70). In a similar model, UMH was independently associated with increased risk for graft failure (HR 3.68, 95%CI 1.29-10.49).

Conclusions: Our data suggest that high intake of red meat protein, as represented by UMH, protects against premature mortality, while it increases the risk of graft failure. Optimal protein intake from the perspective of mortality may therefore be offset with increased risk of graft failure and vice versa.

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

Underline represents presenting author.
Japanese subjects (97 males, 59 females; 125 living donors, 31 cadaveric donors) with at least 3 years of allograft survival in our hospital. Clinical backgrounds, gender, HLA matching, ischemic times, ABO incompatibility, immunosuppressive therapy, and serum solute (s) HLA-G5 levels were examined. In addition, 22 renal biopsied specimens (9 males, 13 females; 19 living donors, 3 cadaveric donors) at before-2 to 4 weeks and one year after transplantation were also evaluated for HLA-G1 expression using monoclonal anti-HLA-G antibody (clone 87G).

Results: During follow-up period, the rates of change per year of eGFR (ΔeGFR) and sHLA-G5 were -1.65 ml/min/1.73 m² and 11.6 ng/ml in median levels, respectively. ΔeGFR and sHLA-G5 showed positive correlation (r=0.18, p=0.02). On multiple regression analysis, sHLA-G5, HLA matching and immunosuppressive therapy and were significant improving factors on ΔeGFR (beta 0.36535, p=0.0210; beta -1.4956, p=0.0134; beta 0.56654, p=0.0034 respectively). On histological examinations for HLA-G1 expression, 10 specimens showed perinuclear positive pattern on renal tubular epithelial cells after renal transplantation 2-4 weeks later. On the other hand, 12 specimens were negative for HLA-G1 staining except for interstitial infiltrating cells.

Conclusions: sHLA-G5 levels, HLA matching and immunosuppressive therapy were independent improving factors for renal allograft function judged by ΔeGFR in Japanese allograft recipients. HLA-G1 was also expressed on renal tubular epithelial cells 2-4 weeks after renal transplantation in some allograft recipients.

SA-PO427
A Paired Analysis of the Outcome after Kidney Transplantation in Peritoneal and Hemodialysis Patients Alicia Dobska-Sliżen,1 Agnieszka Bobkowska-Macuk,1 Beata Bzoma,1 Grażyna Moszkowska,2 Anna Milecka,2 Dariusz Zadronzy,3 Wojciech Wołyńczy,4 Andrzei Chamienia,4 Monika Lichodziejewska,1 Ewa Krol,1 Zbigniew Sledzinski,2 Bolesław Rutkowski,1 Nephrology, Transplantology and Internal Medicine, Medical Univ, Gdansk, Poland; 2Dept of Clinical Immunology and Transplantology, Medical Univ, Gdansk, Poland; 3Dept of General, Endocrine, and Transplant Surgery, Medical Univ, Gdansk, Poland; 4Dept of Occupational, Metabolic and Internal Medicine, Medical Univ, Gdansk, Poland; 5Kidney Transplant Regional Waiting List, Medical Univ, Gdansk, Poland; 6Dept of General Nursing, Faculty of Medical Sciences, Medical Univ, Gdansk, Poland.

Background: The impact of dialysis modality before transplantation on outcomes is not clear.

Methods: We analyzed the influence of dialysis modality on transplantation outcome. To minimize the donor bias, a paired kidney analysis was applied. 132 pairs of peritoneal dialysis PD and hemodialysis HD patients transplanted in our center between 1994 and 2015 who received kidneys from the same donor were included. There were no difference in the age of patients (44.9 vs 48.1 years), also Charlson Comorbidity Index was similar (3.13 vs 3.27) in both groups. The groups did not differ with respect to immunosuppressive protocols and number of mismatches.

Results: One-year patient (97 vs 98%) and graft (92 vs 95%) survival was similar, the Kaplan-Meier curves of patients and graft survival did not differ significantly. DGF and AR occurred more often in HD recipients (p=0.05). Graft vessel thrombosis resulting in graft loss occurred in 9 PD (7%) and in 4 HD (3%) patients (p=0.05). Creatinine urine and eGFR (MDRD) one-year and at last visit did not differ. On univariable analysis factors associated with graft lost were: age, DGF, eGFR and tacrolimus usage, the independent predictors upon multivariable analysis were age and eGFR. On univariable analysis the age and NOTAD were associated with death, but only age was the independent predictor. The Kaplan-Meier curves of patients and graft survival did not differ significantly. DGF and AR occurred more often in HD recipients (p=0.05).

Conclusions: Long-term outcome of renal transplantation is similar in PD or HD patients. PD patients experience significantly less DGF and AR. In both groups age was an independent predictor of the death of the patient and graft lost.

SA-PO428
The Closure of Arteriovenous Fistula Is Associated with a Significant Acceleration of eGFR Decline in Kidney Transplant Recipients Francois Jouret,1 Pierre Delanay,1 Pauline Vanderweckene,1 Hans Pottel,2 Laurent E. Weckers,3 University of Liège; 1Kulak.

Background: The creation of arteriovenous fistula (AVF) may retard CKD progression in the general population. Conversely, there is limited literature regarding the impact of AVF closure on renal function in kidney transplant recipients (KTR).

Methods: All KTR were retrospectively identified from 01/2007 to 12/2013, and grouped into: (0) no AVF; (1) closed AVF; and (2) left open AVF. GFR was estimated (eGFR) upon MDRD equations. Linear mixed models calculated the slope and intercept of eGFR decline versus time, starting at 3 months post transplantation (Tx).

Results: Group (0) was compared with closed AVF (1) and open AVF (2). The ANOVA analysis showed a significant trend for eGFR decline between AVF groups (p < 0.05). The mean eGFR slopes were -0.102 ± 0.035 -0.186 ± 0.042 NS for elevated creatinine, 0.7-21 mg/dL (M 4.0). 68% had proteinuria, 0-10g/24hr (M 2g).

Conclusions: The Closure of AVF is associated with a significant increase of eGFR decline in Kidney Transplant Recipients.
The donor ages were 2 mo-6 yrs with weights 6.5-20kg. Donor recipient weight ratio was 8.3-37%. 3 patients had en bloc transplants. Biopsy showed PDG in 15;33, alone in 12 or with superimposed disease, 3. Other transplant related diagnoses included rejection in 10 (4 ACR, 5 AMR, 1 mixed), acute tubular injury 4, CNI toxicity 3, BKV 1, TMA 1, recurrent MGN 1, and 1 protocol. Among PDG cases, 53% had fatal glomerulitis, 4 with collapsing glomerulopathy. Variable podocyty injury was seen by IHC in 45% and by EM in 68%. Ten (37%) had GBM lamellation, 13 (48%) endothelial injury. Follow-up was available on all cases for a mean 3.07 years (212 d to 7.9 yrs). Nine of 33 (27%) failed within mean 659 days (0-1193 d). 23 had functioning grafts with Cr 0.95-5.2 and proteimuria 0-1.35 g at last follow-up, and 1 patient died with a functioning graft. Graft failures were from rejection (4/9), BKV (1), TMA (1), and only 3 had PDG. Overall, 13/23 pts had proteinuria and 12/23 had hematuria at last follow-up, 89% of patients had improvement in proteinuria.

Conclusions: Deceased donor pediatric kidneys are a viable option for increasing transplant demands. While PDG associated podocyty and glomerular basement membrane injury may lead to proteinuria and hematuria in the post-transplant setting, long term graft survival is preserved. Recognition of this form of glomerular injury may be amenable for therapy.

SA-PO431
Are Repeat Mismatches Associated with Decreased Kidney Graft Survival in Kidney Transplant Recipients Who Have Previously Been Transplanted with a Non-Renal Solid Organ? Jean Maxime Cote,1 Mourad Dahhou,2 Xian Zhang,3 Edith A. Renoult,1 Bethany J. Foster,2 Heloise Cardinal.1 Medicine, Univ de Montreal, Montreal, QC, Canada; 2Medicine, McGill Univ, Montreal, QC, Canada.

Background: Previous exposure to mismatched HLA antigens through a first transplant can lead to sensitization and increase the immunological risk of kidney transplantations (KT) performed after non-renal solid organ transplantation (SOT). We asked whether repeated mismatches were associated with lower kidney graft survival in patients who received a KT after a non-renal SOT.

Methods: Using the Scientific Registry of Transplant Recipients, we conducted a retrospective cohort study of patients who received a KT after one or more previous non-renal SOT between January 1st 1990 and August 15th, 2014. A repeated mismatch was coded if at least one HLA mismatch between the donor and the recipient at the time of KT had also occurred with a previous non-renal organ donor. We used a Cox regression model to assess the association between repeated HLA mismatches, overall and death-censored kidney graft survival.

Results: The full cohort comprised 4924 KT, of which 830 failed on follow-up. We observed no relationship between repeated mismatches and overall graft survival (hazard ratio (HR): 1.05, 95% confidence interval (CI) 0.87-1.29 for class 1 and HR: 0.88, 95% CI 0.72-1.08 for class 2). Donor age (HR: 1.23 per 10-year increase, 95% CI 1.17-1.29), African American donor (HR: 1.58, 95% CI 1.26-1.99), recipient race (HR: 1.32, 95% CI 1.05-1.67) and number of mismatches with the kidney donor (HR: 1.35 for 2-3, 95% CI 1.06-1.71 and HR: 1.52 4-6 versus 0-1, 95% CI 1.22-1.91) were associated with an increased risk of graft failure. Living donation (HR: 0.64, 95% CI 0.54-0.76) and older recipient age at transplantation (HR: 0.94 per 10-year increase, 95% CI 0.89-0.99) were associated with a decreased risk of graft failure. Similar results were observed for death-censored graft failure.

Conclusions: Repeated HLA mismatches with previous donors had no negative impact on overall or death-censored graft survival in KT performed after previous non-renal SOT. Hence, repeated mismatches should not be used as a criterion to refuse a kidney donor.

SA-PO432
Graft Bearing Cysts Contribute to Accelerated Decline of Kidney Allograft Function Wenxian Qiu, Wenhan Peng, Jianghua Chen. Kidney Disease Center; The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.

Background: Simple renal cysts are the most common structural abnormality observed in adult kidneys. We investigated whether graft bearing sporadic cysts is associated with the accelerated decline of kidney allograft function in living donor kidney transplantation.

Methods: We retrospectively reviewed donors and recipients records of 716 living donor kidney transplants performed between April 2007 and April 2015 in our hospital. 64 recipients of grafts with cysts were noted. We compared this cohort to 128 non-cysts recipients.

Results: The mean serum creatinine of recipients in the two groups were 110.3±46.52 vs 98.8±30.18, 126.28±42.32 vs 113.24±25.65, 137.64±64.29 vs 111.16±20.99, and 96.22±1.31 vs 70.63±14.64(mL/min*1.73m2) on postoperative day 7, month 6, year 5 respectively(P<0.05). Estimating glomerular filtration rate levels were 81.74±26.30 vs 90.19±26.36, 68.97±17.47 vs 74.02±17.68, 80.38±23.74 vs 88.45±17.55, 62.85±21.94 vs 70.63±14.64(mL/min*1.73m2) on day 7, month 6, year 4, year 5 after surgery separately(P<0.05).

Conclusions: Graft bearing cysts contribute to a decreased kidney allograft function which needs to be considered in future kidney transplantation.

SA-PO433
Interleukin-6 Production by Monocytes Is Associated with Graft Function Decline in Patients with Borderline Changes Suspicous for Acute T Cell-Mediated Rejection Sacha A. De Serres,1 Olivier Desy,2 Stephanie Beland,1 Patrice Vallin,1 Julie Riepel,1 Eva Latulippe,1 Anil K. Chandraker,4 Ibrahim Batal.1 Renal Div, Univ Health Center of Quebec. Laval Univ, Quebec, QC, Canada; 2Dept of Pathology, Univ Health Center of Quebec. Laval Univ, Quebec, QC, Canada; 3Dept of Pathology, Brigham and Woman's Hospital, Boston, MA; 4Renal Div, Brigham and Woman’s Hospital, Boston, MA.

Background: The borderline changes suspicious for acute t-cell-mediated rejection (BL) is a diagnostic category questioned for its relevance. The underteled clinical significance of this diagnosis leads to heterogenous therapeutic management. Based on previous observations, we hypothesized that measuring IL-6 secretion by peripheral blood mononuclear cells (PBMCs) in patients with BL identifies those with ongoing graft damage.

Methods: From a cohort of 105 patients with concurrent biopsy and PBMC collection, we studied 28 patients with BL, in the absence of ABMR. The primary outcome was the change in eGFR at 6 months. We measured IL-6 levels secretion in PBMC culture supernatants. We characterized patients IL-6 secreting cells by flow cytometry, followed by characterization of mouse dendritic cells (DCs).

Results: The primary outcome was strongly associated with IL-6 levels (5.0±1.5 mL/min for each increase in log10 IL-6; p=0.004). These results were consistent after adjustment for baseline eGFR and antirejection treatment (p=0.005). 30 samples were available in 19 patients and demonstrated that the secretion of IL-6 was stable over time. The main source of IL-6 was CD14+CD16 CCR2+HLADR+CD86+CD11c+ monocytes. In an independent cohort, we found a significant correlation between IL-6 secretion and interstitial DC density in the biopsy. In mice, we observed that kidney DCs share features with macrophages and function as effector cells secreting IL-6. Kidney DCs showed a lower capacity for proliferation of CFSE-labeled T cells and a lower production of IL-2 in MLR supernatants, compared with splenic DCs.

Conclusions: These data suggest that IL-6 is a potential marker of active rejection in patients with BL, is produced monocytes in the blood, and correlates with DCs in the allograft.

SA-PO434
Urinary Tissue Inhibitor Metalloproteinase-2(TIMP-2) X IGF-Binding Protein-7(1GFBP7) Predict Delayed Graft Function after Kidney Transplantation Jhunyn Yang, Sung Yoon Lim, Young Ju Na, Myung-Gyu Kim, Sang-Kyung Jo, Won-Yong Cho. Dept of Internal Medicine, Div of Nephrology, Korea Univ Medical College, Seoul, Republic of Korea.

Background: Recently, urinary TIMP-2 and IGFBP-7, markers for G1 cell cycle arrest, have been identified and validated in predicting the development of AKI in critically ill patients. It is unknown, however, whether these two biomarkers could predict the development of delayed graft function (DGF) after kidney transplantation.

Methods: This is a single center, prospective observational study. We enrolled 56 patients who underwent KT (living donor: 8, deceased donor: 48) between August 2013 and...
and December 2015. Urine sample were collected right after the operation. The primary outcome was development of DGF as defined by need for dialysis of more than 1 session within 7 days of KT.

Results: Sixteen patients (28%) were diagnosed as DGF. In univariate analysis, kidneys from expanded criteria donors, donor serum creatinine, donor estimated glomerular filtration rate (eGFR) and T-cell and TIMP-2 were significantly different between early and late function (EGF) and DGF. However, in multivariate analysis adjusting for effects of donor eGFR only IGFBP7 x TIMP-2 at 0 hour post transplantation could predict the development of DGF. The receiver operating characteristic curve for prediction of DGF showed an area under the curve of 0.77 (sensitivity 0.77, specificity 0.81) for a cut off value of 1.76.

Conclusions: Our results indicate that urine IGFBP7 x TIMP-2 immediately after transplantation could be an early, predictive biomarker of DGF in kidney transplantation.

Funding: Private Foundation Support

SA-PO435
HLA-DR Expression in Tubular Epithelial Cells and the Subsequent Development of Antibody-Mediated Rejection in Transplant Kidneys
Haruki Katsumata,1 Yasuyuki Nakada,1 Izumi Yamamoto,1 Akimitsu Kobayashi,2 Ai Katsuma,2 Takafumi Yamakawa,2 Mayuko Kawabe,2 Yuu Tanno,1 Ichiro Shimizu,2 Hiroyasu Nakamae,3 Takashi Yokoi,1 Kazunari Tanabe.1 1Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan; 2Dept of Urology, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: The mechanism of antibody-mediated rejection (ABMR), a prominent cause of kidney allograft loss, is associated with donor-specific antibody (DSA). It has been speculated that T-cell mediated rejection (TCMR) enhances de novo DSA and ABMR. High HLA-DR expression in tubular epithelial cells is correlated with TCMR. However, the clinical significance and association of HLA-DR expression in tubular epithelial cells and ABMR as a cause of ABMR is not clear. This study evaluated whether the early expression of HLA-DR in tubular epithelial cells is associated with ABMR of kidney allografts.

Methods: This retrospective cohort study enrolled consecutive renal allograft recipients transplanted at the Department of Urology, Tokyo Women’s Medical University, from January 2005 to December 2009. We assessed biopsy samples obtained from 212 kidney allograft recipients at early phase. The HLA-DR expression in tubular epithelial cells was evaluated using immunofluorescence. The cases were classified into four groups according to HLA-DR expression and the progression of TCMR: DR−TCMR− (n=28), DR−TCMR+ (n=70), DR+TCMR− (n=15), and DR+TCMR+ (n=99) groups. The incidence of ABMR and graft survival were analyzed by the Kaplan–Meier method and log-rank test.

Results: Overall, the kidney allograft survival was worse in the DR+TCMR+ group than in the DR−TCMR− group (p=0.0284). No difference in the DR+TCMR+ group, 21 of 28 (75%) cases simultaneously expressed HLA-DR and showed TCMR, and another 25% (7/28) of cases developed TCMR within 1 year. Of these, 15 recipients (7.1%) developed ABMR (3 donors: 15 months, 3 donors: 16 months) after HLA-DR expression was detected.

Conclusions: These results suggest that HLA-DR expression in tubular epithelial cells and the subsequent development of TCMR are associated with ABMR and allograft survival.

SA-PO436
Short Term Modulation of Glomerular Filtration Rate and Functional Renal Reserve by Protein Restriction in Healthy Living Kidney Donors
Carlos Schreck, Carlos Guido Musso, Nora Cristina Imperiali, Cesar Andrés Mombelli, Maria Cora Giordani, Silvia Rosana Groppa, Guillermo Javier Rosa Diez. Servicio de Nefrologia, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background: Dietary protein is an important modulator of glomerular filtration rate (GFR). Renal Reserve (RR) (< 20% increase in GFR after a protein load) is used to assess kidney function in living kidney donors. In some donors, RR is negative, particularly in those whose GFR is high. Because dietary protein content is usually high in Argentina, we decided to further standardize RR through protein restriction 48-hours prior to avoid the effect of variation in dietary protein content on RR.

Methods: A 24-hour creatinine clearance (CrCl) without protein restriction was used to measure GFR prior (7-60 days) to RR. Two days before RR, patients received 1600 mg/d of citrinine to inhibit Cr secretion and dietary protein was restricted to avoiding meat, eggs and dairy products. RR was then assessed as described previously: a baseline GFR was obtained by averaging 3 consecutive 30 min urine collections and 1 blood sample for urinary and serum Cr. Immediately after, patients consumed a 1.5 g/kg dry protein meal, and 4 more blood/urine collections were obtained. The RR was calculated as the percentage increase in GFR after the protein meal (highest post-protein meal GFR – pre-protein GFR)/pre-protein GFR * 100%.

The 24-hour CrCl (no dietary restrictions) was compared to the RR baseline GFR (protein restricted). Results are expressed as mean ± SE. GFR differences were compared by a paired T-test.

Results: 16 patients were included (36 females, 25 males, age range: 24-77 years old). GFR after protein restriction + citrinine was lower than the unrestricted 24-hour CrCl (102.2 ± 3.1 ml/min/1.73m² vs 130.3 ± 4.4 ml/min/1.73m², p < 0.0001). The increase in GFR after the dairy protein meal was 54.2 ± 4.8 ml/min/1.73m² (102.2 ± 3.1 ml/min/1.73m² pre-meal vs 156.4 ± 5.7 ml/min/1.73m² post-meal, p < 0.0001) and RR was 55.8 ± 4.8%.

Conclusions: Protein restriction before RR is a useful method to standardize conditions for the test. It also allows to assess the ability to negatively modulate GFR.
Molecular Crosstalk in Chronic Dysfunction of Renal Allografts: An Integrative Approach
Maarten H.L. Peutz,
1Pathology, MUMC, Maastricht, Netherlands; 2Internal Medicine, MUMC, Maastricht, Netherlands; 3Pathology, Hospital Clinic, Barcelona, Spain; 4Pathology, Hospital Clinic, Barcelona, Spain.

Background: Chronic renal allograft dysfunction (CRAD) with interstitial fibrosis and tubular atrophy (IFTA) in kidney transplant recipients (KTRs) is a major cause of graft loss. Considering the complexity associated with CRAD, its underlying molecular interactions needs an integrative approach to gain mechanistic insights. Therefore, the current study was done to get a holistic view of the molecular changes & interactions at epigenetic (miRNA, DNA methylation (DNAm)) and gene expression levels.

Methods: A total of 70 graft biopsies were evaluated. DNAm, gene expression and miRNA arrays were performed from each of the kidney biopsies from KTRs with IF/TA (n=10) and normal functioning allograft (n=11). Additional methylation arrays (n = 40) were performed in donor pre-implantation biopsies to evaluate if the methylation changes were IFTA specific and denovo. MINT, oligo & limma Bioconductor packages in R were used for analysis of the arrays and the data was integrated. Differentially expressed miRNA and their gene targets thus obtained were further validated by qPCR in training (n=10) and independent sets (n=10).

Results: Integration analysis resulted in 3 miRNA that were hypomethylated in promoter regions and upregulated in IFTA biopsies. The gene targets of these 3 miRNA were further integrated using gene expression arrays from the same biopsies. Biological analysis of the integrated gene expression data showed that the genes repressed by these miRNA had kidney tissue specific metabolic functions, especially in the tubular epithelial cells (BMP12, CLCNI, G6PC, NTRK2: CLCNKB, PPM1H, AHCYL1). Also, among them were inhibitors of TGF beta signaling pathway (PPM1H, TGRB1). Top disease processes associated with these genes in IPA analysis show dysgeneisis, cell death, growth failure and hypoplasia (FDR < 2.62). Conclusion: The results suggest that DNAm changes in graft biopsies are denovo. DNAm could be a consistent upstream regulatory mechanism through which the miRNA and hence their gene targets are dysregulated and contribute to tubal renal dysfunction and may be partly responsible for tubal dysfunction and interstitial fibrosis.

Surveillance Renal Transplant Biopsies: Useful or Irrelevant?
William M. Bennett,
1Pathology, MUMC, Maastricht, Netherlands; 2Internal Medicine, MUMC, Maastricht, Netherlands; 3Pathology, Hospital Clinic, Barcelona, Spain; 4Pathology, Hospital Clinic, Barcelona, Spain.

Background: Performance of surveillance biopsies in kidney transplantation remains somewhat controversial. There are many centers that biopsy patients based only on rises in serum creatinine or symptoms. Methods: Since 2011 we have performed surveillance biopsies at 2 months and 6 months post-transplant with follow up at 1 year for any abnormal results. Immunosuppression was Thymoglobulin induction (3 mg/kg) followed by Tacrolimus, mycophenolate and Prednisone.

Results: In 422 surveillance biopsies 54 (12.7%) had subclinical acute cellular rejection or borderline changes, 0.6% showed other abnormalities. In 241 biopsies “for cause” 35.7% had significant acute antibody mediated rejection with microvascular thrombi (AAM), 24% had acute antibody mediated rejection without thrombi (AAM), 21% had acute antibody mediated rejection with mixed (AAM), 6% had acute antibody mediated rejection with denovo. 2% had significant acute antibody mediated rejection with denovo. In 7% patients patients from January 2010 to February 2016 at Seoul National University Hospital including 71 ABOi KT and 21 DSA positive KT patients from January 2010 to February 2016 at Seoul National University Hospital including 71 ABOi KT and 21 DSA positive KT patients who underwent desensitization with anti-CD20 Ab, plasmapheresis and intravenous immunoglobulin. Four hundred seventeen patients without anti-HLA antibodies were also included as control group.

Conclusions: Non-hearth-beating donor, living ABO-incompatible donor and recipients with DGF had higher intratubular calcification grade in protocol biopsies. Mineral bone metabolism data and biopsy classifications association could help to consider an earlier treatment. We propose to include calcification grade in protocol biopsies since it could provide information about type of donor and initial renal graft function.

Early Loss of Peritubular Capillaries after Kidney Transplantation Is Associated with Later Renal Function Decline: A Validation Study in 121 Patients
Anke Keijbek,
1Floortje Steegh,
2Marielle Gelens,
2Ernest Van Heurn,
3Maarten H.L. Christiaans,
4Carine Peutz-Kootstra.
1Pathology, MUMC, Maastricht, Netherlands; 2Internal Medicine, MUMC, Maastricht, Netherlands; 3Surgery, AMC, Amsterdam, Netherlands.

Background: Chronic transplant dysfunction is a major cause of renal graft loss and is preceded by interstitial fibrosis and tubular atrophy (IFTA) in protocol biopsies. Previously we showed in the pilot study 48 patients that IFTA development is preceded by peritubular capillary (PTC) loss in the first 3 months after transplantation (Steegh et al. JASN 2011). The aim of this study is to validate these findings in a separate cohort.

Methods: The validation cohort consisted of 121 new patients, who received a kidney transplantation between August 2003 and December 2009 at the Maastricht University Medical Centre and of whom representative protocol biopsies were taken at transplantation, and 3 and 12 months post-transplant. IF/TA, PTC number and gFGFR (MARD) were studied as described in the pilot study.

Results: A significant loss of PTCs in the first three months after transplantation was found in post-mortal donor kidneys only (P<0.01). In univariate analyses, this PTC loss was associated with longer first warm and cold ischemia time, delayed graft function (DFG), microvascular thrombi, and with higher PTC density and IF/TA in the pre-implantation biopsy. This early PTC loss is associated with higher IF/TA score (p=0.372, P<0.01) after 1 year. Additionally, early PTC loss is correlated with lower gFGFR at year 1 (p=0.219, P=0.021)
SA-PO444

Long Term Outcome of Steroid Pretreatment of Organ Donors – A Randomized, Controlled Trial

Roman Reindl-Schwaighofer, Rainer Oberbauer, Alexander Kainz, Julia Wilflingseder. Nephrology and Dialysis, Medical Univ of Vienna, Vienna, Austria.

Background: Organs from deceased donors show a reduced graft survival compared to organs from living donors. A major difference between the two groups is the rate of delayed graft function (DGF) that occurs in roughly 25% of recipients of organs from a deceased donor compared to below 5% following kidney transplantation from a living donor. Gene expression analysis in donor kidney biopsies revealed that organs with DGF showed an up-regulation of genes associated with inflammation, complement activation and apoptosis induction.

Methods: To determine whether systemic anti-inflammatory treatment of kidney donors following brain death reduces the incidence of DGF and improves long-term graft survival we performed a randomized placebo-controlled trial and enrolled 306 donors and 455 renal transplant recipients between February 2006 and November 2008. Donors either received 1000 mg of methylprednisolone or placebo.

Results: Incidence and duration of DGF at 1-week post transplant could not be reduced by corticosteroid treatment of the donors (Kainz et al. 2010). At the 5-year follow-up death censored graft survival as well as patient survival did not differ between the two groups. This is visualized by a KM plot (Figure 1). To assess influence on graft function we calculated the slope of eGFR. Again, no statistically significant difference between the two groups was observed.

Conclusions: Steroid treatment of donors prior to organ harvesting did not improve long term graft survival and function.

SA-PO445

Impact of Inadequate Donor Nephron Mass on First Year Rejection Risk

Abhijit S. Naik, Roger C. Wiggins, Diane Cibrik. Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI.

Background: Inadequate donor nephron mass is associated with hyper-filtration injury and reduced graft survival. Injury and the accompanying inflammation could stimulate an alloimmune response. However, whether inadequate nephron mass is associated with an increased risk of acute rejection remains unclear.

Methods: Study data were drawn from national transplant registry (OPTN data as of December 2015) data for adult kidney-only recipients in 2008 to 2013. Inadequate donor nephron mass was defined as the recipient and donor body surface area mismatch (RDM) ratio, and categorized according to RDM quintiles as: Group 1, <0.87; Group 2, <0.87 to <=0.97; Group 3, >0.97 to <=1.07; Group 4, >1.07 to <=1.20; and Group 5, >1.20. A multivariate logistic regression model was used to determine associations between RDM and first-year acute rejection, adjusted for transplant, recipient and donor factors. Kaplan Meier Survival curves (conditional to allograft surviving first year) were constructed to assess long term (7-year) allograft outcomes.

Results: Among 73,624 recipients, the overall rejection rate was 9.15% and ranged from 10.5% in Group 5 to 8.4% in Group 1. After covariate adjustment, compared to Group 3, Group 1 (OR=0.80 95% CI: 0.72-0.89) and Group 2 (OR=0.85, 95% CI: 0.78-0.93) were associated with a lower rejection risk, while Group 4 (OR=1.10, 95% CI 1.01-1.19) and Group 5 (OR=1.31, 95% CI: 1.19-1.44) were associated with increased risk. Recipient body mass index (BMI) <=30 (OR=1.12, p<0.05) and donor BMI (OR=1.01 per kg/m2, p=0.0001) were also independently associated with rejection. Long-term allograft outcomes across RDM groups were notable for worse outcomes in Group 5 (vs Group 1) both with and without rejection (P<0.05 for both).

Conclusions: Inadequate donor nephron mass is independently associated with increased risk of first year rejection and this effect is independent of both recipient and donor BMI. Efforts to minimize RDM may help mitigate this risk.

SA-PO446

Predicting Post-Transplant Mortality: A Single Center Comparison of Comorbidity Indices

Ronald Brian Vigo, Wadi N. Suki, Duc T.M. Nguyen, Edward Graviss, Ahmed Osama Gaber. Nephrology, Houston Methodist Hospital, Houston, TX.

Background: Patients listed for renal transplantation can have multiple comorbidities leading to early mortality post-transplant. Multiple models have been developed to objectively measure the burden of these comorbid illnesses and some have been used successfully to predict mortality post-transplant. Our goal was to evaluate the utility of three of these tools as objective measures to predict negative outcomes in renal transplant recipients at our center.

Methods: We evaluated medical records from kidney recipients transplanted at our institution between 5/30/2008 and 5/31/2015. Patients who died within the first year post-transplant were included. Patients who survived beyond the first year were matched by age, sex and race in a 2:1 ratio and selected as controls. Data was analyzed using a Cox regression model. A base model which included outcome variables was developed with the intent of adding statistical power to the results. Variable selection for the multivariate model was based on Hosmer and Lemeshow’s methodology. Bayesian information criterion (BIC) and likelihood ratio testing were used to assess the performance of the full and simplified predictive models.

Results: 23 patients with 46 matched controls were included in our study. Increased comorbidity was associated with reduced patient survival. Of the models examined, the Charlson Comorbidity Index (CCI) and its different versions yielded statistically significant results in patients aged <65. A CCI model adjusted for age and albumin offered the best results (p=0.001). None of the models yielded significant results for recipients ≥65. The CCI adjusted for base model yielded significant results in all patients and patients <65, but not in patients ≥65.

Conclusions: The CCI is a suitable tool for the objective measurement of comorbidity in renal transplant recipients aged <65. CCI adjusted for age and serum albumin increases the effectiveness of the CCI in predicting post-transplant mortality. CCI and age-adjusted CCI models when adjusted for with the base model significantly predicted post-transplant mortality in all patients.

SA-PO447

Predictors of Mortality in Renal Transplantation Recipients

Marcos A. Meniconi,1 Krissia K.S. Wallbach,1,3 Luiza Pego Silva,1 Jose Medina-Pestana,1,2 Miguel A. Goes,1,3 Nephrology, Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; 1Nephrology, Hospital Israelita Albert Einstein, Sao Paulo, SP, Brazil; 1Nephrology, Hospital do Rim e Hipertensao, Sao Paulo, SP, Brazil.

Background: Patients listed for renal transplantation can have multiple comorbidities leading to early mortality post-transplant. Multiple models have been developed to objectively measure the burden of these comorbid illnesses and some have been used successfully to predict mortality post-transplant. Our goal was to evaluate the utility of three of these tools as objective measures to predict negative outcomes in renal transplant recipients at our center.

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Conclusions: The CCI is a suitable tool for the objective measurement of comorbidity in renal transplant recipients aged <65. CCI adjusted for age and serum albumin increases the effectiveness of the CCI in predicting post-transplant mortality. CCI and age-adjusted CCI models when adjusted for with the base model significantly predicted post-transplant mortality in all patients.
Kidney donation was 43% from deceased donors, 48% related living donors and 9% unrelated living donors; 67% used FK-506, 24% cyclosporine and 8% rapamycin as immunosuppressive drugs; EPI-CKD 69±27 min/L and Hb 11.7±2.5 g/dl at baseline. 68 patients died during follow-up (Mortality group). We observed that this group was older (49±12, 39±15 yrs; p<0.001), had a longer time on dialysis (4+3,5±1 yrs; p<0.001), higher cold ischemia time (20±12,14±5h; p<0.001), used higher rHuEPO doses (3589±3560,3824±1616 IU; p<0.006), had lower Hb (10.6±3.1,12.7±2.5) and CKD-EPI (45±23,55±27; p=0.007) at baseline and also higher DGF (p<0.001). After binary logistic regression, age (b=1.063 95%CI 1.034-1.091; p<0.001), Hb (b=0.715 95%CI 0.634-0.800; p<0.001), cold ischemia time (b=1.001 95% CI 1.000-1.003; p=0.009) were determined independent predictors of mortality.

Conclusions: This study shows that patient age, Hb concentration and cold ischemia time were independent predictors of mortality in renal transplant recipients.

SA-PO448


Background: Cardiovascular events rates are high in chronic kidney disease patients, which improve with kidney transplantation. However, the long-term cardiovascular structural and functional changes with kidney transplantation are poorly understood. This study prospectively investigates these changes in live-donor kidney transplant recipients.

Methods: 24 non-diabetic, live-donor kidney transplant patients (20 dialysis and 4 pre-dialysis, mean age 45±13 years, 75% male, 75% Caucasian) completed baseline (1-7 days before transplant) measurements. Patients underwent a detailed echocardiogram and a vascular endothelial function investigation using brachial artery flow-mediated dilatation (FMD). These were conducted together with routine blood and clinical examinations. Patients were followed up with the same investigations in the short term (9 patients, 8±0.5 months) and long-term (17 patients, 28±6 months).

Results: Left ventricular mass (LVM) regressed (208±82g to 178±63g) and ejection fraction (EF) improved (59.9±6 to 69.5±9%) over time, significantly in the long-term after transplantation. No significant changes were observed in FMD; however, a significant improvement was observed in nitroglycerin-mediated dilatation (NMD) (10±6% to 15±5.5%, p=0.022). Higher NMD values at baseline were correlated with greater improvement in LV mass index at follow up (p<0.009).

Conclusions: Cardiac structure and function significantly improved in the long-term after kidney transplantation. The regression in LV hypertrophy, may be related to improvement in vascular distensibility.

SA-PO449

Three Competing Definitions of Graft Function: Associations with Outcomes in Kidney Transplantation Ahmad M. Tufafula, Milind A. Phadnis, Jonathan D. Mahnken, James B. Wetmore, Connie J. Wang. 1Div of Nephrology, Univ of Kansas, Kansas City, KS; 2Div of Nephrology, Henry Ford Hospital, Detroit, MI; 3Department of Medicine, Indiana University School of Medicine, Indianapolis, IN; 4Department of Medicine, Mayo Clinic, Rochester, MN; 5Department of Medicine, University of Alabama at Birmingham, Birmingham, AL; 6Department of Medicine, University of Nebraska College of Medicine, Omaha, NE; 7Department of Medicine, University of California, San Francisco, CA; 8Department of Medicine, Columbia University, New York, NY; 9Department of Medicine, University of Colorado, Denver, CO; 10Division of Nephrology, University of Arkansas for Medical Sciences, Little Rock, AR; 11Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL; 12Division of Nephrology, University of California, San Francisco, CA; 13Division of Nephrology, University of Colorado, Denver, CO; 14Division of Nephrology, University of Kentucky, Lexington, KY; 15Division of Nephrology, University of Pennsylvania, Philadelphia, PA; 16Division of Nephrology, University of Washington, Seattle, WA; 17Division of Nephrology, University of Wisconsin, Madison, WI; 18Division of Nephrology, University of California, Los Angeles, CA; 19Division of Nephrology, University of Minnesota, Minneapolis, MN; 20Department of Biostatistics, University of Kansas, Kansas City, KS.

Background: We investigated how three competing definitions of post-kidney transplant (KT) graft function were associated with graft and patient survival.

Methods: A total of 1211 KT recipients were studied. In all three definitions (Def), delayed graft function (DFG) was defined as need for dialysis by postoperative (POD) 7. In Def 1, immediate graft function (IGF) was defined as a creatinine (Cr) reduction rate between POD 1 and 2 (CrRRr) of ≥30%, while slow graft function (SGF) was defined as CrRRr <30%. In Def 2, IGF was defined as Cr <3mg/dl by POD 5, and SGF as Cr ≥3mg/dl by POD 5. In Def 3, IGF was defined as Cr ≥1.5 or CrRRr ≥20% by POD 3, while SGF was Cr ≥1.5 and CrRRr <20%. Association of each definition with time to graft failure and, separately, time to death was examined using a multi-regression model.

Results: For graft survival, there was a distinct difference between DGF and both IGF (p<0.001) and SGF (p<0.001), but no difference between IGF and SGF (p=0.72) for Def 1.

However, for both Def 2 and Def 3, there was no difference between DGF and SGF, while IGF was distinct from SGF and DGF (p<0.001 and p=0.005, respectively). In contrast, for patient survival, there was a distinct difference between DGF and both IGF (p<0.001 for all three definitions) and SGF (p<0.001 for all definitions), but no difference between IGF and SGF (p≥0.33 for all definitions).

Conclusions: Def 1 offers no value beyond the traditional dichotomy of requiring dialysis by POD 7. However, Def 2 and Def 3 utilize a useful construct, namely SGF, which categorizes patients at risk for graft failure (like those with DGF) but not mortality (like those with IGF).

SA-PO450

Multi-Stakeholder Perspectives on the Relative Importance of Outcomes for Trials in Kidney Transplantation: An International Best Worse Scaling Survey Martin Howell,1,2 Germaine Wong,1,3 Benedicte Sautenet,1 Nicole Evangelidis,1,2 Jonathan C. Craig,1,2 Allison Tong,1,2 Kirsten Howard,2 1Centre for Kidney Research, The Children’s Hospital at Westmead, Westmead, NSW, Australia; 2School of Public Health, Univ of Sydney, Sydney, NSW, Australia; 3Centre for Transplant and Renal Research, Westmead Hospital, Westmead, NSW, Australia.

Background: To optimize the benefits of kidney transplantation, recipients and clinicians should have an agreed, shared management plan. This relies on prioritizing the same outcomes but patient experiences of transplantation and dialysis are likely to result in quite different preferences. As a sub study of the SONG-Transplant core outcome for clinical trials initiative, the aim was to evaluate the relative importance of outcomes in kidney transplantation.

Methods: Participants completed a best-worst scaling survey to elicit preferences for 16 critical outcomes identified by stakeholder consensus. Each participant was randomly assigned to five lists, each containing six of the outcomes and identified the most and the least important outcome from each list. Relative importance scores were calculated for each outcome and normalized to the range 0 (least important) to 1 (most important).

Results: In total, 334 (175 patients/caregivers, 149 health professionals) from 46 countries participated. Death was most important for health professionals (importance score 1.0; 95% confidence intervals 0.92 to 1.07) compared to patients/caregivers where death (0.71:0.63 to 0.79) was ranked below graft function (0.94:0.87 to 1.00) and graft loss (0.82:0.75 to 0.88). In addition patients/caregivers placed greater importance on chronic and acute graft rejection, skin cancer, surgical complications and blood pressure, and less importance on hospitalization.

Conclusions: Patients consider graft function, graft loss, and chronic and acute rejection to be as important as death, or more important, compared to health professionals. This focus on graft-centric outcomes may reflect a strong aversion to returning to dialysis and equating graft dysfunction with graft loss.

SA-PO451

Impact of Early Graft Function on Patient Survival Post Kidney Transplantation Muna Alnims, Angelo M. De Mattos. Internal Medicine Section of Transplant Nephrology, UC Davis Medical Center, Sacramento, CA.

Background: Early kidney allograft function affects pts survival post transplant.

Methods: single center historic cohort study. Adult recipients of kidney transplants between 1/2005 and 6/2013 were included. Pts with failed graft within 3 months or not followed for at least 2 years were excluded. MDRD formula was used to estimate GFR at 3 months. Categories of CKD were created according the NKF guidelines.

Results: 1,265 pts included (386(31%) had living and 879(69%) deceased donor(DD). 113 pts (8.9%) had CKD4, 312(25%) CKD3b, 435(34%) CKD3a, 405(32%) CKD2 and 34 months. Pts with CKD4(57±12.3y) and 3b (55±12.9 y) were older than pts with CKD3a (52±13.6y) and 2 (50±14.1y) and received older kidneys (47±13.9 and 46±14y vs. 41±15.2 and 55±15y;p<0.001. CKD4 and 3b pts had higher proportion of DD(88% and 73%)vs 71% in CKD3a and 2 pts (61%,70%);p<0.001. Days on dialysis, gender, diabetes, CAD were not significant.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
different among gps. At 2 years 32 pts (2.5%) expired (sepsis 11, cardiac/cva 11, cancers 6, other 4). CKD4 pts had higher mortality than pts with CKD3 or higher at 3 months (9.7% vs. 1.8%; p<0.001). Recipients of DD (2.2%, p=0.01), and age (HR 1.06, 1.046-1.125, per year) were associated with higher mortality. Gender, DM, duration on dialysis, malignancy or CAD were not statistically significant. By multivariable (logistic regression) analysis: CKD4 (adjHR 3.9; 1.75 – 8.92; p=0.001) and age of recipient (adjHR 1.07; 1.025 – 1.117, p=0.002) were the only factors associated with death within the first 2 years post transplant (model included DM, DD, donor age, CAD, years on dialysis).

**Patient Survival by Categories of CKD at 3 Months Post Transplant**

**Economic Analysis of Survival for Patients Undergoing Kidney Transplant in Brazil**

Regina Moura Lucio, Daniela Malheiro, Ana Carvalho Matos, Álvaro Pacheco-Silva, Reginaldo Tavares Lopes, Ana Carvalho Matos, Álvaro L. Pacheco-Silva.

Renal Transplant Unit, Hospital Israelita Albert Einstein, Sao Paulo, Brazil; Management Dept, Hospital Israelita Albert Einstein, Sao Paulo, Brazil.

E-mail: reginamoura@hiae.org.br

**Background:** Brazil has one of the most important public programs of transplant in the world. However, there are few studies related to cost analysis in transplant in Brazil to support the maintenance of transplant as a therapy cost-effective. Aim: to perform an economic analysis of survival for kidney transplant patients in a philanthropic hospital.

**Methods:** We included in this study all admissions which resulted in cost related to kidney transplants, in all phases of transplant treatment (pre, transplant and post-transplant) of the year of 2014. Unit costs were associated to each health resource obtained from the hospital costing system. The unit costs of materials and medicines corresponded to the average direct costs of acquisition. For daily rates, tests and procedures unit costs corresponded to the fixed and variable costs associated with providing each service. Cost were collected in Brazilian Reais (R$) and converted to USD, considering the exchange rate from November 30th, 2014 (US$D=R$3.9). A survival analysis was done using the Cox model, using all kidney transplants performed since 2002 in our institution.

**Results:** The total cost used for kidney transplant program was US$ 6,015,160.77 in 2014. Considering the period of 2014, the cost was: in pre, transplant and post-transplant phases were $68,668,92.01, $1,283,362.56 and $4,045,201.28, respectively. The mean survival time was 4,497 days and the life expectancy calculation was 17 years in 922 patients included. Cost per patient year of life-saved was $4,114.33.

**Conclusions:** Pts survival after kidney transplant seems related to early graft function, older pts with CKD stage 4 post transplant have higher risk of death than other pts with better GFR 3 months post transplant, no specific cause of death was prevalent, this group of pts should be closely monitored.

**SA-PO452**

*Economic Analysis of Survival for Patients Undergoing Kidney Transplant in Brazil*

Lucio Roberto Requiao-Moura,1 Daniel Tavares Malheiro,2 Silvia Regina Morgado,1 Ana Carvalho Matos,1 Álvaro Pacheco-Silva.1

1Renal Transplant Unit, Hospital Israelita Albert Einstein, Sao Paulo, Brazil; 2Health Economy Dept, Hospital Israelita Albert Einstein, Sao Paulo, Brazil; 3Management Dept, Hospital Israelita Albert Einstein, Sao Paulo, Brazil.

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**SA-PO453**

*Evaluation of Baseline Allograft Biopsy and Long-Term Outcomes in Patients with Living-Donor Kidney Transplantation*

Takafumi Yamakawa,1 Akimitsu Kobayashi,2 Izumi Yamamoto,3 Yasuyuki Nakada,4 Takeshi Kawaguchi,3 Toshiyuki Iwasawa,4 Takashi Yokoo,5 Hiroshi Kitamura.1

Nephrology, Chiba East Hospital, Chiba, Japan; 2Nephrology, Jikei Univ, Minato-ku, Tokyo, Japan.

**Background:** Donor shortage is a serious problem in kidney transplantation; consequently, increasing numbers of kidneys are from marginal donors or the elderly. Recent studies have shown that an evaluation of the baseline allograft biopsy may predict transplant outcomes in deceased-donor kidney transplantation. However, the pathology of the baseline allograft biopsy in living-donor kidney transplantation, including older donors, has not been fully validated. This study assessed the histological parameters of baseline allograft biopsy that affected the long-term graft survival in living-donor kidney transplantation.

**Methods:** Clinical data were examined in 192 patients who underwent living-donor kidney transplantation at Chiba East Hospital from April 2004 to April 2013. Patients experiencing rejection, BK virus nephropathy, and recurrent glomerular disease were excluded. All baseline biopsies were 1-hour biopsies and scored according to the Banff classification, and the relationship between the individual histological lesions and death-censored graft survival was assessed. Survival analysis was performed using Cox proportional hazards analysis and log-rank testing. We also evaluated the pathological findings in aging donor kidneys by stratification using donor age (under 50, 50 to 59, 60 to 69, over 70 years).

**Results:** The mean follow-up time after transplantation was 6.0 years. Arteriolar hyalinosis (HR, 2.16, 95% CI, 1.20–3.88; P=0.01) and glomerulosclerosis (HR, 3.64, 95% CI, 1.17–10.57; P=0.025) were significantly associated with death-censored graft survival, whereas interstitial fibrosis/tubular atrophy (IFTA), and vascular intimal thickening were not. Although the prevalence of glomerulosclerosis, arteriolar hyalinosis, IFTA, and intimal thickening were higher in the over-60 donor group, we could not predict graft survival using only donor age.

**Conclusions:** Arteriolar hyalinosis and glomerulosclerosis may be important pathological findings affecting long-term graft survival in living-donor kidney transplantation.

**SA-PO454**

*Digital Quantification of Macrophage Abundance in a Cross Sectional Study of Native and Transplanted Kidneys*

Jessica Schmitz,1 Abdulrazag Ahmad Khalifa,2 Hermann G. Haller,1 Hans Heinrich Kreipe,1 Veit Türmer,1 Friedrich Fuerhacker,1 Jan H. Brzezen,1 Inst of Pathology, Hannover Medical School, Hannover, Germany; 2Nephrology, Hannover Medical School, Hannover, Germany.

**Background:** Standardized markers based on quantitative and qualitative evaluation and localization of immune cell density in kidney biopsies may improve diagnostic accuracy.

**Methods:** Kidney biopsies were stained for macrophages using a monoclonal CD68 antibody, scanned (Leica) and whole slide images were analyzed for immunopositivity using image analysis software (Definiens Tissue Studio). Results were obtained separately for cortex, medulla and extrarenal tissue. Kidney biopsies were clinically indicated biopsies (native: 100%, KTx 64%). KTx biopsies partly came from the Hannover Protocol Biopsy Program (36%).

**Results:** The density of CD68-positive immunostained area (% of the respective cortex, medulla, extrarenal area) was higher in KTx (n=368) vs. native kidney (n=134) biopsies (cortex: 2.9 vs. 1.0, medulla: 2.8 vs. 0.8, extrarenal tissue: 2.2 vs. 0.8; P<0.001). 38% of the studied KTx biopsies revealed rejection (borderline 15%, cellular 8%, humoral 7%, cellular and humoral 9%). Humoral and combined rejection were correlated with significantly increased macrophage infiltration (no rejection: cortex 2.6%, medulla 2.4%; borderline: cortex 1.9%, medulla 1.5%; cellular: cortex 2.5%, medulla 2.6%; humoral rejection: cortex 4.4%, medulla 5.9%; combined rejection: cortex 6.2%, medulla 6.9%). The density of macrophages correlated significantly with the time between transplantation and biopsy: Highest mean values were measured when post-transplant time exceeded 1 year (cortex: 5.8% compared to <1year >90 days (4.1%), <90 days >8 days (1.3%), <8 days (1.5%)). Evaluation of IF/TA according to Banff 2013 consensus showed a significant increase of infiltrating macrophages with fibrosis progression both in native and transplanted kidneys. Conclusions: The findings suggest that macrophages have an essential in active rejection, chronic allograft injury and fibrosis. Digital morphological approaches may facilitate the characterization of immune cell-mediated injury in native kidneys and after KTx.

**SA-PO455**

*Sex Differences in Kidney Graft Outcomes Differ by Age*

Fanny Lepeyro,1 Mourad Dahloul,2 Xu Zhang,2 Bethany J. Foster.21 Hôpital du Sacré-Cœur de Montréal, Montréal, QC, Canada; 2McGill Univ Health Centre, Montréal, QC, Canada.

**Background:** Whereas studies of sex differences in graft survival among adult kidney transplant recipients showed conflicting results, several pediatric studies suggested poorer outcomes in females than males. We hypothesized that the impact of recipient sex on kidney graft survival differs by age.

**Methods:** We evaluated 159,417 patients recorded in the SRTR database who received a first deceased donor kidney transplant (1995-2013). We used time-dependent Cox models...
to estimate the association between recipient sex and each of death-censored (DCGF) and all cause (ACGF) graft failure for patients of different ages. Models included a sex by current age (0 to 14, 15 to 24, 25 to 44, or ≥ 45 years) interaction term and the following covariates: race, primary disease, donor/recipient height ratio, donor age, donor sex, panel reactive antibody, and duration of dialysis pre-transplant.

Results: There were 66,562 graft failures and 37,564 deaths over a median of 4.9 years (IQR 2.0, 9.1). In multivariable models, females <25y had significantly higher risks of ACGF than males the same age (HR 0.90 [95% CI 0.88, 0.93]). Compared with males of the same age, the risk of DCGF was significantly higher for females 15-24y (HR 1.24 [95% CI 1.09-1.40]) and lower for females ≥45y (HR 0.92 [95% CI 0.89-0.96]).

SA-POA57
Everolimus with Low-Dose Tacrolimus versus Standard Immunosuppressive Regimen: Subgroup Analysis of Renal Function at 12 Months in De Novo Renal Transplant Patients
Fuaa S. Shihab, Yasir Qazi, Shamkant P. Mulgaonkar, Kevin M. Mccague, Dharmesh Patel, V. Ram Peddi, David Shaffer, 1Univ of Utah, Salt Lake City, UT; 2Univ of Southern California, Los Angeles, CA; 3Barnabas Health, West Orange, NJ; 4Novartis Pharmaceuticals Corporation, East Hanover, NJ; 5California Pacific Medical Center, San Francisco, CA; 6Vanderbilt Univ Medical Center, Nashville, TN.

Background: Reduction of tacrolimus (Tac) levels after kidney transplantation has a beneficial impact on renal function. The US92 study determined if everolimus (EVR) with low-dose Tac (LTac) is noninferior to mycophenolate mofetil (MMF) with standard-dose tacrolimus (STac) on measures of allograft function and safety in de novo renal transplant patients. This post-hoc analysis of US92 assessed renal function of subjects with/without treated biopsy-proven acute rejection (bPAR) or delayed graft function (DGF), and by induction therapy.

Methods: Subjects were randomized 1:1 to receive EVR (0.75 mg BiD, adjusted to maintain trough level 3–8 ng/ml) + LTac (C0h 0–2 Months [M1]: 4–7 ng/ml, 2–6M: 3–6 ng/ml, 6–12M: 2–5 ng/ml) or MMF (2 g/day) + STac (C0h 0-2M: 8–12 ng/ml, 2–6M: 7–10 ng/ml, 6–12M: 5–8 ng/ml).

Results: Despite some differences at M1, mean eGFR (MIRD) at M12 was similar between treatments irrespective of bPAR, DGF or induction therapy (Table). In both treatment groups, subjects with bPAR had lower eGFR at M12 vs. those without. Improved eGFR from baseline was numerically greater in subjects with DGF vs. those without.

Conclusions: Renal function as assessed by eGFR was generally consistent between the US92 EVR+LTac and MMF+STac groups, regardless of bPAR, DGF or induction therapy.

SA-POA456
Opioid Use, Morbidity and Mortality in U.S. Kidney Transplant Patients
Paul L. Kimmel, Kevin C. Abbott, Chyng-Wen Fwu, Paul W. Eggers,1 DKUH, NIDDK, NIH, Bethesda, MD; 2Social & Scientific Systems, Silver Spring, MD.

Background: Pain is an important symptom for ESRD patients, linked to depression and diminished quality of life. Over the last 10 years, aggressive ESRD patient pain treatment has been advocated. The Medicare prescription drug benefit allows tracking ESRD prescriptions and linkage to outcomes. Few data exist on outcomes associated with pain and opioid medication prescription (OMP) in ESRD. The high prevalence of OMP and associated adverse events are increasingly evident. New Centers for Disease Control guidelines recommend caution in OMP. We assessed prevalence of OMP in kidney transplant patients, and associations between OMP and mortality and hospitalizations, with 2006–2010 USRDS data.

Methods: We limited our study sample to kidney transplant patients (≥365 d) with full Medicare Part A, B, and D coverage in each study year to ensure complete claim data. OMP was confirmed from Part D prescription claims. Cox proportional hazards regression models, controlled for demographic, ethnic, comorbidity and residence data examined associations of OMP in 2010 with subsequent all-cause death and hospitalization (2010 prevalent cohort; N=36,486).

Results: Approximately 14% of patients were prescribed 90+ opioids yearly. The most common OMPs in 2010 contained hydrocodone (6.4%) and oxycodone (3.8%). Patients with OMP for ≥90 d had increased death risk compared with those without (adjusted HR: 1.54 [95% CI, 1.38–1.71]). Short-term (≤1 d supply) and chronic OMP (≥90 d) also had increased hospitalization risk (1.20 [1.16–1.24] and 1.50 [1.44–1.57], respectively), compared with non-users. Rural transplant patients with OMP had higher mortality risk than their urban counterparts. Among individual opioids, hydrocodone, oxycodone, morphine, and hydromorphone were significantly associated with increased death risk.

Conclusions: Opioid drug prescription is associated with increased risk of death and hospitalization of ESRD transplant patients. While a causal relationship cannot be inferred, and opioid prescription may be an illness marker, efforts to treat pain effectively in ESRD transplant patients with less toxic interventions deserve consideration.

Funding: NIDDK Support
SA-PO459
Development of a Bioartificial Kidney Device
Dimitrios Stamatiadis, Natalia V. Chevtchik, Michele Fedecostante, Jitske Jansen, Milos Mihajlovic, Martijn J. Wilmer, Marieke Rueth, Rosalinde Masereeuw, ‘Biomaterials Science and Technology - MIRA Inst, Univ of Twente, Enschede, Netherlands; 2Pharmaceutical Sciences, Utrecht Inst for Pharmaceutical Sciences, Utrecht, Netherlands; 3Biomedical Engineering, Informatics, Radboud Inst for Molecular Life Sciences, Radboud Univ Medical Center, Nijmegen, Netherlands; ‘excelfor GmbH, Oberhagen, Germany.

Background: A key component of a bioartificial kidney device (BAK) is a “living membrane” consisting of a tight renal cell monolayer on an artificial porous membrane.

Results: The upscaling of the L-Dopa/CIV coating and seeding of the cPTECs on the membranes was successful. After one week of culture, reproducible cell monolayers were formed within modules containing 3 HFM and surface area of 4 cm². Tight monolayer cPTEC culture was achieved with limitedulin leakage when compared to modules without cells (301 ± 103 and 812 ± 2 pmol·min⁻¹·cm⁻² respectively, p<0.001, unpaired t-test). The ASP uptake by the cells was reduced by 60% in presence of uremic toxin mix or cimetidine, confirming the functional cell monolayer.

Conclusions: Upscaled HFM modules supporting a functional monolayer of renal cells were successfully developed. Future work will include detailed characterization of protein-bound uremic toxin transport. Acknowledgement. This work is funded by the EU Marie Curie ITN Project BIOART (grant no.316690 EU-FP7-PEOPLE-ITN-2012).

Funding: Government Support - Non-U.S.

SA-PO460
Mixed Matrix Membranes for Removal of Protein-Bound Toxins from Human Plasma
Dimitrios Stamatiadis, Denys Pavlenko, Karin G. Gerritsen, Esmeec Van Geffen, ‘Dept of Biomaterials Science and Technology/MIRA Inst, Univ of Twente, Enschede, Netherlands; 2Biomedical Engineering, Informatics, Radboud Inst for Molecular Life Sciences, Radboud Univ Medical Center, Nijmegen, Netherlands.

Methods: Protein-bound toxins (PBT) accumulate in uremic patients due to their poor removal by conventional hemodialysis. Their removal can be improved by a mixed matrix membrane (MOM), which combines adsorption and diffusion. In this work, we developed a low flux MOM and compared its performance to a conventional low-flux hollow fiber membrane (HFM). Here, we present the development of an upscaled BAK system with “living” HFM supporting the BAK closer to clinical implementation.

Results: MOMs were formed in modules and coated with L-Dopa and Collagen IV (CIV). The culture of cPTECs with organic cation (OCT) transporters was performed under static conditions. The cPTEC morphology and monolayer quality was investigated via expression of tight junction protein Zonula Occludens-1 (ZO-1), permeation of inulin-FITC, fluorescent OCT substrate 4-(4-(dimethylamino)styryl)-N-methylpyridinium iodide (ASP) and of organic cationic solutes.

Conclusions: The upscaling of the L-Dopa/CIV coating and seeding of the cPTECs on the membranes was successful. After one week of culture, reproducible cell monolayers were formed within modules containing 3 HFM and surface area of 4 cm². Tight monolayer cPTEC culture was achieved with limitedulin leakage when compared to modules without cells (301 ± 103 and 812 ± 2 pmol·min⁻¹·cm⁻² respectively, p<0.001, unpaired t-test). The ASP uptake by the cells was reduced by 60% in presence of uremic toxin mix or cimetidine, confirming the functional cell monolayer.

Acknowledgement. This work is funded by the EU Marie Curie ITN Project BIOART (grant no.316690 EU-FP7-PEOPLE-ITN-2012).

Funding: Government Support - Non-U.S.

SA-PO461
Perfused Glomerular Microvascular Unit: A Glomerular Pathophysiology Model
Claire Rigot, Killian Flegeta, Sebastien Rubin, Simon Mucha, Raphael Devillard, Jerome Kalisky, Christian Combe, Biotis, INSERM U0126, Univ de Bordeaux, Bordeaux, France; 2Service de Néphrologie, Transplantation et Dialyse, CHU de Bordeaux, Bordeaux, France.

Background: The development of an artificial glomerular unit may be pivotal for renal pathophysiology studies at a microscopic scale. Using a tissue engineering approach, the project will reproduce the glomerular architecture by performing a glomerular perfused microfluidic unit.

Methods: Human immortalized glomerular cell lines: podocytes and endothelial cells (EC) were used. Cells and 3-dimensional (3D) matrix have been characterized by immunofluorescence (IF) with confocal analysis and Western blot (WB). Optical microscopy was performed to study microfiber compaction and contraction. We also analyzed cell viability and cell metabolism within the 3D construct. Femtosecond laser was used to create the central lumen of microfibers.

Results: Using the microfiber method developed in the unit, we repeatedly obtained a cell culture in perfusion sort human glomerular cells in 3D. Around a central structure made of collagen I, we successively found the internal layer composed by EC, the neoformed glomerular basement membrane rich in collagen IV and the external layer of podocytes. Cell concentration, optimal seeding time and role of physical stresses were appreciated and maintained within the microfiber. Cell viability and cell phenotype were confirmed by IF and WB analysis: expression of specific proteins, vWF, PECAM and VEGFR2 for EC and nephrin, synaptopodin and podocin for podocytes. Cell characteristics were maintained after central lumen formation by femtosecond laser for planned microfiber perfusion.

Conclusions: In summary, with this microfiber technique, endothelial cells and podocytes were better differentiated than in culture dishes, and produced a differentiated GBM. Glomerular fluid stresses and glomerular pathophysiological conditions will be shortly simulated in the glomerular microfibers using the microperfusion method. A glomerular microvascular network will allow us to study cell interactions in a 3D system and increase our knowledge on the glomerular pathophysiology.

Funding: Private Foundation Support

SA-PO462
An Upscaled Bioartificial Kidney Device with an Apically Oriented Inflammatory Response upon LPS Exposure
Michele Fedecostante, Natalia V. Chevtchik, Milos Mihajlovic, Dimitrios Stamatiadis, Rosalinde Masereeuw, ‘Pharmacology, Utrecht Inst for Pharmaceutical Sciences, Netherlands; 2Biomaterials Science and Technology, MIRA Inst for Biomedical Technology and Technical Medicine, UTwente, Netherlands.

Background: The development of a bioartificial kidney (BAK) device for removal of protein-bound uremic toxins in plasma is needed to improve current therapy for end stage renal disease (ESRD) patients. Here, we investigate a monolayer for apical recognition of human conditionally immortalized proximal tubule epithelial cell (cPTEC) when cultured in an upscaled BAK device.

Methods: cPTEC were cultured for 10 days on the outer surface of 3 assembled double-coated (L-Dopa (2 mg ml⁻¹) and collagen IV (25 mg ml⁻¹)) Polyethersulfone hollow fiber membranes (HFM, 4 cm² surface area). Cell barrier integrity was investigated by immunostaining against inulin-FITC leakage. Immune response was assessed by ELISA measurements of IL-6 and IL-8 upon 24h lipopolysaccharide (LPS, 10 μg ml⁻¹) exposure.

Results: Tight monolayer of cPTECs was achieved on HFM-BAK devices as shown by immunostaining and low inulin leakage compared to double-coated control devices (24±68 vs 1575±128 pmol min⁻¹·cm⁻², p<0.001, seeded vs. unseeded devices, resp.). Exposure of BAK devices to LPS at the apical side resulted in pro-inflammatory cytokines release, which was more pronounced in the apical compartment (IL-6: 992±53 vs. untreated: 17±14; IL-8: 74±10 vs. untreated: 5.8±2.5 ng cm⁻²) compared to the basolateral compartment (IL-6: 1.7±1.4 vs. untreated: 2.0±1.2; IL-8: 1.0±0.5 vs. untreated: 0.4±0.2 ng cm⁻²). BAK devices exposed to LPS from the basolateral side, the cytokine response was 10.4±2.4 and 1±0.1-fold lower for IL-6 (p=0.05) and IL-8 as compared to apically exposed devices, respectively. This was also confirmed by immunostaining of Tiel-like receptor 4 at the apical surface.

Conclusions: This study demonstrates an upscaled BAK device of renal epithelial cells on HFM with tight monolayer formation, good barrier function and polarized inflammatory response upon LPS exposure. Funding. EU Marie Curie ITN Project BIOART (grant no.316690 EU-FP7-PEOPLE-ITN-2012).

Funding: Government Support - Non-U.S.

SA-PO463
Genome Engineering of Renal Epithelial Cells with the Goal of Improved Function in an Implantable Artificial Kidney
Matthew H. Wilson, Wentian Luo, Rick C. Welch, Shuvo Roy, William Henry Fissell, ‘Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; ‘Nephrology, VA Medical Center, Nashville, TN; ‘Bioengineering and Therapeutic Sciences, Univ of California San Francisco, San Francisco, CA.

Background: Development of an implantable artificial kidney (IAK) will require renal epithelial cells capable of reabsorption of salt and water. We are using genome engineering to bioengineer cells for improved Na⁺/H⁺ exchange and H2O reabsorption. The piggyBac transposon system offers a simple but highly efficient non-viral strategy for genome engineering cells to stably overexpress one or more transgenes simultaneously. The piggyBac transposase enzyme integrates transposase DNA containing one or more transgenes into the genomic DNA of cells via a cut-and-paste mechanism.

Methods: Standard molecular biology techniques were used to subclone the human sodium hydrogen exchanger 3 (NHE3) and aquaporin-1 (AQP1) cDNAs into piggyBac transposon vectors. The NHE3 fiber was expressed with a C-terminal hemagglutinin (HA) epitope tag. The AQP1 transgene contained flag and myc epitope tags. The transgenes into the genomic DNA of cells via a cut-and-paste mechanism.

Results: Using the microfiber method developed in the unit, we repeatedly obtained a cell culture in perfusion sort human glomerular cells in 3D. Around a central structure made of collagen I, we successively found the internal layer composed by EC, the neoformed glomerular basement membrane rich in collagen IV and the external layer of podocytes. Cell concentration, optimal seeding time and role of physical stresses were appreciated and maintained within the microfiber. Cell viability and cell phenotype were confirmed by IF and WB analysis: expression of specific proteins, vWF, PECAM and VEGFR2 for EC and nephrin, synaptopodin and podocin for podocytes. Cell characteristics were maintained after central lumen formation by femtosecond laser for planned microfiber perfusion.

Conclusions: In summary, with this microfiber technique, endothelial cells and podocytes were better differentiated than in culture dishes, and produced a differentiated GBM. Glomerular fluid stresses and glomerular pathophysiological conditions will be shortly simulated in the glomerular microfibers using the microperfusion method. A glomerular microvascular network will allow us to study cell interactions in a 3D system and increase our knowledge on the glomerular pathophysiology.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: We are currently also overexpressing NHE3 and AQP1 in cultured human renal proximal tubular epithelial (RPTEC) cells. The advantage of this work is to determine if incubation of renal tubular cells with sugars ex vivo alters the mechanical properties of TBM. 

Methods: Tubules were manually dissected from the outer cortex of normal mouse kidneys. Tubules were incubated ex vivo in 100 mM glucose, 100 mM ribose, or PBS for 24 hours. Stress-strain response of individual tubules was evaluated using a microcantilever-based tensile testing method. The stiffness (elastic modulus) of the tubular basement membrane was evaluated at strain ranges of 0-10%, 10-20%, and 20-30% strain by determining the slope of the linear regression of the strain-strain curves over those strain ranges.

Results: Glucose and ribose incubation resulted in a statistically significant (p < 0.05) increase in the TBM stiffness over all strain ranges that were tested. Glucose incubated tubules had stiffness of 767±96 kPa, 124±135 kPa, and 204±200 kPa at strain ranges of 0-10%, 10-20%, and 20-30%, respectively. Ribose incubated tubules had stiffness of 1116±175 kPa, 2773±375 kPa, and 4342±413 kPa over the same strain ranges. This is a 2.2-2.6 fold increase in stiffness for glucose incubated tubules and a 3.8-5.2 fold increase in ribose incubated tubules compared to controls.

Conclusions: These data show that incubation of tubules with sugars is alone sufficient to alter TBM stiffness over a relatively short period of time. Both glucose and ribose increased TBM stiffness. Due to its higher reactivity, ribose had a more pronounced impact on TBM stiffness. These data suggest sugars may alter the biomechanical properties of kidney extracellular matrix. These changes may play a role in disease progression in diabetic nephropathy. 

Funding: NIDDK Support

SA-PO467

Evaluation of Renal Cells for In Vitro Modeling of Proximal Tubule Drug Transport


Background: Active transport by renal proximal tubules plays a significant role in human drug disposition and is therefore important to model when developing drugs. Although several proximal tubule cell lines exist, limited data are available regarding their ability to act as acceptable models of the tubule. Here, several cell lines are compared with respect to monolayer formation, drug transporter expression and function, and cilia function.

Methods: HRTCs were transduced using two lentiviral vectors that carried plasmids for luciferase and qRT-PCR. Transporter function was measured by quantifying cellular uptake and transport of substrates (+/- inhibitor). Cells were deciliated with 30 mM ammonium sulfate.

Results: All cells formed tight junctions as demonstrated by ZO-1 expression, but showed varying levels of monolayer tightness with MDCKCs at ~1%, HPTCs at ~7%, and RPTECs at ~10% monolayer leak. Both human cell types tested had comparable mRNA expression levels of OCT2, MATE1, OAT3 and MRP4 (~ACT of 14-15, 12-13, 15 and 5-9, respectively), while double transduced MDCK cells had high expression levels of OCT2 and MATE1 (~ACT of 2-4 respectively). Both MDCK and HPTC cell types displayed invariable uptake and transport of asp+ and Metiformin. Lastly, both MDCK and HPTC cells grew cilia that could be removed without effects on tight junction formation, RNA expression and function of transporters and cilia.

Conclusions: While overexpressing MDCK cells exhibit the best performance, both human proximal tubule cell lines show promise as potential models of human tubular function. Studies are ongoing to incorporate these cells into an engineered device to mimic renal drug elimination.

Funding: NIDDK Support

SA-PO468

Kidney-Specific Gene Transfer by Hydrodynamic Renal Pelvis Injection

Lauren Elizabeth Woodard, Jinzhong Cheng, Rick C. Welch, Kyle M. Williams, Wenti Lu, Matthew H. Wilson. 1Dept of Medicine, Div of Nephrology, Vanderbilt Univ Medical Center/Veterans Affairs, Nashville, TN; 2Dept of Medicine, Div of Nephrology, Vanderbilt Univ Medical Center/Veterans Affairs, Nashville, TN.

Background: New breakthroughs in the treatment of kidney disease are desperately needed to address the increasing shortage of organs available for transplantation and high mortality associated with dialysis. The first commercial gene therapy products have recently become available. Gene transfer to the mouse kidney is desirable both in terms of providing proof-of-concept for gene transfer to address genetic diseases and for the creation of new disease models.

Methods: We found that a fast injection into the renal pelvis with a DNA solution of sufficient volume was effective for delivery of plasmid DNA to the adult mouse kidney, with greater than 95% of the transgene-expressing cells having an organ expression pattern similar to transgene expression pattern in the mouse. We used the piggyBac transposon system to permanently integrate the luciferase transgene and found that the EF1alpha promoter provided superior long-term gene expression.

Results: Staining for TdTomato revealed expression in a variety of cell types, including proximal tubule epithelial cells. We performed renal pelvis hydrodynamic injections on mice that had undergone a unilateral nephrectomy. We found mice receiving injections had a significantly increased BUN as compared to sham controls at two days following surgery that resolved completely within 7 days.

Conclusions: While overexpressing MDCK cells exhibit the best performance, both human proximal tubule cell lines show promise as potential models of human tubular function. Studies are ongoing to incorporate these cells into an engineered device to mimic renal drug elimination.

Funding: NIDDK Support

SA-PO466

Sugars After the Mechanical Properties of Renal Tubular Basement Membrane

Nicholas J. Ferrell. Div of Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.

Background: Diabetic nephropathy is characterized by loss of extracellular matrix (ECM) homeostasis in the kidney that results in the stiffening of the tubular basement membrane (TBM). In addition, hyperglycemia alters the biochemical structure of the ECM through formation of advanced glycation end-products that can crosslink the ECM and may alter the mechanical properties of the TBM. The mechanical properties of ECM play an important role in maintaining tissue function, and altered biophysical properties may affect disease progression. Cell lines with enhanced renal epithelial cell type for maximal function in the IAK.

Funding: Other NIH Support - NIBIB

SA-PO464

Transport by Renal Tubule Cell Bioreactor Is Dependent on Extracellular Matrix Choice


Background: Renal tubule cell bioreactors are of interest for in vitro disease models, high-throughput drug and toxicity testing, and renal replacement therapy. The parameter space to be exploited in optimizing in vitro cell phenotype is extensive. There are several commercially available extracellular matrix preparations available to facilitate cell-scaffold attachment, leading to the question of whether any one matrix was associated with particular phenotypic features.

Methods: Primary human renal tubule cells (HRTCs) were grown to confluence on Transwell inserts preincubated with Collagen IV, Collagen I, Laminn, Matrigel, or fibronectin, with and without 10 μM acetic acid. TEER and inulin leak rates were measured to verify confluence. Apicobasal volume transport was measured in the presence of ouabain, an inhibitor of basolateral sodium-potassium ATPase.

Results: HRTCs grew to confluence on all substrates. Inulin leak rates were not different from a control well bearing an impermeable substrate. Transport rates were different in the presence and absence of ouabain (p = 5.6 x10^-5 by t test). Transport rates differed between matrices (p=0.006 by one-way ANOVA). Fibronectin and laminin displayed highest volume transport. When cells were cultured in the presence of acetic acid, transport was not significantly different between substrates ( p > 0.08 by one-way ANOVA).

Conclusions: Choice of extracellular matrix substrates influences apicobasal transport in bioreactors, but adding cofactors for basement membrane synthesis to the culture medium abolishes differences arising from initial matrix choice.

Funding: Other NIH Support - NIBIB, Private Foundation Support

SA-PO465

Respiratory Capacities and Differentiation of Novel Gluconeogenic Renal Cell Lines


Background: The renal proximal tubule relies on oxidative phosphorylation to carry out metabolically intensive transport. Cultured primary cells rapidly switch to a less differentiated glycolytic phenotype characteristic of most immortalized renal cell lines. Glucose starvation of non-gluconeogenic cell lines can induce and select for cells that have switched on gluconeogenesis as a survival mechanism, as glucose is essential for the production of ribose-5-phosphate, a precursor for nucleic acid biosynthesis. The selective pressure of glucose starvation not only induces gluconeogenesis, but the cells also exhibit other unique features that are characteristic of renal proximal tubular epithelial cells.

Methods: LLC-PK1 cells were adapted to serum-free media and starved of glucose after the method of Grauenthaler and Handler. Gluconeogenic cell colonies were isolated and expanded. The glucose-free medium. Initial characterization of the mitochondrial oxidative capacity and glycolysis was carried out using a 96-well high-throughput Seahorse Bioscience assay.

Results: Numerous colonies of cells growing in glucose-free medium appeared after 3-4 weeks, and were sub-cloned and expanded. The phenotypic appearance of the colonies was quite variable, with many showing a pronounced differentiation compared to the parental cells. Cells typically formed compact, very dense monolayers, with extensive dome formation, even in very small colonies. Cell proliferation was observed primarily in peripheral cells, while contact inhibited cells rapidly differentiated. Initial characterization of cell lines found significant differences in oxygen consumption rates and glycolysis, compared to parental control cells, with and without glucose.

Conclusions: Gluconeogenic cell lines were induced from LLC-PK1 cells by culturing in glucose-free media. Glucose starvation of LLC-PK1 cells had a marked inhibition on basal and stimulated oxygen consumption with reduced glycolysis, compared to parental cells. Preliminary results suggest that cell lines with enhanced renal function in vitro can be obtained via forced gluconeogenesis.

Funding: Other NIH Support - NIBIB, Private Foundation Support

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but the distribution was equivalent. Dose dependent expression was observed between pericytes, however. Recombinant adeno-associated virus (AAV) is non-integrating and

increase signal. At 10^11 genome copies/mouse, we measured transduction of 17.6±12.4% some cells, we used injected Cre recombinase AAV into R26TdTomato reporter mice to
cells and to SLC12A1+ macula densa epithelial cells. Since GFP expression was low in
dose, AAV2/8-labeled pericytes differentiated intoαSMA+ myofibroblasts after UUO, and

were assessed via transepithelial electrical resistance (TEER), cell viability assay, and

and HPTCs) were grown to confluence on SNM with 7-nm wide slit pores. Transwell

implanted hemofiltration. In this study, we investigated SNM competence for the

dimensions have exhibited superior mass transfer and molecular selectivity characteristics

immunosuppressants. Silicon nanopore membranes (SNM) with precisely engineered pore

requirement for an implantable bioartificial kidney that will circumvent the need for

organ scaffolds for transplantation. A major

Bioengineering, Informatics

two weeks. To test the effect of the immune response on long-term gene expression, we treated mice with cyclophosphamide and observed increased levels of luciferase expression
compared to sham controls.  

Conclusions: Hydrodynamic renal pelvis injection of naked DNA produced transgene expression in many cell types. Higher levels of long-term expression were achieved with transposons for permanent integration and cyclophosphamide for immunosuppression. We are currently testing hydrodynamic renal pelvis injection of biologically relevant transgenes for treatment of cystinuria, acute kidney injury, and anemia. 

Funding: NIDDK Support, VA Support, Private Foundation Support

SA-PO469

Targeting Kidney Pericytes with Adeno-Associated Virus: A Novel Method for Gene Therapy Yoichiro Ikeda,1 Xiao Ru,2 Luk Vandenberghe,2 Benjamin D. Humphreys.1 1Div of Nephrology, Washington Univ in St. Louis, St. Louis, MO; 2Schepens Eye Research Inst, Boston, MA.

Background: Kidney pericytes are the major myofibroblast progenitor population and an important therapeutic target. There is no method to deliver genetic material to kidney pericytes, however. Recombinant adeno-associated virus (AAV) is non-integrating and

expression was maximal

between 2-8 genome copies/mouse without toxicity. Expression was maximal

with increased steady-state elastic modulus of decellularized kidney scaffold sections ~4× compared to uncrosslinked sections. We now report day 1 to 8 culture results, showing fibrolast proliferation was greater on crosslinked scaffolds.

Results: Crosslinking with EDC increased tissue stiffness as we previously described, with increased steady-state elastic modulus of decellularized kidney scaffold sections ~4× compared to uncrosslinked sections. We now report day 1 to 8 culture results, showing fibrolast proliferation was greater on crosslinked scaffolds.

Conclusions: Growth of human lung fibroblasts is enhanced by EDC crosslinking, supporting our hypothesis that stiffness perfusion-decellularized organ scaffolds enhance the proliferation of anchor-dependent cells.

SA-PO472

Visualizing and Quantifying the Luminescent Kidney in 3D Neal A. Paragas,1 Alexander Klose.2 1Medicine, Univ of Washington, Seattle, WA; 2In Vivo Analytics, Inc, New York, NY.

Background: We have developed a platform system to monitor and quantify luminescence with the multispectral bioluminescence tomography (BLT) co-registered to a novel digital mouse atlas. Permitting for the first time quantification of a luminescent signal in a cell specific manner. This will allow us to non-invasively uncover the changes occurring temporally and spatially to tubular and epithelial cells of the kidney.

Methods: We modeled different compartments of the kidney by creating a Podocin, Slc34a1, and HoxB7 luciferase reporter animals. First, we acquired bioluminescence images with a bioluminescent optical imager at six different spectral windows centered at 580, 600, 620, 640, 660, and 680 nm and with bandwidth of 20 nm. The multi-orientation images were acquired using a mirror gantry for simultaneous imaging of the dorsal, ventral and side views. The animal was placed in a fixed position into a novel body shape conforming animal mold, placed onto the mirror gantry and spectral images were acquired. The light intensity imaging data became input to a novel BLT reconstruction algorithm based on an expectation maximization (EM) method and the simplified spherical harmonics (SP3) equations for modeling in vivo light propagation. Post reconstruction, we calculated the total photon emission density of a volume of interest (VOI). We then calculated cell specific luciferase expression co-registering it to a novel digital mouse atlas.

Results: Our new system using the EM method reconstructed the 3D photon emission of Podocin, Slc34a1 and HoxB7-luciferase expressing animals and mapped the signal to a novel organ probability map. For the first time, we could demonstrate the feasibility of quantifying organ number non-invasively in the kidney.

Conclusions: The ability to do non-invasive tomographic reconstruction of the kidney using bioluminescence will be a powerful tool to monitor segmental changes after renal injury.

Funding: NIDDK Support

SA-PO473

Isolation and Transcriptomic Analysis of Distinct Cell Populations from Mouse Renal Collecting Duct Lihe Chen,1 Jae Wook Lee,2 Chung-Lin Chou,1 Susan M. Wall,1 Dennis Brown,2 Mark A. Knepper.1 1National Heart and Lung Inst; 2National Cancer Center, Korea; 'Emory Univ School of Medicine; 'Massachusetts General Hospital; 'National Heart Lung and Blood Inst.

Background: The renal collecting duct contains both principal cells (PCs) and intercalated cells (ICs). To better understand these cells, a reliable, high-yield isolation technique and systematic transcriptomic profiling are needed. To identify cell surface markers for PCs, we previously used transgenic mice that express GFP-driven by the

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Markers that are associated with the advancement of interstitial fibrosis. In addition, we obtained from FT-IR imaging.

Results: The average transcriptome depth was 11500 genes for DBA cells (FFPKM>1, n=2) and 11200 genes for c-kit cells (FFPKM>1, n=2). Based on mean c-kit/DBA FPKM ratio, we clustered the transformed cells into several known IC markers, viz. Slek1, Cx3cl1, Aqp2, Gpr1, Atp6v1b2, Icam1, and Icam5, which have less well defined roles in ICs.

Conclusions: The perlating results confirmed that this flow-sorting method can isolate distinct cell populations that are enriched in PCs and ICs. The idenfication of additional IC and PC specific genes points to additional molecular functions of the two cell types.

Funding: Other NIH Support - NIDDK

SA-PO474
Identification of Biomarkers Associated with Progressive Fibrosis in Renal Transplant Patients Using High-Definition Fourier-Transform Infrared Imaging
Vishal K. Varma, Sanjeev Akkina, Suman Setty, Michael J. Walsh.
1Dept of Pathology, Univ of Illinois at Chicago, Chicago, IL; 2Dept of Nephrology, Loyola Univ Chicago Health Sciences, Chicago, IL.

Background: Renal allografts are often lost due to progressive accumulation of chronic lesions as a consequence of rejection and infection. Close monitoring of graft dysfunction by surveillance biopsies to detect subclinical complications and apply corrective measure may prolong the life of the graft. Here we identify biochemical markers associated with progression of interstitial fibrosis in renal transplant biopsy using label free chemical imaging technique, Fourier-transform infrared (FT-IR) imaging.

Methods: A pilot study focused on identifying 5 patients with no progression of interstitial fibrosis (non-progressors) and 3 patients with an increase in interstitial fibrosis over time (rapid progressors). Serial sections were acquired and stained with Masson trichrome stain and imaged using chemical imaging. An early (3-4 months) and a late (6-24 months) time point protocol biopsy for each patient was analyzed and the difference between the rapid progressors and non-progressors groups were analyzed using the chemical information extracted from areas of fibrosis. Clinical data and other relevant information was used to further increase our understanding of the biochemical signature obtained from FT-IR imaging.

Results: Multivariable analysis of the collected chemical data allows us to use early biopsies to segregate between rapid progressors vs non-progressors. The biochemical signatures between the early biopsies from the rapid progressors and non progressors cohorts were distinct suggesting different underling biochemical reactions in the two groups. In addition, these changes were noted in late biopsies as well.

Conclusions: The data shows promise as we have identified a number of biochemical markers that are associated with the advancement of interstitial fibrosis. In addition, we have highlighted a biochemical-signature that may be predictive of the later interstitial fibrosis, using baseline biopsies. Additional cases should allow us to validate these preliminary findings.

Funding: NIDDK Support

SA-PO475
Differential Urinary Proteome Analysis of IgA Nephropathy Using 2D-LC-MS/MS and iTRAQ Quantification
Ying Sun, Li Siqian, Xuemei Li, Mingxi Li. Nephrology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China.

Background: IgA nephropathy is a common primary glomerulonephritis, more accurate and non-invasive tests for its diagnosis and evaluation are urgently needed. Urinary proteome analysis has been applied to discovering biomarkers for kidney diseases. The aim of this study is to investigate the differential urinary proteome in various stages of IgA nephropathy.

Methods: Eighteen IgA nephropathy patients diagnosed by renal biopsy were recruited. A total of 622 proteins were identified, 108 were found to be up or down regulated in a consistent trend from IgA I to IgA III. 13 of these 108 proteins were highly regulated in microalbuminuria group (n=2) and 11200 genes for c-kit cells (FFPKM>1, n=2). Six patients with membranous nephropathy were included as control (eGFR 90~120ml/min, n=6). The proteins involved in lipid metabolism, APRS, and complement activation significantly increased in the urine of DN patients along the disease progression, as well as proteins related to O-glycosylation defects may involve in the development and progression of IgA nephropathy, and could be potential biomarkers of IgA nephropathy.

Funding: Other NIH Support - NIDDK

SA-PO476
Bioinformatic Analysis of Differential Urinary Glycoproteome of Type 2 Diabetic Nephropathy
Zixuan Zhu, Ying Sun, Xuemei Li, Mingxi Li. Dept of Nephrology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China.

Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease.

Methods: We used DBA and an antibody to c-kit to isolate two populations of cells from mouse renal cell suspensions using FACS. The cell populations were characterized by RNA sequencing (RNA-Seq) using an Illumina HiSeq2500 platform.

Results: The average transcriptome depth was 11500 genes for DBA cells (FFPKM>1, n=2) and 11200 genes for c-kit cells (FFPKM>1, n=2). Based on mean c-kit/DBA FPKM ratio, we clustered the transformed cells into several known IC markers, viz. Slek1, Cx3cl1, Aqp2, Gpr1, Atp6v1b2, Icam1, and Icam5, which have less well defined roles in ICs.

Conclusions: The perlating results confirmed that this flow-sorting method can isolate distinct cell populations that are enriched in PCs and ICs. The idenfication of additional IC and PC specific genes points to additional molecular functions of the two cell types.

Funding: Other NIH Support - NIDDK

SA-PO477
Immunomodulatory Therapy (Rx) Demonstrates Sustained Improvement in Myocardial Contractility in a Canine Model of Chronic Heart Failure (CHF)
H. David Humes, D. Buffington, A. Westover. 1Internal Medicine, Univ of Michigan Medical School, Ann Arbor, MI; 2Innovative BioTherapies, Ann Arbor, MI.

Background: Cardiorenal syndrome (CRS), the most severe subset of CHF patients, is characterized by diuretic resistance in a volume overload. Current therapy is limited and new innovative approaches are needed. CHF is characterized by a proinflammatory state. Monocytes and tissue macrophages are sources of systemic inflammation in CHF and cause a decrease in cardiac contractility. Systemic MO levels correlate with poor outcome. A novel leukocyte (LE) immunomodulating device (SCD), when placed in an extracorporeal circuit with regional citrate anticoagulation has been shown to be effective in acute renoheart failure. The biomimetic membrane device (BMD) is based on the same LE processing premise as the SCD.

Methods: Impact of BMDRx was evaluated in a CHF dog model; 2 groups were evaluated: BMD treated (BT) and untreated control (UC), n=4-5 per group. Dogs were administered either 1-3 BMDRx treatments over a week period, with study termination immediately (Ti) postBMDRx session (n=2-3) or 4 weeks (T4) postRx session (n=2).

Results: Data demonstrated left ventricle (LV) ejection fraction (EF) increased substantially in the BT group from 33.6±1.3 (n=5) to 43.3±2.5 (n=5; 6-48hrs postRx) and 37.0±0.9% (n=2; 4wks postRx) respective of 28.9 and 10.2% increase, respectively. The UC group (n=4) EFs did not change. This effect was not due to a decline in systemic vascular resistance which was similar in both groups. Ventriculograms demonstrated BMDRx to convert viable but non-contracting myocardium to contracting myocardium. The renal effects were also substantive. In the Ti dogs, fractional excretion (FE) Na nearly doubled in the BT group vs. UC group, increasing from 2.2±0.8 to 5.3±0.8. FenaRx went from 59.3±1.0 to 81.1±1.3. T4 dog FE results are not shown. No adverse events of arrhythmia or hypotension were observed during BMDRx.

Funding: Other NIH Support - NIDDK

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Background: Novel renal replacement treatments, such as a bioartificial kidney (BAK), are needed to improve current hemodialysis. When developing a BAK, availability of functional cells and their safety are frequently encountered problems. Here, we evaluated the allomimunization of readily available conditionally immortalized human proximal tubule epithelial cells (ciPTEC) for use in BAK.

Methods: Two ciPTEC lines (urine derived ciPTEC-U, tissue derived ciPTEC-T) were characterized by flow cytometry for HLA-class I expression by cytokine production. Cytokine production was induced by LPS (IL-6: 3.2±0.2 fold, IL-8: 1.3±0.4 fold, p< 0.05). Finally, ciPTEC were not able to induce PBMC proliferation after 5 days of co-culture, compared to positive controls (aCD3/aCD28 dynabeads; 77±8% dividing cells, p<0.001, n=4) and indoxyl sulfate (IL-6: 1.7±0.2 fold; IL-8: 1.3±0.4 fold, p< 0.05). Finally, ciPTEC might have an accessory role in inflammatory responses as shown by cytokine production, the cells are not immunogenic and, therefore, represent a safe choice for BAK application. Acknowledgement: This work is funded by the EU Marie Curie ITN Project BIOART (grant no. 31669 EU-FP7-PEOPLE-ITN-2012). Funding: Government Support - Non-U.S. Government Support

SA-PO478
Lack of Allostimulatory Potential of Conditionally Immortalized Proximal Tubule Epithelial Cells for Bioartificial Kidney Application

Background: Novel renal replacement treatments, such as a bioartificial kidney (BAK), are needed to improve current hemodialysis. When developing a BAK, availability of functional cells and their safety are frequently encountered problems. Here, we evaluated the allomimunization of readily available conditionally immortalized human proximal tubule epithelial cells (ciPTEC) for use in BAK.

Methods: Two ciPTEC lines (urine derived ciPTEC-U, tissue derived ciPTEC-T) were characterized by flow cytometry for HLA-class I expression by cytokine production. Cytokine production was induced by LPS (IL-6: 3.2±0.2 fold, IL-8: 1.3±0.4 fold, p< 0.05). Finally, ciPTEC were not able to induce PBMC proliferation after 5 days of co-culture, compared to positive controls (aCD3/aCD28 dynabeads; 77±8% dividing cells, p<0.001, n=4) and indoxyl sulfate (IL-6: 1.7±0.2 fold; IL-8: 1.3±0.4 fold, p< 0.05). Finally, ciPTEC might have an accessory role in inflammatory responses as shown by cytokine production, the cells are not immunogenic and, therefore, represent a safe choice for BAK application. Acknowledgement: This work is funded by the EU Marie Curie ITN Project BIOART (grant no. 31669 EU-FP7-PEOPLE-ITN-2012). Funding: Government Support - Non-U.S. Government Support

SA-PO479
Neointima Formation in Hemodialysis Grafts: A Role for Abnormal Vein Wall Dynamics?

Background: Neointimal hyperplasia (NIH) is a major cause of vascular graft failure. NIH is characterized by an increase in the thickness of the intima and media, which can lead to stenosis and occlusion of the graft. The development of NIH is thought to be influenced by several factors, including shear stress, inflammation, and smooth muscle cell proliferation. In this study, we investigated the role of abnormal vein wall dynamics in the development of NIH in hemodialysis grafts.

Methods: We used a mathematical model to simulate blood flow in the vein and artery of a hemodialysis graft. The model incorporated a detailed geometry of the graft and realistic boundary conditions. We varied the flow rate and vessel geometry to investigate the effects of different flow patterns on NIH.

Results: We found that abnormal vein wall dynamics, such as uneven wall thickness and increased wall stiffness, significantly increased the risk of NIH. These findings are consistent with clinical observations, which show that hemodialysis grafts with abnormal wall dynamics have a higher risk of failure.

Conclusions: Our findings suggest that abnormal vein wall dynamics may play a significant role in the development of NIH in hemodialysis grafts. These results have important implications for the design and maintenance of hemodialysis grafts to prevent NIH and improve graft survival.

Funding: NIH NIDDK Support

SA-PO480
AFE System Provides Improved Hemodynamic Conditions for Vein Maturation Compared to Conventional AVF

Methods: Using fluid-structure interaction (FSI)-computational fluid dynamics (CFD), we studied blood flow and wall shear stress (WSS) in a simple model of an AFE System and a conventional AVF. The AFE System was designed to provide a controlled dose of WSS to a vein segment, while the conventional AVF was designed to deliver natural blood flow.

Results: The AFE System provided significantly higher WSS at the vein wall compared to the conventional AVF. The WSS at the vein wall was higher in the AFE System than in the conventional AVF, which suggests that the AFE System may be more effective in promoting vein maturation.

Conclusions: The AFE System provides improved hemodynamic conditions for vein maturation compared to conventional AVF. These findings have important implications for the design of renal replacement therapies, particularly for bioartificial kidneys.

Funding: NIDDK Support

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

Underline represents presenting author.
SA-PO481
Loop Mediated Amplification Assay versus Culture for Detection of Escherichia coli in Urine: A Single Center Pilot Study Vinu Kumar Kartiagada,1 Aravindan Arumugam,2 Jennifer Sheyman,3 Christopher J. Webster,3 Kalathil K. Suresh Kumar,2 Richard J. Marcus,4 Abhay N. Vats,5 Michangelo Di Giuseppe,6 Swati Arora,7 1Dept of Medicine- Nephrology, Allegheny General Hospital, Pittsburgh, PA; 2Univ of Pittsburgh, Pittsburgh, PA; 3Atharwa LLC Molecular Diagnostics, Cranberry, PA.

Background: Urinary tract infection (UTI) is a common cause of morbidity in the adult population. Urine cultures could take up to 5 days, thereby, exposing patients to unnecessary broad spectrum antibiotics. Over 80% of outpatient UTIs and 50% of inpatient UTIs are caused by Escherichia coli. Newer assays, such as, loop-mediated amplification (LAMP) assay for detection of E.coli can provide results within 60 minutes. This can potentially be used for point of care (POC) testing in the ambulatory and hospital settings.

Methods: A prospective study was done comparing E.coli LAMP assay and urine culture to detect UTI. LAMP assay was conducted on urine samples using a thermal cycler with incubation for 60 minutes with E.coli DNA primers. E.coli LAMP products were detected using Sybr green dye under UV illumination.

Results: Mean age was 58 years and 73% were females. About 50% of the samples were from outpatient setting, 27% from inpatient and source was not recorded in the remainder. Out of 393 samples, 43 urine cultures were positive for E.coli. Comparison with LAMP assay is shown in the table. Lastly, LAMP assay is designed for one specific organism only. More prospective studies are needed to evaluate utility of LAMP in clinical practice.

<table>
<thead>
<tr>
<th>Comparison standard</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMP vs. E.coli culture</td>
<td>91</td>
<td>24</td>
<td>0.73</td>
<td>0.54</td>
<td>0.001</td>
</tr>
<tr>
<td>LAMP vs. E.coli culture &lt;100,000 cfu/ml</td>
<td>93</td>
<td>21</td>
<td>0.73</td>
<td>0.58</td>
<td>0.001</td>
</tr>
<tr>
<td>LAMP vs. E.coli culture &lt;100,000 cfu/ml</td>
<td>97</td>
<td>3</td>
<td>0.70</td>
<td>0.36</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Conclusions: LAMP assay displayed good sensitivity and could be used as a screening tool to rule out UTI as a POC test. It is not specific and does not provide quantitative information or antibiotic sensitivities to guide management. LAMP assay would pick up even less than 10 copies of E.coli as a “positive” test which is clinically insignificant.

SA-PO483
Remote Monitoring of Patients on Automated Peritoneal Dialysis Saves Healthcare Resources in a Simulation Study Suzanne Laplante,1 Kimberly McLeod,2 Judy A. Danek,1 Timothy L. Kudelka,1 James A. Sloan,1 Mary Gellens,3 Leslie P. Wong,2 1Baxter Healthcare Corporation, Deerfield, IL; 2Xenda, Palm Harbour, FL; 3Cleveland Clinic, Cleveland, OH.

Background: Remote monitoring is useful in chronic diseases, but evidence is scarce in home dialysis. A two-way data exchange platform with remote monitoring capabilities may enable earlier intervention and healthcare savings. This study estimates the nature and importance of the savings in USA.

Methods: Twelve (12) automated peritoneal dialysis (APD) patient profiles (therapy non-adherence, fluid overload, low drain/ unidentified alarms, missing/factitious data entry) were used to simulate healthcare resource usage with remote monitoring information (treatment data, blood pressure, weight) and without. Four US nephrologists (expert in managing APD patients) evaluated the “without remote monitoring” resources. The “with remote monitoring” resources were estimated by 7 APD teams (1 nephrologist, 1 nurse). A Monte-Carlo simulation (1,000 iterations) was run on resources avoided (resources “without remote monitoring” minus those with). US public reimbursement rates or medical literature were used for costing (3 perspectives: public healthcare payer, direct provider costs, provider opportunity costs).

Results: The Monte-Carlo simulation estimated that in these 12 patient profiles (average follow-up: 25 days; range: 7-60 days), remote monitoring could avoid $5,010.5 emergency room visits; 2.0±0.2 hospitalizations; 2.2±0.3 changes to hemodialysis for potential savings of $22,862±$81,384 to the public healthcare payer. Providers could avoid 0.8±0.3 repeat adequacy tests resulting in $19.5±6 direct savings while their opportunity costs resulting mainly from avoidance of 6.7±2.5 unplanned clinic visits and 64±15 unplanned clinic calls would total $1,249±$237. The 12 profiles were estimated to be representative of 17.3-37% of the US APD patient population.

Conclusions: In a simulation, remote monitoring saved healthcare resources in APD patients with treatment non-adherence, fluid overload, volume depletion, low drain/ unidentified alarms, or missing/factitious data entry by enabling earlier medical intervention, avoiding complications and treatment drop-out.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

SA-PO484
Mathematical Modeling Approach to IV Iron Dosing in Hemodialysis Patients Adam E. Gajewski,1 Yelena Z. Ginzburg,1 Yossi Chait,2 John Paul Middleton,3 Michael J. Germain,1 Michael E. Brier,1 1Univ of Louisville; 2UMass Amherst; 3New England Medical Center; 4Duke Univ; 5Renal and Transplant Associates of New England.

Background: Coordinated dosing of Erythropoiesis Stimulating Agents (ESA) and Intravenous (IV) Iron is essential in anemia management of End Stage Renal Disease (ESRD). To aid physicians in this task we are developing a systems biology approach to modeling erythroid- and ferrokinetic marker behavior. Here, we present a mathematical model of Ferritin (ferr) response to IV Iron and ESA.

Methods: A cohort of 23 hemodialysis patients was prospectively followed for 12 months at three dialysis centers in the United States. Data collected included weekly ferr concentration, ESA (EpoGen), and IV Iron (Venofer) dose. We developed patient-specific models of comprising three parameters: 1) ferr sensitivity to iron dose, 2) ferr sensitivity to ESA, and 3) time constant, representing the time to reach 60% of steady state ferr response. We used a nonlinear least squares estimation to maximize the fit between model prediction and data.

Results: IV Iron doses greater than 100 mg/week result in a rapid increase of ferr. ESA dose increases in absence of IV Iron dose result in a decrease of ferr. We obtained the following model parameters: 1) ferr sensitivity to IV iron (median [min-max]): 42 [6.6, 135.2] ng/mL per 100 mg/week, 2) ferr sensitivity to ESA: <36 [1-166.7, -3.2] ng/mL per 1,000 IU/week, 3) time constant: 5.4 [1.2, 16] weeks. The figure below shows an example of model prediction for a selected study subject.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Presented model reliably captures ferr response to IV iron and ESA. The estimated model parameters are consistent with the physiology of erythropoiesis. Next steps involve addition of other ferrokinetic markers such as hepcidin and soluble transferrin receptor 1, and a validation of the model in a larger cohort of subjects.

**Funding:** NIDDK Support

**SA-PO485**

**Discrete Event Model of Fluid Overload Complications in Hemodialysis**

**Victor Andreescu,1 Anca I. Stefan,1 Michelle M.Y. Wong,2 Jarcy Zec,1 Robert Merion,1 John Hartman,2 Bruce M. Robinson,1 1Arbor Research Collaborative for Health, Ann Arbor, MI; 2Visone Data Management, LLC, Green Bay, WI.

**Background:** Fluid overload is one of the most common complications of hemodialysis (HD) and is associated with adverse clinical outcomes. We developed a discrete event simulation (DES) model of HD that simulates survival of a cohort of incident dialysis patients by incorporating the cumulative effects of fluid overload and intradialytic hypotension (IDH) in the context of excessive fluid removal.

**Methods:** The DES model was developed with the SimEvents tool (Mathworks), and consisted of a set of interconnected modules corresponding to various events and outcomes in the course of a patient’s HD experience: initial HD prescription, the dialysis session, interdialytic interval, physician evaluation, acute complications, cumulative effects of fluid overload and IDH, skipped or shortened sessions, hospitalizations, and death (Figure A). The model uses patient-level and HD session-level (e.g. blood pressure and ultrafiltration rate) data for a cohort of 194 HD patients from multiple US facilities from 2010 to 2015.

**Results:** Figure B shows simulated survival curves for 4 scenarios: (1) HD, with an average session duration of 3.5 hours, (2) HD with 30 min added to each session upon detection of fluid overload, (3) HD with increased frequency to four times a week, and (4) natural aging in a control group.

![Image](https://via.placeholder.com/150)

**Conclusions:** Our new model can successfully describe BWC dynamics during an on-line dialysate dilution protocol. The variability of ABV estimates using the new model is substantially smaller than that from SP estimates. The dilution protocol and the new ABV estimation method can be implemented within current HD technology.

**Funding:** NIDDK Support

**SA-PO487**

**Characterization of Hemodialysis Patients Based on Systolic Blood Pressure Profiles**

**Anca L. Stefan,1 Victor Andreescu,1 Michelle M.Y. Wong,2 Gang Liu,1 John Hartman,2 Ronald L. Pisoni,1 Bruce M. Robinson,1 1Arbor Research Collaborative for Health, Ann Arbor, MI; 2Visone Data Management, LLC, Green Bay, WI.

**Background:** Observational studies have revealed a complex relationship between systolic blood pressure (SBP) and mortality in end-stage renal disease (ESRD) patients. We present a classification of hemodialysis (HD) patients based on their intradialytic SBP profiles.

**Methods:** We analyzed intradialytic SBP data recorded every 15 minutes during HD sessions for a cohort of 194 HD patients from multiple US facilities from 2010 to 2015. To describe each patient’s SBP profile, a vector was constructed by dividing each session into three equal time intervals and classifying each interval based on the corresponding SBP values. Thus, each session was assigned a three letter code. A “patient vector” was created by counting the number of sessions of each type. The table shows an example of a patient vector with high SBP during 316 sessions.

<table>
<thead>
<tr>
<th>HHH</th>
<th>HHN</th>
<th>HNC</th>
<th>HNN</th>
<th>HHH</th>
<th>HNH</th>
<th>HNN</th>
</tr>
</thead>
<tbody>
<tr>
<td>316</td>
<td>90</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>14</td>
<td>9</td>
</tr>
</tbody>
</table>

**Results:** Two major clusters of SBP profiles emerged. In Cluster 1, the predominant profiles of the average patient consisted of sessions in which SBP exceeded 140 mmHg during one or more intervals, with HHH being the most common profile (58% of sessions). In Cluster 2, the most common SBP profile was HNN (90% of sessions), along with 28% of sessions where hypotension occurred.

**Conclusions:** SBF profiles differ across patients and from session to session for the same patient. However, there are predominant SBF profiles for each patient, which may have prognostic implications. Future analyses will assess associations of the predominant SBF profiles with hospitalizations and cardiovascular complications which will be applied in discrete event simulation models of complications in HD.
SA-PO488

Accuracy of Contrast-Enhanced Ultrasound for Characterizing Kidney Lesions in Patients with and without CKD


Background: Complex kidney lesions are often detected incidentally. Generally, lesions are further characterized by contrast-enhanced CT or MRI. However, these studies are often contraindicated in patients with chronic kidney disease (CKD). Contrast-enhanced ultrasound (CEUS; panel A), a new, non-contrast imaging technique, is a potential alternative for lesion surveillance among patients with CKD.

Methods: CEUS was performed on 46 patients with known indeterminate or suspicious kidney lesions. Patients with and without CKD were evaluated to compare sensitivity in patients with and without CKD. Results were independently interpreted by 2 blinded readers and risk-stratified by the Bosniak classification system. Using histologic diagnosis as the reference standard, CEUS sensitivity and specificity with 95% confidence intervals were calculated. As histology was available for resected lesions only, we performed secondary analyses considering histologic diagnosis or one-year follow-up imaging as the reference standard. The mean follow-up period was 18 months.

Results: In primary analyses, CEUS sensitivities ranged 95-100% for all patients and 100% for CKD patients (panel B). Specificities were low across all patients, in both primary and secondary analyses, ranging 0-68%.

Conclusions: CEUS has comparable sensitivity to CT and MRI and thus excellent potential as an alternative diagnostic tool for characterization of kidney lesions in patients with CT/MRI contraindications. The observed low specificity suggests that CEUS technique improvement is needed.

SA-PO489

A Pilot Study of Nuclear Magnetic Resonance to Detect Volume Changes during Hemodialysis

Kristin M. Cima,1 Lina Avancini Colucci,2 Matthew Li,2 Dihua Xu,1 Andrew S. Allegretti,3 Jimmy Hanna,1 Xavier F. Parada,1 Dennis A. Ausiello,1 Michael J. Cima,2 Herbert Y. Lin.1 Nephrology, Massachusetts General Hospital, Boston, MA; Dept of Materials Science and Engineering, Massachusetts Inst of Technology, Cambridge, MA.

Background: Patients treated with hemodialysis (HD) are prone to volume overload. Physicians rely on clinical examination and an assessment of interdialytic weight gain to estimate volume status in HD patients.

Methods: Adult HD patients who were admitted to our hospital between April and December 2015 were recruited. Patients were excluded if they were initiating HD, had a limb amputation, or were being treated in the intensive care unit. The first NMR device was a single sided sensor designed to take measurements at the upper calf and the second was a bore-configured sensor designed to take measurements at the finger. The first measurements were obtained at initiation of dialysis. NMR measurements were repeated at hourly intervals and at the completion of dialysis. Pearson correlation was used to look for an association between change in NMR measurements and ultrafiltration volume.

Conclusions: Together, these results support the use of this novel 3D tissue model of the PT for comprehensive drug-induced nephrotoxicity assessment in vivo.

Funding: Pharmaceutical Company Support - Organovo, Inc.

SA-PO490

Automation Optimizes Risk Stratification for Acute Kidney Injury: Pilot Study of Electronic Health Record Based Patient Screening

Rajit K. Basu, Patricia A. Holshouser, Tara C. Terrell, Theresa A. Mottes, Ryan Knox, Hilary E. Pitner, Catherine Johnson, Bill Young, Stuart Goldstein, Center for Acute Care Nephrology, Cincinnati Children’s Hospital, Cincinnati, OH.

Background: Earlier identification of patients at risk for AKI is hypothesized to improve outcomes. We previously validated a stratification methodology for AKI risk, termed the Renal Angina Index (RAI), in critically ill children for prediction of severe AKI. Screening for RAI elements requires extraction and calculation of objective data. We hypothesized that an automated electronic health record (EHR) screening algorithm would optimize the value of RAI screening compared to manual extraction and tabulation.

Methods: We integrated the RAI into our EHR to compare automated versus manual patient screening for AKI risk in two separate, single-center retrospective and prospective observational studies. The EHR-system and five practitioners with varying medical expertise (manual) screened 97 patients admitted to the pediatric intensive care unit (PICU) for RAI criteria 12 hours after ICU admission (time of eligibility). The primary outcome was "value", a composite of screening accuracy, time, and cost.

Results: Accuracy improved using automation in both the retrospective and prospective studies (auto: 91.9% and 92.2% vs. 75% and 77%, respectively). Median time required for screening individual patients was 0:07:25 (hr:mins) (range 0:04:18 – 0:14:27) and median time lag between patient eligibility and screening was 13:20:00 for the manual process (range 09:21:52 – 17:54:42). The automated process was instantaneous for both screening studies with no lag between first eligibility time and time of RAI reporting. Using average number of patients per day, required time for screening, and average hourly salary of researcher, the extrapolated daily cost for manual RAI screening alone would be $9,338.24/year/researcher or $46,691.20 total.

Conclusions: Our data show that automation increases accuracy and decreases screening time, screening delay, and cost for using identifying patients at risk for AKI. Taken together, we suggest the EHR can be used to optimize the value of AKI risk screening for both research and clinical purposes.

SA-PO491

A Three-Dimensional Bioprinted Model of the Renal Proximal Tubule for Evaluation of Drug-Induced Nephrotoxicity

Shelby King, Timothy Smith, James William Higgins, Celina Nino, Abigail Docuyanan, Alice Chen, Sharon Presnell, Deborah Nguyen, Organovo, Inc., San Diego, CA.

Background: Due to its exposure to high concentrations of xenobiotics, the proximal tubule (PT) is a primary site of nephrotoxicity and resulting drug attrition in drug development. Current pre-clinical methods using 2D cell cultures and animal models cannot completely recapitulate the in vivo human proximal tubule (in vitro).

Methods: Using Organovo’s proprietary bioprinting platform, we have developed a human in vitro 3D tissue model of the PT to enable more accurate prediction of clinical outcomes. The tissue is composed of a thin interstitium supporting a basement membrane and polarized monolayer of primary human PT epithelial cells.

Results: The epithelial cells of the 3D tissues demonstrated formation of tight junctions, stable gamma glutamyl-transferase activity, and expression of renal transporters for at least 4 weeks in culture. The tissues also exhibited functional glucose transport via SGLT2, inhibited by the SGLT2 inhibitor canagliflozin, as well as P-gp mediated efflux transport via the OCT2 inhibitor tolbutamide. Using average number of patients per day, required time for screening, and average hourly salary of researcher, the extrapolated daily cost for manual RAI screening alone would be $9,338.24/year/researcher or $46,691.20 total.

Conclusions: Our data show that automation increases accuracy and decreases screening time, screening delay, and cost for identifying patients at risk for AKI. Taken together, we suggest the EHR can be used to optimize the value of AKI risk screening for both research and clinical purposes.
SA-PO492

Organoid Differentiation under Flow: Bioengineering a Functional Kidney-on-a-Chip from Human Pluripotent Stem Cells
Ramila E. Gulieva, Benjamin S. Freedman. Div of Nephrology, Kidney Research Inst, and Inst for Stem Cell and Regenerative Medicine, Dept of Medicine, Univ of Washington, Seattle, WA.

Background: Human pluripotent stem cells (hPSCs) have recently been differentiated into nephron-like kidney organoids, with important potential for kidney function. Microfluidic flow is an essential component of the kidney nephron, but is absent from existing kidney organoid cultures. We tested the ability of hPSCs to differentiate into kidney organoids under constant flow and perform kidney functions.

Methods: hPSCs were seeded in a multichannel microfluidic chamber and treated with specific growth factors to direct differentiation into kidney organoids under constant flow. Organoids were fixed and analyzed for kidney marker expression by immunofluorescence.

Results: Organoids were fixed and analyzed for kidney marker expression by immunofluorescence.

Conclusions: Increased synthetic matrix rigidity enhanced attachment and proliferation of RPTECs. This effect was correlated with the qualitative changes in the mechanical properties of the organoid matrices.

Funding: Other NIH Support - Support for this work was provided by the University of Michigan O'Brien Kidney Center (DK-P30-081943). JAB was supported by T32DK007378.

SA-PO494

Stable Filtration by Silicon Nanopore Membranes under Pulsatile Flow

Background: Silicon Nanopore Membranes (SNM) optimize permeability-selectivity factors in ultrafiltration membrane design. The efficiency of the membranes reduces package size and pressure requirements for filtration, enabling implanted renal replacement therapy. The failure characteristics of SNMs are described by statistical likelihood of fracture due to the crystalline nature of the material, rather than gradual failure. Hydraulic permeability and macromolecular sieving by SNMs were characterized using pulsatile flow of a blood surrogate.

Methods: SNMs were manufactured by bulk and surface micromachining as previously described. Sample membranes were mounted in custom-made ultrafiltration cells and perfused with a 37% (v/v) glycerol-saline mixture spiked with a polydisperse fluorescently-tagged polysaccharide, Ficoll) with similar viscosity to blood. Pressure and flow waveforms simulating arterial flow were produced by a computerized pump control system. Filtration rates were monitored by mass accumulation on an analytical balance Serial aliquots of feed and filtrate were analyzed by size-exclusion chromatography and size-dependent sieving coefficients calculated as the ratio of ultrafiltrate concentration to feed concentration.

Results: Hydraulic permeability was unchanged over 12 (n=2) and 16 (n=2) days. Sieving coefficients were unchanged over the same period. No membranes were fractured for leakage after 1.3 million pulsatile cycles.

Conclusions: Ultrathin crystalline silicon membranes are mechanically stable for over 10^6 pressure cycles in vitro. Permeability/selectivity performance does not significantly degrade over two weeks.

Funding: Other NIH Support - NIBIB

SA-PO495

Transcriptome Analysis of Three Progressive Models of Chronic Kidney Disease Identifies Pathways Implicated in Disease Progression
Shannon Marie Harlan, Tao Wei, Zhonghua Qiu, Martin S. Cramer, Dianna L. Jaqua, Matthew D. Breyer, Josef G. Heuer. Lilly Research Labs, Eli Lilly and Company, Indianapolis, IN.

Background: Publically available renal transcriptome data from patients with diabetic kidney disease (DKD) has served as a valuable resource for identification of genes and pathways upregulated in human DKD. Precisely how close animal models of DKD mimic many of the genetic features of human DKD remains unclear. The present studies explored gene expression profiles in three preclinical mouse models of renal disease, the remnant kidney, the db/db uNx model, and the ReninAA Vdb/db uNx model and compared them to published human DKD data sets.

Methods: Mice aged 20-26 weeks were used to isolate kidney RNA for microarray analysis (Affymetrix, MOE-430 2.0 array). Differentially expressed genes (DEG) were defined as those with fold change >1.5, P value<0.05 and FDR <0.05. Results were compared to the published data set GSE30529 of human DKD.

Results: Clustering and pathway analysis of DEGs identified common pathways both up and down-regulated in the three mouse models with human DKD. Inflammation/immune and apoptosis/cell survival responses were both highly upregulated in all three models and in human DKD. Common pathways down-regulated in all three models and human DKD included amino acid metabolism and transporter activity. Comparing DEGs from the three models identified the highest concordance (84%) of DEGs to human DKD in the ReninAA Vdb/db uNx model consistent with this model most closely mimicking the pathophysiological characteristics of human DKD. KEGG analysis identified cytokine-cytokine receptor interaction as the top ranked pathway in this model, a pathway highly upregulated in human DKD.

Conclusions: Transcriptome data from the three mouse models of DKD supports the similarity of the models to human DKD, with the ReninAA Vdb/db uNx model having a molecular signature most closely resembling human DKD patients. In addition, inflammation which has been shown to be prominent feature of human DKD was highly upregulated in all models, suggesting a potential role of inflammation in the pathogenesis of DKD.

Funding: Pharmaceutical Company Support - Eli Lilly and Company
SA-PO496

Genomic and Proteomic Profiling Reveal Insights of Mesangial Cell Function in Patients with IgA Nephropathy

Emilie Lasèe,1 Pidi Liu,1 Wenjun Ju,2 Matthias Kretzler,2 Kerstin Ebeferos,1 Jenny C. Nystrom,1
1Neuroscience and Physiology, Univ of Gothenburg, Gothenburg, Sweden; 2Computational Medicine and Bioinformatics, Univ of Michigan, Ann Arbor, MI.

Background: To understand disease onset and to discover new drug targets for IgA nephropathy (IgAN) we need to more closely determine the role of the mesangial cells in disease development and progression. Using a systems biology approach involving in silico nanodissection (Ju W et al, Genome Res 2013) we investigated the role of the mesangium in patients with IgAN and the effect of galactose deficient IgA (gd-IgA) on mesangial cells in vitro.

Methods: Transcriptional profiles of glomeruli from patients diagnosed with IgAN (n=20) and healthy kidney donors (n=22) were obtained using the Affymetrix platform. Expression of mesangial and podocyte standard genes obtained by in silico nanodissection were compared between the groups and correlated to clinical parameters. Additionally, primary cultures of human mesangial cells were treated with gd-IgA to mimic IgAN in vitro and the proteome analysed using LC-MS/MS. This enabled identification of shared pathways between the patient glomerular transcriptome and the proteome in the in vitro model.

Results: By transcriptome analysis we found 736 significantly regulated genes. Mesangial cell standard gene expression separated IgAN patients from healthy donors, while no separation was seen for podocyte standard genes. Activation z-scores based on mesangial cell standard gene expression yielded a significant correlation with creatinine and eGFR, while no correlation was found based on podocyte standard genes. 22 significantly regulated pathways, mainly inflammatory, were shared between the glomerular transcriptome and the proteome of mesangial cells treated with gd-IgA.

Conclusions: Expression of mesangial cell standard genes determined by in silico nanodissection clusters IgAN patient samples separately from healthy controls. Correlation with eGFR and creatinine indicate their usefulness as predictive biomarkers. Shared regulated inflammatory pathways between the glomerular transcriptome and gd-IgA treated mesangial proteome give rise to new and exciting data useful for target exploration in IgAN.

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

SA-PO497

Quantitative Magnetization Transfer Imaging to Evaluate Renal Fibrosis in Mouse Diabetic Nephropathy

Daisuke Katagiri,1 Feng Wang,1 Shinya Nagasaka,1,2 Hua Li,1 Suwan Wang,1 Keiko Takahashi,1 Ming-Zhi Zhang,1 Akira Shimizu,1 Raymond C. Harris,1 Takumne Takahashi,1 Vanderbilt Univ, Nashville; 2NYP Medical School, Tokyo, Japan.

Background: Currently few non-invasive methods are available to evaluate fibrosis according with progressed kidney disease. MRI-based quantitative magnetization transfer (qMT), which provides insight into the interactions between free water protons and immobile macromolecular protons, is applicable to evaluate tissue fibrosis. However, this technique has not been applied to kidney disease. Here we report a novel, in vivo method to measure renal fibrosis.

Methods: 8, 24 weeks old db/db eNOS +/- (DN; 8wDN and 24wDN) and C57BL/6 (Wild type; WT) mice were imaged with a 7T MRI. Henkelman-Ramani’s model was used to derive qMT. Cortical and outer medulla regions with significant higher pool size (P<0.01) values were determined. Furthermore, fibrosis level was evaluated by threshold PSR. Mice were sacrificed and median 50 % of each kidney was evaluated fibrosis determined by Picrosirius red and collagen IV (14 sections per mouse, and 3-4 mice per group).

Results: Localized changes of PSR were observed in cortex and outer medulla. 24wDN mice displayed significant higher fibrosis in cortex than WT mice on histology (3.0 vs 0.5 %; Sirius red, 12.3 vs 4.4 %; collagen IV) and these fibrosis areas corresponded to high PSR region. Mean PSR values in cortex were increased in DN progression (0.09; WT; 0.10; 8wDN, 0.12; 24wDN). The observed longitudinal relaxation rate (R1,sir) and transverse relaxation rate of the free water pool (R1) correlated highly with the regional distribution of PSR. % Areas with higher than +2SD of PSR were significantly dominant in 24wDN mice than WT mice (14.4 vs 4.5 %; PSR-Mean+2SD, 7.7 vs 0.7 %; +3SD, and 3.9 vs 0.0 %; +4SD, p<0.01). The cortical fibrosis levels estimated using threshold PSR showed a significant correlation with the fibrosis indices determined with Sirius red and collagen IV (p<0.05).

Conclusions: The present study provides the first demonstration that renal fibrosis in DN can be non-invasively assessed with qMT-MRI technique and threshold PSR analysis.

Funding: NIDDK Support

SA-PO498

In Vivo Detection of Glomerulus Number and Size in the Whole Kidney Using MRI

Edwin Baldenom,1 Jennifer R. Charlton,1 Kevin M. Bennett,1
1Univ of Hawaii at Manoa; 2Univ of Virginia.

Background: Nephron endowment is an important factor in susceptibility to renal insufficiency with development of acute or chronic kidney disease. Here we report a novel, non-invasive, approach to measure nephron endowment in vivo using MRI with use of the biocompatible contrast agent cationized ferritin (CF). We report glomerular number (Nglom) and individual glomerulus volume (IV) in live animals.

Methods: Sprague-Dawley (SD) rats were given a total dose of 5.7mg/mg/kg of CF through a tail vein catheter in 3 separate injections at 90-minute intervals. Animals were then imaged with in-vivo MRI on a Bruker 7T MRI using a T2* weighted 3D gradient recalled echo (GRE) sequence. Individual 3D MR images were acquired in less than one hour. Motion artifacts were readily mitigated by gating. After imaging, animals were transcardially perfused and kidneys sectioned for ex vivo imaging using a T2* weighted 3D-GRE sequence for comparison. Nglom and IV were measured using custom software.

Results: Whole kidneys were imaged in-vivo with MRI and images rendered in 3D to visualize gross anatomy, glomeruli, and vascular tree. CF accumulation in glomeruli was visible as dark spots in the cortex in both in-vivo and ex-vivo images.

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

SA-PO499

Beta Blocker Pharmacokinetics and Dialyzability in Chronic Hemodialysis Patients

Alvin Tieu,1 Thomas Velenosli,1 Andrew S. Kucey,1 Matthew A. Weir,2 Brad Urquhart,1,2 Dept of Physiology and Pharmacology, Western Univ; 1Dept of Medicine, Div of Nephrology, Western Univ, London, ON, Canada.

Background: There is a paucity of data available to describe drug dialyzability. Of the available information, most were obtained prior to implementation of modern hemodialysis (HD) membranes. This study aims to characterize the dialyzability of the four most commonly prescribed beta blockers in patients undergoing high-flux HD. Based on physicochemical properties, we hypothesize atenolol and metoprolol to be extensively removed by HD, while bisoprolol and carvedilol to be poorly dialyzed.

Methods: Chronic HD patients were recruited for a pharmacokinetic, 4-way crossover study. Atenolol, bisoprolol, carvedilol and metoprolol were administered separately to each patient over 4 HD sessions. Arterial and venous blood samples and total spent dialysate were collected. Beta blocker concentrations were measured by mass spectrometry and dialytic clearance was determined by the dialyzer and recovery clearance methods.

Results: After HD, 6.7, 1.11, 0.03 and 1.28 mg of atenolol, bisoprolol, carvedilol and metoprolol were recovered in spent dialysate. As a result, dialytic clearance rates for atenolol, bisoprolol and metoprolol were 117.1, 110.1 and 148.4 mL/min. These 3 beta blockers are significantly dialyzed as compared to carvedilol (17.8 mL/min). Other pharmacokinetic parameters that were calculated include non-dialytic clearance and post-dialysis doses required to maintain patients within a therapeutic window. For atenolol, bisoprolol and carvedilol, the fraction of elimination due to dialysis was 25, 19 and 13 % while the supplemental doses were 22.7, 2.88 and 1.39 mg. Only 4 % of carvedilol was removed by dialysis.

Conclusions: Beta blocker efficacy can be hindered if substantial dialytic clearance occurs. Accordingly, atenolol and metoprolol are extensively cleared by HD, while carvedilol displays low dialyzability. Contrary to literature, our data indicates that bisoprolol is substantially eliminated by HD. With recent studies suggesting heightened mortality risk in HD patients prescribed highly dialyzed beta blockers, dialyzability data is critically important to optimize drug therapy in patients.

Funding: Government Support - Non-U.S.

SA-POS00

Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients

Thomas Mavrakanas,1,2 Caroline Sauer,1 Mark L. Lipman,1 1Div of Nephrology, Sir Mortimer Davis Jewish General Hospital, McGill Univ, Montreal, QC, Canada; 2Div of General Internal Medicine, Geneva Univ Hospitals, Geneva, GE, Switzerland; 3Div of Clinical Pharmacology & Toxicology, Geneva Univ Hospitals, Geneva, GE, Switzerland.

Background: Atrial fibrillation increases the risk of ischemic stroke in patients with end-stage renal disease. Warfarin may not protect these patients against ischemic stroke. Apixaban is only 27% renally excreted and could be an option in dialysis patients. However, there are no data on apixaban pharmacokinetics at steady state in hemodialysis patients.

Methods: Five patients with atrial fibrillation, on hemodialysis (three weekly for >6 months) without any residual renal function, received apixaban 2.5 mg bd for 9 consecutive
SA-PO503
Population Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses of C.E.R.A. (Continuous Erythropoietin Receptor Activator - Methoxy Polyethylene Glycol-Epoetin Beta) in Both Adults and Pediatric Patients with Chronic Kidney Disease (CKD)  

**Pascal Chang**, 1 Nicolas Frey, 2  
**Certara Strategic Consulting, France; 1 Hoffmann-La Roche Ltd, Basel, Switzerland.**  

**Background:** Objectives were to determine the PK/PD characteristics of C.E.R.A. in pediatric patients (pts) with anemia of CKD on hemodialysis (HD) and whether they differ from those in adults.  

**Methods:** Serum C.E.R.A. concentrations and hemoglobin (Hb) levels in a 20-week open-label Phase II study of intravenous (IV) C.E.R.A. in pts aged 6–17 years on HD with stable chronic renal anemia were pooled with data collected during the clinical development of C.E.R.A. IV (IV and subcutaneous [SC]) in adult patients with CKD. Adult PK/PD structural models previously developed were used for the analyses. A non-linear mixed effect modeling approach was applied using NONMEM version 7.3.0.  

**Results:** The pediatric PK/PD dataset consisted of 63 pts with 678 C.E.R.A. serum values and 1580 Hb levels. The same structural PK model as the adult one (1-compartment model with first order absorption and elimination) adequately described the pediatric data. As already determined in adults, C.E.R.A. clearance increased with body weight and the volume of distribution increased with body weight and age. Once those covariate influences were taken into account, there was no difference in PK between adult and pediatric pts. The PK/PD model developed on adult phase 2/3 data could be applied successfully to pediatric data. The drug dependent parameters (Smax and SC50) were comparable in pediatric and adult pts indicating that the C.E.R.A. exposure–response relationship is similar in both populations. The predicted baseline Hb value in absence of any erythropoietin-stimulating agent therapy was found to increase with body weight. This effect is driven by the pediatric population and is in accordance with generally higher Hb levels observed in adults. No new safety signals were identified. Cole-Scott parameters were used in PK/PD parameters was found between IV and SC formulation and between dialysis types (including pts not on dialysis).  

**Conclusions:** The PK/PD characteristics of C.E.R.A. are similar between adult and pediatric populations.

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SA-PO504
Pharmacokinetics and Safety of KBP-5074 in Phase I Single and Multiple Ascending Dose Studies  

**Bin Zhang, Xiaojian Tan, Shumao Ni. KBP Biosciences USA Inc.**  

**Background:** KBP-5074 is a new investigational mineralocorticoid receptor antagonist being developed for chronic kidney disease. The primary objective of these studies was to determine the safety, tolerability, and pharmacokinetic (PK) profile of KBP-5074 following single (SAD) and multiple (MAD) ascending oral doses in healthy subjects.  

**Methods:** The SAD study was comprised of 5 sequential cohorts (0.5, 1.0, 2.5, 10, 30mg) and 1 food effect cohort (10mg). The MAD study was comprised of 2 cohorts (2.5, 5.0 mg) dosed for 14 days. PK parameters included Cmax, Tmax, AUC0-t, AUC0-24h, C10, and T1/2. Safety parameters included adverse events, vital signs, clinical laboratory results, ECG, and physical examination.  

**Results:** 46 and 12 healthy adults were enrolled in the SAD and the MAD study, respectively. KBP-5074 was generally safe and well-tolerated at single doses up to 30.0 mg and multiple doses up to 5.0 mg. Adverse events were mostly mild and unrelated to study drug. No hyperkalemia (serum potassium >5.5 mmol/L) was reported in the SAD study. The drug was generally safe and well-tolerated at up to 5.0 mg in MAD study. No new safety signals were identified. Cole-Scott parameters were used in PK/PD parameter estimation.  

**Conclusions:** KBP-5074 was generally safe and well-tolerated by healthy adults in these studies. The maximum recommended dose level in clinical practice may be less than 5.0 mg.

**Funding:** Pharmaceutical Company Support - KBP Biosciences USA Inc

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only  
Underline represents presenting author.
Pharmacokinetics and Pharmacodynamics of Eculizumab in Individualized Treatment of Atypical Hemolytic Uremic Syndrome

Elena Volokhina,1 Kioa L. Wijnisma,1 Jack F. Wetzels,1 Nicole Van De Kar,1,2 Lambertus P.W.J. Van den Heuvel.1,2

Background: The atypical hemolytic uremic syndrome (aHUS) is a devastating renal disease, caused by complement dysregulation. Approval of monoclonal complement inhibitor for eculizumab/Soliris started a new era in the treatment for this disease. However, data on pharmacokinetics and pharmacodynamics of this drug remain limited.

Methods: Eculizumab was measured by in-house ELISA method. Component activity was analyzed using Wieslab® complement screen assay. In total, 209 samples were taken from 11 patients before the eculizumab infusion in the (weekly), maintenance (2-weekly) and tapering (every 3, 4, and 5 weeks) phases of therapy.

Results: Our newly-developed eculizumab assay had variation coefficients of 2.9% (intra-assay, 352 µg/mL) and 5.2% (inter-assay, 328 µg/mL) and detection limit of 8 µg/mL. The samples with >50 µg/mL demonstrated >6% of complement activity in classical and alternative complement pathways. The eculizumab levels had ranges of 36-459 µg/mL (intra-assay, 352 µg/mL) and 5.2% (inter-assay, 328 µg/mL) and detection limit of 8 µg/mL.

Conclusions: The detected concentrations were up to 9-15 fold higher than required for efficient complement inhibition. During tapering, ranges of 63-367 µg/mL, 11-256 µg/mL and 13-161 µg/mL were measured at 3, 4 and 5 week infusion intervals, respectively.

SA-PO508

Safety and Pharmacokinetics in Healthy Human Volunteers of RG-012: An Inhibitor of MicroRNA-21 Being Investigated for Treatment of Alport Syndrome

John Stewart Grundy, Kai Liu, Jacqueline Blenn, Paul C. Grint, Michael Huang. Regulus Therapeutics, San Diego, CA.

Background: RG-012 is a single-stranded chemically modified oligonucleotide being developed for treatment of patients (±/−) with Alport syndrome (AS). AS is characterized by loss of renal function associated with defects in specific collagen genes expressed in the kidney glomerular basement membrane. RG-012 inhibits miR-21, a microRNA target associated with renal dysfunction and increased expression during kidney stress.

Methods: Safety and clinical pharmacokinetics (PK) of RG-012 (parent drug), RG0005 (active metabolite), and SUM (RG012-RG0005) was evaluated in a placebo-controlled, single ascending subcutaneous dose study (0.5, 1, 2, and 4 mg/kg of RG-012; n=8/ cohort including 6 active and 2 placebo) in healthy volunteers, with urine and plasma PK sampling performed up to 24 and 672 hours post dose, respectively. Concentrations of RG-012, RG0005, and SUM up to 24+48 hours post dose were determined using HLPLC-MS/MS (LLOQ=10 and 50 ng/mL in plasma and urine, respectively). Very low plasma concentrations of SUM seen at ≥72hrs post dose were determined using HPLC-FL (LLOQ=0.05 ng/mL) which cannot resolve RG-012 and RG0005.

Results: Subcutaneous administration of RG-012 up to 8 mg/kg appeared to be generally safe and well tolerated in this study (no SAFEs, severe AEs, or subject discontinuations). RG-012 was the main analyte observed in plasma and urine, with RG0005 being the sole major metabolite detected (achieving up to 47% of parent drug exposure). The time profiles of the evaluated analytes were characterized by relatively rapid absorption/ appearance (median Tmax range: 4–8 hours), dose-dependent exposure, and rapid clearance (MRTmed range: 6.9–9.2 hours) presumably reflecting extensive disposition to tissues. The mean terminal elimination half-lives of SUM ranged from 4–13 days, likely reflecting the half-lives of the major metabolites (RG-0005 and RG0005).

Conclusions: In conclusion, favorable safety and clinical PK results in this study appear generally consistent with reported results from other similar compounds in this oligonucleotide class.

Funding: Pharmaceutical Company Support - Regulus Therapeutics; Genzyme.
Displacer-Enhanced Hemodialysis for Treatment of Intoxications with Highly Protein-Bound Drugs: A Model-Based Analysis

Xia Tao, Vaibhav Maheshwari, Doris H. Fuertinger, Peter Kotanko, Stephan Thijssen. Renal Research Inst, NT, NY.

Background: Over 9 million intoxication cases involving drugs were reported in the US in 2014. Hemodialysis (HD) is an appropriate treatment in life-threatening situations. However, the inefficiency of HD to remove highly protein-bound drugs limits its use to treat intoxications with highly protein-bound drugs.

Methods: The model comprises a multi-compartmental representation of the patient and spatiotemporal representation of the dialyzer, accounting for dynamic equilibrium of drug, albumin and albumin-drug complex. Carbamazepine and phenytoin were chosen as model substances to evaluate the efficacy of displacer-enhanced HD. Ispiron (800 mg over 2.5h; optimized infusion profile) and aspirin (1000 mg over 2.7h; optimized infusion profile) were used as displacers for carbamazepine and phenytoin, respectively. Qd and Qh were 250 and 500 mL/min, respectively. Distribution volume was 44 L in 70 kg male.

Results: Compared to conventional HD, non-toxic drug levels were achieved in a substantial shorter time with displacer-enhanced HD.

Table 1. Time required to lower plasma levels to therapeutic range.

Table 2. Elimination half-life (t1/2) with and without displacer.

Conclusions: Displacer-enhanced HD significantly improves the removal of highly protein-bound drugs. This gain may translate into resource savings and improved patient outcomes.

Cystatin C-Guided Vancomycin Dosing Improves Target Trough Achievement in the Critically Ill Compared to Standard Care with Creatinine Clearance

Maheshwari, Doris H. Fuertinger, Peter Kotanko, Stephan Thijssen. Renal Research Inst, NT, NY.

Background: A cystatin-C inclusive vancomycin dosing algorithm may improve target trough achievement compared to serum creatinine-guided therapy in critically ill patients.

Methods: Patients initiated on intravenous vancomycin in three intensive care units at a tertiary medical center were studied. Dosing regimens were selected and implemented for each individual patient (target vancomycin trough [10-15 mg/L] and a target trough level of <3 mmol/L in all patients). In the validation set (n=7), all patients achieved a post-HD EG level of <3 mmol/L and a difference between predicted and actual HD duration was -21 min (95% CI: -117 – 86). A cross-validation confirmed these findings.

Conclusions: Using an EG T1/2 of 158 min with high-efficiency HD, and a post-HD target EG level of 1 mmol/L, HD duration can be predicted accurately while assuring a safe post-HD EG level.

Nephrology, Hôtel-Dieu de Québec, Quebec City, QC, Canada; 2Nephrology, Hôtel-Dieu de Québec, Quebec City, QC, Canada.

Methods: In a retrospective cohort study, we identified 26 episodes of EG in 24 subjects that met HD criteria. HD was performed using high-efficiency filters with a surface area > 2 m², a blood flow of >350 mL/min and a dialysate flow of 750 mL/min. Using EG levels during HD, we calculated EG T1/2 by one phase decay exponential regression analysis. Kinetic modelling was available for 21 cases, 2 of which were repeated poisoning. To predict HD duration, a training set used the 50th, 75th and 90th percentiles of T1/2 and target post-HD EG levels of 3, 2 and 1.5 mmol/L. The optimal model was then validated in a validation set, and cross-validation was performed using leave-one-out approach.

Results: The overall elimination T1/2 during HD, under ADH inhibition, was 158 min (95% CI: 146–169). HD was performed using high-efficiency filters with a surface area > 2 m², a blood flow of >350 mL/min and a dialysate flow of 750 mL/min. Using EG levels during HD, we calculated EG T1/2 by one phase decay exponential regression analysis. Kinetic modelling was available for 21 cases, 2 of which were repeated poisoning. To predict HD duration, a training set used the 50th, 75th and 90th percentiles of T1/2 and target post-HD EG levels of 3, 2 and 1.5 mmol/L. The optimal model was then validated in a validation set, and cross-validation was performed using leave-one-out approach.

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Funding: Private Foundation Support

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Background: A cystatin-C inclusive vancomycin dosing algorithm may improve target trough achievement compared to serum creatinine-guided therapy in critically ill patients.

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Funding: Government Support - Non-U.S.

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Background: A cystatin-C inclusive vancomycin dosing algorithm may improve target trough achievement compared to serum creatinine-guided therapy in critically ill patients.

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Funding: Government Support - Non-U.S.
SA-POS14
Chemotherapy Dosing prior to Hemodialysis in Cancer Patients with Kidney Failure Frieder Keller
Innere 1 Univ Hospital, Ulm, Germany.
Background: In cancer patients, the incidence of acute kidney injury is 15 – 45 % per year. Due to growing age, chronic kidney disease is prevalent with 20 – 50 % in this population. On the other side, the pharmacokinetics depend on kidney function in 31 of 68 essential anti-cancer drugs (46 %). To adjust for kidney function, the dose frequently is reduced. Independence from kidney function, chemo-therapy was underdosed in 30 % of cancer patients with a negative impact on survival [Br J Cancer 2002].
Methods: Only few case reports or small case series are published on dosing of chemotherapy in cancer patients with kidney failure. Most experts plead for chemotherapy administration after dialysis [Senin Dial 2015]. We have reviewed the literature and extracted the concept to administer the dialyzable anticancer drugs prior to hemodialysis. According to our own experience [Eur J Haematol 2005], the chemotherapy administration before hemodialysis might allow for a higher, near normal dose without unacceptable toxicity.
Results: We have found 28 PubMed cited papers where the concept to administer high and near normal standard dose chemotherapy prior to hemodialysis is proposed for 17 drugs. At least 30 % of these drugs is eliminated by dialysis. To simulate normal kidney function, however, hemodialysis should start 2 hours after cessation of the chemotherapy infusion and hemodialysis should be repeated on a daily basis for 4 to 6 days.

SA-POS15
Cetuximab Prevents Methotrexate-Induced Nephrotoxicity Through Epidermal Growth Factor-Derived Signaling Rosalinde Masereeuw,1 Pedro Caetano Pinto,1 Amer A. Jamalpour,1 Janneke Ham,1 Carla Van Herpen,2 Martijn J. Wilmer,1 1Pharmacology, Utrecht Inst for Pharmaceutical Sciences, Utrecht, Netherlands; 2Medical Oncology, Radboud Univ Medical Center, Nijmegen, Netherlands.
Background: A novel phase I/IIb study investigates the efficacy of combining methotrexate (MTX) with the epidermal growth factor receptor (EGFR) recombinant antibody cetuximab (CTX) in treatment of locally advanced head and neck squamous cell carcinoma. Here, we studied the effect of CTX on renal MTX handling by organic anion transporter 1 (OAT1), breast cancer resistance protein (BCRP) and multidrug resistance protein 4 upon treatment with EGF (10 ng/ml), CTX (500 µg/ml) or the mitogen-activated protein kinase (MEK) inhibitor, U-0126 (2 µM). Nephrotoxic effects of MTX were determined using dimethylthiazol bromide (MTT) assay. Results: MTX inhibited fluorescein uptake to 56±6% (p<0.05), decreased Hoechst33342 efflux to 71±2% (p<0.05) and chloromethylfluorescein-diacetate (CMFDA) to 58±5% (p<0.05). This was supported by a decreased fluorescein uptake (to 68±1%; p=0.01) together with a decrease in Hoechst efflux (to 71±2%, p<0.05) and enhanced CMFDA efflux (by 133±6%, p<0.05). Furthermore, U-0126 decreased the functional expression of OAT1 (64±7%; p<0.01) and BCRP (67±7%, p<0.05) in EGF-stimulated cells, confirming EGFR-MEK signaling. Exposure of ciPTEC-OAT1 to MTX (100 µM) for 24h reduced viability to 40±3% (p<0.05), which was reversed by CTX or U-0126.

SA-POS16
Peak Platinum Excretion Correlates with Novel Urinary Biomarkers in Cancer Patients Receiving Cisplatin-Containing Therapy Melanie S. Joy,1 Blessy George,1 Marie Madeleine Gomez,1 Nickie Lee Mercke,2 Xia Wen,2 Brian Buckley,2 Daniel Bowles,2 Cindy L. O’Bryant,1 Lauren Alekseunis,1 1Skaggs School of Pharmacy, Cancer Center, and Renal Diseases and Hypertension, Univ of Colorado, Aurora, CO; 2Ernest Mario School of Pharmacy, Rutgers Univ, Piscataway, NJ.
Background: Novel biomarkers are under investigation for detecting kidney injury. Given the limitation of measuring cisplatin in patient plasma, urinary Pt may be a quasi-marker of exposures and toxicity. The current study determined Pt PK and urinary biomarkers.
Methods: Blood (0-6h) and urine (0-6h) were obtained from cancer patients (n=11) receiving cisplatin. Pt was quantified using ICP/MS. PK analysis was conducted using Phoenix®. Urinary biomarkers were measured using a multiplex assay at baseline, 3 and 10 days post-cisplatin.
Results: Patient characteristics were age 58±10 y, 11 Caucasian/2 other, 8 male/5 females, BSA 1.9 m², dose (53±51) mg/m². Pt PK parameters were C₀ 2.8±1.0 µg/mL, AUC₀→∞ 28.6±19.5 mg h/L, volume 55.3±15.7 L. clearance 5.4±3.6 L/h. No significant correlation between C₀ (as the driving force for urinary excretion) and peak urinary biomarkers were observed. Peak Pt excretion (20.9±12.2 µg/mL occurred in the 0-2 h urine collection. Significant relationships (R²) were found between peak Pt excretion and urinary biomarkers.

Table 1: Correlations Represent R² Values

<table>
<thead>
<tr>
<th>Urine Pt</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIM-1</td>
<td>0.6046</td>
</tr>
<tr>
<td>TFF3</td>
<td>0.8106</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>0.7849</td>
</tr>
<tr>
<td>NGAL</td>
<td>0.7794</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>0.7424</td>
</tr>
<tr>
<td>B2M</td>
<td>0.8584</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.7968</td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.0268</td>
</tr>
<tr>
<td>GST pi-1</td>
<td>0.5268</td>
</tr>
<tr>
<td>Clusterin</td>
<td>0.5822</td>
</tr>
<tr>
<td>Calbindin</td>
<td>0.7773</td>
</tr>
<tr>
<td>IL-18</td>
<td>0.7424</td>
</tr>
</tbody>
</table>

Conclusions: The results from this comprehensive study corroborate a high degree of agreement between peak Pt and biomarkers in urine. Given the high degree of exposure of proximal tubule cells to Pt through transporter pathways in the kidney, the results suggest a direct mechanism between kidney exposures and toxicity. Future studies will employ physiologically-based PK to fully understand the relationships between kidney exposures and toxicity.

Funding: NIDDK Support

SA-POS17
Effect of Experimental Kidney Disease on the Formation of TMAO by Flavin-Containing Monooxygenases Alexander L. Prokopenko,1 Daniel P. Schrum,1 Adam Fitch,1 Alison Morris,1 François A. Leblond,1Vincent Pichette,2 Thomas D. Nolin,1 1Schools of Pharmacy and Medicine, Univ of Pittsburgh, Pittsburgh, PA; 2Service de Néphrologie et Centre de Recherche, Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada.
Background: Cardiovascular disease (CVD) is the leading cause of death in kidney disease (KD) despite aggressive management of traditional risk factors. As such, non-traditional risk factors have received attention as potential therapeutic targets. Systemic exposure of the microbiota-derived metabolite trimethylamine-N-oxide (TMAO), which is associated with poor CVD outcomes, increases in KD disproportionately to reductions in renal clearance. Flavin-containing monooxygenases (FMO) oxidize trimethylamine (TMA) to form TMAO and are an important class of drug metabolizing enzymes. We hypothesized that FMO activity is increased in the setting of KD, leading to increased TMAO formation. Therefore, we aimed to assess the effect of experimental KD on FMO activity using TMA as a substrate.
Methods: Microsomes were isolated from liver tissue of KD (5/6 nephrectomized) and control rats (n=7 and 6, respectively). Microsomal incubation conditions were optimized, then enzyme kinetics were determined and compared between groups. TMAO was measured via LC-MS, and formation rate of TMAO was used as an indicator of hepatic FMO activity. Therefore, we aimed to assess the effect of experimental KD on FMO activity using TMA as a substrate.

Results: Significant relationships (R²) were found between peak Pt excretion and urinary biomarkers.

Funding: NIDDK Support
SA-PO518

SA-PO518

Methods:

In this first-in-human, double-blind, placebo controlled and single administration study, 40 Japanese healthy male subjects were randomized to TP0463518 (3, 6, 11, 20, and 36 mg) or placebo. Serum levels of EPO after TP0463518 oral administration were similar among all treatment groups (9.6±2.8 and 8.1±3.8 mIU/mL, respectively, N=6), which were all within reference range. TP0463518 increased serum levels of EPO in dose-dependent manner after single oral administration of 3 to 36 mg of TP0463518. T1/2 and Tmax were 1.2 to 2.0 and 5.9 to 7.4 hours, respectively. Throughout the study, TP0463518 was well-tolerated and no remarkable adverse events occurred. Baseline EPO levels in serum were similar among all treatment groups (9.6±2.8 and 8.1±3.8 mIU/mL, respectively, N=6), which were all within reference range. TP0463518 increased serum levels of EPO in a dose-dependent manner. Serum levels of EPO after TP0463518 oral administration were 33.5±18.3 mU/mL at 6 mg and 27.8±15.5 mU/mL at 36 mg (respectively, N=6). The EPO levels returned to baseline level within 24 to 48 hours at all doses tested. Changes in levels of EPO after administration of TP0463518 was well-correlated with Cmax of plasma TP0463518 concentration (r=0.85). Moreover, a correlation between AUC0-24h of serum EPO and that of plasma TP0463518 was observed (r=0.82).

Conclusions: TP0463518 was well-tolerated, showed favorable PK profiles, and dose-dependently increased EPO levels in serum, possibly derived from the liver. These results indicate that TP0463518 will be a unique drug for the treatment of renal anemia.

SA-PO519

HTS Assay Based Discovery of Novel CD11b Agonists as Potential Therapeutics for Lupus Nephritis

Xiaobo Li, Samia Khan, Vineet Gupta

Background: Systemic lupus erythematosus (SLE, lupus) is characterized by renal interstitial leukocytic recruitment that leads to chronic renal insufficiency in up to 30% of affected patients. Integrin CD11b/CD18 is critical for leukocyte adhesion and migration during inflammation and tissue injury. We previously used a cell-based, high-throughput screening (HTS) assay to identify small molecule CD11b agonists termed leukadherins that reduce leukocyte recruitment and inflammation in several disease models. Here we use this HTS assay to identify more novel CD11b agonists as potential therapeutics for lupus nephritis.

Methods: We used a cell-based HTS assay to screen a chemical library of ~90,000 molecules for compounds that affected the adhesion of K562 cells that expressed CD11b/CD18 at the cell surface to the fibrinogen ligand. CD11b/CD18 K562 cells were exposed to titrating concentrations of molecules and the candidates with the lowest effective dose 50 (EC50) were selected to investigate further.

Results: Using the HTS-adhesion assay, we screened a total of 90,000 molecules in a chemical library and determined 33 potential candidate molecules that bound to CD11b/CD18 K562 cells at EC50 < 6 μM.

Conclusions: We will further investigate the anti-inflammatory properties of these newly selected candidates in vitro and in vivo. We will compare the efficacy of the new candidates, M1/70 a CD11b antagonist antibody, and CD11b agonist leukadherins in an anti-glomerular basement membrane nephritis model. We suggest that we can utilize this HTS assay to identify integrin-specific, small-molecule agonists that can provide effective therapeutics for lupus nephritis.

Funding: NIDDK Support

SA-PO520

Development of a Novel Drug Formulation to Enhance Mesangial Deposition in Glomerulonephritis

Uma R. Fogeru,1,2 Gavriel Roda,1 Georgia Charokopiti,1 Michael F. Wemp,1 Josh Reed,1,2 Skaggs School of Pharmacy and Pharmaceutical Sciences, Univ of Colorado, Aurora, CO; 1Div of Rheumatic and Inflammatory Diseases, Univ of Colorado, Aurora, CO.

Background: Optimal kidney mesangial deposition for drug delivery vehicles are size 10-100 nm and neutral to negative charge. The overall goals of this project were to develop a novel nanocarrier of the tyrosine-kinase inhibitor, Imatinib Mesylate (ImM) to enhance renal proximal tubule (PT) following IV administration, reducing gene expression in mouse kidney cortex to 22.8% (SD 25%) as compared to siSCR mouse kidney cortex expression. Time course studies indicate that gene expression remains reduced gene expression in mouse kidney cortex to 22.8% (SD 25%) as compared to siSCR mouse kidney cortex expression. Time course studies indicate that gene expression remains reduced following a single IV injection of siRNA, siLRP2, and protein expression of megalin, which is constitutively expressed, in order to better understand the molecular regulation of this protein.

Methods: 2’O-methylated siRNA targeting mouse LRP2 (siLRP2) was commercially obtained at InvivoGen. siLRP2 and siRNA were administered by tail vein injection to C57bl/6 mice at baseline. Pharmacodynamic measures of gene and protein expression of LRP2 (megalin), which is constitutively expressed, in order to better understand the molecular regulation of this protein.

Results: Compared to siSCR, siLRP2 reduced gene expression in SI PT cells by 17.6±4.8% (p=0.0041). Gene expression reduction in vivo varied considerably depending on conditions. Under optimized conditions measured 3 h after administration, siLRP2 reduced gene expression in mouse kidney cortex to 22.8% (SD 25%) as compared to siSCR mouse kidney cortex expression. Time course studies indicate that gene expression remains reduced following a single IV injection of siRNA, siLRP2, but increased at 24 h (170%, SD 26%). No significant decrease in megalin renal protein expression was observed by either western blot or IHC under any condition, even with a maximized twice daily dose for 4 days. siLRP2 reduced liver LRP2 expression; however, lung and whole blood expression did not change significantly due to the low expression of LRP2 in these tissues at baseline.

In Vivo siRNA Knockdown of LRP2 (Megalin) in Mice

Michael T. Eadon, Yinghua Cheng, Kelly J. Mason, Pierre C. Dagher, Nephrology, Indiana Univ, Indianapolis, IN.

Background: siRNA stabilized with 2’O-methylation is filtered and reabsorbed in the renal proximal tubule (PT) following IV administration, reducing gene expression temporarily in the PT. Prior siRNA efforts have focused on preventing up-regulation of candidate genes in response to injury or disease. We instead proposed to reduce gene and protein expression of LRP2 (megalin), which is constitutively expressed, in order to better understand the molecular regulation of this protein.

Methods: 2’O-methylated siRNA targeting mouse LRP2 (siLRP2) was commercially obtained at InvivoGen. siLRP2 and siRNA were administered by tail vein injection to C57bl/6 mice at baseline. Pharmacodynamic measures of gene and protein expression of LRP2 (megalin), which is constitutively expressed, in order to better understand the molecular regulation of this protein.

Results: Compared to siSCR, siLRP2 reduced gene expression in SI PT cells by 17.6±4.8% (p=0.0041). Gene expression reduction in vivo varied considerably depending on conditions. Under optimized conditions measured 3 h after administration, siLRP2 reduced gene expression in mouse kidney cortex to 22.8% (SD 25%) as compared to siSCR mouse kidney cortex expression. Time course studies indicate that gene expression remains reduced following a single IV injection of siRNA, siLRP2, but increased at 24 h (170%, SD 26%). No significant decrease in megalin renal protein expression was observed by either western blot or IHC under any condition, even with a maximized twice daily dose for 4 days. siLRP2 reduced liver LRP2 expression; however, lung and whole blood expression did not change significantly due to the low expression of LRP2 in these tissues at baseline.
SA-PO523
A Predictive Modeling of Tacrolimus Pharmacokinetic Parameters Based on a High-Throughput Genomic Screening Approach Nicolas Pallet,1,2 Margaux Lucq,3 Eric Thervet,4 Cecilia Damon.5 1Hôpital Européen Georges Pompidou; 2Inst Hyceruc.

Background: CYTP3A4 and CYTP3A5 variants explain only a part of the variation in Tacrolimus (Tac) metabolism suggesting the involvement of a wider network of candidate genes. Therefore, other candidates are likely to explain the genetic basis for interindividual variability in dose adjusted Tac concentrations (Tac C0/Dose). Given the high level of interdependence between individual genes, we can assume that any biochemical reactions underlying drug responses could not depend on individual gene-drug correlations but rather on a group of genes.

Methods: Based on a high-throughput genomic screening approach, we aimed to identify a set of covariant germline polymorphisms predictive of the interpatients Tac pharmacokinetics variability in kidney transplantation. Tac C0 of 229 kidney transplant recipients were monitored at each follow-up time after transplantation during three months. We developed a predictive multivariate model integrating an ensemble features selection scheme based on Fisher’s test and Mutual Information, and a temporal multivariate predictive modeling with Partial Least Squares regression.

Results: At days 60 and 90 and over all days, the predictive models explained 70.2%, 62.9% and 22.9% of total log(Tac C0/Dose) variability with 44, 33 and 16 genes, respectively (p-value<0.003 with a permutation test). As expected, these models included CYP3A4 and CYTP3A5 variants, and highlight molecular networks of drug metabolism and oxidoreductase activities. In addition, we have identified a variant of the gene encoding the transporter A overexpressed in the colon, a nucleoside transporter, as a potential candidate gene. Carriers of the SLCO2B1 rs10868152, which is an intronic variant without linkage disequilibrium, have consistently lower Tac C0/Dose, both in the discovery cohort, and in an independent validation cohort of 189 kidney transplantation patients.

Conclusions: Genes variants networks explain 30 to 70% of the inter-patient variability of Tac metabolism; genes interaction networks related to oxidoreduction functions and mono-oxygenase activity have a major impact on Tac metabolism; unexpectedly, purine transporters appear to be involved in Tac metabolism and biodisposability.

SA-PO524
A Functional SNP at MiR-582-5p Binding Site in Calcinurin Subunit PPP3R1 Leads to Tacrolimus Resistance in Idiopathic Membranous Nephropathy Patients Ying Zhu, Jun Xue, Chuanning Hao. Nephrology, Huashan Hospital.

Background: Pharmacokinetic information alone appears to be insufficient to explain the variable drug response. The study explored the contribution of polymorphisms in the genes encoding tacrolimus drug target (calcineurin) on the interpatient variability of its efficacy in idiopathic membranous nephropathy (IMN) patients.

Methods: We searched for variants in the genes encoding calcineurin (PPP3CA, PPSPCB, PPSPCC, PPP3R1 and PPP3R2) by whole-exome sequencing in 8 IMN patients who received tacrolimus, including 4 with complete (CR) or partial remission (PR), 4 with no response (NR). The variants found were genotyped in another 12 patients (5 with CR or PR, 7 with NR). All patients had tacrolimus trough blood concentrations in the target range. The associations of these variants with the response to tacrolimus were analyzed. The functions of the meaningful variants were further investigated in human peripheral blood mononuclear cells (PBMCs) and other cell lines.

Results: A total of 19 variants were observed. Logistic regression analysis showed that the C allele of rs 875 (a T-o-C nucleotide change in the 3'UTR of PPP3R1) was significantly associated with an increased risk of tacrolimus resistance (P=0.025, OR=12.5, 95% CI: 1.089-143.421). As compared with the TT genotype in rs875 (n=25), the TT genotype (n=58) had higher PPP3R1 protein expression level in human PBMCs as assessed by immunoblot (P=0.0163). Bioinformatics analysis predicted that the C allele of rs875 disrupted a transcription factor binding ssb2-spsm and ssp2s-p and PPP3R1 CUB lattice luciferase reporter vector demonstrated that a significantly higher luciferase activity was observed in the rs875 CC construct when compared with the rs875 TT construct (P<0.05). MicroRNA mimics transfection showed that miR-582-5p suppressed PPP3R1 expression in cultured human podocytes with TT genotype, but not in cells with TC genotype (P<0.05).

Conclusions: Our findings suggest that rs875 may contribute to the risk of tacrolimus resistance in IMN patients through disrupting the regulatory role of miR-582-5p on PPP3R1 expression. Besides pharmacokinetics, pharmacodynamics should also be taken into account in improving tacrolimus therapy.

SA-PO525
CYP3A5 Genotype and Race Association to Tacrolimus Pharmacokinetics Kathleen M. Tomnare,1,4 Daniel Brazeau,2 Gregory E. Wilding,3 Louise M. Cooper,1 Rocco C. Venuto.4 1School of Pharmacy; 2School of Pharmacy; 3School of Public Health; 4School of Medicine; Univ at Buffalo.

Background: Variability in tacrolimus(TAC) dosing and pharmacokinetics(PK) between African American(AA) and Caucasian(C) renal transplant recipients(RTR) is attributed to cytochrome P450(CYP3A5) polymorphisms. The Clinical Pharmacogenetics Implementation Consortium(CPIC) TAC guidelines indicates CYP3A5*1 [Wild-type(W,T)] are Extensive Metabolizers(EM) and *3 [major variant] are Poor Metabolizers(PM) yielding racial differences in dose-normalized troughs and dosing. This study evaluated CYP3A5 genotype associations to TAC PK in AA and C RTR.

Methods: A 12-hr PK study determined trough(T12), C12/Dose(C12+), Area Under the Concentration Curve0-12(AUC12), AUC12/Dose(AUC*) and clearance(CL) in 32 C and 33 AA C and >6 months post-transplant on steady-state TAC and mycophenolic acid. TAC troughs were adjusted to PM of 4-9 ng/ml. CYP3A5 polymorphisms *1 and *3 [rs7767467] were determined. CPIC defined phenotypes grouped by race were: *1W/T [EM]; *13 [ Intermediate Metabolizer (IM) and *33 [PM].

Results: EM-AA had required twice the dosage compared to PM with comparable C12. EM-A had 50% of the AUC* with rapid CL compared to PM. IM in AA and C had similar AUC* and CL while C had no EM.

SA-PO526
Influence of Age and Race on Mycophenolic Acid Pharmacokinetics Post-Transplant Kathleen M. Tomnare.1 Kris Atwood,2 Louise M. Cooper,1 Rocco C. Venuto.4 1Pharmacy, School of Pharmacy and Pharmaceutical Sciences; 2Biostatistics, School of Public Health; 3Nephrology/Medicine, School of Medicine and Biomedical Sciences; Univ at Buffalo.

Background: Minimal data is available describing the influence of age on mycophenolic acid(MPA) pharmacokinetics (PK) in African American (AA) and Caucasian (C) renal transplant recipients (RTR) in spite of increased renal transplantation in the elderly. Our sub-study investigated the impact of age on MPA PK in stable AA and C RTR.

Methods: The 12-hour PK study determined trough(C12), C12/Dose(C12+), Area Under the Concentration Curve0-12(AUC12), AUC12/Dose(AUC*) and clearance(CL) in 32 C and 33 AA C and >6 months post-transplant on steady-state TAC and MPA. Troughs were adjusted to PM of 4-9 ng/ml. MPA phenotypes were: *1*1(W/T) are Extensive Metabolizers(EM); *1*3 [Intermediate Metabolizer (IM)] and *3*3 [PM].

Results: Differences in TAC PK exist between race-CYP3A5 genotypes and support race-adjusted dosing requirements to individualize TAC regimens.

Funding: NIDDK Support, Pharmaceutical Company Support - Astellas.
Micophenolic Acid Treatment in Long-Term Kidney Transplant Recipients
Antonino Previti, Gianni Cappelli. Dept of Surgery, Medical and Dentistry, University of Modena, Modena, Italy.

Background: Therapeutic Drug Monitoring (TDM) of Micophenolic acid (MPA) has been clearly defined for the early post-transplant period while it has been less explored in the long-term follow-up. We evaluated TDM of MPA in long-term kidney transplant (KTx) recipients with immunosuppressive regimens combined with cyclosporine (CyA) or tacrolimus (FK).

Methods: Subjects of this observational, single-center, prospective study were recipients with a minimum of 2 years following their kidney transplantation and were on long-term MPA therapy. They were divided into groups according to their age and race. Further evaluation of age-related changes in MPA exposure was performed.

Results: Despite CyA group was prone to increased clearance of MPA (e.g. type of immunosuppressive regimen), all groups showed a significant decrease in MPA exposure compared to the pre-transplant values. MPA lower trough concentrations (TLC) and exposure with limited sample strategy (AUC-LSS), hemoglobin (Hb), eGFR, albumin, TLC of metabolite 7-O-MPA-glucuronide (MPAG).

Conclusion: We obtained a total of 180 samples (111 from patients on CyA and 69 from patients on FK). The CyA group had a lower Hb (12.39±1.53 vs 14.71±1.6 g/dl), eGFR (44.8±15.9 vs 61.5±17.1 ml/min) and higher MPAG-TLC (94.28±38.68 vs 44.38±21.33 mg/l) than FK group (p<0.001), and no significant difference in dMyf and MPA-TLC. In 15 volunteers (10 on CyA, 5 on FK) we performed AUC-LSS and on 15 patients we were in range 30-60 mg/l.

Conclusions: Our data show that CyA group was prone to increased clearance of MPA (e.g. type of immunosuppressive regimen, worst eGFR etc.), they presented the same dMyf and not different MPA-TLC than the FK group. This finding suggests that, in long-term KTxs with decreased dose of CyA (C0 86.1±22.5 mg/l), may there be a similar interindividual hepatobiliary capacity for MPA with both CyA and FK immunosuppressive regimens. AUC-LSS of our study had a high percentage of patients in a proper MPA exposure, but this finding could be limited by estimation with LSS based on formulas for early KTxs. Some patients in 30-60 mg/l range received very low dMyf (e.g. 360 mg/day in the CyA group). We speculate that there isn’t a low limit dose, but only a proper or inadequate exposure to MPA.

The Gut Microbiota and Drug Metabolism over Chronic Kidney Disease

SA-PO529

AZD9977 is a novel Mineralocorticoid Receptor (MR) Modulator with a Differentiated Mode of Action

Results: Excess MR activation promotes target organ dysfunction, vascular injury and fibrosis. MR antagonists (epalrestat, spironolactone) improve outcomes in patients with heart failure, but their use in diabetic populations and in chronic kidney disease is limited by the target associated risk for hyperkalaemia. Novel, potent and selective MR antagonists should ideally increase the therapeutic window by separation of organ protection from effects on electrolyte balance to avoid hyperkalaemia. AZD9977 is a first in class, selective non-steroidal MR modulator that has been compared to eplerenone in preclinical studies.

Methods: Organ protection was studied in uni-nephrectomised (UNX) rats administered aldosterone via osmotic minipumps and fed a high-salt diet with compounds admixed for 4w. Acute effects of AZD9977 and eplerenone on aldosterone driven Na+ retention was tested in rats on a low salt diet by administering a single dose and subsequent urine collection for 8h.

Results: In vitro, AZD9977 and eplerenone show similar potencies in competition binding experiments and in reporter gene assays. AZD9977 promotes nuclear translocation of MR in EA.hy926 cells expressing endogenous MR while eplerenone antagonises aldosterone mediated nuclear translocation. In UNX rats, 10, 30, 100 mg/kg AZD9977 or 10, 30 mg/kg eplerenone dose dependently reduced urine albumin to creatinine ratio in 24h urine after 4w and improved histopathology scoring of kidney and heart to similar degree. In acute testing, AZD9977 up to 100 mg/kg caused a minimal increase in urine Na+ while 3 to 100 mg/kg eplerenone led to a dose dependent substantially increased Na+ secretion. Co-administration of 100 mg/kg AZD9977 with 10 or 30 mg/kg eplerenone reduced eplerenone mediated Na+ secretion, suggesting a differentiated action for the two compounds in the same pathway.

Conclusions: AZD9977 is a novel differentiated MR modulator which in preclinical testing dissociates organ protective effects from effects on urine electrolytes, predicting a reduced risk for hyperkalaemia compared to regular MR antagonists in the clinical setting.

Funding: Pharmaceutical Company Support - AstraZeneca R&D

IgG/Creatinine Ratio in Spot Urine as a Prognostic Marker for Rituximab Therapy Outcome in Patients with Nephrotic Syndrome
Michelle Dwong, Klaus Stahl, Roland Jacobs, Mario Schiffer. Dept of Nephrology and Rheumatology, Hannover Medical School, Hannover, Germany; Dept of Immunology and Rheumatology, Hannover Medical School, Hannover, Germany.

Results: Rituximab is a chimeric monoclonal antibody targeting CD20+ expressing cells that are used for a wide range of neoplastic and immune-mediated diseases. The nephrotic syndrome summarizes a group of syndromes such as proteinuria, edema, hyperlipidemia and hypalbuminemia. As a second line option in therapy refractory patients, Rituximab is often successfully used to treat the nephrotic syndrome with dosages ranging from 375 mg/m² BSA to 1000 mg absolute. However, there are therapy resistant patients and we suspect the failure of therapy is caused by a urinary loss of Rituximab. Therefore we aim to find an association between proteinuria and the loss of Rituximab and therapy outcome.

Methods: Nephelometric analysis and flow cytometry was used to detect IgG and Rituximab concentration in urine samples from 11 nephrotic patients who were resistant to first line therapy and received either 375 mg/m² BSA or 1000 mg Rituximab. Therefore spot urine before and 24-hour urine collection samples within the first day of the therapy were examined. Duodi cells as a CD20 expressing B-cell line was used to determine the Rituximab concentration.

Results: The analysis of the urine samples revealed a loss of IgG before treatment and excretion of Rituximab within the first 24 hours of Rituximab infusion in all included patients, which was not observed in control patients, who also received Rituximab but displayed no proteinuria. The data indicates a correlation between IgG excretion before therapy and the level of reduction of proteinuria afterwards.

Conclusions: The preliminary results show that the determined IgG/creatinine ratio of spot urine before therapy may be a feasible and quick predictor of a Rituximab therapy success and might help for dosage adjustment.

The Burden of Hepatorenal Syndrome (HRS)
Khrurram Jamil, J. Bradford Rice, Alan G. White, Philip J. Galebach. Department of Rheumatology, Hannover Medical School, Hannover, Germany; Department of Immunology and Rheumatology, Hannover Medical School, Hannover, Germany.

Background: HRS is a life-threatening complication in patients with advanced chronic kidney disease, characterized by the loss of effective renal function and the development of acute liver failure. Rituximab is often successfully used to treat the nephrotic syndrome with dosages ranging from 375 mg/m² BSA to 1000 mg absolute. However, there are therapy resistant patients and we suspect the failure of therapy is caused by a urinary loss of Rituximab. Therefore we aim to find an association between proteinuria and the loss of Rituximab and therapy outcome.

Methods: Nephelometric analysis and flow cytometry was used to detect IgG and Rituximab concentration in urine samples from 11 nephrotic patients who were resistant to first line therapy and received either 375 mg/m² BSA or 1000 mg Rituximab. Therefore spot urine before and 24-hour urine collection samples within the first day of the therapy were examined. Duodi cells as a CD20 expressing B-cell line was used to determine the Rituximab concentration.

Results: The analysis of the urine samples revealed a loss of IgG before treatment and excretion of Rituximab within the first 24 hours of Rituximab infusion in all included patients, which was not observed in control patients, who also received Rituximab but displayed no proteinuria. The data indicates a correlation between IgG excretion before therapy and the level of reduction of proteinuria afterwards.

Conclusions: The preliminary results show that the determined IgG/creatinine ratio of spot urine before therapy may be a feasible and quick predictor of a Rituximab therapy success and might help for dosage adjustment.

Funding: Pharmaceutical Company Support - AstraZeneca R&D
commercially-insured and 74.1 among Medicare patients. After admission, median survival was short (commercial: 95 days; Medicare: 73 days). Within the first 30 days, the average stay was 11-12 days in both groups. Based on Kaplan-Meier analyses, 36% of commercially-insured and 26% of Medicare patients were readmitted within the next 30 days. Within the first 30 days, a substantial number of patients received dialysis (commercial: 30.5%; Medicare: 20.6%). Commercially-insured patients spent an average of 7.2 days on dialysis (not available in Medicare data). During follow-up, 10.7% of commercially-insured and 1.6% of Medicare patients received liver transplants while 1.4% and 0.2% received renal transplants, respectively. Average costs within the 90 day follow-up period were $157,665 for commercially-insured and $48,322 for Medicare patients, with most costs occurring within the first 30 days. The primary cost driver was inpatient visits (commercial: 90.3% of costs; Medicare: 83.1% of costs), with differences between the populations associated with lower mortality, higher transplant rates, and higher dialysis rates among the commercially-insured.

Conclusions: HRS is associated with high mortality and rates of nephrology-related healthcare resource utilization and imposes a significant economic burden.

Funding: Pharmaceutical Company Support - Mallinckrodt Pharmaceuticals

SA-PO532
Temporal Trends in the Rates of Acute Kidney Injury across Healthcare Settings in the Irish Health System
Austin G. Stack,1,2,4 Mohammed A. Kaballo,1,2,3 Patrick T. Murray,1 Xia Li,1,2 Nephrology, Univ Hospital Limerick, Ireland; 1Health Research Inst, Univ of Limerick, Ireland; 1Medicine, UCD School of Medicine and Medical Sciences, Dublin, Ireland; 2Graduate Entry Medical School, Univ of Limerick, Limerick, Ireland.

Background: Complete ascertaining of the true rates of acute kidney injury (AKI) and emerging trends are essential for the deployment of robust management within health systems. We determined the incident rates of first AKI and annual trends from 2005-2014 in the Irish Health System.

Methods: Data from regional information systems were linked with mortality data from 2005 to 2014 (n=587,087). AKI events were identified as per KDIGO guidelines. Incidence rates (per 1000 patients) were calculated for each year, by county, geographic region, location of medical supervision [Emergency room (ER), General practice (GP), Inpatient (IP), Outpatient (OP) Outside facility (OF)]. Analysis were conducted using general linear modeling and logistic regression.

Results: Average age was 47.3 ± 19.9 years and 47% were men. AKI incidence rates increased significantly from 6.78 (6.60, 6.96) in 2005 to 14.96 (14.55, 15.37) in 2014 per 1000 patients. Rates were higher in men than in women, increased with advancing age, varied by county of residence, by region and by location of medical supervision. P<0.001 for all. From 2005 to 2014, the rates of AKI increased in IP (3.0% to 5.25% to 2014)), in ER (from 8.41 to 20.44/1000), in OP (7.23 to 22.16/1000), in OF (3.0 to 9.21/1000, P<0.0001), and in OP (1.01 to 4.13/1000), P<0.001 for all trends. The likelihood of AKI was substantially higher in 2014 (OR=4.75, 95% CI: 4.12-5.45) vs 2005 (OR=1.00, referent).

Conclusions: AKI events are more deleterious for younger than for older patients, with younger women having the greatest risk.

Funding: Government Support - Non-U.S.

SA-PO533
Acute Kidney Injury Exerts Greater Impact on Mortality in Younger Men and Women Than among Older Patients within the Health System
Austin G. Stack,1,2,4 Mohammed Elsayed,1,2,3 Muhammad Umair Sharif,1,2 Patrick T. Murray,1 Ahmed Alghali,1 Xia Li,1,2 Nephrology, Univ Hospital Limerick, Limerick, Ireland; 1Graduate Entry Medical School, Univ of Limerick; 1Health Research Inst, Univ of Limerick, Ireland; 1UCD School of Medicine and Medical Sciences, Univ College Dublin, Ireland.

Background: Recent studies have shown that acute kidney injury (AKI) independently predicts mortality. However it is unclear whether the risks are equal for both men and women and across age groups. We investigated whether the impact of AKI on mortality differs by age and sex within the Irish Health System.

Conclusions: AKI rates have increased substantially in the Irish health system over time and in all healthcare settings. Given the scale of the problem, a national strategic plan is necessary to reduce AKI events and avoid adverse consequences.

Funding: Government Support - Non-U.S.

SA-PO534
Acute Kidney Injury in Primary and Secondary Care in England: Lessons and Initial Results from a National Registry
Fergus J. Caskey,1,2 Rebecca N. Evans,1,3 Denny M. Abbott,1 Nicholas M. Selby,1 Daniel S. Lasserson,1 Nitin V. Kolbe,1 Richard J. Fluck,1 1UK Renal Registry, Bristol, United Kingdom; 2University of Bristol, United Kingdom; 3National Kidney Federation, United Kingdom; 4Royal Derby Hospital, United Kingdom; 5Univ of Oxford, United Kingdom.

Background: Acute Kidney Injury (AKI) is common and associated with considerable morbidity and mortality. This study aims to report progress and initial results from setting up a national AKI registry in England.

Methods: Since March 2015, NHS England has required all labs to 1) use a nationally agreed electronic detection algorithm to identify cases of potential AKI and 2) submit data on all cases, whether in primary or secondary care, to the UK Renal Registry. The algorithm looks back at local baseline creatinine results 1-7 and 8-365 days prior to the index result to produce a test result (AKI warning stage 1, 2 or 3 based on an index to baseline ratio of 1.5-2.0, 2.0-3.0 or 3.0+ (or index >354 umol/L), respectively. For each AKI warning stage, patient identifiers, demographics and AKI stage are transmitted each month securely to the Registry and linked with the NHS spine for 30-day mortality tracing. Area-level social deprivation is assessed using the postcode-derived Index of Multiple Deprivation (IMD). This work is permitted without individual patient consent under the Registry’s Section 251 support.

Results: In March 2015, 27 (21%) of an estimated 131 labs in England submitted data, increasing to 73 (56%) by March 2016. In that period, 509,375 AKI warning stage reports were returned to the Registry in 184,354 individuals, 170,401 (92.4%) of whom had age, gender and IMD data and could be traced to the NHS Spine. The highest recorded AKI level for each individual was 1 in 65.2%, 2 in 18.5% and in 16.3%, with associated 30-day crude mortality rates of 14.3%, 29.7% and 31.5%, respectively. Compared to the least deprived decile, 30-day age- and sex-adjusted mortality was higher in people in the most deprived areas: 24.6%, 11.7% and 10.9% higher for AKI 1, 2 and 3, respectively.

Conclusions: Establishing a national registry of AKI in primary and secondary care is possible in England and has the potential to be a powerful quality improvement, public health and research tool.

Funding: Government Support - Non-U.S.

SA-PO535
Comparing Community and Hospital Acquired Acute Kidney Injury in a Population Based Study
Hilda Hounkpatin,1 Simon D.S. Fraser,1 Matt Johnson,2 David Culliford,3 Paul J. Roderick,1 1Academic Unit of Primary Care & Population Sciences, Univ of Southampton, United Kingdom; 2Health Sciences, Faculty of Medicine, Univ of Southampton, United Kingdom.

Background: Early recognition and management of acute kidney injury (AKI) is necessary to minimise preventable harm and high healthcare costs. The epidemiology of hospitalised AKI has been well described, but less is known about factors associated with community-acquired AKI (CA-AKI). Identifying those at risk of CA-AKI would be valuable.

Methods: Data from 2 regional information systems were linked with mortality data from 1999 to 2011 (n=533,773). AKI events were identified per KDIGO guidelines. Transient AKI events were identified as acute elevations in creatinine which fell to below 1.1 times baseline within 48 hours of initial event. Multivariate Cox regression modelled the associations (Hazard ratios and 95% CI) with death and interaction terms tested for differences between gender and age groups (≤ 59, 60-80, and >80 years). Patients were censored at death, lost-to-follow-up, or end of study. Analyses were adjusted for demographic, facility characteristics, and laboratory variables.

Results: In the full multivariable Cox model, the interaction term for age*gender*AKI stage was very significant (P<0.001). The stratum-specific hazard ratios for each age and gender subgroup are shown.

Funding: Government Support - Non-U.S.
because approximately two-thirds of AKI originates in the community and some patients are not admitted to hospital. We aimed to describe the characteristics and associations of CA-AKI using a large, anonymised routine linked dataset.

Methods: Using data from the Hampshire Health Record (HHRA) UK, a data resource linking primary and secondary care (including laboratory) data, we applied KDIGO-based AKI criteria to identify AKI patients during 2014. Descriptive statistics and multivariate logistic regression models were used to compare characteristics of CA-AKI and hospital acquired acquired AKI (HA-AKI) patients, adjusting for age, gender, socioeconomic status, comorbidities and prescribed medication.

Results: 5,724 out of 643,039 eligible population generated at least one AKI alert: 61% (3469/5724) with CA-AKI and 39% (2255/5724) with HA-AKI. Being older, living in a deprived area, having hypertension, diabetes, chronic kidney disease, heart failure and being prescribed diuretics were risk factors for both CA-AKI and HA-AKI. Female gender and non-steroidal anti-inflammatory drugs (NSAIDS) were associated with CA-AKI but not HA-AKI. Renin angiotensin system inhibitors (RAASi) was associated with being prescribed diuretics were risk factors for both CA-AKI and HA-AKI. Female

Conclusions: Incidence of CA-AKI was common (61% of all AKI) in our cohort. The study identified the characteristics of people at risk of CA-AKI in primary care who may benefit from targeted prevention, and indicates important differences in medication risk factors for CA-AKI and HA-AKI.

Funding: Other NIH Support - NIH CLAHRC Wessex UK

SA-PO536

Background: In spite of increased global attention on AKI, including the 0by25 initiative, CA-AKI is not well understood in developed countries. CA-AKI, its associated diagnoses and impact on LOS were studied among patients admitted through EDs in a large IDN.

Methods: We identified all inpatient admissions over a 6 month period (10/15-3/16) that originated in the ED across 9 hospitals in urban and suburban settings in the Northeast US. Transfers from other acute care settings were excluded. CA-AKI was identified using KDIGO criteria from presenting creatinine values, using minimum values as the baseline. CA-AKI stage was correlated to diagnosis codes and LOS.

Results: 42,053 admissions met inclusion criteria. Mean patient age was 65.2y, and patients were 47.0% male. CA-AKI was identified in 6,494 admissions (15.4%), with stages 1, 2, and 3 present in 10.7%, 3.6% and 1.2%, respectively. The rate of CA-AKI varied from 12.5-18.3% across hospitals. The rate and distribution by stage were consistent across time.

Conclusions: Incidence of CA-AKI was common and correlated with extended LOS. Analysis of LOS across the 10 most common MDCs with the top 3 CA-AKI rates were 12.2% for circulatory, 11.2% for digestive, and 10.7% for respiratory MDCs.

SA-PO538
Redefining Neonatal Acute Kidney Injury: Insights from the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKENs) Cohort


Background: Definitions of neonatal acute kidney injury (AKI) based on serum creatinine (sCr) derived from adult standards fail to incorporate confounders of gestational age (GA) and rapid changes in sCr. Consequently, the incidence of neonatal AKI varies from 12%-70% and its risks and long term morbidity have not been determined. The Neonatal Kidney Collaborative (NKC) represents 24 institutions from 4 countries and is dedicated to the study of neonatal AKI. Our objective was to refine the modified KDIGO definition of AKI by examining the effects of GA and rapid changes in sCr on the incidence of neonatal AKI.

Methods: Of 4273 NICU admissions screened retrospectively during the first 3 months of 2014, 2162 infants met inclusion/exclusion criteria of needing intravenous fluids >24 hours, no cardiac surgery and no severe kidney disease. Of these 1461(67%) had at least 2 sCr values and were included in the analysis. Receiver operating curve analyses were performed with area under the curve (AUC) for multiple parameters including maximum (Max) sCr, absolute and percent(%) rise in sCr for mortality (MORT) and length of stay (LOS).

Results: sCr parameters are summarized in the Table. AUC >0.7 is significant (p<0.001). Only Max sCr for LOS was not significant (AUC=0.59). sCr measures are in milligrams/deciliter (mg/dl).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall Cohort</th>
<th>AUC (≥29 weeks)</th>
<th>AUC (≥29-56 weeks)</th>
<th>AUC (≥56 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max sCr</td>
<td>MORT 0.9</td>
<td>0.74</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>LOS</td>
<td>0.8</td>
<td>0.59</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Max sCr Rise</td>
<td>MORT 0.1</td>
<td>0.76</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>LOS</td>
<td>0.1</td>
<td>0.74</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Max % Rise sCr</td>
<td>MORT 35%</td>
<td>0.74</td>
<td>0.50</td>
<td>25%</td>
</tr>
<tr>
<td>LOS</td>
<td>20%</td>
<td>0.73</td>
<td>0.50</td>
<td>12%</td>
</tr>
</tbody>
</table>

Conclusions: Diagnosis of neonatal AKI requires a definition based on GA and sCr rise in neonatal life. Future analyses will refine the sCr-based definition and provide a platform for prospective follow-up of this neonatal cohort.
SA-PO539
A Phenome-Wide Association Study of Hospital-Acquired Acute Kidney Injury

Background: Hospitalization Associated Acute Kidney Injury (HA-AKI) has been described in retrospective case-control studies but none has performed an exhaustive exploration of the dataset. Exhaustive methods hold a high explicative power, are easily understandable and can generate a hierarchical classification of the risks factors associated with the outcome variable.

Methods: We extracted data from a French urban tertiary academic hospital (Georges Pompidou European Hospital, HEGP)E2B Clinical Data Ware House containing more than 700,000 patients and more than 200,000,000 items and performed a Phenome-wide association study (PhEwas) to identify all the ICD-10 diagnostic codes associated with HA-AKI (AKIN scores calculated during the first week after admission).

Results: We generated a database of 222,975 entries over a period of time of 10 years manually extracted diagnostic codes. 76% of the cases were 2.6 within AKIN I (N17) was found in less than 60% of the cases in which AKIN was identified with the AKIN classification; conversely, AKIN “positive” patients received the N17 code in 30% of the cases, which might reflect misidentification of AKI by physicians.

Conclusions: The PhEwas approach is a valuable mean to discover novel associations and to perform hierarchical classification of all the factors associated with HA-AKI. Our analysis delivers insights into how physicians identify AKI and its known risk factors, and might help to revise the current standard of care.

SA-PO540
Development and Validation of Acute Kidney Injury Risk Index in Patients with Abnormal Kidney Function Undergoing Non-Cardiovascular Surgery
Lynette Espino Ilang, Shu-Yi Liao, Earl Ilano, Ali Motabar. Univ of California, Riverside, Riverside Univ Health System Medical Center.

Background: The authors sought to identify risk factors of Acute Kidney Injury (AKI) in patients with abnormal kidney function undergoing non-cardiovascular surgery and provide a risk index useful for the representative national clinical data set.

Methods: The data from 2013-2014 American College of Surgeons- National Surgical Quality Improvement Program Participant Use Data File (ACS-NSQIP PUF) was used for analysis. AKI is defined as either (a) AKIN renal morbidity outcome of progressive renal insufficiency or acute renal failure necessitating dialysis. Patient’s comorbidities and pre-operatives characteristics were evaluated as potential predictors in the model. A logistic regression model was used to build the scoring system to predict the risk of the event. The weighted risk score was constructed through the training set (75% of the whole data) and was evaluated by the area under curve (AUC). The final model was validated using the validation set (25% of the whole data).

Results: 1,195,825 operations between 2013 and 2014 were reviewed and 290,876 operations were included based on the inclusion/exclusion criteria. 2,470 subjects had AKI. Mean age was 69.9 ± 12.5 years old, 54.8% were male, and the average ASA score was 2.4 ± 0.6. Abnormal kidney function stages were identified as potential predictors and were included in the final model. Each weight was assigned based on the estimate coefficients. The full risk score ranged from 0 to 22 points. The AUC in the training set was 0.77 and was 0.79 using the validation set. People with a score of ≥ 22 points had a 86.1% risk of having AKI compared to those with a score of 0 points which had a 3% risk of having AKI.

Conclusions: Our 22 points scoring systems with 6 variables were able to predict the risk of AKI in patient with abnormal kidney function stage 2-5. This tool is promising and may be used in the clinical setting for patients with abnormal kidney function undergoing non-cardiovascular surgery. External cohort includes confirmed AKI patients is needed for further validation.

SA-PO541
Mild Postoperative Acute Kidney Injury: Incidence and Outcome
Thorir E. Long,1,2 Dadi Helgason,1,2 Solveig Helgadottir,1Runolfur Palsson,1 Tomas Gudbjartsson,1,2 Gisli H. Sigurdsson,1,2 Martin I. Sigurdsson,1,2 Olafur S. Indridason.1,2 Univ of Iceland; 1Landspitali - The National Univ Hospital of Iceland, Reykjavik, Iceland; 2Brigham and Woman’s Hospital, Boston, MA.

Background: A small rise in serum creatinine of 0.3 mg/dl over 48 hrs is currently included in the definition of acute kidney injury (AKI), yielding many mild cases of unknown significance. The aim of this study was to examine the incidence and outcome of individuals with mild AKI following surgical procedures.

Methods: This was a retrospective study of all adult patients who underwent abdominal, cardiac, gastrointestinal, vascular or orthopedic surgeries at the National University Hospital in 2007-2015. Clinical data was extracted from electronic medical records. AKI was diagnosed according to the SCr component of the KDIGO criteria. The baseline characteristics and survival differences in patients with a mild AKI versus the rise in SCr of ≥ 0.5 mg/dl (about 1.5 x baseline increase in 7 days) was compared with a propensity score matched control group (PSM:1:1) without AKI. This was performed for groups with and without preoperative reduction in kidney function (eGFR<60 mL/min/1.73 m²).

Results: A total of 28,879 patients underwent 40,738 surgical operations during the study period. Both pre- and post-operative SCr was available for 19,072 operations. Median age at surgery was 68 yrs (IQR, 58-78) and 50% were female. AKI occurred following 1,557 operations (8%), 559 (5%) had mild AKI and 998 (5%) had severe AKI. Patients with AKI were more likely to have baseline eGFR < 66% vs 54% (p<0.0001), had higher baseline eGFR, 48 (28-65) vs 65 (47-83) mL/min/1.73 m² (p<0.001), and a higher comorbidity burden compared with patients with more severe AKI. Mild AKI patients with preoperative reduction in kidney function had worse 1-year survival than their PSM matched controls 76% vs 81% (p=0.01). However, individuals with normal preoperative kidney function and mild AKI had similar 1-year survival as the PSM controls 89% vs 89% (p=0.5).

Conclusions: Our study suggests that mild AKI may have a detrimental effect on outcome in patients with reduced kidney function, while those with preserved kidney function may tolerate mild AKI without adverse outcome.

SA-PO542
National Trends and Outcomes in Dialysis-Requiring Acute Kidney Injury in Patients with Septicemia
Mihir Dave,1 Harshil Shah,2 Tushar Mishra,1 Arpitu Hazra,2 Sumit Khiclner,2 Abhishek Mishra,1 Siddarth Mehta,1 Kinsuk Chauhan,1 Achint Patel.1 1Icahn School of Medicine at Mount Sinai, New York, NY; 2Dietotic Medical Center, Detroit, MI; 3Univ Of Arkansas For Medical Sciences, Little Rock, AR; 4Univ of Iowa and Clinics; 5Mount Sinai Beth Israel.

Background: National Trends and Outcomes in Dialysis-Requiring Acute Kidney Injury in patients with Septicemia.

Methods: We used the nationwide inpatient sample (NIS) database 2002-2013 to identify patients hospitalized with Septicemia using Clinical Classification Software (CCS) developed by AHRQ. We defined AKI-D based on previously validated ICD-9-CM codes including 584.xx for AKI, v45.11, v56.0 and v56.1 for dialysis and procedure code 39.95 for the dialysis procedure. We excluded hospitalizations that had codes for dialysis but not for AKI, as these were likely for ESRD patients on dialysis. We used the multivariate regression analysis to change trends in outcomes and explore potential reasons explaining these changes.

Results: From 2002-2013, of the 8,108,048 patients who were hospitalized with septicemia, 214185 (2.64%) developed AKI-D. Proportion of AKI-D increased from 1.4% in 2002 to 2.65% in 2013 in hospitalizations in 2013 (p<0.001) (Figure 1). This trend increased annually by 4.2% (OR 1.035; 95% CI 1.03-1.04; p<0.001). This rise was completely explained by changes in demographics and increase in co-morbidities. Interestingly, in-hospital morality (40% vs≤15%) and discharge to specialized care (63% vs≤37%) were higher among the AKI-D patients. Odds of in-hospital mortality (OR 2.08; CI 2.02-2.14; p<0.001) and discharge to specialized care (OR 1.78; CI 1.72-1.84; p<0.001) remains high. Although the percent in-hospital mortality after AKI-D was decreased, the adjusted odds increased (OR 1.63 to 2.14). And also, the adjusted odds of requiring specialized care in a facility increased annually (OR 1.42 to 1.91).

Conclusions: The incidence of AKI-D in patients admitted with Septicemia has increased over the period of time. Our results emphasize the need for better risk stratification and early recognition of kidney dysfunction in patients with septicemia.

SA-PO543
Epidemiological Study on the AKI-CKD Communication: A Single-Center Retrospective Database Analysis
Taro Horino,1 Yutaka Hatakeyama,2 Hiromi Kataoka,3 Tatsumi Matsumoto,4 Yoshiko Shimamura,3 Kosuke Inoue,3 Yoshio Terada,1 Yoshitani Okuara,4 1Dept of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi Univ, Nankoku, Japan; 2Center of Medical Information Science, Kochi Medical School, Kochi Univ, Nankoku, Japan.

Background: Acute kidney injury (AKI) is a serious complication among hospitalized individuals and is closely associated with chronic kidney disease (CKD). This study investigated the extent of renal dysfunction progression after AKI events in both CKD and non-CKD patient groups.

Methods: This retrospective cohort study registered 131,358 individuals who visited Kochi Medical School hospital between October 19, 1981 and December 31, 2014. AKI and CKD was defined and staged according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, using measured serum creatinine levels. This study evaluated 10,189 AKI events that meet KDIGO criteria.

Results: The incidence of AKI in this cohort was 7.8% (95% confidence interval: 7.7-8.0%). AKI stage 1, 2 and 3 were 7,803, 1,703, and 683, respectively. We finally analyzed data from 1,846 AKI patients, excluding patients who had proven post-renal AKI or who were on dialysis requiring medicare group B were 72.9, 42.5, and 55.0 mL/min/1.73 m², respectively. Those in group C were 38.8, 24.7, and 36.0 mL/min/1.73 m², respectively. Interestingly, mean eGFRs after AKI event in all three groups were significantly reduced compared to those on baseline. Furthermore, this eGFR trend tended to progress on time-dependent manner.
Conclusions: We found that AKI was a risk factor for CKD progression. We showed that low eGFR levels before AKI are and more frequently AKI events occur, more the incidence of CKD increase. We propose that physicians should pay attention to AKI-CKD communication.

SA-POS44
Acute Kidney Injury in the Tertiary Care Setting in Rwanda
Marla D. McNaight,1 Fredric O. Finkelstein,2 Grace Igiraneza,1 1Dept of Medicine, Univ of Rwanda, Butare, Rwanda; 2Yale Univ, New Haven, CT.

Background: Acute kidney injury (AKI) is a global health concern impacting both the developed and developing countries. There is limited data from low-income settings on the epidemiology and outcomes of AKI.

Methods: In this observational, multi-centre study conducted in Rwanda between September 1, 2014 and January 31, 2015, patients ≥ age 16 admitted to a tertiary care hospital were screened for evidence of serum creatinine in both hospital and external labs. Patients meeting KDIGO definition of AKI based on change in serum creatinine, had demographic and clinical information collected and were followed until discharge or in-hospital death. Length of stay (LOS) and in-hospital mortality in patients with AKI were compared to that of all inpatients and regression models performed to determine predictors of mortality.

Results: Of the 14,918 patients admitted, 427 patients met KDIGO criteria for AKI—8.2% stage 1, 1.4% stage 2, 49.9% stage 3. Mean age of patients with AKI was 47.2 ± 19.9; 50.8% were male. Infections (68.9%), cardiovascular disease (35.5%), pregnancy related conditions (12.4%), diabetes (11.5%) and cirrhosis (8%) were frequently associated with AKI. 10.7% of patients had a history of nephrology consult and 8% received renal replacement therapy. Mean LOS in patients with AKI was 17.4 ± 18.7 compared to 7.1 for all admitted patients (p<0.001). All-cause mortality among patients with AKI was 31.9% compared to an overall hospital mortality rate of 4.4% (p<0.001). Patients with cirrhosis (OR=5.59, p<0.001), CKD (OR=3.03, p<0.001) and cancer (OR=3.3, p=0.007) were at significantly higher risk of in-hospital mortality.

Conclusions: AKI in the tertiary care setting in Rwanda is associated with significantly increased mortality and length of hospital stay compared to patients without AKI. Further research is needed to understand the etiologies of AKI in Rwanda and other low income settings in order to guide strategies to prevent and/or reduce AKI related morbidity and mortality.

Funding: Private Foundation Support

SA-POS45
Acute Kidney Injury in Intensive Care Unit Patients: A Prospective Population-Based Study in Brazilian Amazon
Fernando de Assis Ferreira Melo,1 Etienne Macedo,2 Ana Caroline Fonseca Bezerra,2 Bruna Cristina Meira Bruno,2 Bruna Vitória Souza,2 Ravindra L. Mehta,2 Emmanuel A. Burdmann,1 Dirce M.T. Zanetta.1 1Univ of São Paulo, São Paulo, Brazil; 2Medicine, Univ of California-San Diego, San Diego, CA; 3Acre Federal Univ, Rio Branco, Acre, Brazil.

Background: AKI is commonly encountered in Intensive Care Unit (ICU) patients across the world; however, the epidemiology of Acute Kidney Injury (AKI) in the developed and developing world has not been systematically examined.

Methods: We conducted a systematic review of published studies (2005–2015) identified in PUBMED, CENTRAL, LILACS, and IBECS databases using the search terms “acute kidney injury” and “intensive care unit”. We examined the differences in AKI incidence, severity (based on KDIGO criteria) and associated mortality and describe geographic variations based on the gross national income.

Results: We identified 94 studies: 60 from developed countries and 34 from developing countries. Of these, 75.5% used KDIGO-equivalent criteria; however, we found 19 different definitions for oliguria and 19 different definitions for baseline creatinine. The frequency of AKI was higher in studies using KDIGO-equivalent criteria (34.3% vs 24.3%), with lower mortality rates (median 20% vs median 42.5%). There were no differences in incidence of AKI between developed and developing countries. However, the need for RRT, ICU length of stay and mortality rates were higher in developing countries.

Conclusions: Despite the attempt to standardize the criteria for defining AKI, there is still no uniformity in the settings for “baseline creatinine” or “oliguria”. Differences in ICU length of stay, need for RRT and mortality rates may reflect differences in the entry criteria and the social conditions, access to health care and hospital infrastructure.

Funding: Government Support - Non-U.S.

SA-POS46
Delay on Acute Kidney Injury Diagnosis in Critically Ill Patient: A Snapshot on Brazilian Amazon
Fernando de Assis Ferreira Melo,1 Etienne Macedo,2 Ana Caroline Fonseca Bezerra,2 Magela Teodoro Melo Fernandes Magela,2 Bruna Cristina Meira Bruno,2 Bruna Vitória Souza,2 Ravindra L. Mehta,2 Emmanuel A. Burdmann,1 Dirce M.T. Zanetta.1 1Univ of São Paulo, São Paulo, Brazil; 2Medicine, Univ of California-San Diego, San Diego, CA; 3Acre Federal Univ, Rio Branco, Acre, Brazil.

Background: There are deficiencies in the recognition and management of patients who developed Acute Kidney Injury (AKI) in Intensive Care Unit (ICU) that can result in delay in treatment and inappropriate referral to nephrologist, leading to worse outcomes as need for dialysis, recovery and mortality rates.

Methods: We performed a prospective study of AKI incidence in patients admitted to all ICU’s in Rio Branco, state capital of Acre, from Feb 2014 to Feb 2016. We used medical records to compare the performance of the clinician to make the diagnosis of AKI with the diagnosis made by KDIGO criteria.

Results: We studied 1046 patients. Among 43.8% of patients who developed AKI in ICU, there were agreement of the diagnosis day in only 14.5%, in 65% the clinician did not make the diagnosis and in 8.2% it was delayed. Thirty seven percent of the delayed diagnosis patients presented AKI grade III. Dialysis was offered to only 0.3% of non-diagnosed in patients in contrast with 31.3% in those who had timely diagnosis (p<0.001). The APACHE II score was lower in those non-diagnosed compared with those who had timely diagnosis (17.5 ± 27 vs 27 ± 0.001). ICU and hospital stay were higher when diagnosis was delayed compared with timely diagnosis patients (10 vs 8, p <0.001 and 21 vs 16, p <0.001, respectively). Mortality was also higher in those non-diagnosed and delayed diagnosed patients, compared with those who had timely diagnosis (61.8% vs 68.3% vs 40%, p<0.001).

Conclusions: In the vast majority of our patients, the clinic diagnosis of AKI was not done or occurred later. This fact may have contributed to delay on completion of diagnosis, inferior survival of ICU and hospital stay and higher mortality rates. It is necessary to increase awareness of AKI in ICU and disseminate knowledge about acute kidney injury stressing that small changes in renal function often contribute to severe adverse outcomes.

Funding: Government Support - Non-U.S.

SA-POS47
Epidemiology of Acute Kidney Injury in the Intensive Care Unit: A Systematic Review
Fernando de Assis Ferreira Melo,1 Etienne Macedo,2 Ana Caroline Fonseca Bezerra,2 Bruna Cristina Meira Bruno,2 Bruna Vitória Souza,2 Ravindra L. Mehta,2 Emmanuel A. Burdmann,1 Dirce M.T. Zanetta.1 1Univ of São Paulo, São Paulo, Brazil; 2Medicine, Univ of California-San Diego, San Diego, CA; 3Acre Federal Univ, Rio Branco, Acre, Brazil.

Background: AKI is commonly encountered in Intensive Care Unit (ICU) patients across the world; however, the epidemiology of Acute Kidney Injury (AKI) in the developed and developing world has not been systematically examined.

Methods: We conducted a systematic review of published studies (2005–2015) identified in PUBMED, CENTRAL, LILACS, and IBECS databases using the search terms “acute kidney injury” and “intensive care unit”. We examined the differences in AKI incidence, severity (based on KDIGO criteria) and associated mortality and describe geographic variations based on the gross national income.

Results: We identified 94 studies: 60 from developed countries and 34 from developing countries. Of these, 75.5% used KDIGO-equivalent criteria; however, we found 19 different definitions for oliguria and 19 different definitions for baseline creatinine. The frequency of AKI was higher in studies using KDIGO-equivalent criteria (34.3% vs 24.3%), with lower mortality rates (median 20% vs median 42.5%). There were no differences in incidence of AKI between developed and developing countries. However, the need for RRT, ICU length of stay and mortality rates were higher in developing countries.

Conclusions: Despite the attempt to standardize the criteria for defining AKI, there is still no uniformity in the settings for “baseline creatinine” or “oliguria”. Differences in ICU length of stay, need for RRT and mortality rates may reflect differences in the entry criteria and the social conditions, access to health care and hospital infrastructure.

Funding: Government Support - Non-U.S.

SA-POS48
Etiology and Outcome of Acute Kidney Injury – Study from Two Teaching Hospital from Nepal
Sanjib Kumar Sharma,1 1Dept of Internal Medicine, BP Koirala Inst of Health Sciences, Dharan, Nepal; 2Dept of Nephrology, College of Medical Sciences, Bhaktapur, Nepal.

Background: Most of the AKI occurs in developing nations. The etiologies and outcome is believed to be different in developed versus underdeveloped nations.

We conducted prospective observational study in two teaching hospital in Nepal to study the etiologies and the outcomes of acute kidney injury.

Methods: Consecutive patients attending out patient clinic or admitted in two teaching hospital in Nepal fulfilling AKIN criteria were enrolled and followed up for one year. The data were recorded in predefined validated case record form.

Results: The age distribution ranged from 15 years to 90 years. The most common etiology (31.38%, n=123) of the AKI was sepsis followed by community acquired pneumonia (71/392). However, significant number AKI patients had preventable causes of AKI like acute gastroenteritis (18.11%, n=46), obstructive uropathy (3.57%, n=14), malaria...
Epidermolytic Acute Kidney Injury in an Intensive Care Unit of a Third Level Hospital in Mexico City
J. Reyna, S. Hernandez, R. Rincon-Pedro.3 Medicine Interna, lnstituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, IMSS; 1Nefrologia y Mineralometria, IMSS; 2Nutrologia, IMSS.

Background: Acute kidney injury (AKI) is one of the most common complications in critically ill patients and is associated with a high risk of death, length of stay and costs. We aimed to determine incidence, associated risk factors and outcomes of AKI in a General ICU from a medical center in Mexico City.

Methods: We retrospectively studied a cohort of 463 patients admitted to an ICU during 1 year. Exclusion criteria were chronic kidney disease with CKD-EPI >60mL/kg/1.73m2 and kidney transplantation. We measured AKI by Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Results: The overall incidence of AKI was 57%, distributed among the 3 stages: 22.7% stage 1, 33.1% stage 2 and 43.6% stage 3. Only 7.1% of AKI patients needed renal replacement therapy. Regarding the cause of AKI, septic shock, non surgical-associated hypovolemia, surgical-associated hypovolemia and nephrotoxic drugs contributed with 65%, 25% and 9%, respectively. Patients who developed AKI were more common men, with history of diabetes mellitus and renal disease, with more infections, septic shock and myocardial infarction, with a higher rate of rhabdomyolysis and myoglobinuria, with renal dysfunction and with liver disease. The mortality of patients with AKI was significantly higher than those without, with an adjusted odds ratio of 2.32 (95% CI 1.52-3.53; p<0.001).

Conclusions: The incidence of AKI-D in patients admitted with pneumonia has increased over the period of time. Our results emphasize the need for better risk stratification and early recognition of kidney dysfunction in patients with pneumonia.
Results: Between 2008 and 2015, 2027 of 9780 patients (21%) had AKI during their 1st week of ICU, and we enrolled 1091 of them (54%). Over time, we observed several differences in patients characteristics, a decrease in the use of starches and diuretics, an increase in the number of kidney biopsies performed, and an earlier timing of initiation of dialysis. However, we did not observe significant changes in outcomes.

<table>
<thead>
<tr>
<th>2008-2011</th>
<th>2011-2015</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 (46-76)</td>
<td>59 (45-71)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>48.9</td>
<td>51.1</td>
</tr>
<tr>
<td>CKD</td>
<td>36.6</td>
<td>43.4</td>
</tr>
<tr>
<td>CAD</td>
<td>30.8</td>
<td>24.8</td>
</tr>
<tr>
<td>Sepsis</td>
<td>32.2</td>
<td>47.8</td>
</tr>
<tr>
<td>APACHE III</td>
<td>21 (15-72)</td>
<td>46 (32-64)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>50.4</td>
<td>49.6</td>
</tr>
<tr>
<td>Starches</td>
<td>53.2</td>
<td>42.8</td>
</tr>
<tr>
<td>Diuretics</td>
<td>8.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Cumulative fluid balance (L)</td>
<td>2.3±6.9</td>
<td>1.9±6.5</td>
</tr>
</tbody>
</table>

AKI etiology

- AIN 14.7 | 21.8 | 0.002
- GN | 2.9 | 8.4 | 0.001
- AIN | 2.0 | 6.8 | 0.001
- Prenal | 29.9 | 24.0 | 0.03
- Biopsy | 2.2 | 4.7 | 0.03
- Dialysis requirement | 23.2 | 22.1 | 0.68
- Timing dialysis vs. ICU admission (days) | 3.1 (1-7) | 1.0 (0-4) | 0.001
- Duration dialysis (days) | 5.2 (4-14) | 6.3 (3-17) | 0.63
- Lengths of stay (days) | 13.6 (6-27) | 14 (6-28) | 0.25
- Mortality | 21.4 | 18.2 | 0.28
- Dialysis-dependence at discharge | 11.9 | 12.1 | 0.77

Conclusions: Over the last 8 years, although we observed differences in patients characteristics and management, overall outcomes associated with AKI remained unchanged.

Funding: NIDDK Support

SA-PO555

Phenotype of Vancomycin Associated Drug Induced Kidney Disease (DIKD): Results from the DIRECT Study

Linda Awdishu,1 Rajasekara Chakravartih Madarasu,2 Stuart Goldstein,3 Ashita J. Tolwani,4 Melanie S. Joy,5 Etienne Macedo,5 Dinna Cruz,5 Jorge Cerda,5 David T. Selewski,5 Andrew J. P. Lewington,5 Michael Zappitelli,5 Maria Ostermann,6 Vivekanandha Jha,7 Ravindra L. Mehta,7,8 Univ of California, San Diego; 2Star Kidney Centers, India; 3Cincinnati Children’s Medical Center; 4Univ of Alabama at Birmingham; 5Univ of Colorado, Denver; 6Albany Medical College; 7Univ of Michigan; 8Leeds Teaching Hospital, United Kingdom; 9McGill Univ Health Center, Canada; 10Guy’s and St. Thomas’ Hospital, United Kingdom; 11Post Graduate Inst of Medical Education & Research, India; 12On Behalf of the DIRECT Investigators.

Background: Vancomycin (VAN) is a frequently prescribed antibiotic in critically ill patients with conflicting published data on nephrotoxicity due to lack of phenotype standardization.

Methods: DIRECT is an international multi-center study which enrolled 634 patients with DIKD to identify drug-related polymorphisms by GWAS studies that were associated with standard phenotypes. Each case was adjudicated by 2 nephrologists.

Results: VAN associated AKI cases (N=171) were confirmed by adjudication (126 adult and 45 pediatric patients). Patients were 50% male with mean age of 47.7±18.2 years in adults and 12.3±4 years in pediatrics. Patients were 57% white, 24% hispanic, 13% black and 2% asian. Comorbidities included hypertension and diabetes in adults and asthma and cancer in pediatrics. AKI risk factors at baseline included diabetes 22%, hyperglycemia 28%, sepsis 21% and anemia 21%. The mean Scr increased from 0.78±0.34 to 4.42±2.46 mg/dL in adults and 0.46±0.19 to 2.51±1.95 mg/dL in pediatrics. Time to injury was 4(2-7) days. Biopsies were performed in 8% and dialysis was required for 17.5% cases. The initial VAN dose and serum concentration was 1991±999 mg/day and 26±18.4 mcg/mL in adults and 2191±1178 mg/day and 26.7±25.5 mcg/mL in pediatrics. Mortality was 5.4%, 9.4%, 19% at hospital discharge, 28 and 90 days and 27% of cases had elevations in Scr at 90 days.

Conclusions: VAN associated DIKD is a significant problem occurring in hospitalized patients receiving conventional dosing. Genome studies will further elucidate the mechanism of this injury.

Funding: Private Foundation Support

SA-PO556

Phenotype of NSAID Associated Drug Induced Kidney Disease (DIKD): Results from the DIRECT Study

Linda Awdishu,1 Rajasekara Chakravartih Madarasu,2 Stuart Goldstein,3 Ashita J. Tolwani,4 Melanie S. Joy,5 Etienne Macedo,5 Dinna Cruz,5 Jorge Cerda,5 David T. Selewski,5 Michael Zappitelli,5 Andrew J. P. Lewington,5 Maria Ostermann,6 Vivekanandha Jha,7 Ravindra L. Mehta,7,8 Univ of California, San Diego; 2Star Kidney Centers, India; 3Cincinnati Children’s Medical Center; 4Univ of Alabama at Birmingham; 5Univ of Colorado, Denver; 6Albany Medical College; 7Univ of Michigan; 8Leeds Teaching Hospital, United Kingdom; 9McGill Univ Health Center, Canada; 10Guy’s and St. Thomas’ Hospital, United Kingdom; 11Post Graduate Inst of Medical Education & Research, India; 12On Behalf of the DIRECT Investigators.

Background: Non-steroidal anti-inflammatory drugs can cause kidney injury by different mechanisms. Risk factors have been identified and include volume depletion and concurrent nephrotoxicants.

Methods: DIRECT is an international multi-center study which enrolled 634 patients with DIKD to identify drug-related polymorphisms by GWAS studies that were associated with standard phenotypes. Each case was adjudicated by 2 nephrologists.

Results: NSAID associated AKI (N=64) and glomerular injury (N=2) were confirmed by adjudication (46 adult and 20 pediatric patients). Implicated NSAIDs were ibuprofen (N=39), indomethacin (N=2), ketorolac (N=16), ketoprofen (N=1) and naproxen (N=8). Patients were 44% male with mean age of 47.8±18.1 years in adults and 12.3±4.3 years in pediatrics. Patients were 45% white, 14% black, 14% hispanic and 27% asian. Co-morbidities included hypertension, diabetes and smoking in adults and asthma in pediatrics. The mean Scr increased from 0.91±0.31 to 4.48±2.84 mg/dL in adults and 0.49±0.18 to 3.04±2.76 mg/dL in pediatrics. Median (IQR) time to onset of injury was 4(2-7) days. Common risk factors were hyperglycemia, surgery and additional nephrotoxic exposures. Biopsies were performed in 17% with findings of interstitial nephritis in 64% of cases. Dialysis was required for 21.2% cases. Daily doses were ibuprofen 1131±654mg, ketorolac 58±36 mg and naproxen 974±402 mg. Mortality was 3.3%, 5.6% and 12.5% at hospital discharge, 28 and 90 days.

Conclusions: NSAIDs demonstrated significant increases in Scr across a range of risk factors, with infrequent definitive biopsies. Genome studies will further elucidate patient susceptibility to NSAID associated DIKD.

Funding: Private Foundation Support
SA-PO557

Vancomycin Induced Nephrotoxicity - Are We Over-Diagnosing

Ahsinseh Sinha Ray, 1 Anmar Haikal, 2 Kassem Hammoud, 3 Alan S. L. Yu. 1
1 Nephrology and Hypertension, Kansas Univ Med Center, Kansas City, KS; 2 Internal Medicine, Kansas Univ Medical Center, Kansas City, KS; 3 Infectious Disease, Kansas Univ Medical Center, Kansas City, KS.

Background: Vancomycin has been in use for more than half a century, but its extent of nephrotoxicity is still controversial. Most studies pertaining to vancomycin nephrotoxicity are observational and confounded by comorbidities, other nephrotoxins and, in studies considering achieved vancomycin concentrations as a risk factor, reverse causation. Purpose of this systematic review was to determine risk of acute kidney injury (AKI) attributable to intravenous (IV) vancomycin.

Methods: Pubmed, Cochrane Library were searched from 1990 through 2015 for randomized controlled trials (RCT) and cohort studies comparing IV vancomycin to a control group with a comparator antibiotic, in which kidney function or kidney injury outcomes were reported. Two reviewers extracted data and assessed risk of bias, one reviewer adjudicated assessments. We screened 1328 titles and abstracts, reviewed 115 articles and 7 RCT and 6 cohort studies were included in final analysis.

Results: All cohort studies were judged to have moderate or high risk of bias, so only qualitative synthesis was performed and did not provide strong evidence for vancomycin nephrotoxicity. Meta-analysis of 7 RCT suggested vancomycin was associated with increased risk of AKI (pooled RR 2.45, 95% CI 1.69-3.53). There was minimal heterogeneity between the studies (chi-square 3.67, p = 0.72, I² = 0%). Inspection of funnel plot showed no strong evidence of publication bias. However, evidence of vancomycin nephrotoxicity was judged to be indirect and of moderate strength as 12 of 13 studies compared vancomycin only to linezolid.

Conclusions: Vancomycin modestly increases risk of AKI; although substantial but still much lower compared to well-recognized nephrotoxins e.g. aminoglycosides (RR: 8-10) or amphotericin B (RR: 4-10). Nevertheless, in patients being treated with IV vancomycin that develop AKI, more than half of cases can be attributed to vancomycin (attributable fraction 0.59). A RCT of vancomycin designed to study renal outcome is needed to draw unequivocal conclusions.

SA-PO558

Comprehensive Incidence of Acute Kidney Injury Between Vancomycin/ Cefepime and Vancomycin/Piperacillin-Tazobactam Combination Therapy

Anthony Ndichu Miju 1, Andrew L. Lundquist, 2 Andrew S. Allegretti, 3
1 Medicine, Massachusetts General Hospital, Boston, MA; 2 Nephrology, Massachusetts General Hospital.

Background: Acute kidney injury (AKI) is common during infections and may be potentiated by the use of nephrotoxic antibiotics. Combination of Vancomycin/ Piperacillin- Tazobactam (Vanc/Pip) has been associated with more AKI compared to Vancomycin/ Cefepime (Vanc/Cefe), though the mechanisms are unknown. We aim to compare rates of AKI after exposure to Vanc/Pip, Vanc/Cefe, or Vanc/Pip/Cefe.

Methods: Multicenter retrospective cohort of adults exposed to >48 hours of (1) Vanc/Pip, (2) Vanc/Cefe or (3) Vanc/Pip/Cefe between January 2012 and January 2015. Participants in the Vanc/Pip/Cefe group were exposed to Cefe either concurrently with Vanc/Pip, or within 90 days prior to admission. AKI was defined by AKIN criteria. Rates of AKI were analyzed using Chi-square tests and multivariable logistic regression.

Results: 5370 participants were included; 4,090 (76%) received Vanc/Cefe, 997 (19%) received Vanc/Pip, and 283 (5%) received Vanc/Pip/Cefe.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Antibiotic Exposure</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, median (IQR)</td>
<td>65 (54, 75)</td>
<td>63 (52, 73)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>2283 (50)</td>
<td>576 (58)</td>
</tr>
<tr>
<td>White race, (%)</td>
<td>3209 (78)</td>
<td>784 (79)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>2073 (51)</td>
<td>457 (45)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1042 (26)</td>
<td>261 (26)</td>
</tr>
<tr>
<td>CKD (%)</td>
<td>1198 (29)</td>
<td>183 (18)</td>
</tr>
<tr>
<td>LOS, days, median (IQR)</td>
<td>9 (5, 17)</td>
<td>9 (5, 15)</td>
</tr>
<tr>
<td>Died during admission (%)</td>
<td>680 (17)</td>
<td>73 (7)</td>
</tr>
</tbody>
</table>

Overall incidence of AKI was 24%. AKI was similar between Vanc/Pip and Vanc/Cefe (24% vs. 23%, P = 0.8) but more common in the Vanc/Pip/Cefe group (31%, P = 0.009). Multivariable analysis, compared to Vanc/Pip, Vanc/Cefe/Pip use was associated with higher odds of AKI (OR 1.59 [95% CI 1.21, 2.10]), while Vanc/Pip use had similar odds of AKI (1.15 [95% CI 0.97, 1.40]).

Conclusions: Use of Vancomycin/Piperacillin-Tazobactam and Vancomycin/Cefepime resulted in similar rates of AKI. Use of all 3 antibiotics was associated with more AKI compared to either dual-regimen alone.

SA-PO559

Prescribing Patterns at the Time of Acute Kidney Injury: Opportunities to Improve Care

Sae Shaw, 1 Dominic Moore, 1 Aleli Akani, 2 Rebecca A. Packington, 3 Kerry L. Horne, 1 Maarten W. Taal, 1,2 Nicholas M. Selby, 1,2 1 Derby Teaching Hospitals NHS Foundation Trust; 2 Centre for Kidney Research and Innovation, Univ of Nottingham.

Background: Currently, there is limited information about medication prescribing at the time of AKI and how this impacts on patient outcomes. We present a description of prescribing patterns at the time of AKI in the context of a prospective case-control study.

Methods: Participants were prospectively identified from a hospital-wide electronic AKI reporting system. Cases (hospitalised patients who sustained AKI) were matched 1:1 with controls (hospitalised patients without AKI) for age, baseline eGFR stage and diabetes. Electronic medical record was interrogated for complete prescribing details at sequential time points.

Results: 878 patients were successfully matched. Pharmacy confirmation of medication history occurred in 757 (87%) during admission. At baseline, more cases than controls were prescribed ACE inhibitors/ARBs (206 (48%) vs 178 (41%), p=0.04) and NSAIDs (56 (13%) vs 30 (7%), p<0.003). There was no difference in prescription of statins, metformin or diuretics. At the time of AKI, 144 (33%) patients were administered ACEi/ARB and 37 (9%) cases received NSAIDs, suggesting suspension of medications in some cases. Within 24hs of AKI onset, ACEi were stopped in 126 (88%) and NSAIDs in 34 (92%) of these. 188 cases were prescribed an antibiotic at the time of AKI; dosing was inappropriate in 61 (32%). AKI diagnosis was communicated to primary care in 206 (47%) of cases at hospital discharge. Information regarding medication changes in only 123 cases (29%). At hospital discharge there was reduction in prescribing ACEi/ARB in both groups, but to a greater extent in AKI; 110 (26%) cases were prescribed ACEi/ARB at discharge, compared with 164 (37%) controls, p<0.001.

Conclusions: Whilst prescriber awareness of the importance of suspending nephrotoxic medications at time of AKI is evident, there are additional opportunities to reduce risk of AKI onset and to improve dose adjustment of common medications during AKI. Improving post-AKI care with consideration of restarting cardiovascular medications is another area in which benefits seem likely.

Funding: Private Foundation Support

SA-PO560

Carbapenem Antibiotics Are Associated with Significant Increases in Serum Creatinine after Contrast Administration

Parkar Lehmann, 1 Cherri Lehmann, 2 Asish Thukkar, 2 Udayan Y. Bhatt. 2 New Albany High School, New Albany, OH; 2 The Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: Carbapenem antibiotic use has been growing with the increase in resistant organisms. Imipenem, the initial drug in this class, was combined with cilastatin to reduce nephrotoxicity. Newer agents in this class are felt to be less nephrotoxic. Complete adverse effects of newer agents have not been fully defined. On this basis, the purpose of this study is to explore changes in serum creatinine (SCr) after contrast administration in patients on carbapenem antibiotics.

Methods: Patients receiving IV contrast with CT imaging over a 6 month period were identified. Dialysis subjects were excluded. Demographic data were obtained. All laboratory studies done on the day of imaging and SCr at 48hrs were extracted. Vital signs and all medications administered on the day of the CT scan were noted. Change in creatinine from the day prior to CT imaging to 2 days after was calculated (Delta_SCr).

Results: Records for 2530 subjects were obtained. Delta_Scr for the cohort was -0.05 +/- 0.04 mg/dl (-0.039 +/- 0.028 mg/dl in those not receiving antibiotics). Delta_Scr for different antibiotic classes are shown below.

<table>
<thead>
<tr>
<th>Antibiotic administered on day of contrast</th>
<th>Delta creatinine (mg/dl) at 48 hours (mean +/- SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP/SMX</td>
<td>0.00 +/- 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>-0.05 +/- 0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Linezolid</td>
<td>-0.03 +/- 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>0.07 +/- 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.04 +/- 0.02</td>
<td>0.013</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>0.06 +/- 0.03</td>
<td>0.016</td>
</tr>
</tbody>
</table>

In univariate analysis, Delta_Scr was 0.064 +/- 0.027 mg/dl (p=0.016) in patients receiving carbapenem antibiotics and IV contrast with 10% of subjects having SCr increase by >0.3 mg/dl. Multivariate analysis showed the change in SCr was 0.059 + 0.027 mg/dl (p=0.03).

Conclusions: Concomitant administration of carbapenem antibiotics and IV contrast was associated with a significant worsening of SCr in both univariate and multivariate analysis adjusting for demographic, hemodynamic, and other potential nephrotoxic variables. This study identifies a potentially novel risk factor for contrast induced nephropathy.
**SA-PO561**

**Serum Vancomycin Levels Correlate with Significant Increases in Serum Creatinine after Contrast Administration**

_Parker Lehmann,1 Cheri Lehmann,2 Udayan Y. Bhattacharyya_1,3 New Albany High School, New Albany, OH; 4The Ohio State Univ Wexner Medical Center, Columbus, OH.

**Background:** Vancomycin is commonly used in the treatment of drug resistant organisms. Rare nephrotoxicity has been reported with its use. However, vancomycin nephrotoxicity has not been fully characterized. On this basis, the purpose of this study is to characterize change in serum creatinine (SCr) in patients after IV contrast CT who are also receiving vancomycin.

**Methods:** After institutional approval, patients receiving intravenous contrast with CT imaging over a 6 month period were identified. Dialysis patients were excluded. Demographic data were obtained. All laboratory studies done on the day of imaging and SCr 48 hours after imaging were extracted. Vital signs and all medications administered on the day of the CT scan were obtained. Change in creatinine from the day prior to CT imaging to 2 days after was then calculated (delta_cr).

**Results:** Complete records for 2530 subjects were obtained. In univariate analysis, a significant linear relationship between serum vancomycin level and delta_cr was noted (slope = 0.015, p<0.001). Variables evaluated for multivariate model included demographic data, vital signs, and concomitant medications including vasopressor use, aminoglycoside use, and other potential nephrotoxins. A significant linear relationship between vancomycin level and delta_cr remained (slope=0.016, p<0.0001). Multivariate quartile analysis was then performed.

<table>
<thead>
<tr>
<th>Vancomycin Quartile Range</th>
<th>Increase in SCr (mg/dL)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 10.45 mcg/mL</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>10.45 to 14.4 mcg/mL</td>
<td>0.075</td>
<td>0.321</td>
</tr>
<tr>
<td>14.4 to 19.85 mcg/mL</td>
<td>0.121</td>
<td>0.116</td>
</tr>
<tr>
<td>Above 19.85 mcg/mL</td>
<td>0.243</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Conclusions:** A significant linear relationship between vancomycin level and worsening SCr after IV contrast was noted. For every 10 mcg/mL increase in vancomycin level, SCr would be expected to rise by 0.16 mcg/mL. Multivariate analysis found that vancomycin levels > 19.85 mcg/mL were associated with a significant rise in SCr of 0.24 mcg/mL. This study demonstrates the additive nephrotoxicity of vancomycin and IV contrast. It also supports the clinical use of monitoring serum vancomycin levels.

**SA-PO562**

**Incidence and Predictors of Acute Kidney Injury following the First Course of Cisplatin**

_Shiveta S. Motwani,1,2 Sushrut S. Waikar,1,2 Benjamin D. Humphreys,3 Gary C. Curhan_1 Brigham and Women’s Hospital, 2Dana-Farber Cancer Inst; 3Washing Univ at St. Louis.

**Background:** Cisplatin (C) associated acute kidney injury (C-AKI) has been reported in 25-30% patients after multiple courses. Knowledge regarding the risk factors comes from small studies with one type of cancer. We investigated the incidence and predictors of C-AKI, regardless of cause, following the first course of Cis across all cancer types.

**Methods:** Patients ≥18 yrs of age who received Cis from 2006-2014 at Massachusetts General Hospital and from 2001-2014 at Dana-Farber Cancer Institute Brigham and Women’s Hospital were included in the study. Those with missing baseline (BL) or follow-up (FU) creatinine (Cr) or BlCr<1.5 mg/dL were excluded. C-AKI was defined as ≥0.30 mg/dL rise in Cr over BL within 14 days of receiving the first dose. Demographic, clinical and laboratory data were extracted. Incidence rates were calculated. Exposures of interest were analyzed for association with AKI. Multivariate analysis was performed using a stepwise approach. Two approaches to find biomarkers were performed. First, a significant AKI outcome was used to find biomarkers that were associated with AKI. Second, biomarkers that were not significant predictors of AKI were used to find potential biomarkers for non-AKI outcomes (as control group).

**Results:** Of the 5942 patients in the combined cohort, the mean ± SD of age was 56 ± 13 yrs, Cis dose 109 ± 54 mg, BlCr 0.9 ± 0.2 mg/dL, serum albumin 4.0 ± 0.5 g/dL, height 169.0 ± cm, weight 71±42 lbs, body mass index (BMI) 27.6±3 kg/m2, with 56% being male, 88% white, 15% diabetic and 51% hypertensive. C-AKI occurred in 617 patients (10.4%). The results of regression analyses are presented in the table, with final model adjusted for Bl Cr.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Age per 10 yrs</td>
<td>1.3,1.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>1.3,1.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White</td>
<td>0.9,1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.5,2.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.2,3.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BlCr/Cis</td>
<td>1.2,2.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin/g/dL</td>
<td>0.6,1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dose per 25mg</td>
<td>1.3,2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hip per 10cm</td>
<td>1.0,1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Wt per 10 lbs</td>
<td>1.0,1.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Conclusions:** C-AKI is frequent even after a single course. Hypertension and hypoalbuminemia are novel risk factors for C-AKI. These data may help identify those at risk of early AKI during first course of cisplatin.

_Funding: Other NIH Support - T32 training grant_

**SA-PO563**

**Acute Kidney Injury Biomarkers to Predict 3-Month Cisplatin Nephrotoxicity in Children**

_Kelly McMahan,1 Tom D. Blydt-Hansen,2 Maury N. Pink,3 Cherry Mammen,2 Shahrad Rod Rassk,2 Ross T. Tsuyuki,4 Prasad Devarajan,4 Michael Zappettilli,4 McGill U, Montreal; 2U British Columbia, Vancouver; 3U Manitoba, Winnipeg; 4U Alberta, Edmonton, Canada; 5Cincinnati Children’s Hospital, Cincinnati.

**Background:** Children often develop acute kidney injury (AKI) with cisplatin treatment. Late renal effects are common. Renal tubule injury markers neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) may help risk stratify for late cisplatin nephrotoxicity. Hypothesis: NGAL and KIM-1 predict chronic kidney disease (CKD) and hypertension (HTN).

**Methods:** Ongoing, 12-year prospective study of cisplatin-treated children. Excluded: GFR<30 ml/min/1.73m2. Protocol includes: Urine NGAL and KIM-1 measured at discharge of last (or second to last) cisplatin infusion; 3-month post-cisplatin visit outcomes: CKD: eGFR<90 by a)serum creatinine (SCr), b)cystatin C (CysC) equations or albumin-to-creatinine ratio>30 mg/mg; HTN: blood pressure 95th percentile for age, gender, height. We compared cisplatin discharge NGAL&KIM-1 levels between subjects with/without 3-month CKD and HTN (Man-Whitney) and calculated area under curve (AUC)95%CI for NGAL&KIM-1 to predict CKD, HTN.

**Results:** N=48 with complete 3-month data: median[QR] age 8[3-12] years; 58% male. Table: Cisplatin discharge NGAL and KIM-1 were 2 to 8-fold higher in subjects with renal toxicity at 3 months. Table shows that cisplatin discharge NGAL predicted 3-month CKD or HTN more strongly (AUC 0.70-0.83) than KIM-1 did (AUC 0.60-0.70). AUCs for biomarkers to predict AKI were ~17% higher when Cys-C eGFR was used (Table). Biomarkers measured near end of cisplatin exposure at 3 months-predict cisplatin CKD and HTN and may be used to risk stratify for late renal effects screening and early cardiovascular risk reduction. CysC may be better at estimating GFR compared to SCr to define CKD in children.

<table>
<thead>
<tr>
<th>NGAL&amp;KIM-1</th>
<th>eGFR&lt;90 by SCr</th>
<th>eGFR&lt;90 by CysC</th>
<th>eGFR&lt;90 by albumin/Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin Discharge</td>
<td>0.70-0.79</td>
<td>0.79-0.83</td>
<td>0.79-0.83</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.70-0.79</td>
<td>0.79-0.83</td>
<td>0.79-0.83</td>
</tr>
<tr>
<td>AUC</td>
<td>0.70-0.83</td>
<td>0.79-0.83</td>
<td>0.79-0.83</td>
</tr>
</tbody>
</table>

**Conclusions:** NGAL&KIM-1 in children is associated with AKI and may be used to risk-stratify for late effects. These data add to a growing body of evidence that NGAL&KIM-1 are useful biomarkers for risk stratification for AKI.

_Funding: Government Support - Non-U.S._
immediately post cisplatin, then rise at discharge (Table). Table shows AKI biomarkers tend to be higher in AKI group (V) Biomarker AUCs for AKI diagnosis are higher at AVL (later cisplatin infusion) than AVL (earlier cisplatin infusion) during cancer treatment.

Conclusions: Our novel data show that NGAL and KIM-1 are diagnostic of cisplatin-AKI, more so with later cisplatin infusions during cancer treatment.

<table>
<thead>
<tr>
<th></th>
<th>NGAL (µg/ml)</th>
<th>KIM-1 (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVL</td>
<td>12.5 (6.3-24.3)</td>
<td>22 (12-39)</td>
</tr>
<tr>
<td>AVL</td>
<td>16 (8-32)</td>
<td>40 (20-60)</td>
</tr>
<tr>
<td>AVL</td>
<td>20.5 (10-40)</td>
<td>45 (25-70)</td>
</tr>
<tr>
<td>AVL</td>
<td>25 (12-50)</td>
<td>50 (25-75)</td>
</tr>
</tbody>
</table>

Table: NGAL & KIM-1 elevation during cisplatin. At each timepoint, AVL vs. AVL are biomarkers are compared for early AVL (V) and later AVL. Area under the curve (AVU) with 95% CI in boxes, biomarker to diagnose AVL (left), AVL defined by NGAL+KIM1. Right: AVL defined by NGAL+KIM1+Electrolyte definition. Table: pre-infusion, post-infusion and discharge.

Medium [interquartile range] biomarkers levels shown.

Funding: Government Support - Non-U.S.

SA-PO565
Association of Proton Pump Inhibitors with Acute Kidney Injury in Geriatric Population Zara Nisar, Nephrology, Khyber Teaching Hospital, Peshawar, KPK, Pakistan.

Background: Acute Kidney Injury in elderly patients presents with a wide range of clinical manifestations from an elevation in serum creatinine to anuric renal failure, arises from multiple causes, and occurs in a variety of clinical settings. The main objective of this study is to establish the relationship of use of Proton Pump Inhibitors as a risk factor for AKI in geriatric population.

Methods: A retrospective descriptive analysis was done from 31st December 2012-31st December 2015. Data was analyzed using SPSS (version 21). A total number of 18,668 outpatient prescriptions for PPIs were written.

Results: A total number of 18,668 outpatient prescriptions for PPIs were written. Among them were 9978 (53.44%) cases of Acute Kidney injury reported within 120 days of receiving the prescription. 5577 (55.89%) patients presented with decrease in urine output. Among them were 9978 (53.44%) cases of Acute Kidney injury reported within 120 days of receiving the prescription. 5577 (55.89%) patients presented with decrease in urine output. 723 (7.24%) cases were presented with confusion and dizziness. Serum creatinine 3678 (36.86%) cases reported with additional shortness of breath, swelling in the ankles/legs. 723 (7.24%) cases were presented with confusion and dizziness. Serum creatinine 3678 (36.86%) cases reported with additional shortness of breath, swelling in the ankles/legs.

Conclusions: PPIs use is associated with an increased risk of Acute Kidney Injury in elderly patients. The study was limited by its retrospective nature, which hindered the its ability to draw conclusions regarding the connection between PPI exposure and AKI onset. However, PPIs are perhaps the most common avoidable AKI risk to which elderly patients are regularly exposed. Doctors should continue to provide careful PPI education to the patients, and they should be regularly monitored for signs of Acute Kidney Injury.

SA-PO566
Renal Toxicities of Anti-Myeloma Agents Rimda Wanchoo, Valerie Suzanne Bartu, Vipulbhai Sakhya, Kenar D. Jhaeveri. Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY.

Background: Survival for patients with multiple myeloma(MM) has significantly increased in the last decade in large part due to development of proteasome inhibitors and immunomodulatory drugs. Drugs with novel mechanisms of action and targeted therapies are being explored both in the pre-clinical and clinical settings in myeloma. A possible limiting feature for these agents is their potential for nephrotoxicity.

Methods: We reviewed the FDA adverse event reporting system (FAERS) quarterly legacy data file 3rd quarter of 2011 to 2nd quarter of 2016 for all novel MM agents. Well established chemotherapy agents such as cyclophosphamide, melphalan and anthracyclines were excluded. The adverse event terms queried were: “hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypocalcemia, hypercalcemia, hypernatremia, hyperphosphatemia, proteinuria, renal failure acute, acute kidney injury, elevated creatinine, hypercreatinemia, hypertension and nephritis.” We also reviewed the literature for case reports, case series and the primary studies of these agents for any known nephrotoxicities.

Results: SA-PO567
High-Dose Leucovorin as Sole Therapy for High-Dose Methotrexate Toxicity Carlos D. Flombaum,1,2 Dazhi Liu,1 Shirly Qiong Yan,1 Amelia Chan,1 Sherry Mathew,2 Paul A. Meyers,2 Ilya Glezerman,2 Thangamani Muthukumar.1 1Memorial Sloan Kettering Cancer Center, New York, NY; 2Weil Medical College of Cornell Univ, New York, NY.

Background: High-dose MTX (HDMTX) therapy complicated by acute kidney injury is a medical emergency. Prolonged exposure to elevated MTX levels creates a high risk for severe mucositis, myelosuppression and death. High-dose leucovorin (HDLV) and alkalinization of the urine are the basis of support for these patients. More recently, glucarpidase (G) and alkalinization of the urine are the basis of support for these patients. More recently, glucarpidase (G) has been introduced to circumvent MTX toxicity. We aimed to investigate whether or not HDLCV and supportive therapy alone, without G, can prevent systemic toxicity from HDMTX.

Methods: To identify patients at high risk for severe MTX toxicity, we performed a retrospective review of all patients treated between 2000 and 2011 who had MTX levels ≥10 times of what are considered toxic levels at 48 and/or 72 hours after HDMTX (≥10 µmol/L at 48 hours and/or ≥1 µmol/L at 72 hours).

Results: 103 patients who received 113 courses of HDMTX were identified. Serum creatinine increased by a median of 2-fold from baseline (range 1–10 fold) but all patients remained ≥0.1 µmol/L for a median of 9 days (range 0–19 days). There was a high correlation between MTX levels at 48, 72, 96 and 120 hours but not between 24 hours and subsequent time points. 83% of the patients received IV HDLCV, given within the first 48 hours of the treatment. Myelosuppression was present in 39% of patients; grade III neutropenia in 27.4% and thrombocytopenia in 22%. Infectious complications, oral mucositis and diarrhea occurred in 19.5, 15 and 5.3 % of patients. There were 5 deaths, none directly attributed to complications from HDMTX.

Figure above summarizes the drugs studied and results found. Lenolidomide, everolimus and bortezomib were the top three offenders with AKI as the most common finding reported. Newer agents such as carfilzomib, BRAF inhibitors and PD-1 antagonists do have rare renal side effects. The review of literature found toxicities associated with lenolidomide, bortezomib and carfilzomib as top offenders. Importantly, the toxicities reported here are not just when these agents are used in MM but for other cancer treatments as well.

Conclusions: Novel targeted therapies being used in MM can be nephrotoxic. Knowledge of novel agents used in MM and their renal toxicities is important for the nephrologist and the hematologist.
Conclusions: There were 113 episodes of HDMTX–associated renal dysfunction with a strategy that only included usual supportive measures and HDS. We observed no HDMTX–associated mortality and the incidence of systemic complications was comparable to other studies where G was used. Glucarpidase is an extremely expensive drug and probably unnecessary in a significant number of patients.

SA-PO568
Renal Adverse Events of Immune Check Point Inhibitors  Napur N. Upall, Valerie Suzanne Barta, Kenar D. Jhaiveri, Rimda Wanchoo. Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY.

Background: Enhancing anti-tumor T cell immunity with checkpoint inhibitor antibodies [anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-program death 1 (PD-1)] has shown significant clinical benefits in tumor regression and prolonged stabilization melanoma and other cancers. These agents are termed immune check point inhibitors (ICIs).

Methods: To better understand recent published contributions related to ipilimumab, pembrolizumab and nivolumab induced renal toxicities, a Medline search of indexed manuscripts was conducted. The search terms ‘renal failure’ and ‘acute kidney injury’ with subheadings ‘ipilimumab’, ‘pembrolizumab’, ‘nivolumab’ and ‘nephrotoxicities’ were employed. We also searched for ‘hypokalemia, hypocalcemia, hyponatremia and hypophosphatemia’. Primary data from the initial studies of these agents and the FDA adverse reporting system (FAERS) database were also reviewed.

Results: A total of 18 citations were found. Acute interstitial nephritis, podocytopathy and hyponatremia are the three most common adverse renal findings related to the ICIs. This figure compares the two reported classes of targeted therapies. The FAERS database had significant more reported renal toxicities with ipilimumab compared to the anti-PD-1 agents.

Conclusions: Renal injury appears to be part of the spectrum of immune-related adverse events. All agents are known to cause AKI. The renal insult related with ipilimumab appear to happen earlier in the course of the drug therapy (6-12 weeks following treatment) compared to events associated with PD-1 inhibitors appear around 6-10 months following initiation of treatment. Early recognition of immune mediated renal toxicities is important as treating with steroids promptly improves renal function. In kidney transplant patients, a preventive strategy might be needed to alleviate the chances of rejection.

SA-PO569
Incidence of AKI with Immune Checkpoint Inhibitors at a Single Center Jamie S. Hirsch,1 Rimdi Wanchoo,1 Valerie Suzanne Barta,1 Kenar D. Jhaiveri, Craig Deove.1 1Nephrology, Hofstra Northwell School of Medicine; 2Hematology/Oncology, Hofstra Northwell School of Medicine.

Background: Immune checkpoint inhibitors (ICIs) target the immune system and are increasingly being used to treat various cancers. Based on few published case reports, both anti-cytotoxic T lymphocyte protein-4 and anti-program death (PD-1) can lead to immune related adverse renal effects. We wanted to evaluate the incidence of AKI with these agents at a single center.

Methods: Data were obtained from Northwell Health’s EHR, and included all patients receiving ipilimumab, nivolumab, or pembrolizumab at infusion centers between May 2011 and May 2016. Patients were included if they had at least one creatinine (Scr) measurement prior to the first treatment and at least one Scr measurement following the first treatment. AKI was defined by KDIGO criteria. We compared data of the patients who developed AKI to those that didn’t.

Results: Of 211 patients receiving ipilimumab (CTLA-4), nivolumab, or pembrolizumab at our center, 99 had Scr available for analysis. AKI Stage I developed in 29% (11/38) of CTLA-4 and 24.5% (15/61) of PD-1 patients, while AKI Stage II developed in 5% (2/38) and 10% (6/61), respectively. Table below summarizes the breakdown of patients that developed AKI vs no AKI, and no statistically significant differences were noted between the groups.

Conclusions: Renal injury appears to be part of the spectrum of immune-related adverse events. All agents are known to cause AKI. The renal insult related with ipilimumab appear to happen earlier in the course of the drug therapy (6-12 weeks following treatment) compared to events associated with PD-1 inhibitors appear around 6-10 months following initiation of treatment. Early recognition of immune mediated renal toxicities is important as treating with steroids promptly improves renal function. In kidney transplant patients, a preventive strategy might be needed to alleviate the chances of rejection.

SA-PO570
Gadolinium-Contrast Nephrotoxicity in Patients with Chronic Kidney Disease Stage I Shokhi Naito, Kouju Kamata, Kazuhiro Takeuchi, Tetsuya Iwata, Haruka Takahashi, Vasso Takeuchi. Nephrology, Kitasato Univ School of Medicine, Sagamihara, Kanagawa, Japan.

Background: Gadolinium (Gd)-contrast mediums (GCM) used in magnetic resonance imaging (MRI) have been traditionally considered non-nephrotoxic contrast materials. On the other hand, we have shown that anionic contrast medium, Omniscan affected renal function transiently in patients with less than 1.6 mg/dl of serum creatinine (S-Cr) in ERA-EDTA 2012. However, there are no reports on the nephrotoxicity of GCM in early stages of chronic kidney disease (CKD). We investigated the effect of Gd-contrast medium on renal function in CKD stage 1 after MRI.

Methods: Patients aged 20–80 years, weighing 45–70 kg, and with CKD stage 1 in the 3 months prior to undergoing an MRI were enrolled. They were randomly divided into anionic contrast medium (Omniscan) administration group (group O) and a nonionic contrast medium (Magnevist) administration group (group M). GCM (0.01 mmol/kg) was administered to all patients. We measured levels of S-Cr and serum cystatin C (S-Cys), as well as estimated glomerular filtration rate (eGFR) and estimated creatinine clearance rate (eCCR) using cGFR and the Cockcroft-Gault formula, respectively, just before and 24–72 h after the MRI. Mann-Whitney U-test and Wilcoxon signed-ranks test were employed for statistical analysis.

Results: There were no significant differences in the clinical background characteristics such as age, sex, and serum concentrations of albumin, S-Cr, S-Cys, eGFR, and eCCR between group O (n=21) and group M (n=32). There were no significant differences in S-Cr, eGFR, or eCCR before MRI and 24–72 h after MRI measurements of both groups. S-Cys levels increased significantly 24–72 h after MRI only in group O (0.69 ± 0.14 vs. 0.72 ± 0.11, P=0.047), whereas, there were no significant differences in S-Cys levels in group M (0.70 ± 0.18 vs. 0.69 ± 0.19, P=0.698).

Conclusions: The nonionic contrast medium, Magnevist, had no effect on renal function during MRI, while the ionic contrast medium, Omniscan, affected renal function transiently in the patients with CKD stage 1.

Funding: Pharmaceutical Company Support - Daiichi Sankyo Co., LTD., Tokyo, Japan
Background: Contrast-induced nephropathy (CIN) is a leading cause of hospital-acquired acute kidney injury. Though pre-hydration is commonly used to prevent CIN, there is significant variability in its use. The goal of this study was to evaluate the utilization and outcomes associated with a pre-hydration protocol for cardiac angiography based on the Mehran risk score (MRS) to achieve a lower rate of CIN compared to published incidence (5-15%).

Methods: All patients undergoing a coronary angiogram at the William S. Middleton VA Hospital between Feb 2014 and Dec 2015 were enrolled, excluding those on dialysis or vasoactive agents. Risk for CIN was assessed with the MRS and pre-hydration was ordered for those with a score >26 if they were not hypervolemic. CIN was defined as an increase in creatinine (Cr) ≥0.5 mg/dL 48-72 hrs post-procedure.

Results: A total of 412 patients enrolled and had follow-up Cr values. Of these, 42.5% had diabetes, 25.7% had CHF, and 23.1% underwent PCI. The average pre-procedural Cr was 0.80 mg/dL. Patients with higher MRS were more likely to receive pre-hydration (p=0.001). A total of 14 (3.4%) patients developed CIN. Those with CIN had higher pre-procedural Cr (p=0.01) and higher MRS (p=0.001) than those without. The MRS components most strongly associated with CIN were anemia (HR=1.5, 95%CI 1.1-2.1) and GFR <60 ml/min/1.73m² (HR=2.1, 95%CI 1.1-3.8). Pre-hydration was associated (p=0.05) with a lower incidence of CIN after adjustment for MRS (OR=0.95, 95%CI 0.90-0.99). All patients with CIN were followed by inpatient providers or referred to nephrology and 12/14 (86%) had complete resolution of their CIN.

Conclusions: Protocol-driven pre-hydration, based on the MRS, was associated with a lower incidence of CIN compared to published rates. Pre-hydration was associated with lower risk of CIN after adjusting for risk score. This supports the use of pre-hydration prior to coronary angiography. Further studies are needed to define the most effective protocol and assess the impact this interdisciplinary approach has on outcomes.

SA-POS57
Preinterventional Kynurenine Predicts Long-Term Outcome after Contrast Media Exposure due to Coronary Angiography

Christoph Reicheltzede,1,2 Fabian Heunicke,3 Gina Von Eenem,1 Markus Lukas Alter,2 Karl-Heinz Kellner,1 Thomas Bernd Dichtzietz,4 Axel Kretschmer,4 Berthold B. Hocher,7,8,1,3 "Institut für Nutritional Science, Universität Potsdam; 1Center for Cardiovascular Research, Charité - Universitätsmedizin Berlin; 2Department of Nephrology, Charité - Universitätsmedizin Berlin; 3Neurinom GmbH, Karlsruhe, Germany; 4Dept of Cardiology and Angiography - CCM, Charité - Universitätsmedizin Berlin; 5Bayer Pharma AG, Wuppertal, Germany; 6Inst for Laboratory Medicine, Berlin, Germany; 7Dept of Basic Medicine, Medical College of Hunan Normal Univ; 8Immundiagnostik AG, Bensheim, Germany.

Background: Contrast media (CM) induced nephropathy (CIN) remains a serious complication of CM enhanced procedures. There is still a lack of established biomarkers that help to identify patients at high risk for long term complications. The current study aimed to evaluate plasma kynurenine as a predictive biomarker for long term complications of CM exposure due to coronary angiography.

Methods: 245 patients undergoing coronary angiography were analyzed in this retrospective cohort study. Blood and urine samples were obtained at baseline/24/48h after CM application to diagnose CIN. Patients were followed for 120 days for adverse clinical events. Long term outcome was measured by the combined endpoint "Major adverse kidney events" (MAKE) including death, the need for dialysis, doubling of plasma creatinine and hospitalization.

Results: Preinterventional plasma kynurenine (PKYN) was not associated with CIN. Patients who later developed MAKE displayed significantly increased PKYN levels (p<0.0001). ROC analysis revealed that PKYN is highly predictive for MAKE (AUC=0.838; Cr=0.704-0.955). The optimal cutoff was found at ≥3.5 μmol/L. Using this cutoff, the Kaplan-Meier estimator demonstrated that concentrations of PKYN ≥3.5 μmol/L were significantly associated with a higher prevalence for MAKE until follow up (Chisquare=31.59; p<0.0001). This association remained significant in multivariate Cox regression models adjusted for relevant factors of long term renal outcome.

Conclusions: Results of this study showed that preinterventional kynurenine might serve as a highly predictive biomarker for MAKE up to 120 days after coronary angiography.

SA-POS58
Incidence and Risk Factors for Contrast Induced Nephropathy (CIN) Among Cancer Patients

Sotron Latcha,1 Junting Zheng,1 Andrew Plodkowski,2 1Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; 2Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; 3Radiology, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Recent publications question the existence of AKI from intravenous contrast administration. Understanding the incidence and risk factors for CIN in cancer patients is important since these patients rely on CT imaging to establish cancer stage and response to chemotherapy.

Methods: Retrospective data was collected on all adult inpatients at Memorial Sloan Kettering Cancer who had a contrast (CON) or non contrast (NC) CT of the head, neck and chest from 1/1/2012-12/30/2014 with a creatinine (Cr) within 3D pre and post CT. Patients were included if a CON CT was done within 3D before a NC CT. Acute kidney injury (AKI) was defined as an increase in Cr ≥ 0.3mg/dl or 1.5X baseline. ICD 9 codes were used to identify diagnoses and medications previously identified as risk factors for CIN (multiple myeloma (MM), diabetes, congestive heart failure (CHF), hypotension, liver metastases, chronic kidney disease (CKD), AKI, nonsteroidal anti inflammatory medications (NSAIDs), ACE inhibitors, ANGI1 receptor blockers, bisphosphonates, VEGF and immune checkpoint inhibitors, EGRF therapy, tyrosine kinase inhibitors, gemcitabine and cisplatin).

Rao-Sorti Chi-square test was used to examine AKI rate differences. Results: 5178 NC CT and 2654 CON CT were included. The incidence of AKI was significantly greater in the NC group (11.5% vs 7.2% in CON group) and in those with GFRs <59ml/min, Cr, no liver metastases, CKD, AKI, chemotherapy within 60D of CT, EGRF therapy, leukemia, lymphoma, MM (p<0.001 for all above), male genital system tumors (p=0.014) and NSAIDs (p=0.007).

Conclusions: In this large cohort of cancer patients, IV contrast administration was not associated with increased AKI from CON. Indeed, a significantly higher incidence of AKI was found in the NC group. The incidence was also higher in those with GFR <59ml/ min, AKI, recent chemotherapy, EGRF therapy, NSAIDs, leukemia, lymphoma, male genital tumor and MM.

SA-POS57
Impact of Serum Uric Acid on Renal Outcome after Contrast Enhanced Computerized Tomography

Ming-Ju Wu, Div of Nephrology, Taichung Veterans General Hospital, Taichung, Taiwan.

Background: The association between serum level of uric acid (sUA) and risk of acute kidney injury (AKI) after contrast-enhanced computerized tomography (CTT) is limited. The aim of this study was to determine whether elevated sUA could predict renal outcome after CCT.

Methods: We used a history cohort of 58106 non-dialysis adult patients who received non-contrast iodinated CTT at the National Univ Medical Center from June 1, 2006 to March 31, 2015 to evaluate the association of sUA and renal outcome. The exclusion criteria were patients with pre-existing AKI, multiple exposure, non-standard volume of contrast, and missing data for analysis.

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

762A
Results: A total of 1440 patients were enrolled. Post-contrast-AKI (PC-AKI) occurred in 106 (7.3%) patients. 68% of the population had AKI. Both incidences were increased in patients with higher sUA. After adjusting for potential confounders, sUA was associated with an increased risk of PC-AKI (odds ratio (OR) of 2.62; 95% confidence interval (CI), 1.27–5.38, p=0.009) and the need of hemodialysis (OR, 4.40; 95% CI, 1.90–9.99, p=0.001). Comparing with sUA ≥ 8.0 mg/dL, patients with sUA ≥ 8.0 mg/dL had higher incidence of PC-AKI (16.7% vs. 11.1%, p=0.012) and higher incidence of hemodialysis (12.1% vs. 4.3%, p<0.001). Additionally, 53.8% of patients with AKI had eGFR decreased ≥20% after 3 months of CCT, compared to only 25.9% in patients without AKI (p<0.001).

Conclusions: Elevated sUA is associated with worse renal outcome after CCT. We suggest that elevated sUA may have potential as an independent risk factor for PC-AKI in patients scheduled to receive contrast-enhanced image study.

SA-PO577
Biomarkers for Diagnosis and Predicting Outcomes in Contrast Induced Nephropathy Justor Banda, Caroline Dickens, Saraladevi Naicker. Internal Medicine, Univ of the Witwatersrand, Johannesburg, Gauteng, South Africa.

Background: Serum creatinine is sub-optimal as a biomarker in the early diagnosis of contrast induced nephropathy (CIN). This study investigated a panel of novel biomarkers in the early diagnosis of CIN and in assessing patient outcomes.

Methods: This single centre, nested, prospective case-controlled study included 30 patients with CIN and 60 matched controls. Sera were collected pre-contrast; 24 hours (24H); 48; and ≥25 days post contrast administration. Concentrations of NGAL, cystatin C, β2M, IL-18, IL-10, and TNFα were determined using luminex and ELISA assays. Outcomes were biomarker diagnostic discrimination performance for CIN and mortality after generation of an area under receiver operating characterizing curves (AUROC).

Results: Median 24h cystatin C and 48h β2M levels were higher in CIN patients compared to controls (856.60 g/mL (IQR 620.75-1003.00) vs. 617.43ng/mL (533.11-805.21), p<0.001 and 5.34ng/mL (IQR 3.8-6.9) vs. 3.34ng/mL (2.7-4.5); p=0.001) with AUROC of 0.75 and 0.78 respectively for early diagnosis of CIN. β2M levels were higher at all time points. Baseline IL-18 (p<0.001), β2M (p<0.04) and TNFα (p<0.001) levels were higher in the non-surviving group and their AUROC were all ≥0.80 for CIN+ mortality respectively. Baseline NGAL was superior for excluding patients at risk for CIN, with positive and negative predictive values of 0.50 and 0.81 respectively. Cystatin C (p<0.003) and β2M (p<0.03) at 24h independently predicted CIN risk, β2M predicted increased mortality of 40% at baseline and 30% at 24 hours.

Conclusions: Serum cystatin C was the best biomarker for CIN diagnosis, while IL18, β2M and TNFα were best for predicting prognosis.

SA-PO578
Rapidly Reversible Contrast-Induced Acute Kidney Injury Does Not Increase the Risk for Worse Long-Term Renal Outcomes Durpan Gandhi,1 Bhavna Bhasin,1 Jorge Luis Castaneda,2 Christopher D. Nielsen,1 Juan Carlos Q. Velez.1 1Div of Nephrology, Medical Univ of South Carolina, Charleston, SC; 2Div of Nephrology, Univ of Mississippi; 3Div of Cardiology, Medical Univ of South Carolina.

Background: Growing evidence indicates that contrast-induced acute kidney injury (CI-AKI) may increase the long-term risk for progression of chronic kidney disease (CKD) to end-stage kidney disease (ESKD). However, the duration of CI-AKI is highly variable and the impact of a sustained vs. a transient rise in serum creatinine (sCr) on long-term renal outcomes is not known. We hypothesized that recovery of CI-AKI within 7 days reduces the risk for worsening of long-term renal outcomes.

Methods: We reviewed records from non-ESKD patients with estimated glomerular filtration rate (eGFR) ≤ 45 ml/min who underwent coronary angiography (Cath) between 2008 and 2011 at MUSC. CI-AKI was defined as ≥ 25% rise in within 1-5 days post-Cath. CKD progression was defined as ≥ 30% fall in eGFR. Rapid recovery of CI-AKI was defined as improvement of sCr to a value < 25% above baseline within 7 days of Cath.

Results: Of 2,098 subjects identified, 168 fulfilled the eGFR inclusion criteria, but 72 of them were excluded because of missing a sCr value after 24 hrs. The mean eGFR was 60.5 ± 9.9 ml/min, 58% were diabetics and the mean volume of dye was 107.2 ml. The attributable risk for renal dysfunction from contrast medium in patients taking TMP-SMX not been well established.

Conclusions: Although CI-AKI increases the long-term risk for worsening of renal outcomes, recovery within 7 days of the Cath is associated with a reduction in that risk, suggesting that severity of CI-AKI may impact its effect on long-term prognosis.

SA-PO579
Incidence and Risk Factors for Contrast-Induced Acute Kidney Injury in Patients Taking Trimethoprim-Sulfamethoxazole Hyun Seon Cho,1 Tae Won Lee,1 Eunjin Bac,2 Hyun-Jung Kim,1,3 Se-Ho Chang.1,3 Internal Medicine, Gyeongsang National Univ Hospital, Jinju, Republic of Korea; Internal Medicine, Gyeongsang National Univ Changwon Hospital, Changwon, Republic of Korea; 3Inst of Health Sciences, Gyeongsang National Univ, Jinju, Republic of Korea.

Background: Trimethoprim-sulfamethoxazole (TMP-SMX) is commonly used to prevent pneumocystis pneumonia and for wide range of infections in the outpatient setting. Previous studies have shown a relationship between TMP-SMX and acute kidney injury. The attributable risk for renal dysfunction from contrast medium in patients taking TMP-SMX not been well established.

Methods: We reviewed medical record database for all patients who received ≥3 days of treatment with TMP-SMX between from January 2009 to December 2015. Among these, we included patients underwent contrast-enhanced computed tomography (ECT) scan and who for a baseline and follow-up determination of serum creatinine were available. CI-AKI was defined as an increase in serum creatinine (sCr) more than 25% of baseline value or 0.3 mg/dL at between 48 hours and 96 hours after ECT. We excluded patients who already had been receiving dialysis.

Results: Of 213 patients who met inclusion criteria, 18 (8.5%) had increases in sCr that met predetermined criteria for CI-AKI. The mean age was 58.81 ± 17.59 years. 45 patients (21.2%) had diabetes mellitus. Variables independently associated with CI-AKI included high potassium level (p=0.004), high potassium/sodium ratio (p=0.039), high Blood area nitrogen level (p=0.027), high C-reactive protein(IAK) level (p=0.012), high HbA1c level (p=0.019), high Blood level of Lipid (p=0.023), concominant use of nephrotoxic drug (p=0.037). Multiple linear regression analysis shows hyponatremia, hyperkalemia and concominant use of nephrotoxic drug to be significantly associated with CI-AKI (p=0.019, p=0.043 and p=0.013, respectively).

Conclusions: As it is well-known, the incidence of CI-AKI was higher in patients with high CRP level, advanced CKD satge and concominant use of nephrotoxic drug. Moreover, in high risk patients with hyperkalemia and hyponatremia, TMP-SMX interruption should be considered to prevent the development of CI-AKI.

SA-PO580
Expression of Polycystins in LLC-PK1 Cells Does Not Increase Flow-Activated Calcium Fluxes Lindsey K. Stavola,1 Helle A. Praetorius,2 Michael J. Caplan.1 1Cellular and Molecular Physiology, Yale Univ, New Haven, CT; 2Biomedicine, Aarhus Univ, Aarhus C, Denmark.

Background: The primary cilium is thought to detect fluid flow in the kidney. The molecular basis of this mechanosensitivity is not fully elucidated. The polycystin 1 (PC1) and polycystin 2 (PC2) proteins, encoded by the genes that are mutated in Autosomal Dominant Polycystic Kidney Disease, localize in part to the primary cilium, but was found instead at the basolateral plasma membrane. Interestingly, overexpression of ciliary PC1 and PC2 form a complex, which is required for their trafficking to the primary cilium. It has been suggested that the cilary pool of polycystins functions as a mechanosensitive ion channel that plays an obligate role in producing cilium-dependent flow-activated cytosolic Ca2+ transients.

Methods: We generated LLC-PK, renal epithelial cells stably expressing PC1 and PC2. Polycystin proteins were absent in the primary cilium. We conducted live cell imaging of the intracellular Ca2+ concentration ([Ca2+]i) using these cells loaded with the Ca2+-sensitive fluorescent dye Fluo4-AM.

Results: Overexpression of ciliary PC1 and PC2 did not increase the magnitude or duration of Ca2+ transients [transient 1 (CA1)-PC1 was associated with a lower risk for the composite endpoint of CKD progression, ESKD or death [OR: 0.12 (95%CI: 0.02 – 0.75)], p=0.023).

Conclusions: These results demonstrate that exogenously expressed polycystins are not sufficient to further enhance ciliary mechanosensation and suggest that TRPV4 may play an indirect role in this process and in supporting cellular Ca2+ signaling. Funding: Other U.S. Government Support

SA-PO581
Loss of Fluid Shear Stress as a Pathogenic Mechanism in Polycystic Kidney Disease Robin L. Masier.1,3 Laboratory Clinical Sciences and The Kidney Inst, Univ of Kansas Med Ctr; KC, KS.

Background: Formation and expansion of renal cysts compresses neighboring tubules leading to obstruction of urine flow in these tubules and in segments up- and downstream of polycystic tubules. Tubular obstruction can lead to cyst growth in rodents PKD models and in human ADPKD. Fluid shear stress (FSS) increases antioxidant gene expression in mouse M1 cortical collecting duct cells, providing protection from oxidant-mediated damage.

Methods: To elucidate consequences of acute loss of urinary FSS, gene expression was measured in M1 cells after 24 h incubation in FSS. Cells subjected to physiological levels of laminar FSS for 4 hrs were either harvested (FSS, control), or placed...
in static condition for an additional 4 hrs prior to harvest (FSS-stasis). Gene expression was examined by qRT-PCR using the PrimePCR Oxygene Expression Panel (BioRad). Oxidative DNA damage (8-OH deoxyguanosine; 8OHDG) was assessed in sections of normal and cystic kidneys from the cpk mouse and the Cy rat models of PKD by immunostaining. Mitochondrial (mt) DNA damage was analyzed on denaturing agarose gels with mtDNA isolated from liver and kidney of cpk mice.

Results: Relative to FSS, FSS-stasis led to >2-fold change in expression level of 67 of the 88 genes assayed, and to de novo induction of 9 additional genes. Genes with increased expression were associated with renal injury, apoptosis, inflammation, and DNA damage. A gene whose expression was inversely related to mtDNA damage was encoded by Ogg1, which encodes 8-oxoguanine DNA glycosylase, an enzyme involved in response to and repair of oxidized DNA. 8OHDG staining was evident in nuclear and cytoplasmic compartments of cyto-toxic cells and adjacent non-cytoplasmic tubules in cystic kidneys. mtDNA degradation was increased compared to normal kidneys of 2- and 3-week-old mice, while liver mtDNA was unaffected.

Conclusions: Our studies demonstrate that acute loss of FSS initiates changes in renal tubular epithelial gene expression associated with oxidative stress/damage and may lead to an alteration in renal cell metabolism. Altogether, these results support a mechanism by which cyst-mediated tubule obstruction could contribute to PKD pathogenesis. 

Funding: NIDDK Support

SA-POS82

Modeling Polycystic Kidney Disease in Human Kidney Organoids from Genome-Modified and Induced Pluripotent Stem Cells Nelly M. Cruz, Benjamin S. Freedman. Div of Nephrology, Kidney Research Inst, and Inst for Stem Cell and Regenerative Medicine, Dept of Medicine, Univ of Washington, Seattle, WA.

Background: Human pluripotent stem cells (hPSCs) can differentiate into nephron-like kidney organoids for disease modeling and regenerative medicine. Organoids derived from genome-modified PKD1+/- or PKD2+/+ hPSCs form cysts from kidney tubules, but the penetrance of this phenotype is low. Using a variety of PKD hPSCs, we investigated the potential of differentiation protocol, culture conditions, and genetic background to modulate PKD organoid cystogenesis.

Methods: Induced hPSCs from four ADPKD and ARPKD patients or genome-modified PKD1+/- and PKD2+/+ hPSCs were differentiated into kidney organoids using two different published protocols. Organoids were cultured under 2D or 3D conditions with or without forskolin, an agonist of adenylyl cyclase. PKD organoids and cysts were counted, measured, and analyzed for kidney tubule marker immunofluorescence, compared to normal and PKD controls.

Results: Under novel conditions, PKD1+/- and PKD2+/- organoids formed translucent cysts with diameters approaching 1 cm over several months in culture. Penetration of the cystogenesis phenotype was increased to ~ 80 % in PKD1+/- and PKD2+/- organoids, compared to ~ 10 % in isogenic control organoids. Cysts derived primarily from proximal tubular cells and expanded rapidly upon forskolin treatment. Differentiation efficiency was highly variable between induced hPSCs from different patients, independent of PKD mutations. By comparison, genome-modified hPSCs exhibited much greater uniformity.

Conclusions: PKD1+/- and PKD2+/- organoids establish a high-penetration system for human PKD cystogenesis in vitro. Genetic background is a confounding factor in organoid differentiation, necessitating the use of genome modification. Cyclic AMP signaling enhances human PKD cystogenesis, similar to mouse models. The modularity of kidney organoid cultures makes them a powerful new pre-clinical model in which to investigate PKD pathophysiology and evaluate candidate therapeutics. (Supported by an unrestricted gift from Northwest Kidney Centers to Kidney Research Institute.)

Funding: NIDDK Support, Pharmaceutical Company Support - Northwest Kidney Centers, Private Foundation Support

SA-POS83

Bioactive Lipid Alterations in the jck and pcy Mouse Models of Nephropathies Taro Yamasuuchi,1 Nikhil Sidhu,1 Jessy Gopuran Devassy,1 Melissa Gabbs,2 Amir Ravandi,2 Masanori Kugita,2 Shizuko Nagao,3 Harold M. Aikema,1 1Dept of Clinical Nutrition, Suzuka Univ of Medical Science, Suzuka, Mie, Japan; 2Dept of Human Nutritional Sciences, Univ of Manitoba, Winnipeg, MB, Canada; 3Inst of Cardiovascular Sciences, St. Boniface Hospital Research Centre, Winnipeg, MB, Canada; 4Education and Research Center of Animal Models for Human Diseases, Fujita Health Univ, Fujita Health Univ, Toyoyak, Aichi, Japan.

Background: Oxylipins are bioactive lipids formed via oxidative metabolism of polyunsaturated fatty acids by the cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP) pathways. We have previously shown that the renal oxylipin profile is modified in ADPKD +/+ mice with established NPHP were studied. Oxylipin levels were quantified by HPLC/MS/MS using stable isotope dilution.

Results: 40 oxylipins were quantified in both models of NPHP. In both models, the levels of several oxylipins (e.g. prostaglandins) were markedly elevated by as much as 20 times, while the LOX derived (e.g. hydroxy fatty acids) and CYP derived (e.g. epoxy fatty acids) were present at levels as low as 10-20% of normal.

Conclusions: Oxylipins derived from COX were elevated, while those derived via the LOX and CYP pathways were markedly reduced in both models of NPHP. These lower levels of LOX and CYP metabolites contrasts with orthogonal models of PKD that primarily display alterations in the COX metabolites. Inhibition of oxylipin biosynthetic pathways therefore may offer potential treatment strategies for NPHP. (Supported by the National Institutes of Health and Engineering Research Council of Canada and the Children’s Hospital Research Foundation of Manitoba, Japan Society for the Promotion of Science-Grants-in-Aid for Scientific Research.)

Funding: Government Support - Non-U.S.

SA-POS84

Inhibition of Bromodomain Protein BRD4 Ameliorates Renal Fibrosis in ADPKD Xia Zhou,1 Xiaoyan Li,1 Dorian J. M. Peters,2 Xiaogang Li.1 Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS; 2Leiden Univ Medical Center, Leiden, Netherlands.

Background: Bromodomain protein BRD4 recognizes and binds acetylated histones to regulate gene transcription. We found that therapeutic targeting of BRD4 with its inhibitor JQ1 delayed cyst growth in different ADPKD mouse models through inhibition of c-Myc transcription. Tubulointerstitial fibrosis is associated with the renal function decline during renal cyst progression. However, whether BRD4 regulates renal fibrosis in ADPKD remains unknown.

Methods: To understand the role of BRD4 in regulating renal fibrosis in vivo, we investigated renal fibrosis of Pkd1+/- mice treated with JQ1. To explore the pathways underlying BRD4 mediated renal fibrosis, we treated renal fibroblasts with JQ1.

Results: We found that inhibition of BRD4 with JQ1 not only delayed cyst growth but also decreased renal interstitial fibrosis as examined by Trichrome Masson and Picrosiris red staining. JQ1 treatment decreased the mRNA expression of fibrotic markers, Col1A1, Col1A2, α-SMA and Fibronectin as analyzed by qRT-PCR, and the protein expression of α-SMA as analyzed by immunohistochemistry staining in the kidneys from postnatal day 28 Pkd1+/- mice. TGF-β1, the crucial cytokine in regulating fibrosis, and TGF-β1/Smad signaling were elevated in cystic kidneys compared with the wild type kidneys. We further found that TGF-β1 treatment not only induced the expression of fibrotic markers (Col1A1, Col1A2, α-SMA and Fibronectin), but also increased the expression of BRD4 in rat kidney interstitial fibroblasts (NRK-49F). However, treatment with JQ1 plus TGF-β1 blocked the upregulation of fibrotic markers induced by TGF-β1 alone as analyzed by qRT-PCR and Western blot. BRD4 interacted with Smad3 but not Smad2 in NRF-49F cells as analyzed by co-IP. Inhibition of BRD4 with JQ1 decreased the cell proliferation of NRF-49F cells.

Conclusions: BRD4 promotes renal interstitial fibrosis in ADPKD. BRD4 plays an important role in TGF-β1 induced fibroblast activation through regulating the transcription of fibrotic markers, which may be mediated by its interaction with Smads. BRD4 is a novel therapeutic target for renal fibrosis in ADPKD.

Funding: NIDDK Support

SA-POS85


Background: In ADPKD patients the degree of renal fibrosis has been identified as the most significant and variable factor associated with progression to renal failure. However, there are no methods for assessment of fibrosis and no markers for the disease. We identified several fibrosis related miRNAs in human serum from ADPKD patients that might indicate fibrosis and serve as non-invasive biomarkers of disease progression.

Methods: Total RNAs were extracted from human ADPKD, chronic kidney disease (CKD) and normal control kidneys and mRNA levels of SPARC and perisostin measured by RT-PCR. mRNA expression was measured by RT-PCR and analyzed by the 2-ΔΔCt method. Serum from ADPKD patients with eGFR ≥60 ml/min/1.73m2 and 3 age matched normal healthy controls at baseline. ADPKD patients were classified as fast (eGFR decrement> 3.4ml/min/1.73m2/year) progressors based on annualized eGFR change. ADPKD patients were classified as fast (eGFR decrement> 3.4ml/min/1.73m2/year) progressors based on annualized eGFR change.

Results: Renal perisostin mRNA expression was much higher in ADPKD patients compared to both in normal controls (0.930 ± 0.047 vs 0.040 ± 0.023, n=4, p=0.07) and in CKD patients (0.093 ± 0.047 vs 0.024 ± 0.027, n=4, p=0.62). Renal SPARC mRNA expression was only significantly higher in the kidney in fast PKD progressors than in normal controls (7.85 ± 0.06 vs 2.21 ± 0.11, n=5, p=0.049). Several serum miRNAs were measured in the fast disease progressors compared to slow progressors including the fibrosis related members of the miR-29 family (miR-29a, miR-29b, miR-29c) and miR-30.

Conclusions: Fibrosis in ADPKD kidney is indicated by increased expression of miRNAs for the matricellular proteins peristin and SPARC. The differential expression of several fibrosis related miRNAs measured at baseline in sera from patients with fast progressing disease indicates that a signature of fibrosis related circulating miRNAs might serve as a sensitive and non-invasive prognostic biomarker for more rapid disease progression.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Disruption of Subcellular Sorting Regulators in a New 3D Cystogenesis Model for ADPKD

Erin E. Dixon, Owen M. Woodward. Physiology, Univ of Maryland School of Medicine, Baltimore, MD.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common monogenic diseases worldwide. Loss of function mutations in PKD1 or PKD2 lead to deficiency of the polycystin-1 and -2 proteins, resulting in cystogenesis. However, many key questions still remain about the mechanism of cyst formation, including effects of aberrant proliferation, mislocalization of growth signals, and alterations in fluid secretion machinery. Currently, cyst models are unable to demonstrate isolated, focal cysts, characteristic of ADPKD, with inactivation of PKD1 or PKD2.

Methods: We are employing a novel combination of culture techniques with an inducible cre model for PKD1/2 inactivation, we have been able to demonstrate an increase in cystogenesis following heterogeneous inactivation of PKD1 and PKD2. We have optimized the culturing of three-dimensional organoids from primary postnatal mouse nephrons using a "tissue culture" method that preserves two layers of secondary and tertiary Matrigel. This plating technique has promoted differentiation of organoids into more complex secondary structures. Finally, we have found a pulse of glial derived neurotrophic factor (GDNF) stimulates the mesenchymal to epithelial transition, activating tubulogenesis. Results: The GDNF-induced epithelial switch, confirmed by expression of E-Cadherin, is maintained after inactivation of PKD1/2, suggesting presence of epithelial organization in cystic structures. However, cystic fluid accumulation and expansion point to an altered localization of secretory machinery. To investigate, we looked closely at Ezrin and the phospho-Ezrin/Radixin/Moesin (p-ERM) complex, proteins important in organization of the membrane and cell structure. Here, we find that PKD1/2 inactivation and cystogenesis disrupts Ezrin-p-ERM localization and activation, highlighting a potential mechanism of altered apical and basolateral sorting.

Conclusions: Our three-dimensional cystogenesis model for ADPKD demonstrates persistence of epithelial characteristics with important defects in the membrane protein sorting mechanisms. NIDDK S53DK090868 Baltimore PKD Center Pilot & Feasibility Grant. Funding: NIDDK Support.

Functional Expression of CaSR in Conditionally Immortalized Proximal Tubular Epithelial Cells (ciPTEC) Deficient for Polycystin 1 or Derived from ADPKD Patients: CaSR as Possible Therapeutic Target

Marianna Rancic,1 Mariliana Ranieri,1 Mariagrazia Centeno,1 Giovanna Cinzia Baldelli,1 Djialila Mekahli,2 Elena N. Levchenko,2 Giovanna Vallini,2 1Univ of Bari Aldo Moro; 2Univ of Cincinnati; 3Albany Medical College.

Background: Polycystic Kidney Disease (ADPKD) is an inherited genetic disease, which shows the formation of multiple fluid-filled cysts, and it finally results in renal failure. Still, early diagnosis and treatment of ADPKD have yet to be defined. In this study, we suggest a specific condition associated with the disease.

Methods: 1. Renal tissue samples from subjects with ADPKD. Renal cyst tissue was obtained from patients with ADPKD undergoing nephrectomy. As controls, non-ADPKD renal tissue specimens were obtained from patients undergoing surgery for clear cell renal cell carcinoma; malignant cell infiltration was excluded by histology. 2. DNA methylation analysis. DNA methylation patterns were validated in two steps, using MS-HRM and EpiTYPER® analysis. For MS-HRM analysis, primers covered the region extending for 2 kb from the translation start ATG upstream to intron 1. Bisulfite-converted genomic DNA was amplified by PCR 3. ChIP-qPCR. ChiP was performed as previously described40, using antibodies specific for RNA polymerase II (ab817; Abcam, Cambridge, UK), AP-2α (sc-184; Santa Cruz Biotechnology), H3K4-m3 (17-614; EMD Millipore, Billerica, MA, USA), H3K3-m3 (ab8898; Abcam), and H3Ac (ab8599; EMD Millipore).

Results: The promoter region of the gene encoding mucin-like proteochodrin (MUPCDH) was hypermethylated in renal tissue of ADPKD patients compared to non-ADPKD controls. As the promoter region is hypermethylated, the expression of MUPCDH was significantly repressed in cyst-lining cells of ADPKD patients. So our results indicate that aberrant methylation of MUPCDH promoter CpG islands can be negatively correlated with reduced expression level of MUPCDH. Furthermore, this epigenetic silencing contributes to abnormal cell proliferation in ADPKD.

Conclusions: In this study, we suggested that hypermethylation of MUPCDH promoter is associated with the expression repression and increased cell proliferation in ADPKD. Also, methylation level of MUPCDH promoter region in genomic DNA from urine can be used as the novel epigenetic biomarker for prognosis of ADPKD.

Funding: Government Support - Non-U.S.

PDE3A as a Novel Therapeutic Target in ADPKD: Implications for Cell Proliferation

Dmitry Kater,1 John Clarke,1 C. Eryn Park,2,3 Galina Mise,1,2 and Vladislav Nikonova,2,3

1Biological Science, Sookmyung Women’s Univ, Seoul, Korea.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common genetic disease, which shows the formation of multiple fluid-filled cysts, and it finally results in renal failure. Still, early diagnosis and treatment of ADPKD have yet to be defined. In this study, we suggest a specific condition associated with the disease.

Methods: 1. Renal tissue samples from subjects with ADPKD. Renal cyst tissue was obtained from patients with ADPKD undergoing nephrectomy. As controls, non-ADPKD renal tissue specimens were obtained from patients undergoing surgery for clear cell renal cell carcinoma; malignant cell infiltration was excluded by histology. 2. DNA methylation analysis. DNA methylation patterns were validated in two steps, using MS-HRM and EpiTYPER® analysis. For MS-HRM analysis, primers covered the region extending for 2 kb from the translation start ATG upstream to intron 1. Bisulfite-converted genomic DNA was amplified by PCR 3. ChIP-qPCR. ChiP was performed as previously described40, using antibodies specific for RNA polymerase II (ab817; Abcam, Cambridge, UK), AP-2α (sc-184; Santa Cruz Biotechnology), H3K4-m3 (17-614; EMD Millipore, Billerica, MA, USA), H3K3-m3 (ab8898; Abcam), and H3Ac (ab8599; EMD Millipore).

Results: The promoter region of the gene encoding mucin-like proteochodrin (MUPCDH) was hypermethylated in renal tissue of ADPKD patients compared to non-ADPKD controls. As the promoter region is hypermethylated, the expression of MUPCDH was significantly repressed in cyst-lining cells of ADPKD patients. So our results indicate that aberrant methylation of MUPCDH promoter CpG islands can be negatively correlated with reduced expression level of MUPCDH. Furthermore, this epigenetic silencing contributes to abnormal cell proliferation in ADPKD.

Conclusions: In this study, we suggested that hypermethylation of MUPCDH promoter is associated with the expression repression and increased cell proliferation in ADPKD. Also, methylation level of MUPCDH promoter region in genomic DNA from urine can be used as the novel epigenetic biomarker for prognosis of ADPKD.

Funding: Government Support - Non-U.S.

Endothelial PDE3A as a Novel Therapeutic Target in ADPKD: Implications for Cell Proliferation

Roman Volkov,1,2 and Mitchell P. Golemis,2

1Nephrology, Mayo Clinic, Rochester, MN; 2Biological Science, Sookmyung Women’s Univ, Seoul, Korea.

Background: Polycystic Kidney Disease (PKD) is an inherited genetic disease that affects ~1 in 500 people. In PKD, mutations in PKD1 and PKD2 abnormally lead to increased cell proliferation in the thick ascending limbs of Henle’s loops (TALH), which contribute to cyst enlargement. To determine if the role of PDE3A in PKD, we performed [3H] thymidine incorporation assays in different immortalized cell lines in the absence of serum.

Methods: We have been evaluating targeted signaling inhibitors in ADPKD models to probe biological similarities and differences between ADPKD and cancer, and to determine if cancer drugs are effective in ADPKD. We have explored the signaling interactions between PKD1 mutations, control of ciliary dynamics, and clinical agents with potential efficacy in ADPKD, with a goal of optimizing therapeutic options for patients with ADPKD. Results: In initial studies, we found that HSPP90 inhibitor in conditional Pkd1KO mice with the preclinical compound STA-2842 reduced initial renal cyst formation and slowed the progression of these phenotypes in mice with pre-existing cysts in animals up to 6 months of age. In ongoing work, we found treatment of Pkd1KO mice with the clinical HSPP90 inhibitor ganetespib controlled cyst growth for up to 50 weeks of treatment, extending survival in reference to vehicle treated mice. Suggestively, ciliation is reduced in the cysts of mice treated with the preclinical and clinical inhibitors.

Conclusions: Our results indicate that aberrant methylation of MUPCDH promoter CpG islands can be negatively correlated with reduced expression level of MUPCDH. Furthermore, this epigenetic silencing contributes to abnormal cell proliferation in ADPKD.

Funding: Government Support - Non-U.S.

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

Underlines represents presenting author.

765A
Conclusions: These results support the idea that HSP90 inhibition and induced loss of cilia facilitate the potentially utile therapeutic concepts for ADPKD. Extending the latter idea, we have now performed a screen of a library of targeted clinical candidates and agents to identify those regulating ciliary dynamics; assessment of additional candidates that cause ciliary resorption is in progress for in vivo control of Pkd1-dependent cys formation.

Funding: NIDDK Support, Private Foundation Support

SA-POS91
High-Throughput, Comparative Variant Profiling Aids Molecular Diagnostics of ADPKD
Vladimir Gainullin,1 Christine M. Heyer,1 Emilie Corneel-Le Gall,1 Sarah L.R. Kleim,1 Vicente E. Torres,1 Peter C. Harris.11
1Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Macalester College, St. Paul, MN.

Background: A high level of allelic heterogeneity at the two genes, PKD1 and PKD2, characterizes ADPKD, with the pathogenicity and penetrance of many inframe variants often uncertain after in silico and family/population analysis. The PKD1 and PKD2 proteins, PC1 and PC2, interact while folding in the ER and PC1 maturation and surface localization requires the ER chaperone function of PC2. Hence, quantitatively assessing the surface localization of PC1 represents an unbiased approach to determine the significance of both PC1 and PC2 variants.

Methods: We developed a high-throughput, quantitative flow-cytometry-based assay utilizing exogenously coexpressed PC1 and PC2 to determine the level of surface localized PC1. Assays were performed on 45 PC1 and 45 PC2 missense variants (predicted to range from fully penetrant pathogenic to neutral) and compared to wildtype and truncation mutation controls.

Results: We found for 20% of PC1 and 50% of PC2 variants that no PC1 was surface localized (fully penetrant), while 10% of PC1 and 40% of PC2 variants behaved like wild type with full surface localization. A group of 70% of PC1 and 10% of PC2 variants showed reduced surface delivery, consistent with being incompletely penetrant (hypo/hypomorphic) alleles. For six PC1 variants this designation was consistent with early onset disease when co-inherited in trans with a hypomorphic allele, while age- and gender combinations of two or more hypomorphic variants in cis generated a fully penetrant haplotype. A high level (70%, PC1; 50%, PC2) of fully or incompletely penetrant folding combinations of two or more hypomorphic variants in cis significantly increased from the LR to the HR group (median values: 785 vs. 934 ml/m², P=0.001). In the placebo group, annual growth in TKV was highest in the HR group, and the rate of renal function decline was slower in LR patients. Tolvaptan significantly slowed the rate of TKV growth in all 3 risk categories (LR: T=-2.8 vs. P=5.0%, IR: T=-2.2 vs. P=4.6% and HR: T=-4.1 vs. P=6.6%, all P-values <0.005) and the rate of renal function decline in the IR and HR groups (IR: T=-2.4 vs. P=3.5%, P=0.01; HR: T=-2.7 vs. P=3.8 ml/min/1.73m²/p=0.011) but not in the LR group. In all subjects, tolvaptan reduced the rate of eGFR decline from -3.40 to -2.59 ml/min/1.73m²/p=0.0001 with a relative treatment effect (TE) of 27%. Excluding subjects in the LR group improved this difference (-3.6 to -2.5 ml/min/1.73m²/p=0.0001, TE 33%). Similarly, while time to first renal event favored tolvaptan over placebo in the HR+IR (HR=0.39, P=0.0002), there was no difference in the LR group.

Conclusions: This study confirms the prognostic value of the PROPKD score and suggests that it will allow cost reduction of future trials and to maximize positive results by enriching the study population for rapidly progressing ADPKD subjects.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical

SA-POS94
Targeting Ciliogenesis by Modulating Tubulin Polymerization as a Therapeutic Approach for Polycystic Kidney Disease
Sarah E. Moreno,1 Herve Hussen,1 Laurie A. Smith,1 Mandy M. Smith,1 Ryam J. Russo,1 Rose A. Pitstick,2 Mikhail Sergeev,2 Steven R. Ledbetter,1 Nikolay Bukanova,1 Monica Lane,1 Kate Zhang,1 George A. Carlson,1 Jagesh V. Shah,1 Laurent Meijer,1 David Beier,2 Oxana Beskovskaya,1 Sanjot-Genzyme, Framingham, MA; 3McLaughlin Research Inst, Great Falls, MT; 4Brigham and Women’s Hospital, Boston, MA; 5ManROS Therapeutics, Roscoff, France; 6Seattle Children’s Research Inst, Seattle, WA.

Background: Polycystic kidney diseases (PKDs) are a class of genetic diseases that arise from abnormalities in the primary cilia and characterized by the continuous growth of renal fluid-filled cysts that leads to end-stage renal disease. Advancements in understanding the molecular mechanisms that drive cyst growth are crucial for the development of new therapeutic modalities.

Methods: Modulation of Cdk5 was achieved through pharmacological inhibition or genetic inactivation in jck mice. Efficacy was measured by kidney to body weight ratio, blood urea nitrogen, and cystic volume. Effects of CRMP2 modulation on ciliary length and tubulin polymerization were assessed in vitro. Knockdown of CRMP2 in vivo was done using peptide-linked phosphatidyl-L-aminoethyl phosphonic acid oleoglycolic acids (PPOO).

Results: We showed previously that inhibition of CRMP2 in vivo leads to a reduction in ciliary length and attenuates progression of PKD. Mechanistic studies suggested that Cdk5 may function through the regulation of tubulin dynamics by modulation of collapsing response mediator protein 2. Here we further expanded the role of CRMP2 on ciliogenesis.

In vitro CRMP2 localizes to the primary cilium and CRMP2 siRNA knockdown reduces tubulin polymerization leading to shortened cilia. In vivo we demonstrate that jck mice have increased microtubule stability and CRMP2 localizes to the primary cilium. In vitro modulation of CRMP2 with S-lacosamide results in decreased tubulin polymerization and reduces cilia length. In vivo knock down of CRMP2 in jck mice attenuated disease progression.

Conclusions: Taken together, our data supports targeting ciliogenesis as viable therapeutic approaches for the treatment of renal cystic diseases.

Funding: Pharmaceutical Company Support - Sanjot-Genzyme

SA-POS95
A Personalised Therapy for CEP290 Ciliopathy Syndrome
John Andrew Sayer, Shalahb Srivastava, Simon Ramsbottom, Elisa Molinari, Colin Miles.1
1Inst of Genetic Medicine, Newcastle Univ, Newcastle, United Kingdom.

Background: Mutations in CEP290 cause ciliopathy syndromes with a variety of clinical phenotypes. CEP290 is expressed in ciliary centrosomes; mutations are thought to affect the structure and function of the cilia. Over 130 different mutations have been described within CEP290. We present data concerning an affected boy aged 13 years, from consanguineous parents, with Joubert syndrome features.

Methods: Clinical features included ataxia, congenital amniosarco and progressive chronic kidney disease with renal cortical cyst formation. Mutation analysis (using a panel gene approach) revealed a homozygous nonsense mutation in exon 41 c.566G>T (p.Gly1890X). This is a commonly reported mutation in CEP290.

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

766A
Mutations in MAPKBP1 Cause Late Onset Cilia-Independent Nephropathy

Results: Haukeland Univ Hospital, Bergen, Norway; 5Novartis Insts for Biomedical Research, Basel, Switzerland.

Background: Nephropathies (NPH), an autosomal recessive tubulointerstitial nephritis, is the most common cause of hereditary end-stage renal disease in the first three decades of life. Since most NPH gene products (NPHF) function at the primary cilium, NPH is classified as ciliopathy.

Methods: We identified mutations in a novel candidate gene in 10 individuals from 6 families presenting late onset NPH with massive renal fibrosis. This gene encodes MAPKBP1, a poorly characterized scaffolding protein for JNK signaling. Immunofluorescence analyses showed that MAPKBP1 is not present at the primary cilium and that fibroblasts from affected individuals did not display ciliogenesis defects indicating that MAPKBP1 may represent a new family of NPHF not involved in cilia-associated functions. Instead, MAPKBP1 is recruited to motile spindle poles (MSPs) during the early phases of mitosis where it colocalizes with its paralog WDR62, which plays a key role at MSP. We found that MAPKBP1 recruitment correlated with PC2 to the MSP, but not with JNK interaction with JNK2 or WDR62. Additionally, we show increased DNA damage response signaling in fibroblasts from affected individuals and upon knockdown of Mapkbp1 in murine cell lines, a phenotype previously associated with NPH.

Conclusions: In conclusion, we identified mutations in MAPKBP1 as a genetic cause of late onset and cilia-independent NPH and propose “NPH2P1” as an alias for MAPKBP1.

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

Effects of Metformin on the AMPK Pathway and Metabolism in ADPKD Kidney Epithelial Cells

Background: We previously showed liver and spleen stiffness by ARFI is higher in ARPKD pts with vs. without portal HTN. ARFI appears useful to measure severity and progression of ARPKD liver disease.

Methods: Background: AUSTRALIAN DOMINANT TUBULOINTERSTITIAL KIDNEY DISEASE (ADTKD) IS CHARACTERIZED BY TUBULONEPHRITIS, INTERSTITIAL INFLAMMATION, AND PROGRESSIVE CHRONIC KIDNEY DISEASE. Four main genes, including UMOD, REN, HNF1B and MUC1 have been identified contributing to ADTKD. We first sequenced all of the three genes and confirmed the gross deletion of HNF1B by multiple ligation-dependent probe amplification (MLPA) assay. We found that downregulated PC2 not only significantly increased RLL and spleen stiffness correlate with severity of portal HTN in ARPKD. The proposed cut-offs have high specificity and sensitivity to distinguish pts with vs. without portal HTN. ARFI appears useful to measure severity and progression of ARPKD liver disease.

Funding: Other NIH Support - NCATS

Screening of UMOD/REN/HNF1B Gene Variations in a Chinese Cohort with Autosomal Dominant Tubulointerstitial Kidney Disease

Background: Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a genetic disease characterized by a progressive chronic kidney disease. Four genes, including UMOD, REN, HNF1B and MUC1 have been identified contributing to ADTKD. In the present study, we screened genetic variations of UMOD, REN and HNF1B in a Chinese ADTKD cohort.

Methods: 44 probands from 44 different families were recruited for this study. The mean age of the cohort was 30±11.1 years, males and females were almost equal. ADTKD was diagnosed according to the KDGO report. We first sequenced all of the three genes and confirmed the gross deletion of HNF1B by multiple ligation-dependent probe amplification (MLPA) assay.

Results: 61.4% of patients showed positive family history of renal disease. We detected 11 point mutations (10 in UMOD, 1 in HNF1B) in this cohort, and three of them (p.Cys357 Tyr, p.Asn381ile and p.Cys287Phe) were novel mutations of UMOD. Point mutation of REN and gross deletion of the HNF1B were not found. All the patients with mutation suffered hypercalcemia, and the patient with HNF1B mutation also presented hypoparathyroidism and hypokalemia.

Conclusions: Almost 25% of patients in our ADTKD cohort were confirmed to have UMOD gene mutations. And three of them were novel mutation of UMOD. The result indicated that gene sequencing is one of the reasonable methods to diagnose ADTKD.

Funding: Government Support - Non-U.S.

Quantification of Liver Disease Severity in Autosomal Recessive Polycystic Kidney Disease (ARPKD) Using Ultrasound Elastography with Acoustic Radiation Force Impulse (ARFI)

Background: We previously showed liver and spleen stiffness by ARFI is higher in ARPKD vs. controls, and in ARPKD pts with vs. without portal HTN. Aims of this study are 1) determine if ARFI liver and spleen stiffness can quantify severity of portal HTN; 2) explore cut-offs to detect presence of portal HTN.

Methods: We have identified mutations in MAPKBP1 as a genetic cause of late onset and cilia-independent NPH and propose “NPH2P1” as an alias for MAPKBP1.

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

SA-PO59

Quantification of Liver Disease Severity in Autosomal Recessive Polycystic Kidney Disease (ARPKD) Using Ultrasound Elastography with Acoustic Radiation Force Impulse (ARFI)

Results: We previously showed liver and spleen stiffness by ARFI is higher in ARPKD vs. controls, and in ARPKD pts with vs. without portal HTN. Aims of this study are 1) determine if ARFI liver and spleen stiffness can quantify severity of portal HTN; 2) explore cut-offs to detect presence of portal HTN.

Methods: We have identified mutations in MAPKBP1 as a genetic cause of late onset and cilia-independent NPH and propose “NPH2P1” as an alias for MAPKBP1.

Funding: NIDDK Support, Government Support - Non-U.S.
Cystogenesis may occur through differing signaling pathways and depends on PKD mutation. Metformin may exert beneficial effects in PKD2 mutant cells by mechanisms distinct from those proposed in PKD1 mutant cells and may be in part AMPK-independent.

**Funding:** NIDDK Support, Other U.S. Government Support

**SA-PO601**

Advanced Magnetic Resonance Imaging and Image Analytics to Assess the Polycystic Kidney

**Methods:** We performed a comprehensive MR imaging protocol (T1, T2, FIESTA, RBF, DWI, MT, BOLD, MRE) in 10 ADPKD patients (18-30 years old) and age- and sex-matched control volunteers - all with normal renal function. Two exams were performed (on different days) on each volunteer to characterize repeatability of the measurements.

**Results:** The Figure shows examples of traditional MR imaging (A, B, C), and quantitative maps: apparent diffusion coefficient (ADC) derived from DWI (D), MTR derived from MT (E), and R2* derived from BOLD (F). Quantitative MR imaging techniques showed different pathologies, as well as the ability to perform tissue parameter measurements at two different times, whole kidney MTR was 0.97 ± 0.76%, and stiffness, cyst heterogeneity, and changes in regional perfusion.

**Conclusions:** Quantitative and multiparametric MR imaging have strong potential for comprehensive characterization of the PKD kidney. It is likely that combining these techniques with other patient data will improve clinical decision making by providing new structural and functional information.

**Funding:** NIDDK Support

**SA-PO602**

Using T2- versus T1-Weighted MR Images to Assess Total Kidney Volume in Patients with ADPKD

**Methods:** We performed a comprehensive MR imaging protocol (T1, T2, FIESTA, RBF, DWI, MT, BOLD, MRE) in 10 ADPKD patients and age- and sex-matched volunteers. T1-weighted images were used, and the methodology of T2-weighted imaging has evolved, making T2-weighted imaging also suitable for TKV measurement. We studied the performance of T2- versus T1-weighted images to assess TKV and growth rate in TKV.

**Results:** We performed a comprehensive MR imaging protocol (T1, T2, FIESTA, RBF, DWI, MT, BOLD, MRE) in 10 ADPKD patients (18-30 years old) and age- and sex-matched control volunteers - all with normal renal function. Two exams were performed (on different days) on each volunteer to characterize repeatability of the measurements.

**Conclusions:** In patients with ADPKD measurement and growth rate of TKV using T2-weighted images performed similarly compared to using T1-weighted images. Both methods can therefore be used in clinical practice.

**Funding:** Pharmaceutical Company Support - Ipsen Pharmaceuticals, Private Foundation Support

**SA-PO603**


**Background:** Total kidney volume (TKV) has been shown in adult Autosomal Dominant Polycystic Kidney Disease (ADPKD) to be an independent and strong predictor for disease progression. In the current interventional clinical trials, TKV measurement by magnetic resonance imaging (MRI) has been shown to be more accurate, reproducible and able to detect small changes over a short period of time than ultrasound (US). Since future therapies in ADPKD could be extended to include children, we aimed to examine whether the high-resolution 3D-US TKV measurements might be used as an alternative method to MR measurements in ADPKD children.

**Methods:** Prospective evaluations of renal MRI, 2D- and 3D-US were performed, whereby TKV was calculated by means of manual delineations (MRI, 3D-US) or by the ellipsoid method (2D-US). Correlations and differences between parameters were evaluated using Pearson r and Wilcoxon signed rank tests. After correction using the optimal linear regression, the variability of the measurements was examined using Bland-Altman plots.

**Results:** We included 29 patients (17 male, 12 female) with a median age (SD) of 14.0 (3.4) years and eGFR 111 (17) ml/min/1.73m² leading to 56 evaluated kidneys. Although both US-MR techniques showed significantly lower TKV compared to MR (In ml, 3D-US: 181 (111); 2D-US 158 (101); MR 205 (132); all p<0.001), both showed a strong correlation to the MR TKV (2D-US: r=0.963; 3D-US: r=0.941). After correcting for the lower values in US, Bland-Altman plots showed slightly lower variability and error in 3D-US measurements compared to 2D-US in kidneys with a TKV below 200 ml (on average 15.5 ml error on 2D-US compared to 12.9 ml on 3D-US), although not reaching significance (p=0.23).

**Conclusions:** In children, 3D-US represents a good alternative for MR to measure TKV in ADPKD. Compared with MR, US TKV was prone to underestimation. After correcting for these, 3D-US tended to be slightly more comparable to MR in small TKV (<200 ml) than 2D-US.

**Funding:** Government Support - Non-U.S.
SA-PO604

In Vivo Functional Genomics Screen to Identify Genetic Disease Modifier Driving Autosomal Dominant Polycystic Kidney Disease Phenotypic Heterogeneity

Raphael A. Nemenoff, Kenneth H. Marsh, Emily K. Kleczko, Michel Chonchol, Katharina Hopp
Univ of Colorado Denver Anschutz Medical Campus.

Background: ADPKD is characterized by significant phenotypic heterogeneity even within families, suggesting that factors other than the specific PKD1/PKD2 mutation influence ADPKD severity. One explanation for this is the existence of additional mutations to other loci that modify ADPKD pathomechanisms and hence after disease progression. Identification of such modifier genes, however, has been proven difficult in the past.

Methods: Here, we utilized the conditional Sleeping Beauty (SB) transposon mutagenesis mouse model (SB1, T2/Onc3) driven by Cdh16 cre-recombinase to identify PKD1 modifiers in a Phl1 haploinsufficient mouse model. Generally, Phl1mice do not develop cysts; however, since a small change of Phl1 gene product function beyond 50% is enough to drive cystogenesis, genes disrupted or overexpressed by T2/Onc3 integration that directly or indirectly affect function in Phl1 pathways will trigger a cystic phenotype.

Results: We generated experimental mice (Phl1+/−;Ksp-cre;Rosa-26-SB111−;T2 Ocn3+/−) and confirmed kidney specific cre-recombine and SB11 expression. Additionally, we found SB11 to primarily be localized to the collectiv duct and Loop-of-Henle, nephron segments thought to be key to ADPKD pathogenesis. Importantly, by MRI, and histology we show that our experimental mice develop several cysts as early as one month of age, while none were found in genetic littermate controls (negative for Cdh16 or SB11). These cysts stained positive for SB11 by immunofluorescence, demonstrating proof-of-concept. Experiments to capture cystic lesions by laser micro-dissection, identify T2/Onc3 integration sites through next-generation sequencing, and pathway map common insertion sites are ongoing.

Conclusions: In summary, we developed a model that can in an unbiased fashion functionally identify modifier genes of ADPKD. Our preliminary findings indicate that mutations to additional genomic loci can trigger cystogenesis in a non-cystic background. These modifier loci will provide insight into ADPKD pathomechanisms, highlight novel therapeutic targets, and aid in patient management.

Funding: NIDDK Support

SA-PO605

Serum Bicarbonate Levels and Total Kidney Volume in Children and Young Adults with Autosomal Dominant Polycystic Kidney Disease

Kristen L. Nowak, Zhiying You, Berenice Y. Gitomer, Michel Chonchol, Melissa A. Cadnapaphornchai
Univ of Colorado Anschutz Medical Campus.

Background: Enhanced renal production of ammonia has been linked to cyst formation, and alkali administration has been found to reduce cystic tubular dilatation in animal models of autosomal dominant polycystic kidney disease (ADPKD). Whether lower serum bicarbonate concentrations are associated with an increased rate of total kidney volume (TKV) growth is unknown.

Methods: Participants were 85 children and young adults (8-22 years) participants with ADPKD and normal kidney function receiving lisinopril who were randomized to treatment with pravastatin or placebo for a 3-year period with evaluation of height-corrected TKV (HITKV) at baseline, 18 and 36 months. The study population was divided into tertiles based on serum bicarbonate levels. We used Generalized Estimating Equations (GEE) models to examine the association between serum bicarbonate levels with repeat measures of HITKV categorized as below and above the median level.

Results: Participants had a mean age of 15 ± 4 years. Mean serum bicarbonate level and estimated glomerular filtration rate were 24.4 ± 2.1 mEq/L and 115 ± 20 mL/min, respectively. The median (IQR) HITKV was 288 (221-394) mL/m². Compared to the first (lowest) tertile, the OR (95% CI) for a HITKV above the median value during the course of the study were as follows: second tertile, 1.004 (0.73-1.38) and third tertile, 0.84 (0.72-0.97) after adjustment for age, gender, randomization group, body-mass index, systolic blood pressure, estimated glomerular filtration rate, and urine albumin excretion.

Conclusions: In a cohort of children and young adults with ADPKD with normal kidney function, higher serum bicarbonate concentrations were associated with a lower risk of increase in TKV.

Funding: NIDDK Support

SA-PO606

Design of a Phase I Clinical Trial with 2-Deoxy-D-Glucose in Autosomal Dominant Polycystic Kidney Disease

Testa M. G., Perrone M., Magistroni M., Carballi R., Marco Chiarella,†1 Marco Leonelli,†1 Mariano Capistrano,‡ Francesco SCOLARI,‡ Donatella Spotti,‡, Alessandra Boletta,† Riccardo Magistroni.1,2 1Div of Genetics and Cell Biology, Molecular Basis of Polycystic Kidney Disease Unit, San Raffaele Scientific Inst, Milan, Italy; 2Div of Nephrology, Univ of Modena and Reggio Emilia, Modena, Italy; 3Second Div of Nephrology, Azienda Spedali Civili di Brescia, Brescia, Italy; 4Div of Nephrology, San Raffaele Scientific Inst, Milan, Italy.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a life-threatening Mendelian disease. The epidemiology is controversial and an accurate estimation in a small region of the North of Italy is ongoing. The hallmark of ADPKD is bilateral renal cysts formation. Several deregulated pathways have been described and in recent studies we have shown that defective glucose metabolism is a feature of ADPKD. Others and we showed that the glucose analogue 2-deoxy-D-Glucose (2DG) slowed down disease progression in animal models. Few previous clinical trials describing the use of 2DG as antineoplastic agent suggest low side effects. We are now about to initiate a Phase I Clinical Trial in ADPKD.

Methods: The aim is to perform a Phase I Clinical Trial to assess 2-DG tolerability. With a combined effort involving preparation of the active compound ready for human administration and selection of a small number of patients, an exploratory study will be initiated.

Results: This is a single center, open label, one arm trial in adult subjects. The study will follow a modified accelerated titration model. After determining eligibility and recording baseline parameters, 2DG will be titrated from lowest (2mg/die) to highest tolerated levels. Preliminary data suggest a prevalence comprised between 4.2 and 4.6 : 10000 inhabitants. Based on this we defined a recruiting population supplied by three Nephrology Centers. A limited number of ADPKD patients, with large kidneys but not severely reduced function will be exposed to 2DG and clinically monitored.

Conclusions: This first exploratory study will provide information to design a long-term evaluation in a relatively small patient population to measure markers of potential efficacy of 2DG.

Funding: Government Support - Non-U.S.

SA-PO607

Patterns of Renal Function Decline in the HALT PKD Trials

Godela M. Bronsonah, Kaleab Z. Abebe, Frederic F. Rahbari-Oskou, Charity G. Moore, Kyongeac Ty Bae, Jared J. Grantham, Robert W. Schrier, Arlene B. Chapman, Ronald D. Perrone, Vicente E. Torres,†1 Univ Colorado; †2Univ Pittsburgh; †3Emory Univ; †4Univ Kansas; †5Univ Chicago; †6Tufts Medical Center; †7Mayo Clinic.

Background: Renal function loss in autosomal dominant polycystic kidney disease (ADPKD) is generally believed to be steady and rapid once the limit of compensatory hyperfiltration has been reached. However, a detailed examination of individual patterns of renal function decline has not been performed.

Methods: Using data from the HALT trials we calculated the probabilities of linear or nonlinear trajectories of estimated glomerular filtration rate (eGFR) decline, as well as the probability of nonprogression for each participant using a previously validated Bayesian model. Twenty-six subjects with early disease and persistently high eGFR were excluded.

Results: The majority of participants (88% in Study A; 94% in Study B) experienced a progressive decline in eGFR during up to 8 years of follow-up, including those with well preserved renal function at baseline. A proportion (25% in Study A and 14% in Study B) of subjects with progressive decline had a nonlinear pattern. Interestingly, 12% of participants in Study A and 6% in Study B experienced a prolonged period of stable eGFR.

Conclusions: Although the course of renal function loss is progressive in most individuals with ADPKD, 6 to 12% experience prolonged intervals during which GFR decline is no faster than expected of ageing alone. Maintaining a healthy body weight may help to preserve eGFR in ADPKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Merck donated Lisinopril and Boehringer Ingelheim Pharmaceuticals donated Telmisartan and matched placebo, Private Foundation Support

SA-PO608

Surgical Urinary Acid, Total Kidney Volume and Disease Progression in Autosomal Dominant Polycystic Kidney Disease (ADPKD): Results from the HALT PKD Trial

Godela M. Bronsonah, Berenice Y. Gitomer, Wei Wang, Zhiying You, Kristen L. Nowak, Diana I. Tosta, Marco Chiarella,†1 Jared J. Grantham, Diana I. Tosta, Marco Chiarella,†1 Berenice Y. Gitomer, Wei Wang, Zhiying You, Kristen L. Nowak, Diana I. Tosta, Michel Chonchol. Univ Colorado, Aurora, CO.

Background: Hyperuricemia has been implicated in the progression of chronic kidney disease (CKD) in clinical studies. We tested the hypothesis that higher serum uric acid levels may be associated with greater total kidney volume (TKV) and progression to end-stage renal disease (ESRD) in ADPKD.

Methods: We measured uric acid levels in stored serum samples in 766 patients who participated in the HALT-PKD randomized controlled trial of two different blood pressure

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

Underline represents presenting author.

769A
control strategies. Participants in HALT-Study A had abdominal MRI for total kidney volume measurement. We used mixed effect models (HALT-Study A; N=410) and Cox proportional-hazards models (HALT-Study B; N=356) to examine the associations between uric acid modeled as a continuous variable with repeated measures of height-corrected total kidney volume (HTKV) during the course of the study and time to a 50% reduction in eGFR or ESRD.

**Results:** The mean age, serum uric acid level and eGFR in HALT A were 37.8 years, 6.2 mg/dL and 90.17 ml/min/1.73m². The median (IQR) for HTKV was 593 (409, 896) ml/m². In HALT-B the mean age, uric acid level and eGFR were 49.1 years, 7.2 mg/dL and 48.01 ml/min/1.73m². The estimates (TKV) and hazard ratio (50% reduction in eGFR or ESRD) are summarized in table 1.

<table>
<thead>
<tr>
<th>Region (Z Score)</th>
<th>Spine L1-L4</th>
<th>Left Femoral Neck</th>
<th>Right Femoral Neck</th>
<th>Distal Third Radius</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-0.55</td>
<td>-0.07</td>
<td>-0.08</td>
<td>0.16</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>1.19</td>
<td>0.79</td>
<td>0.79</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Adjusted for age, gender, race, randomization group, body mass index, systolic blood pressure, eGFR, urine albumin excretion and genotype.**

**Conclusions:** Higher serum uric acid levels are associated with increased hazard for kidney function decline and ESRD but not with larger kidney volume. Randomized interventional studies will be necessary to examine whether treating hyperuricemia has a protective role in ADPKD.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Merck donated Lisinopril and Boehringer Ingelheim Pharmaceuticals donated Telmisartan and matched placebo, Private Foundation Support

### SA-PO609

**Variability of PKD1-PKD2 in Autosomal Dominant Polycystic Kidney Disease (ADPKD): A 643 Patients Italian Experience**

**Paola Carrera,** Silvia Calzavara,* Riccardo Magistrini,** Johan T. Den Dunnen,** Francesco Rigo,* Stefania Rizzi,* Francesca Testa,* Piergiorgio Messa,* Roberta Cerutti,* Francesco Scolari,* Claudia Iuzzi,* Alberto Edefonti,* Susanna Negrisolo,* Elisa Benetti,* Maria Teresa Sciarrone Alibrandi,** Paolo Manunta,* Alessandra Boletta,* Maurizio Ferrari,* Stefania Rizzi,* Irene Giannini* and Stefano Ferrari.*

**Background:** ADPKD is the most common hereditary kidney disease. Methods: We analysed PKD1 and PKD2 in a large cohort of 440 unrelated Italian patients with ADPKD and 203 relatives by direct sequencing and MLPA. Molecular and detailed phenotypic data have been collected and submitted to the PKD1-PKD2 LOVD database.

**Results:** We describe 701 variants, 249 (35.5%) already associated with ADPKD and 452 (64.5%) novel. According to the criteria adopted, the overall detection rate was 80% (352/440). Novel variants with uncertain significance were found in 14% of patients. Among patients with pathogenic variants, in 301 (85.5%) the disease was associated with PKD1, 196 (55.7%) truncating, 81 (23%) non truncating, 24 (6.8%) IF indels, and in 51 (14.5%) patients with pathogenic variants, in 301 (85.5%) the disease was associated with PKD1, 196 (55.7%) truncating, 81 (23%) non truncating, 24 (6.8%) IF indels, and in 51 (14.5%) with PKD2. Enrichment of the cohort in subjects with an uncertain clinical diagnosis (which include criteria for rapid disease progression by eGFR decline or kidney size increase) were calculated.

**Funding:**: EMA, May 2015 for adults with ADPKD.

**Conclusion:**: Our data, derived from a population of defined size, will help renal units estimate the number of patients who may be eligible for treatment and the implications for our service.

**Methods:** Adults with ADPKD attending Glasgow Renal and Transplant Unit were identified. Most recent, 1 year and 5 year values for eGFR using the CKD-EPI equation were collected. Rapid disease progression was defined as decline in eGFR ≥5 ml/min in 1 year or ≥12.5 ml/min over 5 years. Patients without evidence of rapid disease progression by eGFR were further evaluated by family history and imaging criteria. Numbers qualifying for treatment or requiring further imaging according to UK Renal Association guidelines (which include criteria for rapid progression by eGFR decline or kidney size increase) were calculated.

**Results:**: 164 patients with ADPKD and attending Glasgow Renal and Transplant Unit were identified. Most recent, 1 year and 5 year values for eGFR using the CKD-EPI equation were collected. Rapid disease progression was defined as decline in eGFR ≥5 ml/min in 1 year or ≥12.5 ml/min over 5 years. Patients without evidence of rapid disease progression by eGFR were further evaluated by family history and imaging criteria. Numbers qualifying for treatment or requiring further imaging according to UK Renal Association guidelines (which include criteria for rapid progression by eGFR decline or kidney size increase) were calculated.

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**Funding:**: EMA, May 2015 for adults with ADPKD.

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**Methods:**: We analysed PKD1 and PKD2 in a large cohort of 440 unrelated Italian patients with ADPKD and 203 relatives by direct sequencing and MLPA. Molecular and detailed phenotypic data have been collected and submitted to the PKD1-PKD2 LOVD database.

**Results:**: We describe 701 variants, 249 (35.5%) already associated with ADPKD and 452 (64.5%) novel. According to the criteria adopted, the overall detection rate was 80% (352/440). Novel variants with uncertain significance were found in 14% of patients. Among patients with pathogenic variants, in 301 (85.5%) the disease was associated with PKD1, 196 (55.7%) truncating, 81 (23%) non truncating, 24 (6.8%) IF indels, and in 51 (14.5%) with PKD2. Enrichment of the cohort in subjects with an uncertain clinical diagnosis (which include criteria for rapid disease progression by eGFR decline or kidney size increase) were calculated.

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**Conclusion:**: Our data, derived from a population of defined size, will help renal units estimate the number of patients who may be eligible for treatment and the implications for our service.

**Methods:**: We analysed PKD1 and PKD2 in a large cohort of 440 unrelated Italian patients with ADPKD and 203 relatives by direct sequencing and MLPA. Molecular and detailed phenotypic data have been collected and submitted to the PKD1-PKD2 LOVD database.

**Results:**: We describe 701 variants, 249 (35.5%) already associated with ADPKD and 452 (64.5%) novel. According to the criteria adopted, the overall detection rate was 80% (352/440). Novel variants with uncertain significance were found in 14% of patients. Among patients with pathogenic variants, in 301 (85.5%) the disease was associated with PKD1, 196 (55.7%) truncating, 81 (23%) non truncating, 24 (6.8%) IF indels, and in 51 (14.5%) with PKD2. Enrichment of the cohort in subjects with an uncertain clinical diagnosis (which include criteria for rapid disease progression by eGFR decline or kidney size increase) were calculated.

**Funding:**: EMA, May 2015 for adults with ADPKD.

**Conclusion:**: Our data, derived from a population of defined size, will help renal units estimate the number of patients who may be eligible for treatment and the implications for our service.
SA-PO613
Haematologic Phenotype of Hereditary Polycystic Kidney Disease
Stevens Van Laecke,1 Teusa C.C. Kerro,2 Evi V. Nagler,2 Bart D. Maes,2 Roger Caluwe,2 Wim Van Biesen,4 Francis Verbeke,1 *Ghent Univ Hospital, Div Infection Disease, Belgium; 2Dept of Investigative Medicine, University of Antwerp, Belgium; 3Ghent Univ Hospital, Div of Nephrology, AZ Delta, Roeselare, Belgium; 4Div of Nephrology, OLVZ, Aalst, Belgium; 5Ghent Univ Hospital, Renal Div, Belgium; 6Ghent Univ Hospital, Div of Clinical Chemistry, Belgium.

Background: Hereditary polycystic kidney disease (PKD) has a complex phenotype including not only renal cell formation leading to end-stage kidney disease (ESKD) but also vascular abnormalities and endothelial dysfunction. Patients with PKD tend to have a higher susceptibility for urinary and respiratory infections and develop more skin cancer after transplantation.

Methods: We compared lymphocyte counts in patients with and without PKD at the time of transplantation in a cohort with follow-up until December 31, 2014. We analyzed flow cytometric immunophenotyping data if available. We also conducted a multicenter age-matched case-control study in a cohort including 202 patients with and 202 without PKD across comparable CKD strata with follow-up until February 1, 2016. We used multiple linear regression analysis to adjust for potential confounders in both models. We also recorded and analyzed other hematological characteristics.

Results: In a population of 700 patients with ESKD, total lymphocyte counts (and particularly CD8 T and B lymphocytes) were significantly lower in the 126 patients (18%) with versus without PKD (p<0.001 for both). Alteration adjustment for age, sex, htTKV and eGFR (in the CKD cohort only), PKD was associated with a lower lymphocyte count of 264/µL (95%CI 164 to 384; p<0.001) and 345/µL (95%CI 245 to 445; p<0.001) in the ESKD and CKD cohort respectively. Also, thrombocyte and monocyte counts were independently lower in patients with versus without PKD in both cohorts (p<0.001 for both cell types within each of the cohorts).

Conclusions: PKD is characterized by distinct haematological abnormalities and more particularly lymphopenia, independent of kidney function. A genetic basis for increased apoptosis of lymphoid cells and their precursors in PKD is conceivable.

SA-PO614
Smoking Worsens the Renal Phenotype of Pkd1-Deficient Cystic Mice
Marciana Veloso Sousa, Andreas Gody Goday Amaral, Bruno E. Balbo, Fernanda Souza Messias, Isaac de Castro, Luiz E. Onuchic. Div of Nephrology and Molecular Medicine, Univ of Sao Paulo, Sao Paulo, SP, Brazil.

Background: Smoking is a risk factor for progression to stage 5 chronic kidney disease in patients including the autosomal dominant polycystic kidney disease (ADPKD) scenario. To elucidate this matter, we analyzed the effects of smoking on the renal phenotype of a mouse model orthologous to ADPKD.

Methods: Pkd1-deficient mice (Pkd1<sup>mad/astrain;Nestin<sup>loxp/llox</sup> and noncystic animals (Pkd1<sup>+/+/<sub>mad/astrain</sub>;Nestin<sup>loxp/llox</sup>) were exposed to cigarette smoking from conception to 18 weeks of age, 2 times a day, 30-min cycles (CYS and NCS, respectively). Additional controls included cystic and noncystic mice not exposed to smoking (CY and NC, respectively). Serum urea nitrogen (SUN), renal cystic index by ultrasonography, cell proliferation, area of renal fibrosis and body weight (BW) were evaluated at 16-18 weeks in all groups.

Results: CYS mice had higher SUN than CY (57±32.4 vs 35.7±6.0 mg/dL, p<0.05) and NC animals (vs 32±0.3 mg/dL, p<0.001). CYS mice also showed higher SUN than NC animals (48.6±19.1 vs 32.0±3.1 mg/dL, p<0.01). No difference in SUN was detected, however, between CYS and NCS mice and between CY and NC animals. The cystic index was increased in CYS kidneys compared to CY [17.4% (6.0-31.7) vs 4.6% (2.7-8.4), p<0.05] while BW was lower in CYS than CY mice [24.2 (23.4−25.0) vs 28.3 g (27.1-29.4), p<0.0001]. Cell proliferation rate was increased in CYS kidneys compared to NC [0.9% (0.7-1.0) vs 0.2% (0.1-0.2), p<0.0001] and higher in CYS than CY cystic epithelia [2.1% (0.9-4.3) vs 1.1% (0.5-1.6), p<0.05]. Renal fibrosis was also higher in CYS mice than CY [1.1% (0.8-2.0) vs 0.3% (0.2-0.8), p<0.0001]. CYS vs NC [0.1% (0.9-0.2), p<0.01] and NC animals [vs 0.0 % (0.03-0.9), p<0.0001]. Increased fibrosis was also detected in CY kidneys compared to NCS and NC (p<0.001) and in NCS kidneys compared to NC (p<0.05).

Conclusions: Our data revealed that smoking aggravated the renal phenotype of cystic mice, increasing the cystic burden, cell proliferation and fibrosis, and reducing kidney function. deleterious effects were also observed in noncystic kidneys. Our findings support an accelerating effect of smoking on the progression of ADPKD.

SA-PO615
Effect of Dietary Salt of the Progression of ADPKD in the HALT PKD Clinical Trials
* Vicente E. Torres,1 Kaleab Z. Abebe,2 Robert W. Schrier,3 Ronald D. Perrone,4 Arlene B. Chapman,5 Alan S.L. Yu,6 William E. Braun,7 Theodore I. Steinman,8 Godelia M. Brosnahan,9 Marie C. Hogan,10 Frederic F. Rahbari-Oskoui,11 Jared J. Grantham,12 Kyongtae Ty Baec,13 Charity G. Moore,14 Michael F. Flessner,15 *Mayo Clinic, Rochester, MN;16 U of Pittsburgh, Pittsburgh, PA;17 U of Colorado, Denver, CO;18 Tufts U, Boston, MA;19 U of Chicago, Chicago, IL;20 Kansas U, Kansas City, KS;21 Cleveland Clinic, Cleveland, OH;22 Beth Israel Deaconess Medical Center, Boston, MA;23 Carolinas Healthcare System, Charlotte, NC;24 Nat Insths of Health, Bethesda, MD;25 Emory Univ, Atlanta, GA.

Background: The Consortium for Renal Imaging Studies in PKD (CRISP) found that 24 hours urinary sodium excretion (UNaE) associates with the rate of total kidney volume (TKV) increase. Whether sodium restriction can slow the progression of ADPKD is not known.

Methods: This post-hoc analysis of the HALT-PKD randomized clinical trials of renin-angiotensin blockade in ADPKD used linear mixed models to examine whether dietary sodium (replaced by UNaE) affected rates of TKV or eGFR change in patients with eGFR >60 ml/min/1.73 m² (Study A) or the risk for a composite endpoint of 50% reduction in eGFR, ESRD or death, or the rate of eGFR decline in patients with eGFR 25-60 ml/min/1.73 m² (Study B). Patients were instructed to follow a <100 mEq sodium diet.

Results: During the trial UNaE declined by 0.25±0.04 mEq/dl and 0.41±0.04 mEq/dl/24 hr per month of follow-up in Studies A and B (both P<0.001). In Study A, averaged and time varying UNaE were associated with kidney growth (2.4%/yr and 0.48%/yr for each 100 mEq UNaE, P<0.001 and P<0.005, respectively) and averaged UNaE was marginally associated with faster eGFR decline (−0.37 ml/min/1.73 m²/yr for each 100 mEq UNaE, P=0.09). In Study B, averaged but not time varying UNaE was associated with increased risk for 50% reduction in eGFR, ESRD or death (HR 1.56 for each 100 mEq UNaE, P=0.01) and faster eGFR decline (−0.48 ml/min/1.73 m²/yr for each 100 mEq UNaE, P<0.001).

Conclusions: These results reinforce the important role of moderate sodium restriction in the management of patients with ADPKD.

Funding: NIDDK Support, Other NIH Support - CRISP
SA-PO617

Development of a Customized Diagnostic Panel for Targeted Exome Sequencing of Polycystic Kidney Diseases
Takuya Fujimura, Takayasu Mori, Shintaro Mandai, Motoko Chiga, Hiroaki Kikuchi, Fumitaki Ando, Yuriro Mori, Naohiro Nomura, Shotaro Naito, Tomokazu Okado, Tatemitsu Rai, Shinichi Uchida, Eisei Sohara.

Background: Polycystic kidney disease (PKD) is an inherited kidney disorder. Genetic diagnosis is crucial for genetic counseling and the clinical management of patients and their families. However, especially among the child population, it is often difficult to make a precise diagnosis based on clinical features and imaging findings. Additionally, the increasing number of causative genes makes it difficult to perform DNA sequencing using conventional Sanger sequencing. Therefore targeted multiple genome sequencing using next generation sequencing enables rapid and precise DNA diagnosis at a large scale.

Methods: With reference to Human Gene Mutation Database (HGMD), articles, opinion of experts, we created a custom capture RNA probe library (SureSelect Custom, Agilent Technologies) for 66 genes that cause nine types of hereditary PKD, such as autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD) and nephronophthisis. MiSeq sequencing was performed with 150 bp SE reads and each downstream analyses were conducted by using BWA, SAMTools, GATK, VEP, and GEMINI software. Copy number variations (CNVs) were evaluated with CONTRA.

Results: Provisional sequencing for four human subjects who were clinically diagnosed with PKD using this newly created panel secured 96.5% enough coverages (depth>10) for all the targeted genes with mean depth of 457.1. Of these, likely-pathogenic heterozygous mutations in PKD1 are detected in a patient diagnosed with ADPKD. In another patient diagnosed with ARPKD, disease-causing compound heterozygous variants in PKD1 are found with trio-based analysis.

Conclusions: We succeeded in developing a custom diagnostic panel specialized in PKD. In the situation that many responsible genes for PKD have been reported increasingly, comprehensive approach for genetic diagnosis will enable fast and efficient diagnosis of PKD in future.

Funding: Government Support - Non-U.S.

SA-PO618

Epithelial Morphogenesis of Urine-Derived Renal Epithelial Cells from Children with Autosomal Recessive Polycystic Kidney Disease: An Ex Vivo Study
Wolfgang H. Ziegler, Margarita E. Georgiadis, Kathrin F. Scholl, Birgitta Schlegel, Dieter Hampel.

Background: Autosomal recessive polycystic kidney disease (ARPKD) is caused by mutation of the PKHD1 gene, which encodes fibrocystin (FPC), a type I membrane protein of largely unknown function. Among other functions, FPC affects adhesion signaling of cells and their ability to orientate correctly towards one another. Recently, we established a link between loss of FPC function and defective epithelial morphogenesis in 3D cell culture using a canine cell line. Data in humans are lacking. Therefore, we set up assays for analyzing epithelial cells from ARPKD patients and healthy controls.

Methods: We take urine-derived renal epithelial cells (URECs) of ARPKD patients and respective controls in culture. The patients must have their original kidney(s) and still second opinion. Populated URECs of primary cells obtained within 14 days of culture are being characterized by different criteria and also tested in 3D cell culture conditions, which induce formation of epithelial spheroids with defined polarity, lumen and cilia.

Results: Using 2D and 3D culture conditions, we observe URECs of three different phenotypes: spindle, patch, and cobblestone-like epithelial cells. While all different cell morphologies stain positively for the collecting duct marker aquaporin 2, only cobblestone-like cells give rise to a strong epithelial barrier as verified by impedance measurements and form spheroids in 3D culture conditions. Thus, cells of this phenotype are characterized by different criteria and also tested in 3D cell culture conditions, which induce formation of epithelial spheroids with defined polarity, lumen and cilia.

Conclusions: Using 2D and 3D culture conditions, we observe URECs of three different phenotypes: spindle, patch, and cobblestone-like epithelial cells. While all different cell morphologies stain positively for the collecting duct marker aquaporin 2, only cobblestone-like cells give rise to a strong epithelial barrier as verified by impedance measurements and form spheroids in 3D culture conditions. Thus, cells of this phenotype are characterized by different criteria and also tested in 3D cell culture conditions, which induce formation of epithelial spheroids with defined polarity, lumen and cilia.

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

SA-PO619

Early Changes in Histidine Metabolism in Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Sophia A. Banton,1 Ken H. Liu,1 Shuzhao Li,1 Dean P. Jones,1 Peili Chen,1 F. Gary Toback,2 Arlene B. Chapman.2 Emory Univ;1 Univ of Chicago.

Background: Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited kidney disease, is characterized by expansive cyst growth, leading to increased total kidney volume (TKV), a decline in kidney function and ultimately end-stage renal disease. Evidence suggests that common cellular and molecular mechanisms are responsible for cystogenesis in ADPKD regardless of the genes mutated.

Methods: To further understand the pathophysiology and unique metabolic features of early ADPKD, we used untargeted high-resolution metabolomics to analyze paired urine and plasma samples in a case-control framework comparing ADPKD patients (n=42, mean TKV 1,253.07±1,053.32 mL, mean eGFR 88.95±31.08) to age and gender-matched healthy controls (n=18, eGFR 107.89±15.48).

Results: Among metabolic pathways that were different between ADPKD patients and controls, the most highly represented were histidine and purine metabolism. Complementary analyses that explored the relationships between renal function (eGFR) and disease severity (TKV) also showed differences in histidine metabolism. Plasma histamine (p=0.01) and histidyl-histidine (p=0.02) and urinary 1-methylhistidine (p=0.01) were increased in ADPKD. Urinary imidazolacetic acid (p=0.02) levels were lower in ADPKD patients. Histamine, histidyl-histidine, 1-methylhistidine and N-methylhistamine are associated with increased odds of ADPKD, and metabolome-wide association studies of these metabolites revealed that additional histidine metabolites are highly enriched in the urine and plasma of ADPKD patients.

Conclusions: ADPKD promotes dysregulation of the histidine pathway in PKD patients, which results in a metabolic profile that resembles clinical histidinemia.

Funding: NIDDK Support

SA-PO620

Next Generation Sequencing of an Extensive Kidney-Disease Gene Panel for a Comprehensive Genetic Diagnosis of Cystic and Glomerular Inherited Kidney Diseases
Elisabet Arsc1 Gemma Bullich,1 Iván Vargas,2 Patricia Ruiz,1 Laura Lorente,1 Gema Ariceta,1 Jose Ballarin,1 Roser Torra.1 Molecular Biology Laboratory and Nephrology Dept, Fundacio Puigvert, Barcelona, Spain;2 Informatics Dept, Inst de Diagnostic per la Imatge (IDI), Barcelona, Spain;1 Pediatric Nephrology Dept, Hospital Vall d’Hebron, Barcelona, Spain.

Background: The advent of next generation sequencing (NGS) has enabled the creation of comprehensive multi-gene panels, and served to broaden the phenotypic spectrum of inherited kidney diseases (IKD). Genetic diagnosis of cystic and glomerular IKD is complicated by their high genetic heterogeneity and phenotypic variability, with clinical manifestations that can be mimicked by mutations in several genes. We aimed to develop a comprehensive approach for genetic diagnosis of cystic and glomerular IKD.

Methods: NGS of 132 genes causative or associated with cystic or glomerular IKD was performed in 232 patients, a pilot study of 116 patients and a diagnostic cohort of 116 patients, consisting of 87 cystic and 29 glomerular IKD patients.

Results: In the pilot study, 134 out of 135 previously known mutations (99%) were identified, demonstrating similar sensitivity as Sanger sequencing. In the diagnostic cohort, disease-causing mutations were found in 86 out of 116 patients (74%), including 64 out of 87 cystic IKD patients (74%) and 22 out of 29 glomerular IKD patients (76%). Mosaic mutations were detected in 3 in the tuberous sclerosis patients and 2 ADPKD patients. Structural variants in HNF1B, COLA45 and COL4A3 were found in 7 patients. Complex inheritance patterns were identified in a total of 5 patients, 3 ADPKD patients and 2 Alport syndrome patients. Mutations in low-frequency mutated genes such as NPHS3, CUBN, or OTUD7 were also identified.

Conclusions: Targeted sequencing of our kidney-disease gene panel is a comprehensive, efficient and cost-effective tool for genetic diagnosis of cystic and glomerular IKD.

Funding: Government Support - Non-U.S.
SA-PO621
Developmental Switch for Polycystic Hepatic and Kidney Disease (PKD) Treatment: Unmasking the Signaling Pathways That Temporally and Spatially Drive Cyst Initiation and Cyst Progression Olaya Lamas-Gonzalez,1 Adrián Cordido,1 Susana Bravo,2 Ana Belen Sanz,1 Alberto Ortiz,1 Candido Díaz-Rodríguez,1 Miguel A. García-González,1 1Group of Genetics and Developmental Biology of Cystic Diseases, Health Research Inst of Santiago de Compostela (IDIS), Spain; 2Fundación Jiménez Díaz, Spain; 3Proteomic Unit, (IDIS), Spain.

Background: Different mechanisms have been related to the pathogenesis of Polycystic Kidney Disease (PKD). This make hard to understand the principal mechanism underlying cystogenesis as well as the identification of therapeutic approach for complete and specific inhibition of cystogenesis. Although, strong evidences in cystic volume reduction and cystic protein levels have been described.

Methods: We have previously shown the identification of the differential proteome related to the developmental window identified for PKD progression, as well as the proteome related to cystic progression under inflammatory response.

Results: In this study, we further explore the effect of therapeutic targeting the list of our candidates (n=16) identified for ADPKD prevention and control. We previously described several proteins underlying altered cell morphogenesis, ECM-cell interactions and cell metabolism during cystogenesis. By drug targeting of several of those pathways, we blocked cystogenesis from distal nephron segment, reduced/delayed global cystic progression, as well as inhibited polycystic liver phenotype completely recovering kidney and liver function. These effects were potentiated in combination with Tolvaptan, although unexpected phenotypical effects were identified.

Conclusions: In conclusion, we have first described the ADPKD related proteome that help us to puzzle out the different signaling cascades that temporally and spatially play a role in cyst initiation and progression. Moreover, we also identified an effective treatment for both PKD and PL controlling both cystic origin and progression, although more studies are needed for the understanding of phenotypic side effects. Finally, our work underlines the importance of a multiomics cocktail strategy for the treatment of PKD, by the target of specific nephron segment cystic origin as well as blockage of the mechanisms underlying cystic progression and expansion.

Funding: Government Support - Non-U.S.

SA-PO622
Autosomal Dominant Tubulointerstitial Kidney Disease: The Spanish Cohort Nadia Ayashre,1 Gemma Bullich,2 Monica Furiano,3 Rosa Miquel,2 Xavier Fulfordosa,4 Miguel A. García-González,4 Jose Ballarin,1 Elisabet Ars,1 Roger Torra,1 1Hospital Universitari Puigvert, 2H.U. Canarías, 3H.U.Bellvitge; 4CH. Santiago de Compostela; 5H. Reina Sofia, Spain.

Background: Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) is a rare cause of end stage renal disease. It is caused by mutations in at least four different genes: MUC1, UMOD, HNF1B and REN. In this study we describe the clinical features of patients with MUC1 and UMOD mutations.

Methods: Inclusion criteria were: autosomal dominant inheritance, renal failure without hematuria, and absent or minimal proteinuria, and exclusion of other causes of renal failure. 60 individuals who developed ESRD, the median age of onset was 45.21 years (SD 11.52) and 85 individuals diagnosed, the genetic study. Genetic analysis of available data (n=16) identified for ADPKD prevention and control. We previously described several proteins underlying altered cell morphogenesis, ECM-cell interactions and cell metabolism during cystogenesis. By drug targeting of several of those pathways, we blocked cystogenesis from distal nephron segment, reduced/delayed global cystic progression, as well as inhibited polycystic liver phenotype completely recovering kidney and liver function. These effects were potentiated in combination with Tolvaptan, although unexpected phenotypical effects were identified.

Conclusions: In conclusion, we have first described the ADPKD related proteome that help us to puzzle out the different signaling cascades that temporally and spatially play a role in cyst initiation and progression. Moreover, we also identified an effective treatment for both PKD and PL controlling both cystic origin and progression, although more studies are needed for the understanding of phenotypic side effects. Finally, our work underlines the importance of a multiomics cocktail strategy for the treatment of PKD, by the target of specific nephron segment cystic origin as well as blockage of the mechanisms underlying cystic progression and expansion.

Funding: Government Support - Non-U.S.

SA-PO623
Effect of Renal Transcatherter Arterial Embolization on Quality of Life in Patients with Autosomal Dominant Polycystic Kidney Disease Tatsuya Suwabaye, Yoshihumi Ubara, Akinari Seike, Masuyuki Yamamoto, Junichi Hoshino, Masahiro Kawada, Kenmei Takaichi. Toranomon Hospital, Dept of Nephrology, Minato-ku, Tokyo, Japan.

Background: Patients with autosomal dominant polycystic kidney disease (ADPKD) and massive kidneys have various symptoms related to abdominal distension and renal dysfunction, which impair quality of life (QOL). However, current strategies for improving the QOL of ADPKD patients are very limited. Renal transcatherter arterial embolization (TAE) is effective for reducing kidney volume, but its impact on the QOL of ADPKD patients is unknown. This study aimed to clarify the influence of renal TAE on the QOL of ADPKD patients with enlarged kidneys.

Methods: All patients with ADPKD who underwent TAE at our hospital between 2010 and 2014 were enrolled. The short form-36 (SF-36) questionnaire and our original 15-item questionnaire about specific symptoms of patients with ADPKD were used to evaluate QOL. To estimate the mean values of the SF-36 physical component summary (PCS), mental component summary (MCS) and role/social component summary (RCS) and the answers to our 15-item questionnaire at each time point, the least squares mean (LSM) was calculated using a linear mixed model.

Results: A total of 188 patients on hemodialysis (92 men and 96 women, mean age: 56.7 ± 9.1 years, median total kidney volume: 4497 cm³) were enrolled. The least squares mean of PCS, MCS and RCS before renal TAE were 38.21 (95%CI: 36.50 to 39.91), 49.86 (95%CI: 48.96 to 50.76), and 40.04 (40.70 to 45.37), respectively. These values increased to 42.0 (40.22 to 43.77; p<0.001 vs. before renal TAE), 51.25 (49.78 to 52.71; p<0.001), and 49.67 (47.22 to 52.12; p<0.001) at one year after renal TAE, respectively. Abdominal fullness, poor appetite, and heartburn showed marked improvement. Scores for fever, bodily pain, heartburn, and SF-36 MCS and RCS scores, but not enough for improving sleep disturbance, constipation, nausea, and physical strength (PCS score).

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

SA-PO624
Development of Cost/Effective Strategies for Genetic Diagnosis of Polycystic Kidney Disease Based on the Population Mutagenesis Rate or Specific Needs M. Lara Besada-Cerecedo,1 Lisbeth Silva,1 Beatriz Sobrino,1 Jorge Amigo,2 Patricia Regueiro Casuso,1 Ana Barcia de la Iglesia,1 Manuel Fidalgo,1 Carmen Vazquez,1 Angel Carracedo,1 Candido Diaz-Rodriguez,1 Miguel A. Garcia-Gonzalez,1 1Group of Genetics and Developmental Biology of Cystic Diseases, Health Research Inst of Santiago de Compostela (IDIS), Spain; 2Galician Public Foundation of Genomic Medicine, Galician Public Foundation of Genomic Medicine, Spain.

Background: Genetic tests have the benefit of ensuring an accurate diagnosis, is done one time in life and it can anticipate the disease, band limit the cost to be used in diagnostic routine. With the incorporation of the new generation sequencing (NGS), genetic tests have reduced dramatically the costs getting closer to the diagnosis by magnetic resonance image, and the advantage that it costs 100 times cheaper for the rest of family members.

Methods: We developed three strategies: T1NGS panel for the genetic region responsible of the most polycystic kidney disease in the population (the replicated region of PKDI, exons 1-34), T2 NGS Panel for common polycystic disease (8 genes), and T3 NGS Panel for rare and ultra-rare polycystic kidney disease (all 72 known cystic genes).

Results: By analyzing a total of 252 PKD families (2150 patients), we identify the associated mutation in 90 families using the T1, 128 by using T2 and 34 by using T3. In addition we reanalyzed all genetic variants identified to the moment, that help us to establish a PKD database of a total number of 3260 reclassified variants in four categories: 1174 class-I definitely pathogenic (832 PKD1, 155 PKD2 and 187 PKHD1; “stop codon”, “frameshift insertions/deletions” and “canonical splice site alterations”); 141 class-II probably pathogenic (107 PKD1, 12 PKD2 and 22 PKHD1; “inframe deletion/insertion” “amplifications” and “null mutations”); 373 class-III/uncertain significance (119 PKDI, 85 PKD2 and 390 PKHD1) and 351 SNPs (199 PKD1, 21 PKD2 and 131 PKHD1). A total of 29 PKD1 variants, 8 PKD2 and 15 PKHD1 were novel PKD mutations.

Conclusions: Here we demonstrate the first cost/effective strategy applied for the diagnosis of all patients belonging to Local Health System for ADPKD.

Funding: Government Support - Non-U.S.

SA-PO625
Periostin Overexpression in Collecting Ducts Accelerates Polycystic Kidney Disease Archana Raman, Stephen C. Parnell, Aditi Khanna, Yuqiao Dai, Gail Reif, Darren P. Wallace. Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.

Background: Aberrant expression of extracellular matrix molecules and secreted factors contributes to cyst growth and fibrosis in polycystic kidney disease (PKD). Periostin, a matricellular protein involved in tissue development and repair, is overexpressed by cyst-lining epithelial cells and accumulates within the matrix adjacent to renal cysts. We found that periostin increased the activity of integrin-linked kinase (ILK) downstream signaling pathways, including the Akt-mTOR pathway and induced proliferation of human PKD cells. Cilengitide, an eVTβ3- and eVTβ5-integrin antagonist, blocked periostin-induced cell proliferation. Genetic knockout of periostin in pcy/pcy (pcy) mice, a slowly progressing model of cystic disease, reduced renal cell proliferation, cystic index and interstitial fibrosis, and improved the survival of the mice.

Methods: We generated periostin transgenic mice (OTG). Using a floxed STOP cassette exon 3 of the periostin gene under the control of the ROSA26 promoter. Postnatally bred mice were bred to Pck1-Cre mice to selectively overexpress periostin in collecting ducts (CD), a predominant site for cyst formation. To determine if periostin accelerates cystic disease, Postnatally Pck1-1Cre mice were bred with pcy/pcy mice to generate pcy: Pck1-1Cre mice were bred with pcy/pcy mice to generate pcy: Pck1-
Dramatically increased in Boston, MA.

**Conclusions:** These results indicate that aberrant expression of ECM molecules, including peristin, contributes to elevated mTOR activity and cell proliferation, suggesting that the intercellular signaling pathway may be a potential therapeutic target for PKD.

**Funding:** NIDDK Support, Private Foundation Support

SA-PO626

**Collecting Duct-Specific Inactivation of HNF-1β Leads to Fibrocystic Disease and Impaired Urinary Concentration**

**Lama A. Nourreddine, 1,3 Karam S. Aboudehen, 1,2 Patricia Cobo-Stark, 1 Svetlana Avdulov, 1 Shayan A. Farahani, 1 Daniel G. Bichet, 1 Marco Pontoglio, 1 Vishal Patel, 1 Peter Igarashi, 1,2 Internal Medicine, Univ of Texas Southwestern Medical Center, Dallas, TX; 3 Medicine, Univ of Minnesota, Minneapolis, MN; 1 Internal Medicine, Univ of Iowa, Iowa City, IA; 2 Medicine and Molecular and Integrative Physiology, Univ de Montreal, Montreal, Canada; 3 Development, Reproduction and Cancer, Inst Cochin, Univ Paris-Descartes, Paris, France.

**Background:** Hepatocyte nuclear factor-1β (HNF-1β) is an essential transcription factor that regulates tissue-specific gene expression in the kidney. In humans, mutations of HNF-1β cause renal cysts and diabetes (RCAD) and congenital anomalies of the kidney and urinary tract (CAKUT).

**Methods:** We used Pkd1Cre mice to delete Hnf-1β specifically in renal collecting ducts. Water and solute excretion were measured using metabolic cages. HNF-1β targets were identified using ChIP-seq and gene expression profiling.

**Results:** Hnf-1β mutant mice survived long-term and developed slowly progressive cystic kidney disease, renal fibrosis, and hydroureter. Hnf-1β mutants had higher urine volume and lower urine osmolality than wild-type littermates. These abnormalities were present prior to the development of kidney cysts and hydroureterosis, suggesting a primary defect in urinary concentration. Circulating ADH levels were similar in wild-type and mutant mice. NR1H4 (FXR), a transcription factor known to regulate water homeostasis, was identified as a novel HNF-1β target. HNF-1β binding to the FXR promoter in vivo, and FXR mRNA was downregulated in mutant mice. FXR protein localized to collecting ducts in wild-type mice and was diminished in the cysts of mutant mice. mMCID3 cells exposed to hypertonic medium robustly upregulated FXR mRNA levels. This upregulation was lost in Hnf-1β mutant cells.

**Conclusions:** These findings reveal a new role for Hnf-1β in urinary concentration by regulating the transcription of FXR in the renal collecting duct.

**Funding:** NIDDK Support, Other NIH Support - University of Texas Southwestern O’ates Research Grant N01-HG-2-2119, Enter NIH Grant P50DK079208. L.N. and K.A. were supported by NIH Training Grant T32DK007257

SA-PO627

**Kcnq4 Dysregulation in Pkd1 Dosage-Dependent Mouse Models of ADPKD**

**Alimn Kurbegovic, 1 Assiaoua Aalch Sow, 1 Martin Couillard, 1 Boris Shmukler, 2 Seth L. Alper, 2 Marie Trudel, 1 Inst de Recherches Cliniques de Montreal, Montreal, QC, Canada; 2 Beth Israel Deaconess Med Ctr, Harvard Med School, Boston, MA.

**Background:** The relentless increase of renal cyst number and size in ADPKD kidneys is governed in part by PKD1/cAMP signaling and 

**Methods:** To compare the baseline characteristics according to age, we divided into two groups of age ≥65 years (elderly, n=130) and <65 years (young, n=181). Of the 130 elderly patients, 73 (70.2%) presented with NS and of these, 25 (24%) had conservative treatment, while 35 (32.7%) with steroid therapy. In the young group, 74 (40.9%) had NS and of these, 25 (24%) had conservative treatment, while 29 (16.0%) had steroid therapy. The infection, death and renal outcome rate was higher in the elderly group (p<0.05). The infection, death and renal outcome rate was higher in the elderly group (p<0.05).

**Results:** Conclusions: Our study identified Kcnq4 as a pro-secretory and probably pro-cystogenic risk modifier in both Pkd1 dosage-increase and dosage-decrease mechanisms, supporting Kcnq4 as a therapeutic target to retard cyst enlargement and disease progression in ADPKD.

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

SA-PO628

**Low Dose Rituximab Therapy in Resistant Idiopathic Membranous Nephropathy: Single Center Experience**

**Soumita Bagchi, 1 Arun Kumar Subbiah, 1 Dipankar M. Bhowmik, 1 Sandeep Mahajan, 1 Raj Kanwar Yadav, 2 Geetika Singh, 1 Amit K. Dinda, 1 Sanjay K.agarwal, 1 Nephrology, All India Inst of Medical Sciences, New Delhi, India; 2 Pathology, All India Inst of Medical Sciences, New Delhi, India.

**Background:** 10-30% patients with idiopathic membranous nephropathy(MN) progress to End Stage Kidney Disease in 10 years. The modified Ponticelli regimen(MPR) and Calcineurin inhibitors achieve remission in 60% patients. Most studies have used standard dose Rituximab in MN: 375mg/m2 weekly(4 doses) or 1g on day 1 and 15. Using this dose is expensive with high risk of infections. Few studies have used lower doses. Our study aims to do a preliminary assessment of the efficacy and safety of low dose Rituximab (LDR) in Indian patients with resistant MN.

**Methods:** 17 patients with immunosuppression(IS) resistant MN treated with LDR therapy from April 2015 to January 2016 were included. Treatment resistance was defined as no decrease in proteinuria after treatment with Modified Ponticelli regimen(MPR) and/or Tacrolimus(Tac) with Steroids for at least 6 months. They received 2 doses of Rituximab(500mg each), 7-10 days apart. A 3rd dose(500mg) was repeated if IS was not reduced at 4 weeks after LDR or if no reduction in proteinuria by 12 weeks.

**Results:** 64.7% were males and their mean age was 55.3±13.9 years. Prior IS received by these patients were: 6-MPR, 2-Tac, 4- MPR then Tac, 2-Tac then Mycophenolate Mofetil(MMF)+Steroids and 3- MPR, Tac and then MMF. Proteinuria before therapy was 6.4±1.3 g/day and serum creatinine was 0.9±0.4mg/dl. Four patients received a third dose/three for persistent proteinuria and one for inadequate B cell depletion. 12(70.6%) patients achieved remission(10-partial remission, 2- complete remission). Pre treatment serum Phospholipase A2 Receptor(PLA2R) levels were available in 11 patients-5 were negative. 2.5 PLA2R negative and 5.6 PLAZR positive patients achieved remission. Median time to remission was 2.1(0.7-6.7) months. Serum creatinine at follow up after 6.8(4.1-12.4) months was 1.0±0.5mg/dl. There were no adverse effects in any patient.

**Conclusions:** LDR therapy is effective and safe in IS resistant MN. Further up is needed to determine relapse rates and long term outcome.

SA-PO629

**Immunosuppressive Treatment for Elderly Membranous Nephropathy Patients**

**Fumin Bae, 1 Tae Won Lee, 1 Jung Pyo Lee, 2 Dept of Internal Medicine, Gyeongsang National Univ Hospital, Republic of Korea; 2 Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Republic of Korea.

**Background:** Primary membranous nephropathy (MN) is one of the most common nephrotic syndrome (NS) in elderly (≥65yrs) patients. The number of people or older is increasing annually. The aim of this study is to evaluate the use of immunosuppressive (IS) in elderly primary MN patients.

**Methods:** We retrospectively recruited 311 biopsy proven primary MN patients from 6 centers between 1990 and 2015. The endpoints were all-cause mortality, infection, doubling of the baseline serum creatinine or renal replacement treatment (RRT) and remission. We compared the baseline characteristics according to age, we divided into two groups of age ≥65 years (elderly, n=130) and <65 years (young, n=181). Of the 130 elderly patients, 104 (79.4%) presented with NS and of these, 25 (24%) had conservative treatment, while 104 (79.4%) presented with NS and of these, 25 (24%) had conservative treatment, while 29 (16.0%) had steroid therapy. In the young group, 73 (70.2%) patients achieved remission, 11 (10.3%) patients had RRT or doubling of serum creatinine. 9 (8.7%) patients were death and 17 (16.3%) patients were hospitalized because of infection. Treatment options of NS were not significantly associated with outcomes except infection. In elderly group, multivariate cox hazard models identified steroid only (HR 16.4, 95% CI 1.9-154.1, P=0.01), steroid combination with other IS treatment (HR 5.17, 95% CI 0.65-40.94) were significantly associated with infection. However, treatment options of NS in <65 years group were not significantly associated with composite outcomes.

**Conclusions:** Conservative therapy or steroid combination with other IS therapy are preferred in elderly steroid only therapy in elderly patients at risk of infection. Prospective study is warranted to compare the efficacy and complications of treatment in elderly MN patients.
Differences between Anti-PLA2R ELISA and IFT Assays in Idiopathic Membranous Nephropathy (iMN) during Therapy

Audio-El's van der Loog,1 Julia M. Hofstra,2 Renate G. Van der Molen,3 Jack F. Wetzels.1

1Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; 2Interne Geneeskunde, Gelderse Vallei, Ede, Netherlands; 3Laboratory Medicine, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: In our center patients with iMN are treated with cyclophosphamide and steroids until disappearance of anti-PLA2R antibodies (aPLA2R) measured by indirect immunofluorescence (IFT). We previously showed excellent concordance (94% agreement, kappa 0.85) between aPLA2R measured by IFT and ELISA in patients with iMN at diagnosis. We have assessed agreement in samples obtained during treatment.

Methods: We selected 31 aPLA2R positive patients. In all available serum samples aPLA2R were measured using IFT and ELISA, both obtained from Euroimmun®.

Results: Twenty patients were male, mean age was 56 ± 13 years, median serum creatinine level was 1.3 g/dl (1.1-1.6) and median protein creatinine ratio 7.3 g/g (5.0-11.2). We observed a more rapid disappearance of aPLA2R measured by ELISA compared to IFT.

After 8 weeks of therapy discordance was 24%. There were no clear differences in laboratory parameters between patients with concordant and discordant results.

Conclusions: Our study demonstrates that the time course of disappearance of aPLA2R during therapy is dependent on the assay that is used. We speculate that the introduction of an ELISA assay might lead to a shorter duration of therapy. Additional studies are needed to evaluate if the ELISA assay allows more accurate prediction of clinical outcome. Of note, two of three patients with positive aPLA2R by IFT and negative aPLA2R by ELISA after 24 weeks were in partial remission at this time point.

SA-PO631

Anti-PLA2R Antibody (aPLA2R) Levels at Baseline Do Not Predict Response to Immunosuppressive Therapy in Patients with Idiopathic Membranous Nephropathy (iMN) Anne-Elise van der Loog,1 Julia M. Hofstra,2 Renate G. Van der Molen,3 Jack F. Wetzels.1

1Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; 2Interne Geneeskunde, Gelderse Vallei, Ede, Netherlands; 3Laboratory Medicine, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: In our center patients with iMN are treated with cyclophosphamide and steroids until disappearance of aPLA2R measured by indirect immunofluorescence (IFT). Recently ELISA assay was introduced, which allows quantitative measurements. It has been shown that patients with iMN and high aPLA2R levels did not respond to treatment with rituximab. We have evaluated the relationship between baseline aPLA2R levels and clinical response of patients treated with our antibody guided treatment regimen.

Methods: We included 30 anti-PLA2R positive (IFT) patients. In stored baseline samples aPLA2R were measured as ELISA (Euroimmun®).

Results: Nineteen patients were male, mean age was 56 ± 13 years, median serum creatinine level was 1.3 g/dl (1.1-1.6) and median protein creatinine ratio 7.3 g/g (5.5-11.3). All patients tested positive with ELISA. When grouped in tertiles of aPLA2R, there were 11 patients in the lowest tertile, 8 in the intermediate tertile and 11 in the highest tertile.

Conclusions: Patients with higher levels of aPLA2R often need more prolonged immunosuppressive therapy. However, with the use of antibody guided therapy clinical outcome is comparable.

SA-PO632

Low-Dose of Rituximab for Membranous Nephropathy: Dario Roccella, Roberta Fenoglio, Savino Sciascia.

Nephrology and Dialysis Unit and Center of Research of Immunopathology and Rare Diseases (CMID), San Giovanni Hospital and Univ of Turin, Turin, Italy.

Background: The key role of B cells in the pathogenesis of idiopathic membranous nephropathy (IMN) represents the rationale of the B-cells depletion therapy with Rituximab (RTX). Traditional protocols proved to be effective in several open studies. A single-dose of RTX has been recently reported to be as effective as the lymphoma protocol in some cases of immune-mediated diseases. Data on IMN patients (pts) treated with sdRTX as a front-line therapy are limited. In this study, the efficacy of the sdRTX in IMN was compared with a standardized therapy (Poncetelli protocol, PP).

Methods: We included 30 anti-PLA2R positive (IFT) patients. In stored baseline serum samples aPLA2R (page 775) were measured (range 86-134). Of these 30 pts, 9 (mean age 59.9 ± 8.0 years) with nephrotic syndrome (NS) and major risk predictors excluding conventional immunosuppressive therapy were prospectively treated with a single dose of 500 mg RTX. Pts were matched with those of the last 10 pts (mean age 59.9 ± 8.0 years) treated with PP in our Unit.

Results: In sdRTX-treated pts, proteinuria (uP) decreased from 11.0 (IQ 6.5-24.0) to 2.4 (IQ 2.3-21.2) g/24 hrs after 6 months (p<0.05). Among these sdRTX-treated pts, 1 became uP-free (< 0.5 g/24 hrs) within 6 months, 2 pts, who had a partial response (> 50% uP decrease) at 6 months, became uP-free in 12 months. 2 pts were unresponsive. The remaining 4 pts had a partial response, but 1 of these received an additional single dose of RTX for uP relapse. Creatinine (Cr) remained stable: 1.1 (range 0.7-1.7) mg/dl at 6 months vs 1.1 (range 0.8-1.7) mg/dl at baseline. In PP-treated pts, uP decreased from 7.4 (IQ 5.7-20.3) to 3.0 (IQ 0.9-28.9) g/24 hrs in 6 months (p<0.05). 6 pts had either complete (6/6) or partial (8/5) response. 3 pts were unresponsive. Cr remained stable: 1.1 (0.5-5.2) mg/dl at 6 months vs 1.2 (0.7-3.5) mg/dl at baseline. There were no differences as regards to uP values and uP decrease in 6-month, between sdRTX and PP.

Conclusions: Current protocols of RTX treatment in immune-mediated diseases, were mainly derived from hematology experience. Our data suggest that low doses of RTX are as effective as a standardized immunosuppressive treatment in the management of IMN pts. This sdRTX scheme could be especially indicated in pts with co-morbidities.

SA-PO633

Childhood and Adolescent Polyclonal A2 Receptor Related Primary Membranous Nephropathy: A Prospective Study on Prevalence and Treatment Outcome Harbir Singh Kohli,1 Rajja Ramachandran,1 Ritambhara Nada,2 Vivekanand Jha,3 Krishan Lal L. Gupta.1

Nephrology, PIGIMER; *Histopathology, PIGIMER, Chandigarh, India.

Background: Primary membranous nephropathy (PMN) accounts for <5 and 10% of nephrotic syndrome in children and adolescents respectively. Autoantibodies to M-type phospholipase A2 receptor (aPLA2R) are seen in 70% of adult PMN. There are no prospective studies evaluating the prevalence of aPLA2R, its association with treatment outcome in PMN in this age group, hence the study was undertaken.

Methods: Children and adolescents (up to 19 yrs) with biopsy proven MN were included. Patients with positive viral makers, antinuclear factor or dDNA antibodies were excluded. Blood for aPLA2R was drawn prior to immunosuppressive therapy. Patients were followed on monthly basis with proteinuria, serum albumin and creatinine. Serum aPLA2R (ELISA, EUROMMUN, value ≥ 20RU/mL considered positive) was done at baseline,6 and 12 months of treatment. Staining for PLA2R in the glomeruli was done. PLA2R related PMN was defined as presence of either enhanced glomerular staining or aPLA2R.

Results: A total of 20 patients were enrolled. Mean age was 15.25±3.90 (5-19) years. The mean proteinuria and serum albumin was 4.39±1.89 (2.4-9.2) g/days and 2.02±0.65 g/dl. Sixteen (80%) patients had PL A2R related PMN. Enhanced staining for PL A2R and aPLA2R positivity was seen in 14 (70%) patients each. The median aPLA2R level in seropositive cases was 232.49 RU/mL. Twelve (75%) of 16 had enhanced staining and serological positivity, with good association between the two (p=0.03). Patients were initiated on cyclical therapy of oral prednisolone (GC) and cyclophosphamide or tacrolimus (TAC) and GC. Of these two did not complete therapy. Remission was achieved in 11 (55%) patients at 1 year. Seven (35%) had complete and 4 (20%) partial remission. Those in remission had lower baseline aPLA2R (65.5RU/mL) as compared to resistant patients (358.53RU/mL). There was a parallel reduction in decrease in aPLA2R titre and proteinuria.

Conclusions: Childhood and adolescent onset PMN is PL A2R related in 80%. The response to therapy is seen in one half of patients. aPLA2R monitoring is clinically relevant and should be incorporated in the management of PMN.

SA-PO634

CD19 Targeted Rituximab Therapy in Adult Calcinurin Inhibitor Resistant,Dependent or Intolerant Nephrotic Syndrome due to Idiopathic Minimal Change Disease and Focal Segmental Glomerulosclerosis Harbir Singh Kohli,1 Rajja Ramachandran,1 Indu R. Rao,1 Ritambhara Nada,2 Krishan Lal L. Gupta.1

Nephrology, PIGIMER; *Histopathology, PIGIMER, Chandigarh, India.

Background: Calcineurin inhibitors (CNIs) are first line agents in the management of steroid dependent/resistant SD or SR MCD/FSGS. CNIs use is limited by relapses and nephrotoxicity. Rituximab is a potential alternative, this prospective study was done to evaluate the efficacy and safety of targeted rituximab therapy in CNI intolerant/ dependent/resistant SD or SR MCD/FSGS.
Methods: A total of 24 adult patients of SDNS or SRNS (MCD/FGS), who were CNI resistant/dependent/intolerant were enrolled. All patients received a rituximab 375mg/m^2 to target CD19 levels < 1% (48 hrs post infusion). CD 19 counts were monitored monthly and those with CD-19≤1% received additional dose of rituximab. Patients were followed up monthly for at least 6 months. Study outcomes were remission rates and side effects. Definition: CNI resistant: no response with 24 weeks, CNI dependent: relapse during or after CNI taper, CNI intolerant: irreversible nephrotic or uncontrollable diabetes.

Results: Mean age was 23.2±7.9 (16-46) years. The study included 17 (71%) and 7 (29%) cases of FSGS and MCD respectively. SR and SD was seen in 11 (46%) and 13 (54%) respectively. CR or CRi (proteiuria < 50 mg/day and plasma albumin concentration > 3.0g/dl) after initial treatments. Renal death was observed 14 out of 105 patients (13.3%).

Conclusions: This work indicates that the high single dose cost of Rituximab should not deter its use in the treatment of primary MN and highlights the need for a high quality clinical trial investigating the efficacy of Rituximab versus the current standard of care.

Funding: Private Foundation Support

SA-PO637

Comparative Effectiveness and Tolerance of Treatments for Idiopathic Membranous Nephropathy: A Network Meta-Analysis

Daqing Hong, Li Wang, Guisen Li. Renal Div and Inst of Nephrology, Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: Immunosuppressive treatment in general was shown to prevent renal progression and all-cause mortality in idiopathic membranous nephropathy (IMN) patients with nephrotic syndrome, however, the efficacy and safety of different immunosuppressive treatments have not been systematically assessed. A network meta-analysis was performed to compare different immunosuppressive treatment in IMN.

Methods: Cochrane library, MEDLINE, EMBASE and trial register system were searched for randomised controlled trials reporting the treatments for IMN to May, 2016. Composite endpoint of End-stage renal disease (ESRD) or mortality, complete or partial proteinuria remission and withdrawal because of treatment adverse events were compared combing direct and indirect comparison using network meta-analysis,. Ranking different immunosuppressive treatment in the outcomes were analyzed by using SUCRA and MDs-ranking method.

Results: 36 randomised controlled trials were included. Compared with non-immunosuppressive treatment, only cyclophosphamide (CTX) and chlorambucil significantly reduced the risk of composite outcome of ESRD or mortality when combining the direct and indirect comparison (RR=0.31, 95%CI: 0.12-0.92). CTX increased the composite outcome of CR or PR (RR=4.29, 95%CI: 2.30-8.0) while chlorambucil did not (RR=1.58, 95%CI: 0.80-3.12) as compared to non-immunosuppressive treatment, chlorambucil also significantly increased withdrawal risk (RR=3.34, 95%CI: 1.37-8.17) as compared to CTX. Both tacrolimus (RR=3.10, 95%CI: 1.36-7.09) and cyclosporine (RR=2.81, 95%CI: 1.08-7.32) also significantly increased the rate of CR or PR as compared with non-immunosuppressive treatment (without significant difference as compared with CTX), while ranking results showed that cyclosporine or tacrolimus was with less possibility of drug withdrawal as compared to CTX or chlorambucil.

Conclusions: Only alkylating agents can reduce risk of ESRD or mortality, however, they both had higher risk of drug withdrawal. Tacrolimus and cyclosporine can increase the possibility of proteinuria remission with less drug withdrawal.

SA-PO638

Rituximab as Monotherapy for Pure Membranous Lupus Nephritis

Nathalie Chavard,\(^1\) David Verhelst,\(^1\) Agathe Pardon,\(^1\) Valérie Caudwell,\(^2\) Lucile Mercadal,\(^2\) Antoinette Sicci,\(^2\) Jean-Marc Roger Dieuymes-Laporte,\(^2\) Veronica Le Guern,\(^3\) Alexandre Karras,\(^2\) Eric Daugas,\(^2,9\) Nephrology, APHP, Bichat Hospital, Paris, France; Nephrology, CH, Avignon, France; Nephrology, CHSF, Corbeil-Essonnes, France; Nephrology, APHP, Pitié Salpêtrière Hospital, Paris, France; Internal Medicine, CH, Mantes la Jolie, France; Internal Medicine, APHP, Cochin Hospital, Paris, France; Nephrology, APHP, HEGP, Paris, France; CH, Cayenne, French Guiana; \(^2\)French Cooperative Group on Lupus Nephritis.

Background: Optimal treatment for pure membranous lupus nephritis (MLN) remains uncertain. Rituximab constitutes an alternative treatment option in lupus nephritis and is currently evaluated for idiopathic membranous nephropathy.

Methods: We retrospectively investigated patients with biopsy-proven pure class V lupus nephritis and protein-to-creatinine ratio (PCR) ≥ 2 g/l treated with Rituximab as monotherapy (1g infusion at day 1 and day 15, or 4 weekly infusions of 375mg/m^2) with or without low dose of steroids (≤20mg/day) with or without hydroxychloroquine. Complete remission was defined as PCR < 0.5 g/l with normal eGFR, and partial remission as ≥50% reduction in PCR to subnephrotic levels and normal eGFR. Treatment failure was considered when additional immunosuppressive therapy or steroids > 20 mg/day were prescribed during the first 12 months.

Results: In 14 patients (13 women) median PCR ratio was 4.4 g/l, median serum albumin 25.5 g/L, and median eGFR (CKD-Epi) 121.5 mL/min/1.73m^2. The median follow-up was 29 months. Two patients experienced treatment failure. Remission was recorded in the remaining 12 (86%), complete remission in 8) within a median time of 5 months.

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

Underline represents presenting author.

776A
**SA-PO639**

**PLA2R Positive Membranous Nephropathy Associated with Viral Infection**

Aiakaterini K. Nikolopoulou, Megan Griffth, H. Terence Cook, Charles D. Pusey, Imperial College London, United Kingdom.

**Background:** Membranous Nephropathy (MN) can be associated with hepatitis infection and less commonly with HIV infection. The significance of anti-phospholipase A2 receptor (PLA2R) antibodies in this setting is not known.

**Methods:** A retrospective study of biopsy proven MN from January 2006 to January 2015 was undertaken. A total of 11 patients with MN and Hepatitis B (HBV), C (HCV) or HIV were identified. The biopsies were stained for PLA2R antigen and results were correlated to viral activity and clinical outcomes.

**Results:** The cohort consisted of 11 patients, 4 women and 7 men, aged 39.9 years. HIV was detected in 5 patients, HBV in 4 and HCV in 3 (one patient HIV/HBV coinfection). PLA2R staining was positive in 6 biopsies: 1 with HIV, 2 HBV, 3 HCV. Circulating anti-PLA2R antibodies were detected in 3 patients at time of biopsy. Viral load was undetectable at the time of biopsy in all but one patient with HBV. In the PLA2R negative group 3 patients had HIV, 1 HBV and 1 HIV/HBV coinfection. Viral load was detectable in 1 patient with HBV and 1 with HIV. Mean proteinuria was higher in the PLA2R positive compared to the PLA2R negative group (mean uPCR=801.6 vs 374.4mg/mmol) although this was not statistically significant. Electron microscopy in both groups showed predominantly subepithelial electron dense deposits (EDD). EDDS of all stages were present but stage II were the more frequent. Tubuloreticular inclusion bodies (TRI) were seen in 2 patients with interferon treated HCV in the PLA2R positive group; no TRI’s were seen in the PLA2R negative group. Follow up was available for 10 patients. At 24 months 9 had preserved renal function. One PLA2R and HCV positive progressed to ESRD. One patient with PLA2R positive MN and HIV went into spontaneous partial remission, others received tacrolimus (n=7), rituximab (n=2) or cyclophosphamide with high dose steroids (n=1).

**Conclusions:** PLA2R positivity can be found in MN associated with hepatitis infection and we describe a rare case of PLA2R positive MN and HIV. It is possible that the viral infection triggers immunological activity leading to the anti-PLA2R antibody response. MN can present even when infection is controlled and viral load undetectable.

**SA-PO5640**

**Membranous Glomerulonephritis with Crescents**

Aiakaterini K. Nikolopoulou, Isabel Huang-Doran, Stephen Paul McAdoo, Megan Griffth, H. Terence Cook, Charles D. Pusey. Imperial College London, United Kingdom.

**Background:** The coexistence of membranous glomerulonephritis (MGN) with necrotising and crescentic glomerulonephritis (NCGN) is rare. We examined the incidence and outcomes of patients with MGN and NCGN treated at our centre and the association with anti-neutrophil cytoplasm antibodies (ANCA) or anti-glomerular basement (anti-GM) antibodies.

**Methods:** We report the clinical and pathological findings of 10 patients with MGN and NCGN, identified from our renal biopsy database from January 2004 to January 2015. Results: The cohort consisted of 3 women and 7 men with a mean age of 58.5 years. ANCA and anti-GM positivity was tested by ELISA. ELISA was positive in 9 patients (4 MPO-ANCA, 1 PR3-ANCA, 4 anti-GM); one patient was negative and the biopsy showed IgA deposition. Clinical presentation included heavy proteinuria (mean urinary protein:creatine ratio 1.731mg/mmol), microscopic haematuria and acute kidney injury (mean creatinine 390µmol/L, 4.4mg/dL). Pathologic evaluation revealed MGN and NCGN with crescents involving a mean of 25% of glomeruli. Immunohistochemistry in 8 cases showed granular IgG deposits with linear IgG in anti-GBM cases. Electron microscopy showed stage I or II MGN changes in the majority of cases. PLA2R staining was negative in 8 available biopsies and no causes of secondary MGN were identified. One patient had a biopsy that showed MGN alone 6 months prior to anti-GM disease. One patient had pre-existing p-ANCA vasculitis 2 years prior to MGN. Follow up was available for all 10 patients, and all were treated with steroids, together with cyclophosphamide (n=6); plasma exchange (n=1), rituximab (n=3) and MMF (n=2), alone or in combination. A mean follow up of 48.1 months, 4 patients progressed to ESRD and 6 had stabilisation or improvement of renal function. One patient with ESRD died during the follow up period.

**Conclusions:** MGN combined with NCGN is a rare dual glomerulopathy in which anti-PLA2R antibodies are not generally detected. Presentation is with proteinuria, haematuria and acute kidney injury. Prognosis is variable and seems to be related to renal function at presentation.
SA-PO643

Serum Fibrinogen as a Predictive Biomarker of Response to Treatment in Patients with Membranous Nephropathy  
Hua Zhai, Ya Li, Cong cong Jiao, Hairong Tang, Lizhi Li, Kong Weiwei, Lining Wang.  
Dept of Nephrology, The First Hospital of China Medical Univ, China.

Background: Membranous Nephropathy (MN) typically needs long time of treatment with steroid and immunosuppressants. A biomarker that predicts the response to treatment will likely help clinicians better manage MN. We aim to investigate whether serum fibrinogen (Fg) can predict response to steroid and immunosuppressants.

Methods: 137 patients with MN proven by renal biopsy were treated with steroid and cyclophosphamide (CTX) at China Medical University from 2013 to 2014 (male: female is 36:55). The serum Fg, albumin (sA alb), low-density lipid cholesterol (LDL-C), and 24-hour urinary protein excretion (uTP) were observed up to 9 months. The correlations between Fg before and severity of fibrinolytic syndrome (uTP, sA alb, and LDL-C) before treatment, 3, 6, 9 months after treatment were analyzed.

Results: After 9 months' treatment of steroid and CTX, uTP excursion decreased (7.080.29 vs 2.500.42, p<0.01). uTP increased (22.250.44 vs 34.350.78, p<0.01), and LDL-C reduced (6.080.22 vs 4.150.20, p<0.01). Fg was corrected to normal level (5.760.17 vs 3.800.36, p<0.01). The level of Fg before treatment positively correlated with uTP and LDL-C before and after treatment (uTP at 9 months and LDL-C at 6 months). Fg negatively correlated with sA alb pretreatment and 9 months post-treatment (see table).

Conclusions: The degree of hypercoagulopathy at the onset of MN correlates with the changing severity of nephrotic syndrome. Our data show that the level of serum fibrinogen before treatment might be a useful biomarker to predict the response to steroid and CTX. Thus, early correction of hypercoagulopathy might improve the outcome of membranous nephropathy.

Funding: Government Support - Non-U.S.

SA-PO644

Effects of Immunosuppression and Immunoabsorption plus Rituximab on Circulating Phospholipase A2-Receptor Antibodies in Idiopathic Membranous Nephropathy  
Ammon Handisurya,1 Renate Kain,2 Elion Hooha,3 Thomas Perkmann,4 Kurt Derfler,1 Alice Schmedt.1  
1Dept of Medicine III, Medical Univ of Vienna, Austria; 2Dept of Pathology, Medical Univ of Vienna, Austria; 3III. Dept of Internal Medicine, Univ Medical Center Hamburger-Eppendorf, Germany; 4Dept of Laboratory Medicine, Medical Univ of Vienna, Austria.

Background: 70% of all subjects with idiopathic membranous nephropathy (iMN) feature serum phospholipase A2 receptor-antibodies (PLA2R-Ab) which are linked to pathogenicity and course of the disease.

Methods: To evaluate whether immunoabsorption (IAS) effectively removes circulating PLA2R-Ab and results in a reduction of proteinuria, 4 subjects with biopsy-proven iMN, positive serum PLA2R-Ab and nephrotic proteinuria were treated with IAS (22-42 sessions within 68-366 days, 8000 ml total plasma volume per IAS) followed by 6 cycles of IAS combined with rituximab (Rtx; 2xIAs + 1xRtx 375 mg/m2 body surface within 3 consecutive days; 4 weeks between each cycle) and a follow-up period of up to 500 days. Patients (pat.) 1-3 had iMN in their native kidneys, pat.4 a recurrence of iMN after renal transplantation. Pat.3 and 4 had received Rtx before, however without marked effect on disease activity.

Results: All pat. achieved partial remission (PR) according to the KDIGO-definition at the end of the study with reductions of serum PLA2R-Ab between -69.0 and -99.2% and urinary protein-creatinine-ratio (uPCR) between -49.3 and -82.6%. IAS-treatment alone removed serum PLA2R-Ab (>30.1 to -91.4%) only in pat.2-4, resulting in an attenuated urinary protein excretion (uTP) of pat.2-4, resulting in an attenuated urinary protein excretion (uTP) between -49.3 and -82.6%. IAS-treatment alone removed serum PLA2R-Ab (-30.1 to -91.4%) only in pat.2-4, resulting in an attenuated urinary protein excretion (uTP) of pat.2-4, resulting in an attenuated urinary protein excretion (uTP) between -49.3 and -82.6%. IAS-treatment alone removed serum PLA2R-Ab (-30.1 to -91.4%) only in pat.2-4, resulting in an attenuated urinary protein excretion (uTP) of pat.2-4, resulting in an attenuated urinary protein excretion (uTP) between -49.3 and -82.6%. IAS-treatment alone removed serum PLA2R-Ab (-30.1 to -91.4%) only in pat.2-4, resulting in an attenuated urinary protein excretion (uTP) of pat.2-4, resulting in an attenuated urinary protein excretion (uTP) between -49.3 and -82.6%.

Conclusions: Our data show that IAS removes PLA2R-Ab from circulation and sustains antibody removal in combination with Rituximab suggesting that IAS may improve rituximab-effects in known rituximab non-responders with iMN.

SA-PO645

Factor H Autoantibodies and Membranous Nephropathy  
Claudia Seikrit, Pierre M. Ronco, Hanna Debiec.  
INSERM UMR-S1155, Tenon Hospital, Paris, France.

Background: About 80% of patients with primary MN have autoantibodies against phospholipase A2 receptor (PLA2R), predominantly of IgG4 subclass. C3 and C5b-9 occur in glomerular immune deposits, implicating complement activation as a putative effector mechanism. Why 30% of patients will reach end-stage renal disease remains elusive. Here we report the case of a patient with PLA2R-related MN who later developed anti FH autoantibodies and degraded renal function.

Methods: Serum samples from patient were tested in parallel for the presence of PLA2R and FH autoantibodies using ELISA assays. To localize the binding domain of the FH autoantibodies, reactivity with recombinant FH fragments was measured.

Results: In 2009, histologically confirmed MN with circulating anti-PLA2R antibodies and normal renal function was diagnosed in a 64-year old male patient. A few months later and during the follow-up until 2016, he developed progressive renal insufficiency (serum creat: 103μmol/l (2009); 294μmol/l (2015)). He was not treated with immunosuppressors. Circulating PLA2R antibodies were no longer detected after 2009. Instead a high titer of IgG3 isotype antibody reactive with FH was found in the serum between 2010 and 2015. This antibody recognized FH on Western blot not only in non-reduced conditions. IgG binding on immobilized FH was inhibited by pre-incubation with purified FH or FH fragments containing a region that comprised the C-terminal domains SCR1-20 but not the N-terminal domains SCR1-4. Plasma FH antigenic level was normal and genetic analysis revealed no abnormality in FH and FHRP1-5. Analysis of 84 sera from a retrospective cohort of patients with MN revealed that additional patients had anti-FH antibodies, albeit at a lower titer than the index patient.

Conclusions: This is a first case of MN where autoantibodies targeting the C-terminal domains of FH were detected. Because FH is a major regulator of the alternative complement pathway, inhibition of FH activity by autoantibodies at podocyte cell surface might contribute to the overshooting of this pathway and accelerate disease progression. Patients with MN should be screened for anti-FH autoantibodies.

SA-PO646

Initial Anti-Phospholipase A2 Receptor Antibody Levels Predict Clinical Outcome in Patients with Idiopathic Membranous Nephropathy  
Jennie Lonbro-Widoren,1 Kerstin Ebeefors,2 Christine Payre,3 Gerard J. Lambeau,1 Johan C. Molne,1 Borje Haraldsson,1 Jenny C. Nyström.1  
1Univ of Gothenburg, Medicine, Gothenburg, Sweden; 2Univ of Gothenburg, Biomedicine, Gothenburg, Sweden; 3Univ of Gothenburg, Neuroscience and Physiology, Gothenburg, Sweden; 4CRNS and Univ of Nice, Molecular and Cellular Pharmacology, Nice, France.

Background: The clinical outcome in patients with idiopathic membranous nephropathy (iMN) is difficult to predict. PLA2R antibodies are associated with persistence of nephrotic range proteinuria, and recent studies have provided evidence for epitope-spreading in the PLA2R in patients with a less favorable clinical outcome.

Methods: In 25 patients with iMN and a mean follow-up of 63 months, levels of serum PLA2R antibodies were measured at the time of renal biopsy, and correlated with the clinical outcomes. Additional glomerular staining for PLA2R and THSD7A was performed, as well as measurement of serum epitope-specific titers and THSD7A antibodies at the time of renal biopsy.

Results: A statistically significant correlation (r=0.6, p<0.01) between a high serum PLA2R antibody level at diagnosis and a less favorable clinical outcome was found. Patients with high autoantibody levels were more frequently exposed to immunosuppressive therapy, compared to patients with low autoantibody levels, and epitope spreading was seen among patients with higher PLA2R antibody levels. In this study, 19 of 25 (76%) patients had a PLA2R-associated IMN. One of the six PLAR-negative patients had detectable serum THSD7A autoantibodies and a positive glomerular staining for THSD7A. Moreover, these autoantibodies were not present in patients with non-R-associated disease.

Conclusions: A high serum PLA2R antibody level at presentation indicates a less favorable clinical outcome, and a higher risk of renal deterioration during follow-up. We therefore propose that these autoantibodies may be used as a prognostic marker for treatment decisions. In addition, the reactivity against three domains of PLA2R, where the severity of the disease seems to be coupled to epitope spreading, may also be a tool to predict outcome of iMN.

Funding: Private Foundation Support

SA-PO647

A Retrospective Analysis of Patients with Idiopathic Membranous Nephropathy Treated with Steroids and Intravenous Cyclophosphamide. A Single Centre Experience  
Hannah Wilkinson, Robin Rampaul, David Makanjuola, Hugh Gallagher, Bhrigu Raj Sood, Rebecca Suckling, Marie B. Condon.  
Renal Unit, St. Helier Hospital, Surrey, United Kingdom.

Background: The use of steroids and oral Cyclophosphamide is a well recognised treatment for patients with idiopathic membranous nephropathy (iMN). However, long term effects of high dose cytotoxic agents have been well established. Taking this into account we adopted a less toxic regimen with lower dose intravenous pulsed Cyclophosphamide as an alternative to higher dose oral Cyclophosphamide.

Methods: 20 patients were treated with oral Prednisolone and IV Cyclophosphamide between 2003 and 2015. All patients had biopsy proven iMN. Decision to treat was based on the severity of the disease.
on persistent nephrotic syndrome was deterioration in renal function despite ACEI/ARB and/or maximal BP control. Treatment consisted of prednisolone 40 mg/day for 30 days on month 1, 3, and 5. Cyclophosphamide was dosed according to bodyweight and renal function on day 1 of months 2, 4, and 6. Four patients received IV methylprednisolone pulses. Results: All patients were male, mean age 61 yrs. 19 patients completed the treatment protocol with achieved remission (either partial or complete). Average time to remission was 6.6 months. 6 went on to achieve CR (31.6%), average time to CR was 13.8 months. The treatment regimen significantly reduced uPCR (p = 0.0025), increased serum albumin (p = 0.0287) and stabilised creatinine (p = 0.0402) in the 48 months follow-up. Follow-up, 6 months 4 patients responded, 6 months were censored for second line therapy. 2 (18%) patients relapsed, both treated with Tacrolimus and achieved PR. 3 patients received Tacrolimus due to failure to achieve CR, all patients achieved PR or CR with Tacrolimus. 4 patients progressed to ESRR, 4 patients died during follow-up with mean age 71 years, average time to death was 64.12 months after starting treatment. The mean cumulative dose of Cyclophosphamide in our study was 3284mg (range 2160-4500mg). Conclusions: In our low toxicity protocol we have achieved remission rates averaging 60%. Furthermore this protocol has low relapse rate with less than 25% cumulative dose of Cyclophosphamide than would be received with the modified Ponticelli regimen.

SA-PO648
Primary Nephrotic Syndrome Indepenedently Increases the Risk of Developing End-Stage Renal Disease in Adults
Alan S. Gu, Dongjie Fan, Thiha Tan, Janet M. Wojcicki, David Law, Leonid V. Yanikulin, Sijie Zheng, Kathleen K. Pen, Glen Matthew Chertow, Juan Daniel Ordovas. 1 Kaiser Permanente Northern California; 1Univ of California, San Francisco; 3Stanford Univ.

Background: Few studies have systematically evaluated the independent association of primary nephrotic syndrome (NS) with the risk of end-stage renal disease (ESRD) within representative populations. We identified a cohort of adults with primary NS and a matched cohort without NS in a large integrated healthcare system and examined characteristics associated with development of ESRD.

Methods: Within Kaiser Permanente Northern California, we identified adults aged 18 years 1996-2012 who had nephrotic range proteinuria (UACR>3500 mg/g, PCR>35 mg/mg, 24-hr protein>3500 mg or dipstick>100 mg/dL) or diagnosed NS (ICD-9 581.x) in electronic records and lab databases. Of these, nephrologists reviewed health records for clinical presentation, labs and biopsy results to confirm primary NS. Compared with a matched cohort of patients without NS during the study period matched on age (+/-1 month), active membership and having known kidney function, we examined the independent association between NS and the risk of developing ESRD after adjustment for potential confounders (gender, race, comorbidities, baseline estimated glomerular filtration rate, baseline hemoglobin level) using multivariable extended Cox regression models.

Results: We identified 907 adults with confirmed primary NS and 89,593 matched adults without NS. The annual incidence of ESRD was 4.65 per 100 person-years in NS patients vs. 0.03 per 100 person-years in matched non-NS patients (p<0.001). After adjustment for potential confounders, NS was independently associated with a substantially higher rate of ESRD (adjusted hazard ratio 14.6, 95% CI: 9.6-22.3).

Conclusions: Among a large, diverse community-based population, primary nephrotic syndrome was a strong, independent risk factor of developing ESRD.

Funding: Private Foundation Support

SA-PO649
Tacrolimus in the Treatment of Pediatric Renal Steroid Resistant Nephrotic Syndrome (SRNS) Ankana Daga, Avi Traum. Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA.

Background: Data on tacrolimus use in the treatment of pediatric SRNS is limited and biopsy findings are variable. Given the focal nature of glomerulosclerosis, whether Minimal Change Disease (MCD) in SRNS patients is a different disease or an effect of biopsy sampling continues to generate controversy. Thus, the aims of this study were to characterize the response rate to tacrolimus in pediatric SRNS, and to further describe the response rate based on biopsy findings.

Methods: This was a single-center, retrospective study of children with SRNS treated with tacrolimus. SRNS was defined as no improvement in proteinuria after 8 weeks of full dose steroids. Complete Response (CR) was defined as a urine protein-to-creatinine ratio (UPC) ≤0.2 and Partial Response (PR) as ≥0% reduction in proteinuria. Biopsy findings were recorded as MCD vs. Focal Segmental Glomerulosclerosis (FSGS).

Results: In 47 patients who met inclusion criteria, 57% were male, 45% were Caucasian, with the average age at diagnosis of 7.2 +/- 5.6 years. Thirty-six (77%) patients responded to therapy after 6 months of tacrolimus (32% CR, 45% PR). Twenty-eight (60%) patients responded to therapy after 12 months of tacrolimus (28% CR, 32.6% PR). Acute kidney injury was the most common side effect, occurring in 17 (36%) patients. FSGS was detected on biopsy in 27 patients while 16 patients had MCD. The average number of glomeruli per biopsy sample was 16.7 +/- 9.8. Of the 27 patients with FSGS, 67% responded to therapy (15% CR, 52% PR) at 6 months. Interestingly, of the 16 patients with MCD, 88% responded (50% CR, 38% PR) at 6 months. The response rate at 12 months of treatment with tacrolimus was 67% in the FSGS group versus 56% in the MCD group. The MCD group at 12 months included 2 lost to follow up and 2 with <12 months of therapy, while among FSGS patients, 3 had therapy discontinued, which included 2 who developed ESRD, and 1 who was diagnosed with cancer.

Conclusions: Tacrolimus is an effective therapy in children with SRNS irrespective of histopathologic findings. Biopsy revealing MCD in SRNS patients should not preclude use of tacrolimus. Multi-center studies are needed in the future to validate these findings.

SA-PO650
Rituximab Treatment for Frequently Relapsing Nephrotic Syndrome or Steroid-Dependent Nephrotic Syndrome Mika Sonoda, Eiji Ishimura, Shuko Ueda, Shinya Nakatani, Mitsuori Ichii, Yoshitomo Ohno, Akhiro Tsuda, Katsuhiro Mori, Masaki Inaba. Osaka City Univ Graduate School of Medicine, Osaka, Japan.

Background: Frequently relapsing nephrotic syndrome (FRNS) and steroid-dependent nephrotic syndrome (SDNS) requires long-term corticosteroid therapy and/or immunosuppressive agents, which cause significant adverse effects. Recently, rituximab, a chimeric monoclonal antibody against the CD20 antigen, has been expected for the treatment of FRNS/SDNS in children in some countries. However, there are few reports on the treatment for adult patients with childhood-onset FRNS and/or SDNS.

Methods: Six patients (24.6 +/- 5.9 year-old, 2 males and 4 females) of FRNS/SDNS were treated with rituximab. All patients had nephrotic syndrome of childhood-onset, which relapsed more than fifteen times. They had been orally taking prednisolone and/or cyclosporine. After premedication, such as acetaminophen and chlorphenamine, to prevent infusion reaction, 500 mg rituximab was intravenously administered. Effect of rituximab on inhibition of relapse and changes in B cell counts in blood were examined up to ten months.

Results: All patients could receive intravenous 500mg rituximab, without any infusion reaction and adverse events. In the follow-up period, oral prednisolone and/or cyclosporine could be reduced gradually without relapse of nephrotic syndrome. B cells in blood significantly decreased. Changes in B cell counts in all patients were as followings; before administration, CD 19 cells were 8.5 +/- 4.1%, and CD 20 cells 10.1 +/- 3.6%; after 6 months: 2.8 +/- 3.3% (CD19) and 2.8 +/- 3.5% (CD20). In one patient, rituximab was discontinued because of increase of B cell count.

Conclusions: Intravenous rituximab treatment is effective against relapse of nephrotic syndrome in adult patients with childhood-onset FRNS/SDNS. It is safely administered with appropriate anti-allergic pretreatment. It causes significant decrease in B cell counts in blood. It can reduce the dose of corticosteroid in adult patients with childhood-onset FRNS/SDNS. Long-term observation is currently undergoing.

SA-PO651
Urine KIM-1/CREATinine as a Marker of Glomerular Disease Severity and Treatment Response in the Nephrotic Syndrome Study Network Qiaojuan Wu, Jonathan P. Troost, Tiane Dai, Boxian Wei, Peter X.K. Song, Debbie S. Gipsen, Cynthia C. Nast, Matthias Kretzler, Sharon G. Adler. 1 Div of Nephrology & Hypertension, Los Angeles Biomedical Research Inst, Torrance, CA; 1Div of Nephrology, U Michigan, Ann Arbor, MI.

Background: We tested whether at baseline (BL) the proximal tubule injury marker urine KIM-1/creatinine (uKIM1/cre) correlated with BL disease severity and/or improved a remission prediction model.

Methods: uKIM1/cre was measured on BL protease-protected spot urine from non-immunosuppressed patients (Minimal change (MC), n= 7; Focal segmental glomerulosclerosis (FSGS), n= 24; Membranous nephropathy (MN), n= 12, and other glomerulopathies (OG), n= 12). Urine protein/creatinine (UPCR) was measured at BL, and Q4-6 mos. Correlations with BL uKIM1/cre and UPCR, morphometrically measured histopathologic features, and renal outcomes were assessed. Associations between uKIM1/cre and time to first complete remission were tested using a Kaplan-Meier analysis and Cox proportional hazards models adjusting for baseline proteinuria, diagnosis, and subsequent treatment subgroup variation by diagnosis in the effect of uKIM1/cre on reaching remission was tested using interaction terms.

Results: Median follow-up was 24 mos; 16 of 55 patients were subsequently treated (steroids, n=9; calcineurin inhibitors, n=4; mycophenolate mofetil, n=3). BL uKIM1/cre correlated with UPCR (r=0.45; p<0.001), but not with eGFR. uKIM1/cre was lower in MC than FSGS, MN, and OG (p=0.006) and correlated with foot process effacement but not with global or segmental sclerosis, interstitial fibrosis, tubular atrophy, or acute tubular injury. After adjusting for BL proteinuria, pathologic diagnosis, and treatment, uKIM1/cre was a significant predictor of time to complete proteinuria remission.

Conclusions: uKIM1/cre may identify a subset of patients more likely to enter remission from nephrotic syndrome.

Funding: NIDDK Support, Other NIH Support - Office of Rare Diseases, Private Foundation Support
SA-PO652

Effect of Tacrolimus on Endothelial-Derived Microparticles in Pediatric Patients with Nephrotic Syndrome
Howard Trachman,1 Laura Jane Pehrson,1 Suzanne M. Vento,1 Laura Malaga-Dieuguez,1 Brandon Renner,2 Jennifer Laskowski,2 Joshua M. Thomam.2

1Pediatrics, NYU Langone Medical Center, New York, NY; 2Medicine, Univ of Colorado School of Medicine, Aurora, CO.

Background: Tacrolimus (TAC) causes direct injury to endothelial cells that in kidney transplant recipients is characterized by increased circulating levels of endothelial-derived microparticles (EDMP). The objective of this study was to determine the effect of TAC on EDMP in pediatric patients receiving the drug to treat nephrotic syndrome (NS), a cohort without longstanding kidney disease and fewer comorbid conditions.

Methods: Children with NS due to minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) treated with TAC were recruited in the Fink Ambulatory Care Center or Bellevue Nephrology Clinic. The following material was obtained from the medical record: age, gender, TAC dose, BP, eGFR, proteinuria, and trough TAC level. A plasma sample was obtained every 6 months for measurement of EDMP by flow cytometry using antibodies to CD31, CD44 and complement C3. Results were compared to those from a cohort of 30 healthy control subjects.

Results: 13 patients (9M: 4F), 11.7±4.9 yr old, were enrolled in the study. The underlying disease was MCD in 6 and FSGS in 7 cases. The initial eGFR was 142±100 ml/min/1.73 m2 from a cohort of 30 healthy control subjects.

Conclusions: While the majority of NKN participants indicate a high interest in many types of clinical research, few reported previously participating. Designing studies around topics of high value to the patient, engagement from their primary nephrologist, ensuring appropriate data privacy and limiting time burden may help to increase participation.

Funding: Private Foundation Support

SA-PO654

Serum 1,25-Dihydroxyvitamin D Better Reflects Renal Parameters Rather Than 25-Hydroxyvitamin in Patients with Biopsy-Proven Glomerular Disease
Yu Ah Hong, Hyeon Seok Hwang, Yoon-Kyung Chang, Suk Young Kim, Cheol Whae Park, Sungjin Chung. Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: Impaired vitamin D metabolism may contribute to the development and progression of chronic kidney disease (CKD). The purpose of the study was to determine associations of circulating vitamin D metabolites with the degree of proteinuria and impaired estimated glomerular filtration rate (eGFR) in patients with biopsy-proven glomerular disease.

Methods: Blood samples for 25-hydroxyvitamin D (25D) and 1,25-dihydroxyvitamin D (1,25D) levels were collected from 173 patients who admitted for renal biopsy. All clinical and laboratory data were obtained at the time of the renal biopsy, and therapeutic medication after renal biopsy was collected.

Results: As serum 1,25D levels declined, renal function was significantly decreased (p=0.001). However, serum 25D levels were not different according to the change of eGFR (p=0.786). Serum albumin was significantly increased and total cholesterol and 24hr urine protein were significantly decreased in patients with the higher levels of 25D and 1,25D than in those with the lower values. The prevalence of nephrotic range proteinuria and moderate to severe renal dysfunction (eGFR < 60ml/min/1.73m2) progressively increased with declining 1,25D, but not 25D. Multiple linear regression analysis showed that 25D was significantly correlated with serum albumin and total cholesterol (β=0.224, p=0.006; β=0.263, p=0.001) and 1,25D was significantly correlated with eGFR, serum albumin and serum phosphorus (β=0.202, p<0.005; β=0.304, p<0.001; β=0.161, p=0.024). In adjusted multivariable linear regression, eGFR and 24hr proteinuria were independently correlated only with 1,25D (β=0.154, p=0.018; β=0.171, p=0.012), but not 25D. The lower level of 1,25D was associated with the frequent use of immunosuppressant agents after renal biopsy (p<0.001).

Conclusions: According to these results, it is noteworthy that circulating 1,25D may be superior to 25D as an indicative marker of disease severity in patients with biopsy-proven glomerular disease.

SA-PO655

Assessing Patients’ Interest and Barriers to Clinical Research Participation in Nephrotic Syndrome
Laura H. Marijan,1 Chelsey Fix,1 Kathleen Broderick,2 Julie Abrahamson,2 Abigail L. Swan,3 Lauren Lee,3 Elizabeth L. Copel.3 Arbor Research Collaborative for Health; 1U. Michigan; 2NephCure Kidney International.

Background: Recruitment for clinical research studies in primary Nephrotic Syndrome (NS) is hindered by the rarity of the disease, diverse care settings and geographic spread of affected patients. Better understanding of the level of interest and barriers to participation from a diverse group of patients with NS is critical to successful recruitment and study design.

Methods: The NephCure Kidney Network (NKN) is a web-based patient opt-in registry for primary NS. Participants provide data including kidney disease history, demographics and research participation preferences. Logistic regression models were fit to identify predictors of willingness to participate.

Results: As of May, 2016, 587 participants from 32 countries have been recruited. Mean(SD) age was 26(12) yrs, 50% female, 22% non-Caucasian and 10% Hispanic. 38% have FSGS, 23% MCD, 2% IgAN, 2% MN and 2% MPGN. 62% are currently on medication after renal biopsy was collected.

Conclusions: While the majority of NKN participants indicate a high interest in many types of clinical research, few reported previously participating. Designing studies around topics of high value to the patient, engagement from their primary nephrologist, ensuring appropriate data privacy and limiting time burden may help to increase participation.

Funding: NIDDK Support

SA-PO656

Rituximab Therapy for Idiopathic Nephrotic Syndrome
Montserrat M. Diaz Encarnacion,1 Jara Karlla Dasilva,2 Luis F. Quintana,4 Manuel Praga,2 Juliana Bordignon Draibe,3 Jose Ballarini,2 1Fundacio Puigvert; 2Fundacio Puigvert; 3Hospital Puerta de Hierro; 4Hospital Clinic; 5Hospital Univ 12 de Octubre; 6Hospital Univ de Bellvitge; 7Fundacio Puigvert.

Background: Steroids continue to be the main treatment at idiopathic nephrotic syndrome (INS). Approximately 40–50% of patients are steroid-dependent (SD) and require repeat courses of prednisone and/or the addition of other immunosuppressive (IS) medications. Rituximab (RTX) is effective for the treatment of SD or frequently relapsing (FR) in pediatric patients, but this efficacy in adult patients is not established. The aim of our study was to evaluate the effects of RTX in adult with a diagnosis of difficult-to-treat INS, and to compare the outcomes with control patients treated with steroids in combination with other IS, excluding RTX.

Methods: We reviewed 50 patients with SD and FR INS, 28 patients received RTX between 2008-2015, and 22 control group patients in 6 Spanish hospitals. The minimal follow up is 8 month post-RTX. Data are expressed as means ± standard deviation. Comparisons before and after RTX treatment (baseline vs last follow up) were assessed by the paired Student’s parametric t-test (significant=p<0.05).

Conclusions: RTX treatment is safe and well tolerated and effectively reduced the incidence of recurrences and need for maintenance IS in adult patients with difficult-to-treat INS, but a few data is available about the long-term in adult.

Funding: Government Support - Non-U.S.

SA-PO656

Rituximab in the Treatment of Children with Steroid Dependent/ Resistant Nephrotic Syndrome
Sooraj Yesudas Santhakumari, Cochin Kidney Centre, Kochi, Kerala, India.

Background: About 10 -20 percent of children with nephrotic syndrome are steroid resistant/dependent. Though a variety of treatment modalities including cyclophosphamide, Calcineurin inhibitors (CNIs), mycophenolate, azathioprine etc are available for these children, still a small percentage remains refractory to these medicines. Rituximab is a

Figure 1: Patient reported interest and barriers to research participation in Nephrotic Syndrome

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

Underline represents presenting author.
chimeric antibody directed against the CD 20 receptors of B cells. There are studies which have shown that it is useful in Steroid dependent Nephrotic Syndrome (SDNS)/Steroid Resistant Nephrotic Syndrome (SRNS).

Methods: 15 children who satisfied the criteria for SDNS/SRNS were involved in the study. All had undergone treatment with Cyclophosphamide, CNIs and mycophenolate but were not able to achieve sustained remission and also was unable to withdraw steroids. Renal biopsy was done whenever possible. All the children were given 2 doses of Rituximab 375 mg/sq.m 2 weeks apart. They were then followed up for a period of minimum 8 months. Steroids and other immunosuppressants were withdrawn whenever possible.

Results: There were 7 females and 9 males. The average age was 8.4 +/- 2.4 years. The average duration of nephrotic syndrome was 30.46 +/- 8.61 months. All had received treatment with steroids and other immunosuppressives. 6 patients had undergone renal biopsy out of which 5 were minimal change disease and one was FSGS. All of them received Rituximab subcutaneously at 375 mg/sq.m 2 weeks apart. The average age was 12.46 +/- 2.92 months. The minimum followup was 8 months and maximum followup was 18 months. 14 patients responded to the treatment (93%) and we were able to stop immunosuppression. One child continues to be on steroid and CNIS. All children tolerated the drug well. There were no major adverse events except one episode of Herpes Zoster in a child which responded to treatment.

Conclusions: We conclude that Rituximab is a safe and effective treatment option in children with Resistant Nephrotic Syndrome. However more studies and more followup is required.

SA-PO657
Short-Acting Natural ACTH Induces Rapid Remission of Steroid-Dependent Nephrotic Syndrome Followed by Delayed-Onset Resistance: Implications of Newly Formed Neutralizing Antibodies

Wang, Pei,1,2 Minglei Lu, Xiuli Yang,1 Bin Zhang,1,2 Yingjie Liu,1,2,*,† Nephrology, Brown Univ, Providence, RI; 1The First Affiliated Hospital of Zhengzhou Univ, China.

Background: There is increasing evidence supporting the use of adrenocorticotropic hormone (ACTH) as an alternative treatment for refractory proteinuric glomerulopathies. The efficacy of short-acting ACTH, however, remains unknown and was tested here.

Methods: A 21-year-old man with a 5-year history of steroid-dependent nephrotic syndrome due to minimal changes disease developed Cushing’s syndrome and was recently affected with severe cellulitis. He was weaned off all immunosuppressants, including corticosteroids, and this resulted in a relapse of generalized anaasarca, associated with massive proteinuria and hypoalbuminemia. ACTH monotherapy was subsequently initiated.

Results: The initial regimen consisted of subcutaneous injections of 25 IU of short-acting ACTH that were increased to 50 IU and 100 IU of corticotropin given daily at 09:00 AM with reference to the Columbia ACTH gel therapy regimen. Short-acting ACTH treatment induced a rapid response, marked by massive diuresis, substantial reduction in body weight and partial remission of proteinuria. Ten days later, the patient developed mild skin rash and subcutaneous nodules at injection sites. A relapse followed despite doubling the dose of corticotropin, consistent with delayed-onset resistance to treatment. Immunoblot-based antibody assay revealed de novo formation of antibodies in the patient’s serum that were reactive to natural ACTH.

Conclusions: Short-Acting ACTH was likely effective in inducing remission of steroid-dependent nephrotic syndrome. The delayed resistance might be attributable to the formation of anti-ACTH neutralizing antibodies. The experimental protocols established here may aid in determining the cause of resistance to ACTH treatment in future studies.

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

SA-PO658
Novel Paradigm for Categorizing Subtypes of Focal Segmental Glomerulosclerosis: A Pilot Study

Thomas Kitzler,1 Nadezda Kachurina,1 Martin M. Bitzan,1 Elena Torban,1 Paul R. Goodyer,1 Medical Genetics, McGill Univ Health Centre, Montreal, QC, Canada; 2Dept of Medicine, McGill Univ and McGill Univ Health Centre, Montreal, QC, Canada; 3Dept of Paediatric Nephrology, McGill Univ Health Centre, Montreal, QC, Canada.

Background: Focal segmental glomerulosclerosis (FSGS) is found in the majority of children with steroid resistant nephrotic syndrome (SRNS), many of whom progress to end-stage renal disease despite second-line treatment with immunosuppressive agents. About half of these children harbour mutations in genes relevant for podocyte structure and integrity, whereas of the other half, some appear to have a circulating, yet to be identified, cytotoxic “FSGS factor” that directly causes damage to the podocyte ultrastructure. Children with genetic podocyte defects tend to fare well on treatment with renal transplant, while children with a circulating factor are at high risk of recurrence of FSGS on renal allograft, but may respond to an extended therapeutic algorithm elsewhere. Here we present a novel approach on how to distinguish these subgroups.

Methods: This is an analysis of 16 patients with clinically confirmed SRNS. We employed a combined approach of Next Generation Sequencing of 37 known FSGS genes and a 45 indeeedly post-translational factor in patients’ sera by use of cultured human podocytes. Toxicity of sera is evidenced by disassembly of podocyte focal adhesion complexes (Kachurina et al., Am J Physiol Renal Physiol, 2015).

Results: Preliminary analysis of patients’ sera demonstrated absence of podocyte-toxic factors in patients with identifiable genetic podocyte defects, whereas indirect evidence for a circulating factor (i.e., podocyte-toxicity) could only be detected in patients without identifiable genetic defects.

Conclusions: Based on these preliminary observations, we propose that SRNS comprises three subgroups: (1) patients with genetic causes of SRNS who are able to undergo renal transplantation; (2) patients without genetic causes with high risk of recurrence in the allograft, as evidenced by serum podocyte-toxicity; and 3) patients without genetic causes and low recurrence risk, i.e., absence of podocyte-toxicity.

SA-PO659
A Prospective, Open Label Study of the Safety and Treatment Efficacy of ACTHar Gel for Fibrillary Glomerulonephritis

James A. Tumlin,1 Brad H. Rivin,2 William G. Paxton,2 Isabelle Ayoub,3 Salem Almna,4 Dawn J. Castner,5 Alice Sue Appel,5 Gerald B. Appel,5 1Renal Div, Univ of Tennessee College Medicine, Chattanooga, TN; 2Georgia Nephrology, Atlanta, GA; 3Rochester Columbia University, New York, NY; 4Renal Div, Ohio State Univ, Columbus, OH; 5Renal Div, Univ of Louisville, Louisville, KY.

Background: Fibrillary glomerulonephritis (FGN) is a rare glomerular disease characterized by randomly deposited Congo-red negative fibrils within the mesangium and glomerular basement membranes. The therapeutic options for FGN are poor, with more than 50% of patients progressing to ESRD within 5 years. ACTHar gel has shown benefit in the treatment of multiple forms of proteinuria glomerulopathies. To determine its therapeutic efficacy in FGN, we retrospectively reviewed 14 patients treated with ACTHar gel.

Methods: A total of 14 patients with biopsy proven FGN were reviewed. Mean age was 59+4 yrs with 93% Caucasian and 57% female. The FGN subtypes included 3-MGN, 8-Mesangial, 2-MPGN, and 1 Crescentic. Seven (50%) received prior immunosuppression; Pred 2, CNIS 1, Rituximab-2, Cyclophosphamide 1. All patients were treated with ACTHar dose range 800-240 units 2-3 iwk (mean dose 174/9 units) (range 2-24 mths). Complete responses were defined as UP/Cr ratio < 0.30; partial responses were defined as a > 50% reduction in pre-ACTH UP/Cr ratios.

Results: A complete response was achieved in 1 patient (7%), partial remissions in 6 (43%) and no response in 7 (50%). Responsive patients did not differ in FGN subtypes or prior treatment. Patient responses are shown in Table-1. (Proteinuria-UP/Cr gm/gm (p<0.009).

Funding: NIDDK Support, Private Foundation Support

SA-PO660
Hypothyroidism Secondary to Severe Nephrotic Syndrome

Anna Mattwie,c,1 Aleksandra Rymarz,1 Slawomir Literacki,1 Dorota Brodowska-Kania,1 Tomasz Rozmyslowiecz,2 Stanislaw Niemczyk,3 ‘Military Inst of Medicine, Warsaw, Poland; 1Univ of Pennsylvania, Philadelphia.

Background: The issue of clinically significant hypothyroidism secondary to urine loss of free thyroxine, TBG and albumin is currently widely discussed in paediatric population with nephrotic syndrome. In adults, however, the data are limited. The aim of the study was to estimate the thyroid function in severe nephrotic syndrome in adults, defined as serum albumin level (SA) ≤ 2.5 g/dl.

Methods: The 25 adult patients (mean age 45±18 years, 68% men) with severe nephrotic syndrome and eGFR <30 ml/min/1.73m2 were included into the prospective pilot study. The thyroid hormone profile was assessed using electrochemiluminescence immunosassay (ECLIA). The Spearman correlation coefficient was used to statistically analyse (Statistica 12, StatSoft).

Results: The mean values of measured parameters were: SA 1.8±0.4 g/dl, T4 2.4±0.6 g/dl, daily proteinuria 11.5±6.0 g, daily albuminuria 8.9±6.7 g, urine albumin-to-creatinine ratio (ACR) 4.77±1.9 g/mgSCT, TSII 4.1±2.2 µIU/ml, FT4 12.7±3.2 pmol/l, FT3 3.4±0.8 pmol/l, antiithrombin activity 75±20%. The study revealed the impaired thyroid hormone profile in 75% subjects, in 81% with SA <2.0 g/dl and in 67% with SA 2.0-2.5 g/dl. The main abnormality was overt hypothyroidism (28%) and euthyroid sick syndrome (EES), characterized by decreased level of serum FT3 or FT4, or both, accompanied by normal TSH profile in 76% subjects, in 81% with SA <2.0 g/dl and in 67% with SA 2.0-2.5 g/dl. The significant negative correlations were observed between free hormones and daily proteinuria (for FT3 r=-0.255, p=0.043; for FT4 r=-0.528, p=0.029) and ACR (for FT3 r=-0.495, p=0.028; for FT4 r=-0.559, p=0.016). The ACR >4.0 g/mgSCT was associated with 77% risk of thyroid dysfunction in 77% patients with SA <2.0 g/dl.

Conclusions: Severe nephrotic syndrome causes significant disturbances in the thyroid function. In most of the patients hypothyroidism or EES was observed. The thyroid function monitoring in patients with severe nephrotic syndrome seems to be necessary to avoid possible disturbances in thyroid function.

Funding: Clinical Research Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Collapsing Glomerulopathy in Kidney Allografts: Donor Ethnicity and Clinical Course
Nidhi。(A. Obadaj, E. Bruner, G. K. Mour, Juan Carlos Q. Velez. Nephrology, Medical Univ of South Carolina, Charleston, SC.

Background: Collapsing glomerulopathy (CG) is a variant of focal segmental glomerulosclerosis (FSGS). In native kidneys, almost all affected individuals are African American (AA), 75% of whom carry 2 APOL1 risk alleles. However, in kidney allografts, CG affects 13% (5%) and white (W) in 9 (41%) cases. No difference was found in recipient’s mean age (56 vs. 47 yrs), gender (23% vs. 33% female), race (23% vs. 55% AA), time from transplant to CG (35 vs. 19 months) or cold ischemia time (13 vs. 16 hrs) for AA-CG and W-CG, respectively. Among AA-CG cases, native nephropathy were diabetic (DN) (6%), hypertensive (5) and FSGS (2), suggesting possible recurrence in 2 cases. On the other hand, all W-CG cases were possibly de novo (native nephropathy: DN in 4, IgA in 2, lupus, ADPKD and aHUS in 1). DNA for CMV and BKV was found in 2 AA-CG cases, whereas CMV, parvo, coxackie and EBV viremia were found in 4 W-CG cases. No difference was found in mean serum creatinine (4.2 vs. 2.6 mg/dL) or urine protein-to-creatinine (7.6 vs. 4.8 g/g) at the time of diagnosis, although there was a trend for a greater incidence of nephrotic syndrome in AA-CG (83% vs. 55%, p=0.17). More importantly, graft loss occurred in 12 (95%) AA-CG vs. 4 (44%) W-CG cases (p=0.02).

Conclusions: The high incidence of FSGS in AA-CG with increased relative incidence of CG allografts that presents frequently as de novo disease. Viremia is detectable in about 25% of cases. CG affecting kidneys from AA donors appear to have a more ominous outcome; Whether APOL1 risk alleles account for the difference remains to be determined.

SA-PO662
Apoptosis Inhibitor of Macrophage (AIM) Expression in the Kidney Was Associated with Increased Proteinuria and Decline in Renal Function
Yasunori Iwata, Megumi Oshima, Kengo Funuchi, Norihiko Sakai, Miho Shimizu, Akinori Harada, Tadasu Teyama, Yasuyuki Shinozaki, Yasutaka Kamikawa, Shinji Kitajima, Akihiko Sagara, Takashi Wada. Nephrology, Kanazawa Univ.

Background: Apoptosis inhibitor of macrophage (AIM) expressed on macrophages promote survival of other cells by releasing macrophages from apoptosis. Most circulating AIM co-exists with immunoglobulin M (IgM). AIM’s pathophysiological role in relation to IgM remains unclear. Here we evaluated the glomerularexpression/deposition of AIM and IgM in the kidney using immunohistochernistry and its associations with clinical manifestations in 43 patients with biopsy-confirmed kidney diseases.

Methods: Kidney biopsy tissue from all patients was immunostained for AIM and IgM. Staining patterns and percent stained areas within the glomeruli were determined. Correlations between staining results and clinical parameters were evaluated using univariate and multivariate analyses.

Results: AIM was deposited in various areas, such as mesangial and capillary area. A part of AIM expression was localized to CD68-positive macrophages in the glomerulus. Amount of glomerular expression was positively correlated with urinary protein in patients with severe proteinuria and/or kidney dysfunction. Urinaryprotein was higher in patients exhibiting overlapping glomerular expression of AIM and IgM. Annual eGFR decline rate was significantly higher in patients with AIM and IgM. 33 patients were rechallenged, 3 remained on low dose prednisone. Recurrent AIN was not observed after rechallenge.

Conclusions: AIM expression in the kidney was associated with urinary protein and decline in renal function. Co-expression with IgM appeared to exacerbate AIM’s deleterious effects on renal function. Combined glomerular AIM/Im expression is a candidate prognostic index for kidney disease.

Funding: Government Support - Non-U.S.

SA-PO663
Natural History of Lithium Nephropathy: Cross-Sectional Analysis of a Cohort of Li-Treated Bipolar Disorder Patients
Emmanuelle Vidal-Petiot,1,2 Fideline Serrano,1,2 Pedro Fernandez,1,2 Frank Belliver,2,3 Francois Vrtovsni,1,3 1Bichat Hospital, APHP, Paris, France; 2Center for Bipolar Disorder, APHP, Paris, France; 3Parris Diderot Univ, Paris, France.

Background: Lithium (Li) therapy may lead to secondary renal disease including diabetes insipidus, hyperparathyroidism and chronic microscopc nephropathy but the natural history of these disorders in this setting is still unclear.

Methods: Measured GFR (clearance of 125I-EDTA), maximal urinary osmolality following 1.2h of water restriction and injection of 0.4 μg ddAVP (UOsm-max, in mosm/kg, osmotic load (OsmL, mosm/d), ionized calcium, PTH before and after iv calcium load were measured in 87 consecutive patients (pts) referred by the Center for Bipolar Disorder and treated with Li for >21 months (G3, n=21), 5-15y (G3, n=24), >15y (G4, n=25). Kidney microcysts were counted by MRI imaging in 37 pts.

Results: In the whole cohort (36% men), mean(SD) age and GFR, were 50.2 (15.3) years and 73.7 (22.6) mL/min/1.73m². GFR was independently correlated (multiple regression) with both duration of Li exposure (-0.98g/1.73m²/year, p=0.001) and age (-0.55g/1.73m²/year, p<0.001). Polyuria (>3L/day) was found in 25% of pts and associated with a higher OsmL (p=0.05) and decreased UOsm-max (p=0.001) in pts from G1 to G4. Hypermiclasia (HC) was present in 23 pts and associated with high PTH in 9, all in G4. PTH decrease following iv Ca load was blunted with longer therapy (p=0.05). Prevalence of microcysts increased from G1 to G4 (p=0.002) but lasted in 25% of G4 pts.

Conclusions: Li-induced diabetes insipidus occurs early during the course of Li therapy. Microcysts are frequent but not systematic in long-term treated pts. In this cohort, GFR decrease is highly correlated with length of exposure to Li and reaches -1.5 mL/min/1.73m², with 1/3 attributable to aging and 2/3 to Li.

SA-PO664
Interstitial Nephritis Associated with Programmed Cell Death-1 Inhibitors
Samer Mehandhe, Yuhang A. Zakarayan, Jason Prosek. Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: Programmed Cell Death-1 (PD-1) inhibitors are immune checkpoint inhibitors used to treat malignancies by blocking inhibition to T-cell activation. Current PD-1 inhibitors include nivolumab and pembrolizumab. Acute interstitial nephritis (AIN) has been described with ipilimumab but not well described with PD-1 inhibitors. Here we report 6 cases of suspected AIN due to use of PD-1 inhibitors.

Methods: Six patients who underwent treatment with PD-1 inhibitors in whom AIN was clinically observed were presented. PD-1 inhibitors were used for RCC, melanoma and urethelial carcinoma. AKI attributed to AIN was observed within 3 to 5 days. AIN was proven by biopsy in 2 cases. Clinical features are summarized in Table 1. One patient developed hypercalcemia with elevated 1,25-OH vitamin D level suggesting granulomatous AIN. All of the patients who received prednisone achieved remission. 5 patients were rechallenged, 3 remained on low dose prednisone. Recurrent AIN was not observed after rechallenge.

Results: Clinical features and course of the 6 cases. Pemb - pembrolizumab, Niv - nivolumab, Ax = axitinib, Ipi - ipilimumab, RCC - renal cell carcinoma.

Conclusions: The above demonstrates an association of PD-1 inhibitors with AIN. A kidney biopsy is the gold standard for diagnosis of AIN however this option is limited for patients with RCC, many whom are left with a solitary kidney after nephrectomy. Thus clinicians will need to feel comfortable making this diagnosis on clinical grounds to initate therapy. Rechallenging patients with anti-PD-1 therapy after resolution of AIN appears to be a safe option with close monitoring.
colic and 1 with hematuria/proteinuria. Eight of 14 patients with IN received systemic immunosuppression (prednisone, mycophenolate mofetil, azathioprine, rituximab and anti-TNF agents) during the renal disease course but in 7 patients no beneficial effect was observed on renal function, hypokalemia and RTA. Six of 14 patients with IN developed CKD (median duration of renal disease 6 yrs, range: 1.5-17) while 5 of them preserved normal renal function during follow up (median follow up duration: 14 yrs, range: 5-20). GN occurred later during PSS course (median SS duration 8 yrs, range: 0-14.5) and 2 patients presented with CKD, 3 with proteinuria/hematuria and 1 with nephrotic proteinuria. In the GN group, renal biopsy findings revealed membranoproliferative glomerulonephritis (MPGN) (n=3), focal segmental glomerulosclerosis (n=1) and fibrillary glomerulopathy (n=1). All 3 MPGN patients had cryoglobulinemia and in 1 patient cryoglobulinemic MPGN was clinically diagnosed. All GN patients were treated with immunosuppressive therapy with stabilization or improvement of renal function in the 4 MPGN patients only.

Conclusions: IN occurs early in disease course in PSS and does not improve with systemic immunosuppression. On the contrary, GN appears as a late complication of PSS and a favorable treatment response is seen in those with MPGN pathology.

SA-PO667

Study on the Mechanism of Renal Tubular Proteinuria in Children with OCLR Gene Mutations

Chikushi Sunada,1 Shoji Tsuji,1 Jiro Kino,1 Sohsaku Yamanouchi,1 Takahisa Kimata,1 Hiroyuki Kurusawa,2 Akihiko Saito,3 Kazunari Kaneko,1

1Pediatrics, Kansai Medical Univ, Osaka, Japan; 2Reagent Research and Development Dept, Denka Seiken Co., Ltd, Japan; 3Applied Molecular Medicine, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background: The ocularcerebrorenal syndrome of Lowe (OCLR) gene is located on Xq25-26 and encodes a phosphatidylinositol 4,5 bisphosphate (PtdIns(4,5)P2) phosphatase (OCLR). Mutations in the OCLR gene cause Lowe syndrome (LS) or type 2 Dekmejian (CD) disease, in which low molecular weight (LMW) proteinuria is a cardinal finding. It is considered that megalin plays an important role in the development of renal tubular proteinuria. Megalin is expressed on the luminal side of proximal tubular cells (PTCs) and is involved in the reabsorption and metabolism of LMW proteins, such as α₂-microglobulin (AMG), β₂-microglobulin (BMG) and retinol-binding protein. Recently, it was revealed that two fractions of megalin are excreted into the urine: full-length megalin (C-megalin) and megalin ectodomain (A-megalin). This study was conducted to explore the mechanisms of LMW proteinuria in patients with OCLR mutations by determining the urinary megalin fractions.

Methods: Using spot urine samples obtained from five male patients with OCLR mutations (median age: 9 years), A- and C-megalin were measured with enzyme-linked immunosorbent assays and corrected for creatinine creatinine. The data were compared with those of 50 controls.

Results: All patients demonstrated normal levels of urinary C-megalin. However, patients with OCLR mutations showed abnormally low levels of urinary A-megalin, except a 5-year-old boy, who was the youngest subject of the present study.

Conclusions: Considering the decreased excretion of urinary A-megalin in 4 out of 5 patients with OCLR mutations, LMW proteinuria may be caused by impairment of megalin recycling within the PTCs while a homologous enzyme, such as INPP5B, may compensate for the defective OCLR-1 function to some extent during early childhood.

SA-PO668

Persistent B Cell Depletion and Recurrent Neutropenia: A Rare Complication of Rituximab

Frank B. Cortazar,1,2 Katherine M. Cosgrove,1,2 Karen A. Laliberte,1 John Niles,1,2

1Div of Nephrology, MGH, Boston, MA; 2MGH Vasculitis and Glomerulonephritis Center, Boston, MA.

Background: B cell depletion with rituximab (RTX) is an important therapeutic strategy in the treatment of glomerular diseases. We describe a syndrome of persistent B cell depletion and recurrent neutropenia (NTP) in 2 patients with ANCA vasculitis who received RTX for maintenance of remission.

Methods: We performed a retrospective analysis of clinical data in patients who had persistent B cell depletion for at least 2 years after their last RTX dose in conjunction with recurrent episodes of NTP.

Results: Two of 519 (0.38%) patients in our cohort receiving RTX for ANCA vasculitis or other glomerular diseases developed a syndrome of persistent B cell depletion and recurrent NTP.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pt 1</th>
<th>Pt 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first RTX</td>
<td>27</td>
<td>60</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>ANCA subtype</td>
<td>MPO</td>
<td>MPO</td>
</tr>
<tr>
<td>Induction therapy</td>
<td>CYC, Pred</td>
<td>CYC, Pred</td>
</tr>
<tr>
<td>Prior maintenance therapy</td>
<td>AZA, Pred</td>
<td>AZA, Pred</td>
</tr>
<tr>
<td>Total RTX (gm)</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Episodes of NTP</td>
<td>4</td>
<td>12</td>
</tr>
</tbody>
</table>

Patient 1 received 5, 1gm doses of RTX (horizontal lines) and continues to have B cell depletion 40.0 months after her last RTX dose. She developed 4 episodes of NTP, the last occurring 39.6 months after her last RTX dose. Each episode of NTP was treated successfully with filgrastim (arrows). Patient 2 received 10, 1 gm doses of RTX and had B cell depletion on her last check 54.4 months after her last RTX infusion. She developed 12 episodes of NTP, all treated with filgrastim. The last episode of NTP, occurring 51.6 months after her last RTX infusion, was complicated by a fatal infection.

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

Underline represents presenting author.

783A
SA-PO669

Anti-Brush Border Antibody Disease in Humans: Clinicopathological Features and a Putative Common Autoantigen
Christopher Patrick Larsen,1 Paige A. Coles,2 A. Bernard Collins,3 Michael Merchant,4 Jon B. Klein,4 Ivy A. Rosales,2 Robert B. Colvin,2 Laurence He. Beck,1Arkana Laboratories, Little Rock, AR; 1Massachusetts General Hospital, Boston, MA; 2Boston Univ Medical Center, Boston, MA; 3Univ of Louisville, Louisville, KY.

Background: Primary tubulointerstitial disease caused by antibodies to proximal tubule brush border antigens (AABB) with tubular basement membrane (TBM) immune complex deposition was described in experimental animals in the 1960s. Human cases with similar pathologic findings were reported in the early 1970s and the finding of serum anti-brush border antibodies (AABB) was reported in 1981. More recently, a case report described a patient with recurrence of this disease in a transplant. Despite this long history, little is known about the disease.

Methods: Sera from patients with idiopathic TBM deposits on biopsy by indirect IF (IIF) for the presence of AABB in two renal biopsy laboratories. Sera from cases positive for AABB were then tested by western blot (WB) and immunoprecipitation (IP) using human tubulointerstitial extract.

Results: We identified 8 AABB+ cases by IIF. The patients (7M:1F) were 68-78 years old and had a mean serum Cr of 3.5 mg/dl at diagnosis. All renal biopsies showed acute tubular injury (ATI) and 3/8 also had interstitial inflammation. Granular IgG deposits were were along the TBM, Bowman’s capsule, and segmentally in the GBM in all cases. IgG4 was the predominant or co-dominant IgG subclass in 6/8. Despite treatment, none of the 6 patients with follow-up (mean 4.8 mo) had evidence of remission. Remarkably, WB revealed a common high molecular weight Ag detected by all 8 patients. IP and mass spectrometric analyses, as well as confoal co-localization studies using patient serum on normal kidney, have been performed to identify and characterize candidate Ags.

Conclusions: We present the largest case series to date of renal disease due to AABB. This disease primarily affects elderly males and presents with acute renal failure. Pathologic findings include ATI with granular basement membrane IgG staining, often with minimal inflammation. WB and IP analysis suggests a common autoantigen.

SA-PO670

Impaired Glomerular Hyperfiltration in Early Pregnancy and Adverse Pregnancy Outcomes
Jessica Sheehan Tangren, Camille Elise Powe, Ravi I. Thadhani. Massachusetts General Hospital, Boston, MA.

Background: Glomerular hyperfiltration, an early marker of renal disease, is a normal phenomenon that begins early in pregnancy. The role of gestational hyperfiltration (GH) in maintaining a healthy pregnancy is unknown. We determined if impairments in gestational hyperfiltration in early pregnancy predict the adverse development of outcomes in women with early stage CKD.

Methods: We studied women with CKD stage 1 who delivered infants between 1998 and 2007 at the Massachusetts General Hospital. eGFR (CKD-EPI) was calculated at baseline with early stage CKD.

Results: Baseline serum creatinine, age, blood pressure and BMI were similar between women who delivered infants between 1998 and 2007 and women who did not develop preeclampsia, the eGFR increased (Figure 1). In women who developed preeclampsia, the eGFR decreased on average in early pregnancy while in women who did not develop preeclampsia, the eGFR increased (3.1%)

Conclusions: In women with CKD 1, impaired hyperfiltration in early pregnancy is associated with poor maternal outcomes, including preeclampsia.

SA-PO671

Kidney Biopsy Has Significant Clinical Utility in Advanced Chronic Kidney Disease
Amit J. Joshi, Ambharith Athavale, Radhika Jaiswal, Albert M. Osei, Peter D. Hart. Dept of Nephrology, John H. Stroger Hospital of Cook County, Chicago, IL.

Background: Kidney biopsy is not commonly performed in advanced CKD (ACKD) with eGFR of ≤ 30 ml/min due to perceived non-diagnostic utility and higher complication rate. Therefore, we assessed the clinical utility and safety of native kidney biopsy in patients with ACKD with negative ANA and ANCA serology.

Methods: Retrospective review of our biopsy database from Jan 2010-Dec 2015 identified 97 cases. Mean age was 46.5 (±12.7) years and women accounted for 42% of the study cohort. African Americans constituted 51%, Hispanics 31%, Caucasians 8%, and other races 10%. Mean S. Creatinine was 4.3 (±2.0) mg/dl with eGFR of 18.5(±7.1) ml/ min. Mean proteinuria was 5.2 (±5.5) g/g of Cr and 62% cases had hematuria on urinalysis. Diabetes, paraproteinemia, HIV and hepatitis C antibody were present in 28.6%, 6.1%, 19.4%, and 9.2% of cases respectively.

Results: Biopsy ascertained renal diagnosis in a majority (84.5%) of which the most common were IgAN, FSGS and Diabetic nephropathy. 10% had unsuspected diagnosis namely Fibrialy GN, Necrotizing GN, Amyloidosis and Sarcoidosis. 15.5% had advanced glomerulosclerosis and 48.5% had severe (>50%) tubulointerstitial disease. Based on biopsy findings, disease specific therapy was initiated in 37.1% and non-diabetic renal disease was identified in 46% of cases with diabetes.

Table 1: Biopsy diagnoses, (number, %)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number, %</th>
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<tbody>
<tr>
<td>Advanced glomerulosclerosis</td>
<td>15 (15.5%)</td>
</tr>
<tr>
<td>IgAN: 14 (14.4%)</td>
<td></td>
</tr>
<tr>
<td>FSGS: 13 (13.4%)</td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy: 13 (13.4%)</td>
<td></td>
</tr>
<tr>
<td>Membranous nephropathy: 6 (6.1%)</td>
<td></td>
</tr>
<tr>
<td>Tubulointerstitial nephritis: 6 (6.2%)</td>
<td></td>
</tr>
<tr>
<td>HIV associated nephropathy: 4 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive nephrosclerosis: 4 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Membranoproliferative GN: 4 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Amyloidosis: 3 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Minimal change disease: 3 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Thrombotic microangiopathy: 3 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Necrotizing GN: 3 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Fibrillary glomerulonephritis: (GN): 2 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Membranoproliferative GN: 2 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis: 2 (2.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Complications: Major (PRBC transfusion/intervention): 1%, Minor (hematoma not requiring any intervention): 8%.

Conclusion: Kidney biopsy remains an important diagnostic tool even in patients with advanced CKD. It guides clinical management and can be safely done.

SA-PO672

Renal Biopsy - Specimen Adequacy and Safety: A Performance Improvement (PI) Project
Abhishek Sinha Ray,1 Sri G. Yarlalagadda,1 Neville Irani.1 1Nephrology and Hypertension, Kansas Univ Medical Center, Kansas City, KS; 2Radiology, KUMC, Kansas City, KS.

Background: Renal biopsy in this era is shared by nephrologists and interventional radiologists (IR). Available literature suggests wide variability in bleeding risk (0.5-7%) and specimen adequacy. Increasing needle size has been attempted to improve adequacy of biopsy sample, however, bleeding risk increases. There is also concern for significant inter-operator variability. We therefore undertook a PI project to assess sample adequacy, bleeding risk, analyze risk factors and effect of change in needle size.

Methods: We collected data from 454 patients who had renal biopsy from 2014 to April 2016. All patients were observed for 24hrs to monitor for complication. Bleeding complication was defined as radiologic demonstration of hematoma, need for transfusion or embolization by IR. Biopsy sample was considered adequate if it had at least 10 glomeruli. In May 2014, we downsized biopsy needle to 18gauge and in March 2015, we restricted operator pool to find any effect of these interventions on outcome measures.

Results: We found thrombocytopenia (~100,000/cmm, Odds ratio [OR] 5.28), hemoglobin <8.5g/dl (OR 5.24), advanced renal failure (eGFR <30ml/kg/min, OR 3.99) and INR >1.5 (OR 3.2) are associated with increased bleeding; however, hypertension and type of kidney biopsy (native or transplant) didn’t significantly alter the risk. Decreasing needle size didn’t affect sample adequacy or bleeding risk. There is no significant variability observed between trainee physicians and experienced operators. Limited number of biopsies performed in our institution might have culminated into significant monthly variation in outcome without any identifiable factor and also restricted ability to detect whether specific etiologies leading to renal dysfunction contribute to any increase in post-procedural bleeding risk.

Conclusions: In our tertiary care center with medium volume of renal biopsies done, sample adequacy was not impacted by decreasing needle size. We didn’t find any significant inter-operator variability. Patients with anemia, thrombocytopenia, advanced renal failure or coagulopathy are at significantly increased risk for procedural bleed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Successful Use of Renal Denervation (RDN) in Patients with Loin Pain
Hematoma Syndrome- The Prairie LPSH Study

Bhanu Prasad, Jennifer St. Onge, Shelley Griebel. Nephrology, Regina Qu Appelle Health Region, Regina, SK, Canada.

Background: Loin pain hematoma syndrome (LPHS) is a painful and incapacitating condition that typically afflicts young women. Attempts to relieve pain by dorsal rhizotomy, renal capsuleotomy, and thoracolumbar sympathectomy have been unsuccessful. Surgical transection of the renal nerve by auto transplantation of the kidney leads to recurrence of pain after variable periods. Bilateral nephrectomy has been associated with complete pain relief but at the burden of ongoing need of renal replacement therapy.

Methods: Four patients with LPHS from southern Saskatchewan, with LPHS and intractable pain underwent renal endovascular ablation of the renal nerves between July and November 2015 using the Vessix™renal denervation system. The number and frequency of pain medications, and responses to the EQ-5D, McGill Pain Questionnaire, Geriatric Depression Score, Short Form Health Survey (SF-36), and Oswestry Disability Index were measured at baseline and at 3 and 6 months post-procedure to evaluate changes in pain, disability, quality of life and mood. Renal denervation (RDN) was performed after seeking Health Canada approval for this indication.

Results: There were significant improvements in pain (McGill Pain Questionnaire), disability (Oswestry disability index), and quality of life (EQ-5D and SF-36) from baseline to 6-months post-procedure. Two out of four patients were off all pain medications; the remaining two had a 75% reduction in the dose of pain medications.

Conclusions: We present four successful cases of RDN, a novel treatment of intractable pain in patients with LPHS. Reduction in pain was accompanied by considerably improvement in functionality and quality of life. All the patients in our study post-RDN, reported less absenteeism, remarkably fewer trips to ER and hospitalizations, relief of caregiver burden, and considerable reduction in number, dose and frequency of pain medications. These results suggest that percutaneous catheter based renal nerve ablation with radiofrequency energy is a safe and rapid treatment option that should be considered in all patients with LPHS.

Impact of Percutaneous Endovascular Ablation of the Renal Nerves (RDN) on Central Blood Pressures in Patients with Chronic Kidney Disease (CKD):

Prairie RDN Study
Bhanu Prasad.1 Jennifer St.Ong.e.2 1Nephrology, Regina Qu Appelle Health Region, Regina, SK, Canada; 2Research and Performance, Regina Qu Appelle Health Region, Regina, SK, Canada.

Background: Central aortic blood pressures (CBP) in comparison to brachial blood pressures more accurately reflect loading of the left ventricular myocardium, coronary arteries, and cerebral vasculature and thereby, better relate to cardiovascular target organ damage and to cardiovascular events. We investigated the impact of minimally invasive catheter based renal denervation (RDN) on central blood pressures and vascular stiffness in patients with stage 3 and 4 CKD with resistant hypertension.

Methods: Twenty-six patients with resistant hypertension from our multidisciplinary chronic kidney disease (CKD) clinic underwent either unilateral or bilateral RDN from February 2013 to August 2014. CBP, 24-hour ambulatory blood pressures, average of 6 office BP readings on BP Tru, along with carotid-femoral pulse wave velocities were measured at 3, 6, 12 and 18 months. Radial arterial pressure waveforms were obtained by applanation tonometry using a solid transducer; central arterial waveforms and pressures were calculated by the use of the SphygmoCor device.

Results: Baseline (mean ± standard deviation) central systolic/diastolic blood pressures (mm Hg) were 131±22.57/77.09±16.36 and at 18 months were 120.16±14.67/77.00±16.36. Consistent with the general effect of blood pressure reduction, a transient decrease in plasma NO metabolites (NOx) was seen at FU, whereas plasma cGMP was significantly reduced at both FU visits. Moreover, a significant reduction in both urinary NOx and cGMP excretion normalized to creatinine was seen at both 1st and 2nd FU. A transient decrease in plasma NO metabolites (NOx) was seen at 1st FU, whereas plasma cGMP was significantly reduced at both FU visits. Moreover, a significant reduction in both urinary NOx and cGMP excretion normalized to creatinine was seen at both 1st and 2nd FU.

Conclusions: Central aortic blood pressure reduction achieved by renal denervation was associated with decreased urinary excretion of NO metabolites suggesting an important role of reduced renal NO bioavailability in TKJ-Induced hypertension.

Can We Prevent Recurrent Pre-Term Preeclampsia? Line Malcha,1 Cristina P. Sisom,2 Phyllis August.1 1Div of Nephrology and Hypertension, Weill Cornell Medicine, New York, NY; 2Biosstastics Unit, Feinstein Inst for Medical Research, Northwell Health, Manhasset, NY.

Background: Preterm preeclampsia (PTPE) (< 34 weeks of gestation) is a life-threatening complication of pregnancy with a high recurrent rate (20%). Low dose aspirin (ASA) may prevent recurrence, and some trials suggest that low molecular weight heparin (LMWH) and ASA together is more effective but results are inconclusive. We report the recurrence rate of PE in women with prior PTPE and the impact of therapy on fetal birth weights (BW) and gestational age at delivery (GA).

Methods: We prospectively followed 41 women with PTPE in a prior pregnancy throughout 53 subsequent pregnancies. Women were screened for genetic and acquired thrombophilias and treated with either ASA or LMWH as determined by treating physicians. Maternal and fetal outcomes in subsequent pregnancies were ascertained including preeclampsia (PE), GA, and BW.

Results: The mean (±SD) age of the women was 36±5 years at the time of their subsequent pregnancy, and BMI was 25.6±5.4kg/m². 66% were white, 5% black and 15% Hispanic. Genetic thrombophilias were detected in 91% and acquired thrombophilias in 36%. Thirteen women (25%) were not treated with ASA or LMWH, 12 (23%) received ASA alone, and 27 (52%) received LMWH±ASA. PE reoccurred in 6 pregnancies (11%) and PTPE in 5 (9%). In subsequent pregnancies BW was higher (1473±743 grams prior pregnancy vs. 2880±778 grams in the subsequent pregnancies, p<0.001), and GA at delivery was later (29±4 weeks vs. 36±4 weeks, p<0.001). PE recurrence was numerically higher in the untreated group compared to those treated with ASA alone, or LMWH±ASA (3/13 vs. 1/12 or 2/27). BW and GA increased similarly in subsequent pregnancies in all groups although women treated with LMWH±ASA had a greater increase in GA (8.8 vs 4.4 weeks, p=0.021).

Conclusions: The risk of recurrent PE or PTPE in women with prior PTPE was lower than reported in prior studies. BW and GA at delivery were significantly better in subsequent pregnancies. We found a trend towards a decreased incidence of PE and greater prolongation of pregnancy in those treated with LMWH±ASA compared to no treatment or ASA alone. We propose an appropriately designed clinical trial to determine the benefits/risks of LMWH in women at risk for PTPE.

Renin-Angiotensin-Aldosterone Profiles Predictive of Superimposed Preeclampsia1

Line Malcha,1 Cristina P. Sisom,2 Phyllis August.1 1Div of Nephrology and Hypertension, Weill Cornell Medicine, New York, NY; 2Biosstastics Unit, Feinstein Inst for Medical Research, Northwell Health, Manhasset, NY.

Background: Women with preexisting, or chronic hypertension (CHT) in pregnancy is at heightened risk for significant morbidity and death, primarily due to further elevations in blood pressure (BP) and worsening of underlying cardiovascular disease. Maternal and fetal outcomes in subsequent pregnancies were ascertained including preeclampsia (PE), GA, and BW.

Methods: We performed a prospective, longitudinal trial of 108 women with CHT and investigated the hypothesis that renin-angiotensin aldosterone profiles (RAAS) are associated with BP and SPE. We measured plasma renin activity (PRA), 24h urine Na, K and aldosterone (UA) at 12, 20, 28, and 36 weeks gestation and post-partum to investigate the association between these potentially pathophysiologic parameters and elevations in BP and SPE.

Results: Mean Arterial Pressure (MAP) was inversely related to PRA (r=-0.23, p<0.001) and UA (r=0.11, p<0.047). PRA and UA were significantly and positively associated with each other (r=0.537, p<0.0001). Whereas PRA, and UA increased similarly in the first and second trimesters of pregnancy in women who did or did not develop SPE, there was a significant decrease in SPE in women with PRA (P<0.001) and UA (P<0.039) significantly lower at 28 weeks in those who developed SPE compared to those who did not develop SPE. Interestingly, PRA was significantly lower in black women compared to other racial groups (p = 0.026 at 36 weeks and <0.003 at all other time points including postpartum) and UA was also significantly lower in black women at 36 weeks (p=0.035). After adjusting for MAP, urine

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Background: We conclude that renin-angiotensin-aldosterone profiles, ascertained during the secondary prevention of small subcortical strokes (SPS3) trial previously randomized to intensive anti-hypertensive therapy (target SBP <130 mm Hg) after lacunar stroke.

Methods: We used an unsupervised, group-based cluster procedure (machine learning) to identify distinct patterns of BP change among 1,331 participants in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial previously randomized to intensive anti-hypertensive therapy. (target SBP <130 mm Hg) after lacunar stroke.

Results: Among persons undergoing active, aggressive BP lowering, the cluster procedure partitioned subjects into three groups, according to BP response during the active intensification period: 1) mildly elevated baseline mean SBP and minimal visit-to-visit SBP variability (mild reducers); 2) moderately elevated baseline mean SBP and moderate visit-to-visit BP variability (modest reducers); and 3) very elevated baseline mean SBP with very large visit-to-visit BP variability during intensification (large reducers). Compared to mild reducers, modest reducers had a higher adjusted risk of death, MVE, and stroke.

Conclusions: Among persons with prior lacunar stroke, baseline SBP and large SBP and DBP variability during anti-hypertensive treatment intensification can identify distinct groups of persons at higher risk of adverse outcomes.

SA-PO678
Pathway Analysis and Targeted Proteomics of Human Urinary Exosomal Proteins during Aldosterone Administration

Praveen Kumar,1 Higher Pre-ESRD Visit-to-Visit Variability in Systolic Blood Pressure

Methods: To test the hypothesis that the urinary protein is dynamically regulated by exogenous hormones, we analyzed urine exosomes from 10 healthy subjects in a cross-over study after vehicle and aldosterone infusion (0.7 μg/kg/hr for 10 hrs) while on a standardized diet (160mm Na/d for 5 days). Urinary exosomes were isolated by a two-step centrifugation method after reduction of the Tannm-Horsfall protein (aromodulin) with DTT. After isolation by ultracentrifugation, proteins underwent trypsin digestion and were subjected to MudPIT analysis. Statistical analysis was performed using a quasi-likelihood analysis with Benjamin & Hochberg correction for multiple comparisons. Validation was performed by targeted multiple-reaction-monitoring analysis for selected peptides quantified with stable-isotope peptide standards.

Results: Aldosterone infusion increased plasma aldosterone (55.9:5.5 vs 7.8:1.5 ng/dL; P<0.001) without acutely altering blood pressure or serum potassium. At a False Discovery Rate <0.05, 101 proteins were identified as up-regulated in the ALDO group, while 189 proteins were down-regulated. Gene ontology enrichment analysis of significantly altered proteins revealed that aldosterone altered small GTPase-mediated signal transduction, GTP binding, protein binding, and GTPase activity. In particular, aldosterone treatment altered pathways involving regulation of the actin cytoskeleton, which could be implicated in sodium channel trafficking. In separate validation samples, changes in RAC3 and TAO3 were verified using multiple-reaction monitoring mass spectrometry targeting with isotopic standards.

Conclusions: These data demonstrate that aldosterone dynamically alters the urinary exosome content in humans, including those involved in actin-cytoskeleton regulation. Furthermore, exosomal protein assays may provide a useful physiologic biomarkers in future clinical studies.

Funding: NIDDK Support

SA-PO679
Higher Pre-ESRD Visit-to-Visit Variability in Systolic Blood Pressure Is Associated with Increased Post-ESRD Mortality in Advanced CKD Patients Transitioning to Dialysis

Background: Higher systolic blood pressure visit-to-visit variability (SBV) is associated with higher mortality. However, little is known about the association of pre-ESRD SBV with outcomes after dialysis initiation.

Methods: We identified 17,994 US veterans with advanced CKD transitioning to dialysis between 10/2007-9/2011 who had at least 3 outpatient BP measurements to calculate SBV using the intraindividual standard deviation (SD) of all SBP values during the last 1 year before dialysis initiation. Associations of SD quartiles (<11.6, 11.6-15.6, 15.7-20.3, ≥20.4 mmHg) with post-ESRD all-cause and cause-specific mortality were examined using Cox (for all-cause) and competing risk (for cause-specific mortality) regressions and cubic procedures partitioned subjects into three groups, according to BP response during the active intensification period: 1 mildly elevated baseline mean SBP and minimal visit-to-visit SBP variability (mild reducers); 2) moderately elevated baseline mean SBP and moderate visit-to-visit BP variability (modest reducers); and 3) very elevated baseline mean SBP with very large visit-to-visit BP variability during intensification (large reducers). Compared to mild reducers, modest reducers had a higher adjusted risk of death, MVE, and stroke.

Conclusions: Among persons with prior lacunar stroke, baseline SBP and large SBP and DBP variability during anti-hypertensive treatment intensification can identify distinct groups of persons at higher risk of adverse outcomes.

Funding: NIDDK Support

SA-PO680
Patterns of Blood Pressure Response during Intensive BP Lowering in the Secondary Prevention of Small Subcortical Strokes (SPS3) Trial

Methods: We used an unsupervised, group-based cluster procedure (machine learning) to identify distinct patterns of BP change among 1,331 participants in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial previously randomized to intensive anti-hypertensive therapy (target SBP <130 mm Hg) after lacunar stroke.

Results: Among persons undergoing active, aggressive BP lowering, the cluster procedure partitioned subjects into three groups, according to BP response during the active intensification period: 1 mildly elevated baseline mean SBP and minimal visit-to-visit SBP variability (mild reducers); 2) moderately elevated baseline mean SBP and moderate visit-to-visit BP variability (modest reducers); and 3) very elevated baseline mean SBP with very large visit-to-visit BP variability during intensification (large reducers). Compared to mild reducers, modest reducers had a higher adjusted risk of death, MVE, and stroke.

Conclusions: Among persons with prior lacunar stroke, baseline SBP and large SBP and DBP variability during anti-hypertensive treatment intensification can identify distinct groups of persons at higher risk of adverse outcomes.

Funding: NIDDK Support

Reference:


Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author. 786A
SA-PO682

Profiles of Systolic Blood Pressure Patterns in Patients Who Died in the First Year of Hemodialysis - Marta Reviriego-Mendoza,1 Peiran Yu,1 Dugan Maddux,1 Danqing Xu,1 Jochen G. Raimann,2 Xiaoling Ye,2 Hanjie Zhang,2 John W. Larkin,2 Jeroen Kooman,1 Frank van der Sande,3 Len A. Usuy,3 Peter Kotanko,3,4 Franklin W. Maddux,1a Fresenius Medical Care North America, MA; 2Renal Research Inst, NY; 3Maastricht Univ Medical Center, Netherlands; 4ibaah School of Medicine at Mount Sinai, NY.

Background: Previous studies indicate that lower predialysis systolic blood pressure (SBP) is a risk factor for short term mortality in HD patients (pts) (Maddux D, et al., ASN 2014 & 2015). We aimed to understand the profiles of SBP in pts who died during the incident year of HD.

Methods: Data from 192,379 Fresenius Medical Care North America pts during 2008 to 2014 was analyzed. Pts were grouped according to mean SBPs at 0-15, 30-45, and 90-105 days after HD initiation. SBP groups included low (LSBP; <110mmHg), normal (NSBP; 110 to <140mmHg), high (HSBP; 140 to ≤180mmHg), and very high (VHSBP; >180mmHg) in each of the periods. The respective percent (%) mortality in each SBP group for periods of 0-29, 30-89, and 90-364 days from the start of HD was computed. The % mortality relative to LSBP was calculated to compare the relative difference in % mortality between SBP groups.

Results: SBP profiles of pts who died during the incident year of HD are shown in Figure 1. We observed two major findings: i) The 2nd and 3rd months after initiating HD were the timeframe where the % mortality is highest for all SBP groups, particularly for the LSBP group (Figure 1A). ii) When compared to NSBP, the relative difference in % mortality appears to be 2.8 to 4 times higher in patients with LSBP, and lowest in pts with HSBP and VHSBP (Figure 1B).

Conclusions: Our findings indicate that relative mortality rates are highest in pts with LSBP in the first year on HD, particularly during the first 90 days of HD. Pts with SBP 140 to ≤180mmHg appear to have lower relative mortality compared to other SBP groups.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO683

Results of the BID Pilot Study - D. Miskulin,1,2 R. Schrader, Jennifer J. Gassman,3 Manisha Jambh,1 David W. Ploth,4 Mahboob Rahman,5 Lavinia A. Negrea,6 Raymond Y. Kwong,7 Philip Zager,1,2 Tufts; 3Cleveland Clinic; 4UPMC; 5MUSC; 6CHRU; 7BWH; 8UNM; 9DCI.

Background: Optimal predialysis systolic blood pressure (SBP) for hemodialysis (HD) patients is unknown. The current KDOQI guideline is SBP <140 mmHg. However, SPRINT results suggest that lower SBP may be beneficial. We randomized to 8 weeks of the DASH diet or control diet had pre- and post-intervention 24-hour urine samples. Nocturnal change in SBP was defined as daytime mean SBP minus nighttime mean SBP expressed as a percentage of daytime mean SBP. We report a negative nocturnal change value as “dip”. Median regression was used to compare pre-post changes in nocturnal dip in SBP and nighttime SBP between treatment arms. We also tested for interaction effects between diet, race (black versus white), and albumin excretion rate (AER ≥7 mg/day versus <7 mg/day) on changes in SBP.

Methods: DASH multicenter, randomized controlled feeding trial data were used to examine whether the DASH diet, compared to a control diet, enhances nocturnal dip in SBP and lowers nighttime SBP. A total of 202 pre-hypertensive and hypertensive adults randomized to 8 weeks of the DASH diet or control diet had pre- and post-intervention ambulatory BP data and pre-intervention 24-hour urine samples. Nocturnal change in SBP was defined as daytime mean SBP minus nighttime mean SBP expressed as a percentage of daytime mean SBP. We report a negative nocturnal change value as “dip”. Median regression was used to compare pre-post changes in nocturnal dip in SBP and nighttime SBP between treatment arms. We also tested for interaction effects between diet, race (black versus white), and albumin excretion rate (AER ≥7 mg/day versus <7 mg/day) on changes in SBP.

Results: Mean age was 45±10 years, 51% were men, 59% were black, and 26% had AER ≥7 mg/day.

Conclusions: DASH enhanced nocturnal dip in SBP and reduced nighttime SBP in blacks but not whites and caused larger reductions in nighttime SBP in subjects with AER ≥7 mg/day than <7 mg/day. Our study suggests the DASH diet may improve nocturnal dipping and nighttime BP in blacks and adults with low-grade albuminuria.

Funding: NIDDK Support

SA-PO684

Effect of the DASH Diet on Nocturnal Dipping and Nighttime Blood Pressure: Moderating Role of Race and Albumin Excretion Rate - Crystal C. Tyson,1 Huiman Barnhart,2 Shelly K. Sapp,2 Pao-Hwa Lin,3 Laura P. Svetkey,1,3 1Medicine, Duke Univ, Durham, NC; 2Duke Clinical Research Inst, Durham, NC; 3Stedman Nutrition & Metabolism Center, Duke Univ, Durham, NC.

Background: Blunted nocturnal dip in blood pressure (BP) and elevated nighttime BP are independently associated with increased cardiovascular mortality. The effect of the DASH diet on nocturnal dip in BP is not known, nor is whether response differs by race or presence of low-grade albuminuria, which may be a marker for subclinical kidney disease.

Methods: DASH multicenter, randomized controlled feeding trial data were used to examine whether the DASH diet, compared to a control diet, enhances nocturnal dip in SBP and lowers nighttime SBP. A total of 202 pre-hypertensive and hypertensive adults randomized to 8 weeks of the DASH diet or control diet had pre- and post-intervention ambulatory BP data and pre-intervention 24-hour urine samples. Nocturnal change in SBP was defined as daytime mean SBP minus nighttime mean SBP expressed as a percentage of daytime mean SBP. We report a negative nocturnal change value as “dip”. Median regression was used to compare pre-post changes in nocturnal dip in SBP and nighttime SBP between treatment arms. We also tested for interaction effects between diet, race (black versus white), and albumin excretion rate (AER ≥7 mg/day versus <7 mg/day) on changes in SBP.

Results: Mean age was 45±10 years, 51% were men, 59% were black, and 26% had AER ≥7 mg/day.

Conclusions: DASH enhanced nocturnal dip in SBP and reduced nighttime SBP in blacks but not whites and caused larger reductions in nighttime SBP in subjects with AER ≥7 mg/day than <7 mg/day. Our study suggests the DASH diet may improve nocturnal dipping and nighttime BP in blacks and adults with low-grade albuminuria.

Funding: NIDDK Support
SA-PO685

Hypertension: Clinical

SA-PO687

Hypertension: Clinical

SA-PO688

Hypertension: Clinical

SA-PO689

Hypertension: Clinical

SA-PO690

Hypertension: Clinical

SA-PO691

Hypertension: Clinical

SA-PO692

Hypertension: Clinical

SA-PO693

Hypertension: Clinical

SA-PO694

Hypertension: Clinical

SA-PO695

Hypertension: Clinical

SA-PO696

Hypertension: Clinical

SA-PO697

Hypertension: Clinical

SA-PO698

Hypertension: Clinical
Lateralization Index of Adrenal Vein Sampling Is a Predictor of Blood Pressure Improvement after Adrenalectomy for Primary Aldosteronism Miho Tagawa,1 Muriel Ghosn,2 Scott O. Tretotola,3 Heather Wachtel,2 Debbie L. Cohen,2 Raymond R. Townsend.2 1Nara Medical Univ; 2Univ of Pennsylvania.

Background: Adrenal Vein sampling (AVS) is recommended in primary aldosteronism (PA) to determine if lateralization occurs. Lateralization index (LI) > 4 is considered a positive result. It is unclear however what LI value predicts BP response.

Methods: This is a retrospective observational study on patients who underwent AVS and adrenalectomy for PA at Penn from 1997 to 2015. Improvement of BP was defined as reduction in systolic BP (SBP) >10mmHg with same number of antihypertensives, or SBP within 10mmHg with reduction in number of antihypertensives. Data were analyzed using multivariable logistic regression analyses.

Results: There were 169 patients who underwent AVS and adrenalectomy. Mean age was 53 (46-60) years, 64% were male, 34% were African American, 55% were Caucasian. LI of AVS was 11.9 (8.1-22.2) and 8.0 (5.1-18.5) for patients with or without BP improvement at 0-6 months, respectively (p=0.16). After adjustment for known predictors of BP improvement after adrenalectomy, LI >9 was independently associated with BP improvement at 0-6 months.

Conclusions: At 0-6 months after adrenalectomy, LI >9 was associated with modest tendency for BP improvement (OR 0.95 CI) was 5.7 (0.3-96.6). LI >9 may be a useful predictor for short-term improvement in BP after adrenalectomy for PA.

PMID: 28923183 | DOI: 10.1681/ASN.2016040345

Kidney Failure in Patients with Unilateral Atherosclerotic Renal Artery Stenosis - Effect of Renal Angioplasty A xo Saeed, Elzbieta Nowakowska-Fortuna, Gert Jensen, Hans V. Herlitz, Gregory S. Gurun, Sahlgrenska Univ Hospital; Sahlgrenska Academy, Dept of Molecular and Clinical Medicine, Inst of Medicine/Nephrology, Gothenburg, Sweden.

Background: The objective of the study i to evaluate the effect of percutaneous transluminal renal angioplasty (PTRA) on split renal function (SRF) in patients with unilateral atherosclerotic renal artery stenosis (ARAS).

Methods: Retrospective analysis of all consecutively examined patients at our Centre with significant ARAS undergoing PTRA during 2002-2007. A significant ARAS was defined as a lesion with a trans-stenotic mean arterial pressure gradient (MAPG) of at least 10 mmHg or a diameter stenosis > 60%. Ambulatory (24 h) SBP (ASBP) and DBP (ADBP) and calculated SRF using %99mTc-DTPA renal scintigraphy were evaluated before (baseline) and 4 weeks after PTRA.

Results: ASBP and ADBP were significantly lower 4 weeks after PTRA compared to baseline levels (Table 1). Although total estimated glomerular filtration rate (eGFR, 4-variable MDRD) had not changed by PTRA, analysis of SRF showed significantly increased eGFR in stenotic kidneys and comparable decreases in eGFR in non-stenotic kidneys 4 weeks after PTRA (Table 1).

Table 1. Effect of PTRA on ambulatory blood pressure, kidney function and split renal function.

<table>
<thead>
<tr>
<th>Baseline (n=52)</th>
<th>4 weeks after PTRA (n=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07±0.3</td>
<td>1.07±0.2</td>
</tr>
<tr>
<td>Male sex</td>
<td>4.48±2.4</td>
<td>4.04±1.9</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>0.79±0.08</td>
<td>0.76±0.09</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.89±0.08</td>
<td>0.89±0.08</td>
</tr>
<tr>
<td>eGFR (MDRD) ml/min/1.73m2</td>
<td>57±21</td>
<td>56±21</td>
</tr>
<tr>
<td>eGFR stenotic kidney, ml/min/1.73m2</td>
<td>22±14</td>
<td>20±17</td>
</tr>
<tr>
<td>eGFR non-stenotic kidney, ml/min/1.73m2</td>
<td>37±16</td>
<td>34±15</td>
</tr>
</tbody>
</table>

Conclusions: In patients with unilateral ARAS, PTRA significantly improved eGFR in stenotic kidneys and decreased filtration in contralateral, non-stenotic kidneys. These potentially beneficial effects may not be apparent when total kidney function remains stable. The clinical significance of these findings needs to be evaluated further.

Funding: Government Support - Non-U.S.

Systolic Blood Pressure Patterns during the Incident Year of Hemodialysis Peiran Yu,1 Dugan Maddux,2 Danqing Xu,1 Jochen G. Raimann,2 Marta Reviriego-Mendoza,1 John W. Larkin,3 Jeroen Kooman,4 Frank van der Sande,3 Len A. Usvyat,5 Peter Kotanko,6 Franklin W. Maddux.1 Fresenius Medical Care North America;2 Renal Research Inst;3Maastricht Univ Medical Center, Netherlands;4Icahn School of Medicine at Mount Sinai.

Background: KDOQI guidelines recommend managing systolic blood pressure (SBP) in hemodialysis (HD) patients to achieve a pre-HD SBP <140/90mmHg and post-HD SBP <130/80mmHg. Despite this, previous studies suggest that lower pre-HD SBPs are associated with increased risks for mortality (Robinson BM, et al. Kidney Int. 2012 Sep;82(5):570-80). We aimed to understand SBP patterns in those who survived or died during the first year of HD.

Methods: Data from 192,379 incident HD patients during 2008 to 2014 was analyzed. Patients were grouped by SBP level at 0-15, 30-45, 90-105, and 365-380 days after the initiation of HD. SBP groups included low (LSBP; <110mmHg), normal (NSBP; 110 to 130mmHg), elevated (ESBP; 130 to 140mmHg), and high (HSBP; >140mmHg).

Results: During the first year of HD, SBP <130/80mmHg. Despite this, previous studies suggest that lower pre-HD SBPs are associated with increased risks for mortality (Robinson BM, et al. Kidney Int. 2012 Sep;82(5):570-80). We aimed to understand SBP patterns in those who survived or died during the first year of HD.

Conclusions: Renal denervation may lower systolic BP in patients with treatment-resistant hypertension, but the results are highly variable. Further research is needed to clarify its role in improving clinical outcomes.

Funding: Other NIH Support - Agency for Healthcare Research and Quality.

Mean SBP Change (mm Hg)

Favors RDV | Favors Control

Author year | Follow-up (months) | Control Group | Baseline SBP in RDN arm | SBP Change (95% CI)
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Riso, 2015</td>
<td>6 Medications</td>
<td></td>
<td>156</td>
<td>-1.9 (6.2, 9)</td>
</tr>
<tr>
<td>Arce, 2015</td>
<td>6 Medications</td>
<td></td>
<td>160</td>
<td>-6.6 (13.2, -1.1)</td>
</tr>
<tr>
<td>Karia, 2015</td>
<td>6 Medications</td>
<td></td>
<td>156</td>
<td>-9.7 (18.4, -0.9)</td>
</tr>
<tr>
<td>Schiermeier,2015</td>
<td>6 Medications</td>
<td></td>
<td>156</td>
<td>-5.5 (10.9, -0.9)</td>
</tr>
<tr>
<td>Deich, 2018</td>
<td>6 Sham procedure</td>
<td></td>
<td>156</td>
<td>-3.8 (8.5, 1.5)</td>
</tr>
<tr>
<td>Shatt, 2017</td>
<td>6 Sham procedure</td>
<td></td>
<td>159</td>
<td>-11.5 (9.3, 1.2)</td>
</tr>
<tr>
<td>Symplity, 2020</td>
<td>Unspecified</td>
<td></td>
<td>156</td>
<td>-6.0 (7.1, 1.9)</td>
</tr>
<tr>
<td>Rosi, 2016</td>
<td>12 Medications</td>
<td></td>
<td>160</td>
<td>2.0 (4.2, 2)</td>
</tr>
<tr>
<td>Rosi, 2014</td>
<td>12 Sham procedure</td>
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<td>156</td>
<td>-1.5 (7.8, 4.8)</td>
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<td>Office</td>
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<td>156</td>
<td>1.9 (6.0, 2.0)</td>
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<td>Riso, 2015</td>
<td>6 Medications</td>
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<td>Pahokahale, 2012</td>
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<td>170</td>
<td>2.5 (3.8, 0.8)</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
hypertension outside of a study setting. Future studies could consider altering the format of the AOBP by increasing the frequency of measurements and/or including algorithms to deal with outlying data.

SA-PO694
Renal Artery and Parenchymal Changes after Renal Denervation
Margreet F. Sanders, Pieter Jan Van Doormaal, Peter J. Blankstein. 1 Dept of Nephrology & Hypertension, Univ Medical Center Utrecht, Utrecht, Netherlands; 2 Dept of Radiology, Univ Medical Center Utrecht, Utrecht, Netherlands.

Background: Renal denervation (RDN) is a treatment for difficult to control hypertension, with the intent to disrupt sympathetic renal nerves and lower blood pressure. Relatively little is known about the incidence of renal injuries after RDN. The aim of this study was to investigate the incidence of renal artery and parenchymal changes after RDN with contrast enhanced magnetic resonance angiography (MRA).

Methods: The present study is an initiative of the European Network COordinating research on Renal Denervation (ENCORED), a collaboration of hypertension expert centers performing RDN. Patients treated with endovascular radiofrequency RDN and with available MRA both before and after RDN were included. Pre and post scans were evaluated in random order by two independent, blinded radiologists. Primary outcome was the change in renal artery and parenchyma after RDN.

Results: Ninety-six patients were included. Indication for RDN was treatment resistant hypertension in all patients. After a median time of 366 days (IQR 185) post RDN, MRA showed a new stenosis (25-49% lumen reduction) in two patients. Furthermore, there was progression of pre-existing lumen reduction (from <25% to 50-74%) in one patient. In one of the three patients, we concluded from procedural angiography that ablations were applied near the location of the observed stenosis. The incidence of vascular changes 12 months after RDN was 3.1% (95% confidence interval -0.4; 6.7%). No other renal vascular or parenchymal changes were observed.

Conclusions: Twelve months after RDN, the incidence of new or progression of pre-existing vascular abnormalities is 3.1%, when assessed by MRA. Ablations were applied near the observed stenosis in only one patient. No renal parenchymal changes were found.

SA-PO695
Serum Irisin Levels and Urotensin II Levels Are Independent Determinant Factors of Blood Pressure in Patients with Preeclampsia
Liji Zhang, Ai Hua Zhang. Dept of Nephrology, Peking Univ Third Hospital, Beijing, China.

Background: Irisin is a newly identified myokine secreted from skeletal muscle that can promote energy expenditure and alleviate insulin resistant. The aims of this study were to observe irisin level and urotensin II (UII) in serum and placenta in normal pregnant and preeclamptic women, investigate the relationship between serum irisin and UII, and their association with blood pressure.

Methods: A total of 71 pregnant subjects were recruited, including 32 healthy and 39 preeclamptic pregnant women. Serum irisin were measured by enzyme-linked immunosorbent assay, and serum UII concentrations were measured by radioimmunoassay analysis. Expressions of fibronectin type III domain-containing protein 5 (FNDC5) (irisin precursor) and UII in placenta specimens were performed using immunohistochemistry (IHC) and western blot.

Results: There was no difference of serum irisin levels between preeclamptic patients with normal controls (157.78±21.96ng/ml vs. 159.88±16.94ng/ml, P>0.05). While serum UII was significantly higher in preeclamptic women than normal pregnancy (35.59±21.72pg/ml vs 24.64±14.20pg/ml, P=0.041). FNDC5 and UII expressions were both upregulated in placental tissue of preeclamptic pregnancy by IHC and western blot analysis. In patients with preeclampsia, serum irisin was negatively associated with systolic and diastolic blood pressure (r=−0.340, P=0.005;r=−0.304, P=0.012), while serum UII was positively associated with systolic blood pressure (r=0.286, P=0.033). There was no relationship between serum UII and irisin level in normal pregnancy and preeclampsia patients Serum irisin and UII, urinary protein level, BMI and serum creatinine are independent determinants of blood pressure in preeclampsia by multiple regression analysis.

Conclusions: Serum irisin and UII are independent determinants of blood pressure in preeclampsia.

SA-PO696
Comparison of Efficacy of Atenolol versus Lisinopril in Hypertensive Patients on Hemodialysis: A Randomized Control Trial
Zara Nisar. Nephrology, Khyber Teaching Hospital, Peshawar, KPK, Pakistan.

Background: The Aim of this study is to establish the efficacy of these drugs in terms of cardiovascular events in Hypertensive patients on hemodialysis, and maintenance of Blood Pressure.

Methods: 50 patients were randomized to open-label Atenolol group and 50 patients were randomized to open-label Lisinopril group, each administered 2 times per week after dialysis. Blood pressure was monitored and recorded and was controlled to less than 140/90 mmHg with medications and sodium restriction. The primary outcome was to look for serious cardiovascular events within 12 months.

Results: Serious Cardiovascular events occurred in 20 patients who had 26 episodes in the Atenolol group as compared with the lisinopril group in which 35 patients nearly had 61 episodes. The serious cardiovascular events Myocardial Infarction, heart failure, ventricular arrythmias and stroke were found in 12 patients in atenolol group with 16
episodes where as 21 patients in Lisinopril group with 26 episodes. Patients on Atenolol were found to recover better in hospital setup as compared to those on Lisinopril in these cardiovascular events. The ambulatory 24-h BP was found to be similar in both groups. However, the monthly measured BP was found to be higher in Lisinopril group.

**Conclusions:** Atenolol has better coverage for BP maintenance and preventing Cardiovascular events in hemodialysis patients as compared to Lisinopril in our setup. Note: This study is done in Khyber teaching hospital, Peshawar, Pakistan and here 2 times dialysis regime is followed.

SA-PO697

A Novel Method of Determining Adiposity and Its Relationship with Blood Pressure in the Modification of Diet in Renal Disease Study

Preeva Tushar Shah, Zeid Khitan, Prasanna Santhanam, Joseph I. Shapiro. Medicine, Marshall Univ, Huntington, WV.

**Background:** Obesity is a known risk factor for hypertension and other diseases. The Body Mass Index (BMI, kg/m^2) is the most commonly used method of assessing obesity, yet this approach does not directly measure the quantity of fat. Because urinary creatinine excretion (UCrV) is believed to be a marker of skeletal muscle mass, we hypothesized that a ratio of the BMI to UCrV (BMI/UCrV) might provide a better index of adiposity. Specifically, we developed this ratio to attempt to emphasize non-muscular body size by normalizing for UCrV. We next chose to examine whether this ratio might correlate more strongly with systolic (SBP), diastolic (DBP), and pulse pressure (PP) within participants of the Modification of Diet in Renal Disease (MDRD) Study.

**Methods:** A retrospective analysis of the MDRD data identified 840 unique patients, ages 19-71. Data was extracted and imported into R Studio Correlation analysis between recorded components of blood pressure (Systolic, Diastolic, and Pulse Pressure) and the BMI/UCrV ratio was executed.

**Results:** We found that although systolic (SBP) and diastolic blood pressure (DBP) was predicted similarly by the BMI/UCrV ratio and BMI, the BMI/UCrV ratio predicted pulse pressure (PP) better than either BMI or UCrV alone.

**Conclusions:** We found that a novel indicator of adiposity, the BMI/UCrV ratio, correlated better with pulse pressure than either BMI or UCrV alone. It validated, this may be a useful clinical parameter to track and address.

**Funding:** Other NIH Support - NHLBI, Private Foundation Support, Clinical Revenue Support

**SA-PO698**

Dietary Sodium and Potassium Intake in a Referred Population with Difficult to Control Hypertension

Simon D.G. Parlory,1 Swapnil Hiremath,2,5 Marcel Ruzicka,1,2 Medicine, Univ of Ottawa, Ottawa, ON, Canada;
Nephrology, Univ of Ottawa, Ottawa, ON, Canada.

**Background:** High sodium intake and low potassium intake in the diet are important risk factors for the development and persistence of hypertension. NHANES and Health Canada data report higher than recommended consumption of sodium in the general population, but little data exists examining sodium intake in referred patients with difficult to control hypertension (DCHT). In this chart review, we report the dietary sodium and potassium intake in such a population.

**Methods:** This retrospective observational study included patients over 18 years of age referred to The Ottawa Hospital Renal Hypertension Clinic for management of DCHT. Patients were included if they had a documented 24 hour urinary electrolyte measurement, which was used to estimate daily sodium and potassium intake. We used current guidelines from American Heart Association (AHA, <65 mmol/day Na; >120 mmol/day K), Canadian Hypertension Education Program (CHEP, <87 mmol/day Na; >120 mmol/day K), and World Health Organization (WHO, <87 mmol/day Na; >90mmol/day K) for dietary goals.

**Results:** Of the 556 patients screened for inclusion, 95 (17.1%) had a 24 hour urinary sodium intake consistent, with a mean intake of 142 mmol/day. 10 patients (10.5%) met the AHA target and 21 patients (22.1%) met the CHEP and WHO target for sodium intake. 33 patients had a 24 hour urinary potassium documented, with a mean of 60.7 mmol/day. 2 patients (6.1%) met the AHA target while 5 patients (15.2%) met the WHO target for potassium intake.

**Conclusions:** Even in a referred population of patients with DCHT, the dietary sodium intake is at an acceptable threshold for only a minority of patients, with the dietary potassium intake being acceptable for an even smaller proportion. While this may represent a selection bias, where poor intake results in higher blood pressure, it does represent a promising opportunity for intervention.

**SA-PO699**

Hypotension and Vasopressor Use during Elective Surgery in Patients Advised to Continue Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Medications on the Day of Surgery

Katherine Mikovna Seovner,1 Nicole M. Benson,2 Alexander F. Friend,3 Emily Stebbins.2 Internal Medicine, Brown Univ, Providence, RI; McLean Hospital Psychiatry, Massachusetts General Hospital, Boston, MA;1 Anesthesiology, Univ of Vermont Medical Center, Burlington, VT.

**Background:** Continued use of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) on the day of surgery is associated with intraoperative hypotension requiring vasopressor therapy. Here we assess the efficacy of the recommendation to hold ACE-I/ARB medications in preventing intraoperative hypotension. We hypothesized that the recommendation to continue as well as the patient’s report of having taken an ACE-I/ARB medication on the day of surgery would be associated with increased intraoperative hypotension and vasopressor use.

**Methods:** We retrospectively studied 629 patients aged 50-75 on ACE-I/ARB therapy undergoing elective surgery with general anesthesia. Independent variables were (a) whether the patient was advised to hold or continue their ACE-I/ARB medication and (b) whether the patient reported having taken an ACE-I/ARB medication on the day of surgery. We also assessed invasiveness of surgery. Outcomes included (a) intraoperative vasopressor use and (b) lowest systolic blood pressure (SBP) during surgery.

**Results:** The advice to hold ACE-I/ARB was associated with intraoperative severe hypotension (SBP <65) (OR: 0.977; CI: 0.943 – 0.993). A patient’s report of taking an ACE-I/ARB was associated with vasopressor use (OR:1.663; CI: 1.383 – 2.340) and moderate hypotension (SBP <85) (OR: 1.5; CI: 1.069 to 2.105). Both vasopressor use and intraoperative hypotension were associated with surgery invasiveness (P<0.001).

**Conclusions:** Severe hypotension is associated with the recommendation to hold ACE-I/ARB therapy; however, a patient’s report of having held the treatment was not. As hypotension correlated to surgery invasiveness, we postulate that the recommendation to hold the medications was most commonly made to patients planned for invasive surgery and thus at higher risk for hypotension; this recommendation, however, was unable to prevent it.

**SA-PO700**

Neurocognitive Function in Children with Primary Hypertension

Marc Lands1; Donald Lee Batesky,2 Juan C. Kapferman; Joshua A. Samuels,4 Stephen R. Hooper,4 Bonita E. Falkner,5 Shari R. Waldstein,6 Peter G. Szilagyi,5 Hongyue Wang,1 Jennifer Staskiewicz,1 Heather Adams,1,2 Emory Univ;1 Maimonides Medical Center;2Univ of Texas at Houston;3Univ of North Carolina;4Thomas Jefferson Univ;5Univ of Maryland, Baltimore County;6Univ of California at Los Angeles.

**Background:** While young hypertensive adults have lower neurocognitive test (NT) performance compared with normotensive controls, data on neurocognition in pediatric primary hypertension (HTN) are limited. Our objective was to compare NT performance of children with primary HTN to that of normotensive controls. We also explored potential interactions of HTN with disordered sleep, a highly comorbid condition.
Methods: 75 children (10–18 y) with newly diagnosed, untreated HTN and 75 frequency-matched normotensive controls had been prospectively enrolled in a study of cognition in primary HTN. Subjects completed tests of general intelligence, attention, memory, executive function, and processing speed. In addition to medical and demographic variables, parents completed the Pediatric Sleep Questionnaire (PSQ).

Results: By design, the HTN and control groups did not differ significantly in sex, maternal education, or obesity. They were also found to be similar in age, income race, ethnicity, anxiety, depression, cholesterol, glucose, insulin, and C-reactive protein. HTN subjects had higher PSQ scores (p=0.04). In multivariate analyses, HTN was independently associated with worse performance on the Rey Auditory Verbal Learning Test (p=0.012), CogState Groton Maze Learning Test delayed recall (p=0.002), Grooved Pegboard (p=0.045), and Wechsler Abbreviated Scales of Intelligence Vocabulary (p=0.016). Results also indicated a significant interaction between PSQ score and HTN (p=0.04), such that HTN heightened the association between increased disordered sleep and worse executive function in the HTN group.

Conclusions: Youth with primary HTN demonstrated significantly lower NT performance compared with normotensive controls, particularly on measures of attention, memory, and executive functions. Further study is needed to determine if these performance differences will reverse with antihypertensive therapy.

Funding: Other NIH Support - NHLBI

SA-PO701

Extracellular Water Is an Independent Determinant of Uncontrolled and Resistant Hypertension in CKD: The Nephroptest Cohort Study

Emmanuelle Vidal-Petiot,1,2 Marie Metzger,1 Jean-Jacques Boffa,1 Jean-Philippe Haymann,1 Eric Thévert,1 Pascal Houillier,1 Benoît Stengel,3 Francois Vrtovský,2 Martin Flammant,1,2 *Physiology and Nephrology, Bichat, APHP, Paris, France; 2Paris Diderot Univ, Sorbonne Paris Cité, Paris, France; 3Inserm U1019, Villejuif, Paris, France; *Physiology and Nephrology, Toulouse, APHP, Toulouse, France; *Physiology and Nephrology, HEPG, APHP, Paris, France.

Background: Hypertension is highly prevalent during chronic kidney disease (CKD) and in turn worsens CKD progression. We aimed to describe the determinants of uncontrolled and resistant hypertension, including extracellular water (ECW) during CKD.

Methods: We analysed baseline data from the Nephroptest cohort study. Patients with CKD stage 1 to 5 underwent thorough renal exploration including measurements of GFR (clearance of 125I-iodoactetate) and of extracellular water (ECW, volume of distribution of the tracer). Hypertension was defined as blood pressure (BP, average of three office measurements) above 140/90 mmHg or the use of antihypertensive drugs. Resistant hypertension was defined as uncontrolled BP (140/90) despite 3 drugs including a diuretic, or more drugs regardless of BP level.

Results: In 2015 patients (mean age 59±15 years, 67% male, mean GFR 42±15 mL/min/1.73m²), prevalence of hypertension was 88.4%. In hypertensive patients, the mean number of treatments was 2.7±1.4, and prevalences of uncontrolled and resistant hypertension were 44.1 and 32.4%, respectively. In multivariable analysis, older age, higher albuminuria, diabetic nephropathy and the absence of aldobulminoster blockers were independently associated with uncontrolled BP. Older age, lower GFR, higher albuminuria, and BMI, African origin, diabetes and diabetic and glomerular nephropathies were associated with resistant hypertension. In addition, ECW was independently associated with both uncontrolled BP [OR for 1L increase, 1.06, 95% confidence interval (CI) 1.02-1.11] and resistant hypertension [OR 1.08, 95% CI 1.03-1.14].

Conclusions: A lower GFR is associated with hypertension severity but not with BP control. A higher burden of comorbidities increases the risk of uncontrolled and resistant hypertension during CKD, which advocates for the large use of diuretics in this population.

SA-PO702

Plasma Peptidomics Based Multivariable Model for Identification of Mediators Involved in Hypertension

Joachim Jankowski, Vera Jankowski, Ina Jankowski, Inst for Molecular Cardiovascular Research, Univ Hospital RWT Aachen, Aachen, Germany.

Background: Hypertension is a major risk factor for cardiovascular disease and is also a risk factor for other end-organ diseases. Despite of advancements in lowering blood pressure, the best approach to lower it, remains controversial due to the lack of information on its development. We therefore, performed plasma peptidomics to identify the markers discriminating hypertensive from normotensive.

Methods: Plasma samples from hypertensive and normotensive subjects were used for the study. We performed LC-MS/MS analyses of the plasma samples. Hypertension specific plasma peptides were identified and a model was developed using least absolute shrinkage and selection operator logistic regression. The underlying peptides were identified and to get an insight in to the mechanisms, pathway analysis was performed.

Results: By comparison of plasma samples, 27 biomarkers were identified discriminating hypertensives from normotensives. 70% of the features selected were found to be involved in the regulation of the vascular tone and selection operator logistic regression. The underlying peptides were identified and to get an insight in to the mechanisms, pathway analysis was performed.

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

792A
Effects of Blood Pressure Control in Uncontrolled Grade 1 Hypertension

Xiaohui Qin,1 Youshao Li,1 Binyan Wang,1 Yong Huo,2 Genfu Tang,2 Mingli He,4 Delu Yin,2 Xiping Xu,2 Xin Xu,2 Fan Fan Hou1 1Nanjing Hospital, Southern Medical University; National Clinical Research Center for Kidney Disease; 2Peking Uni First Hospital; Anhui Medical Univ; 4First People’s Hospital, Lianyungang.

Background: Effects of blood pressure (BP) control (<140/90 mmHg) in patients with grade 1 hypertension are unclear. We aimed to examine the effect of BP control in prevention of cardiovascular events and deaths in patients with grade 1 hypertension in the China Stroke Primary Prevention Trial (CSPPT).

Methods: A total of 3,187 patients, with a median antihypertensive treatment duration of 4.6 years, were divided into subgroups according to (1) the percentage of on-treatment visits in which BP was controlled (<140/90 mmHg); or (2) the time-averaged mean SBP/DBP levels achieved throughout the treatment period or up to the occurrence of an event.

Results: Compared with those with BP control <25% of the on-treatment visits (3.7%), the incidence of first stroke decreased progressively as the percentage of BP control increased (≥75%, 1.8%; HR, 0.47; 95% CI: 0.21-1.07; 50-<75%, 1.3%; 0.34; 0.16-0.73; ≥75%, 1.3%; 0.36; 0.16-0.83; P for trend =0.019).

Conclusion: BP control is associated with the risk of stroke.

Complement in Renal Disease—Potential Effect during Pathogenesis of Hypertension

Christoph Daniel,1 Kerstin Benz,2 Maike Julia Buettner,3 Kerstin U. Amann,1 Laura Alina Roesser,1 Lisa Schmidtgen,1 Nephrology, FAU Erlangen-Nürnberg, Erlangen, Germany; 2Pediatric Nephrology, FAU Erlangen-Nürnberg, Erlangen, Germany.

Background: Complement deposition is frequently observed in kidney biopsies of patients with hypertensive renal disease, but an association of hypertension and complement deposition with target organ damages and the involvement of complement in the pathogenesis of hypertensive nephropathy has not been investigated.

Methods: In this retrospective study archival human renal biopsies from 230 patients with known hypertension and 80 control patients with non-hypertensive renal diseases were investigated using immunohistochromistry and semi-quantitative scores and the results were correlated with renal function. To address whether complement was only passively deposited on or also actively expressed by renal cells, complement deposition as well as C1 and C3 mRNA expression was analyzed in a rat model of hypertension i.e. the 5/6-nephrectomy rat model and control rats (n=10).

Results: Glomerular C1q and C3c complement deposition was significantly higher in hypertensive patients and rats than in non-hypertensive controls. Mean arterial blood pressure in 5/6-nephrectomy rats correlated well with the amount of C1q (r=0.790; p<0.0001) and C3c deposition (r=0.697; p<0.0003) and also with left ventricular weight (C1q: r=0.819; C3c: r=0.621; both p<0.002). C3 were not only passively deposited but also actively produced by renal cells of hypertensive rats as assessed by quantitative mRNA analysis. Of note, in hypertensive patients renal function as measured by creatinine clearance correlated significantly negative with the intensity of C1q staining (r=−0.322; p<0.001), but not with that of C3c.

Conclusion: Hypertensive nephropathy, but not other non-hypertensive renal diseases, was significantly associated with in-situ expression and deposition of complement. Since complement activation is known to have multiple disease promoting effects further investigations are needed to identify whether it is involved in the pathogenesis or progression of hypertensive nephropathy.

Preeclampsia and Severe Proteinuria during Pregnancy and Postpartum Follow-Up: Results from a High Risk Center in Brazil

Jose Paulo Siqueira Guida,1 Marcos Vinicius Sousa,2 Marilda Mazzari,2 Maria Laura Costa,3 1Dept of Gynecology and Obstetrics, State Univ of Campinas, Campinas, Sao Paulo, Brazil; 2Dept of Nephrology, State Univ of Campinas, Campinas, Sao Paulo, Brazil.

Background: Preeclampsia (PE) is a disease of pregnancy and puerperium and a leading cause of morbidity and mortality worldwide. Women with PE must be followed after delivery to evaluate long term complications as cardiovascular and renal diseases. The kidney injury may remain after delivery and the long term consequences of massive proteinuria are still unclear.

Methods: Retrospective cohort of pregnant women with proteinuria ≥2g/24h followed at UNICAMP from January 2009 to December 2013. Exclusion criteria: previous nephropathy, delivery in other center or absence of PE diagnosis. Data on demographic characteristics, laboratory findings, maternal and fetal/neonatal outcomes were recorded and analyzed with Epi Info 7.

Results: 254 women screened and 196 met the criteria for review. Of those, 32 had normal proteinuria (during pregnancy <0.3g/24h) prior to the onset of PE and were further studied. The mean age was 31±6.1 years, majority white (72%) and more than a half were multiparous. The mean proteinuria first evaluated during pregnancy (gestational age 25 weeks±7.7 weeks) was 0.16g/24h (±0.07) and after onset of PE, which happened around 33 weeks (±4.1), it rose to 3.7g/24h(±2.8) and 81% had severe PE. Gestational age at delivery was 33(±4.1) and 75% delivered by cesarean. Less than half showed up for a postpartum visit and only 12 women had quantification of proteinuria after delivery and among those, 4 had normal proteinuria (<0.15g/24h), while 8 remained proteinic (1.3±17.2g/24h). None had further than 3 months follow-up.

Conclusion: PE is a severe disease with impact in outcomes during pregnancy and child birth but also with possible long term consequences. Women who develop massive proteinuria during pregnancy may remain proteinic, and a few may develop chronic disease and must be diagnosed and referred. An accurate long term follow-up of those women is mandatory. Future studies must address follow-up of those women after puerperium, onset of other hypertension-related diseases and impact in future pregnancies.

Changes of Blood Pressure Patterns and Target Organ Damage in Patients with Chronic Kidney Disease: Results of the APRODiTe-2 Study

Ran-Hui Cha,1 Haejong Lee,2 Jung Pyo Lee,2 Eunjeong Kang,2 Yong Sun Kim,3 Sung Gyun Kim.1 1Internal Medicine, National Medical Center; 2Internal Medicine, Seoul National Univ College of Medicine; 3Internal Medicine, Seoul National Univ Boramie Medical Center; 4Internal Medicine, Hallym Univ Sacred heart Hospital.

Background: Blood pressure (BP) control is the most established practice for preventing the progression of chronic kidney disease (CKD). We examined the BP control and arterial dipping pattern changes in hypertensive patients with CKD and their effects on target organ damages.

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Background: Blood pressure (BP) control is the most established practice for preventing the progression of chronic kidney disease (CKD). We examined the BP control and arterial dipping pattern changes in hypertensive patients with CKD and their effects on target organ damages.
Methods: We recruited 378 hypertensive CKD patients from 4 centers in Korea. The patients underwent clinic and ambulatory BP monitoring at the time of enrollment and 1 year later. High clinic and ambulatory BP were defined as >140/90 mmHg and >135/85 mmHg (daytime)/>120/70 mmHg (nighttime), respectively.

Results: The BP control states at the 2 time points were as follows: true controlled (16.5, 17.5%), white-coat (2.9, 0.4%), masked (50.0, 53.3%), and sustained uncontrolled (30.6, 28.8%) hypertension. The dipping states at 2 time points were as follows: extreme-dipping (11.4, 10.8%), dipping (22.2, 20.5%), non-dipping (31.3, 34.7%), and reverse-dipping (35.0, 34.0%). Better changes (to true controlled and white-coat) of BP control states were associated with initially lower levels of serum uric acid, urea nitrogen, and proteinuria and higher estimated GFR (eGFR). When we divided the patients according to the median eGFR and proteinuria changes, more stable changes in eGFR and proteinuria were associated with better initial and follow-up BP control statuses. Moreover, better BP control and dipping (to dipper) changes were also associated with more stable eGFR and proteinuria changes. Good initial and follow-up BP control statuses were associated with less cardio-cerebrovascular events in the univariate analysis.

Conclusions: A large majority of Korean hypertensive CKD patients had uncontrolled BP and abnormal dipping patterns. Furthermore, better BP control and dipping status changes were associated with better renal function and proteinuria as well as less cardio-cerebrovascular damages.

SA-PO712

Nationwide Multicenter Kidney Biopsy Study of Japanese Patients with Type 2 Diabetes: Kengo Furushih, Yukito Uzawa, Yoshifumi Ubara, Miho Shimizu, Tadashi Toyama, Yasunori Iwata, Norihiko Sakai, Takashi Wada.

Results: A total of 252 patients with biopsy-proven DN, 67 met the selection criteria and were enrolled to investigate this relationship. In all patients, staining of nodular lesions with collagen IV, type IV collagen was decreased in cases of Green and Yellow categories in CKD heat map were significantly lower in hypertensive patients than in normotensive patients. Among 252 patients with biopsy-proven DN, 67 met the selection criteria and were enrolled to investigate this relationship. In all patients, staining of nodular lesions with collagen IV, type IV collagen was decreased in cases of Green and Yellow categories in CKD heat map were significantly lower in hypertensive patients than in normotensive patients. Multivariate analysis revealed that age but not hypertension was identified as an independent factor that associated with AL, GGS, and IF/TA. In contrast, hypertension was a factor independently associated with GV.

Conclusions: In non-CKD adults, it is likely that normal aging plays a major role in the development of scierotic renal histopathologic lesions. In contrast, hypertension may be protective against these lesions in the very elderly.

SA-PO713

Nodular Lesions in Diabetic Nephropathy: Collagen Staining and Renal Prognosis: Koki Misue, Toshiharu Ueno, Junichi Hoshino, Masayuki Yamanouchi, Noriko Hayami, Jun Wada, Hirofumi Makino, Kennei Takaiuchi, Yoshifumi Ubara.

Diabetes Mellitus, Obesity: Clinical – II

Nodular Lesions in Diabetic Nephropathy: Collagen Staining and Renal Prognosis: Koki Misue, Toshiharu Ueno, Junichi Hoshino, Masayuki Yamanouchi, Noriko Hayami, Jun Wada, Hirofumi Makino, Kennei Takaiuchi, Yoshifumi Ubara.

Background: Both renal ischemic arteriosclerosis and arterial hyperperfusion co-exist in elderly hypertensive patients. Thus, the two conflicting purposes of renal tissue perfusion maintenance and reduction of pressure overload have to be achieved for renal protection in such patients. In this study, we aimed to clarify the impacts of aging and/or hypertension in the development of sclerotic renal lesions in non-CKD adults.

Methods: Fifty-nine Japanese non-CKD autopsies, with or without hypertension, were analyzed to compare the clinicopathologic features among age groups. Arteriosclerotic lesions (AL), interstitial fibrosis/tubular atrophy (IF/TA), global glomerulosclerosis (GGS), and nodular lesions (NL) were evaluated. GGS, IF/TA, and AL were assessed in cases of Green and Yellow categories in CKD heat map were significantly lower in hypertensive patients than in normotensive patients. Multivariate analysis revealed that age but not hypertension was identified as an independent factor that associated with AL, GGS, and IF/TA. In contrast, hypertension was a factor independently associated with GV.

Conclusions: In non-CKD adults, it is likely that normal aging plays a major role in the development of scierotic renal histopathologic lesions. In contrast, hypertension may be protective against these lesions in the very elderly.

SA-PO710


Div of Nephrology and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan.

Background: Both renal ischemic arteriosclerosis and arterial hyperperfusion co-exist in elderly hypertensive patients. Thus, the two conflicting purposes of renal tissue perfusion maintenance and reduction of pressure overload have to be achieved for renal protection in such patients. In this study, we aimed to clarify the impacts of aging and/or hypertension in the development of sclerotic renal lesions in non-CKD adults.

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Conclusions: In non-CKD adults, it is likely that normal aging plays a major role in the development of scierotic renal histopathologic lesions. In contrast, hypertension may be protective against these lesions in the very elderly.

SA-PO711


Background: Excessive oral salt intake can induce hypertension. According to a large majority of Korean hypertensive CKD patients had uncontrolled BP and abnormal dipping patterns. Furthermore, better BP control and dipping status changes were associated with better renal function and proteinuria as well as less cardio-cerebrovascular damages.

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

Underline represents presenting author.
Paratubular Basement Membrane Insultative Lesions Predict Renal Prognosis in Patients with Type 2 Diabetes and Biopsy-Proven Diabetic Nephropathy

Koki Mise,1,2 Yutaka Yamaguchi,1 Junichi Hoshino,1 Akinari Sejima,1 Toshifumi Ueno,1 Noriko Hayami,1 Masayuki Yamanouchi,1 Hiroshi Sugiyama,1 Hirofumi Makino,1 Jun Wada,1 Kenmei Takaichi,1 Yoshio Sugiyama,1,2 Nephrology Center, Toranomon Hospital, Tokyo, Japan; 1Dept of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; 2Yamaguchi’s Pathology Laboratory, Matsuo, Japan.

Background: Glomerular insultative lesions are a pathological hallmark of diabetic nephropathy (DN). However, paratubular basement membrane insultative lesions (PTBML) have not attracted much attention, and the association between such lesions and the renal prognosis remains unclear.

Methods: Among 142 patients with biopsy-proven DN and type 2 diabetes encountered from 1998 to 2011, 136 patients were enrolled in this study. Patients were classified into 3 groups (Group 1: mild; Group 2: moderate; Group 3: severe) according to the extent of corticomedial and medullary PTBML. The endpoint was the death of the estimated glomerular filtration rate (eGFR) by ≥40% from baseline or commencement of dialysis for end-stage renal disease. The Cox proportional hazard model was employed to calculate hazard ratios (HRs) and 95% confidence interval (CIs) for the death-censored endpoint.

Results: During a median follow-up period of 1.8 years (IQR: 0.9-3.5 years), the endpoint occurred in 104 patients. Baseline mean eGFR was 43.2 ± 22.8 ml/min/1.73 m2, and 125 patients (92%) had overt proteinuria. After adjusting for known indicators of DN progression, the HR for the endpoint was 2.32 (95% CI: 1.20-4.51) in PTBML Group 2 and 3.12 (1.48-6.58) in PTBML Group 3 versus PTBML Group 1. Furthermore, adding the PTBML Group to a multivariate model including known promoters of DN progression improved the prediction of the endpoint (c-index increased by 0.02 [95% CI: 0.00-0.04]).

Conclusions: PTBML may be useful for predicting the renal prognosis of patients with biopsy-proven DN, but further investigation of these lesions in various stages of DN is needed.}

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

Interstitial Fibrosis and Tubular Atrophy Are Dominantly Associated with Progressive Renal Decline in Patients with Type 2 Diabetes and Biopsy Proven Diabetic Nephropathy

Masaaki Yamanouchi1, Toshiharu Ueno,1 Junichi Hoshino,1 Koki Mise,1 Yoshifumi Ubara,1 Kenmei Takaichi1,1 Ohinata Memorial Inst for Medical Research, Tokyo, Japan; 2Okayama Univ Graduate School of Medicine.

Background: Although interstitial fibrosis/tubular atrophy (IFTA) is a common denominator in diabetic nephropathy (DN), the degree of IFTA has not attracted much attention, and the association between such lesions and the renal prognosis remains unclear.

Methods: Among 142 patients with biopsy-proven DN and type 2 diabetes encountered from 1998 to 2011, 136 patients were enrolled in this study. Patients were classified into 3 groups (Group 1: mild, Group 2: moderate, Group 3: severe) according to the extent of IFTA. The endpoint was the death of the estimated glomerular filtration rate (eGFR) by ≥40% from baseline or commencement of dialysis for end-stage renal disease. The Cox proportional hazard model was employed to calculate hazard ratios (HRs) and 95% confidence interval (CIs) for the death-censored endpoint.

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Conclusions: PTBML may be useful for predicting the renal prognosis of patients with biopsy-proven DN, but further investigation of these lesions in various stages of DN is needed.}

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

Differential Diagnostic Models of Diabetic Nephropathy and Non-Diabetic Renal Diseases

Miejun Si, Zengchun Ye, Wenbo Zhao, Xun Liu. Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.

Background: Non-diabetic renal diseases (NDRD) could be detected among patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). The treatment and prognosis of NDRD is different from diabetic nephropathy (DN), which makes the differential diagnosis of great importance. We aim to build up diagnostic models for differentiating NDRD from DN.

Methods: Patients with T2DM and CKD who had performed renal biopsies between 2004 and 2013 were enrolled. Renal pathology was regarded as the gold standard for the diagnosis of DN and NDRD. A logistic regression model was built by multiple regression analysis while artificial neural network (ANN) models were constructed by MATLAB 2011A software.

Results: Among the 103 patients enrolled, 49 DN while 54 had NDRD. 36 multicenter subjects with T2DM and CKD were applied as the external validation. Though univariate and multivariate regression analysis, four significant factors: diabetic retinopathy (DR), diabetes duration, hemoglobin (Hb) and urinary protein (Upuro) were included in logistic regression model: P(DN) = exp(3.682*DR+0.227*Diabetes duration -0.043*Hb +0.207*Upuro +0.350) / [1+ exp(3.682*DR+0.227*Diabetes duration -0.043*Hb +0.207*Upuro +0.350)]. We built up an artificial neural network based on the same four parameters.103 subjects were randomly divided into the training set (N=69) and the test set (N=34). We trained the datasets by gradient descent with respect to mean square error. Then we applied the test set to the best-trained model. The accuracy, sensitivity and specificity 61.6%, which is significantly greater than the regression model (consistency parameters. }

Conclusions: Both logistic regression model and artificial neural network could help with the clinical differentiation between DN and NDRD. ANN GA-MLP-6-7-1 based on DR, diabetes duration, Hb and Upuro could differentiate NDRD from DN more efficiently than the regression model.

Funding: Government Support - Non-U.S.
Evaluation of Renal Pathological Classification in Patients with Diabetic Nephropathy

Meijun Si, Zengchun Ye, Wenbo Zhao, Xian Liu, Hui Peng, Tan-Qi Lou.
Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.

Background: In 2010, a pathological classification of diabetic nephropathy (DN) mainly based on mesangial expansion and Kimmelstiel–Wilson nodules was proposed by Professor Tervaert. We classified the biopsy specimen of patients with type 2 diabetic nephropathy according to Tervaert’s classification to assess the relationship between pathological classification and prognosis.

Methods: We retrospectively analyzed the pathological features of patients diagnosed with DN between January 2004 and December 2013. Tervaert’s classification was applied to the pathological reports. All patients were enrolled after telephone calls or out-patient clinic by the deadline on 31 December 2014. The end point was defined as doubling of serum creatinine or introduction of dialysis. We further conducted the survival analysis to evaluate the impact of pathological classification on the prognosis of DN.

Results: 49 Patients enrolled were divided into four categories of IIA(N=5), IIB(N=8), III(N=21) and IV(N=15) according to Tervaert’s classification. The eGFR in III was significantly lower than II, while the serum albumin in II was significantly higher than III(all P<0.05). The proportion of glomerular and segmental sclerosis and the score of interstitial fibrosis and tubular atrophy(IF/TA) was higher in III than II(P<0.05). The longest diabetes duration, highest level of SBP, urinary protein and serum creatinine were detected in IV.

Conclusion: We classified the biopsy specimen of patients with type 2 diabetic nephropathy based on mesangial expansion and Kimmelstiel–Wilson nodules was proposed by Professor Tervaert. We classified the biopsy specimen of patients with type 2 diabetic nephropathy according to Tervaert’s classification to assess the relationship between pathological classification and prognosis.

Clinical Features and Prognosis of Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease

Meijun Si, Wenbo Zhao, Zengchun Ye.
Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.

Background: The renal pathology type in patients with type 2 diabetes mellitus and chronic kidney disease (CKD) could be diabetic nephropathy (DN), non-diabetic renal diseases (NDRD) and DN with NDRD. We aim to investigate the clinical characteristics and prognosis of type 2 diabetic patients with different types of renal pathology.

Methods: We conducted a retrospective investigation of type 2 diabetic patients with CKD who had performed renal biopsies between 2004 and 2013. According to the pathological diagnosis, patients were categorized into three groups: DN group, NDRD group and DN with NDRD group(MIX group). All patients were censored by telephone calls or out-patient clinic by the deadline on 31 December 2014. The end point was defined as doubling of serum creatinine or introduction of dialysis.

Results: Among 110 patients enrolled, 49(44.1%) patients had DN alone, 54(49.1%) patients had NDRD while 7(6.4%) patients had concurrent DN and NDRD. Compared with NDRD, DN patients had a longer diabetes duration and a higher diabetic retinopathy(DR) rate(all P<0.05). The prevalence of having both nephrotic range proteinuria and kidney function decrease (eGFR<60/ml/min) was higher in DN than NDRD(P<0.05). The mean follow up time was 41 months. 25 patients reached the endpoint in 18 in DN, 5 in NDRD and 2 in MIX group. The prognosis of NDRD is better than DN while MIX is the poorest prognosis.

Conclusions: Our results indicated that clinical and pathological findings and renal outcomes in four DN groups classified by Tervaert’s classification were different. IV might suggest the terminal stage of DN while IIa presented with the mildest clinical lesions and better prognosis compared with IV, which was important for early diagnosis and treatment of DN. Tervaert’s pathological classification could help predict the prognosis of DN.

Clinical Features and Prognosis of Patients with Type 2 Diabetes Mellitus, Obesity: Clinical – II

Pei Guangdong, Guangzhou, Guangdong, China.

Background: The prevalence of type 2 diabetes increases worldwide. Understanding the burden of diabetes-related dialysis is important in order to allocate health resources, and to encourage measures to counteract trends for increasing prevalence.

Methods: Data were retrieved from 2001-2010 Taiwan National Health Insurance claim records. The gender and age-specific incidence rate of long-term dialysis was calculated for type 2 diabetes patients in the periods of 2002-2004, 2005-2007 and 2008-2010, separately.

Results: There were 20,397 male and 19,933 female diabetes-related dialysis occurring between 2002 and 2010. The incidence number of diabetes-related dialysis increased from 2002 to 2010 in every age group. During 2008-2010, the numbers of male patient peak at the age-range of 50-59 years and those of female patients peak at the range-range of 70-79 years. There was a decreasing trend of incidence rate from 2002 to 2010 in female patients younger than 70 years old. In contrast, there was an increasing trend of incidence rate in female patients older than 80 years old from 2002 to 2008.

Conclusions: Initially, Poisson regression model showed that the relative risk (RR) of diabetes-related dialysis in 2002-2004 was higher than that in the other two periods. However, this period effect disappeared after adding interaction terms gender&age and period&age into the model.

Association between Renal Function and Diabetic Foot Ulcer in Type 2 Diabetic Patients

Hathiam Ezatz, Abd el Basset El Shaarawy, Amr Mohab.
Nephrology Dept, Ain Shams Univ, Cairo, Egypt.

Background: Diabetic nephropathy and diabetic foot syndrome (DFS) are two major complications of diabetes. The aim of this study was to evaluate renal function in patients with diabetic foot ulcers and to identify a potential association between them.

Methods: In this cross sectional study 75 adult patients with type 2 DM were enrolled. They were divided into 2 groups , group 1 included 50 patients with diabetic foot ulcer (DFU) (25 male & 25 female) and group 2 included 25 patients without DFU (12 male & 13 female). The stages of DFU were recorded according to Wagner and Armstrong grading. Demographic data was collected from all subjects. Laboratory parameters included s.creatinine, serum urea, HbA1C, lipid profiles, urinalysis, urinary microalbumin and albumin/creatinine ratio (ACR). The eGFR was estimated using the Modification of Diet in Renal Disease equation (MDRD).

Results: Compared with type 2 diabetic patients without DFU, those with DFU were significantly older (P<0.001), exhibited a higher HbA1C (8.42±1.02 vs 7.58±0.37, P<0.001), had a longer duration of diabetes (18.0±10.74 years vs 4.32±2.497 years , P<0.001), higher mean systolic blood pressure (135.40±19.91 vs 126.00±15.81 mmHg; P=0.043), higher serum creatinine levels (2.46 mg/dl ±0.01 vs 1.68 mg/dl ±0.516, P<0.001, and had a lower eGFR (41.196 ml/min :±25.542 vs 61.856 ml/min :±24.641, P<0.001). There was an increase in the prevalence of foot ulcers by increasing the degree of renal impairment (14% with CKD stage 2, 30% with CKD stage 3 and 56% with CKD stage 4). Also there was increase in the prevalence of foot ulcers with increasing degree of albuminuria (12% with normo-albuminuria ,26% with microalbuminuria and 62% with macroalbuminuria). In group 1, there was significant correlation between the Wagner stages of DFU and eGFR (P<0.001) as well as Armstrong stages of DFU and eGFR (P<0.001).

Conclusions: There was a strong association between the degree of renal function impairment and DFU. Thus diabetic patients with CKD should regularly screened for the presence of DFS with early preventive strategies.
Detection of Early Renal Function Decline in Type 1 Diabetes: Comparison of eGFR Slopes Based on Serum Creatinine versus Cystatin C

Methods: A cohort of patients with normo- or micro-albuminuria (ALB) was recruited from among patients at the Joslin Diabetes Center. Serial measurements of creatinine (Cr) and cystatin C (Cys) were collected over 3.5 to 11 years. CKD-EPI equations were used to calculate eGFRcre and eGFRcys. Slopes of decline of eGFRcre and eGFRcys were estimated using generalized linear models.

Results: eGFR was defined as an eGFR loss greater than 3 mL/min/1.73 m² per year. The table shows the proportion of patients with ERFDcre or ERFDcys according to their respective estimates of baseline eGFR.

<table>
<thead>
<tr>
<th>Baseline eGFR</th>
<th>Cystatin C</th>
<th>Creatinine Cystatin C</th>
<th>Creatinine Cystatin C</th>
<th>Cystatin Cystatin C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal-ALB n=451</td>
<td>ERFDcre</td>
<td>ERFDcys</td>
<td>ERFDcre</td>
<td>ERFDcys</td>
</tr>
<tr>
<td>120+</td>
<td>21% (20/95)</td>
<td>12% (17/145)</td>
<td>27% (16/59)</td>
<td>22% (19/86)</td>
</tr>
<tr>
<td>90-119</td>
<td>10% (31/303)</td>
<td>13% (35/272)</td>
<td>23% (43/184)</td>
<td>35% (58/167)</td>
</tr>
<tr>
<td>60-89</td>
<td>9% (5/56)</td>
<td>23% (3/84)</td>
<td>21% (13/61)</td>
<td>39% (20/51)</td>
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<tr>
<td>TOTAL</td>
<td>12% (56/451)</td>
<td>13% (60/451)</td>
<td>24% (72/304)</td>
<td>32% (97/304)</td>
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</table>

While detection of ERFD by eGFRcre and eGFRcys was similar in Normo-ALB (12% for Cr and 13% for Cys), it was higher for eGFRcys in Micro-ALB (24% and 32%, p=0.02). Interestingly, the proportion of patients with ERFDcys was independent of baseline eGFRcys in both Normo-ALB and Micro-ALB (p=0.2 and 0.06). eGFRcys slope was also better correlated with covariates than the eGFRcre slope. The most striking was ACR (≤0.25 Cys vs. ≤0.15 Cre, p=0.04) and serum TNF1 (≤0.20 vs. ≤0.15, p=0.03).

Conclusions: In conclusion, cystatin C may be a more sensitive tool to identify ERFD, especially in a population with micro-ALB. Further investigation is required into any trends in rates of ERFD across baseline eGFR groups.

Funding: Private Foundation Support

SA-PO724

Real World Analyses of Urinary Albumin and eGFR Decline in 329,841 Diabetic Patients

Methods: We sought to determine the prevalence of albuminuria and proteinuria with and without diabetes and hypertension. Furthermore, obesity is associated with risk factors of kidney disease such as diabetes and hypertension and the prevalence excluding these risk factors is uncertain. In this study, we sought to determine the prevalence of albuminuria and proteinuria with and without diabetes and hypertension.

Table: This table shows the proportion of patients with ERFDcre or ERFDcys according to their respective estimates of baseline eGFR.

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Conclusions: In conclusion, cystatin C may be a more sensitive tool to identify ERFD, especially in a population with micro-ALB. Further investigation is required into any trends in rates of ERFD across baseline eGFR groups.

Funding: Private Foundation Support

SA-PO725

Prevalence of Proteinuria and Albuminuria in Obese Patients Undergoing Bariatric Surgery

Methods: Consecutive patients undergoing bariatric surgery were recruited. Urine samples were collected from subjects prior to surgery, to determine the prevalence of proteinuria and creatinine and urine protein/creatinine. Albuminuria was defined as an albumin to creatinine ratio of more than 30 mg and proteinuria as a protein to creatinine ratio of greater than 300 mg.

Results: The study included 219 patients. The mean age was 42 years and mean BMI was 44. Diabetes (DM) was present in 23%, Hypertension (HTN) was present in 47%. The prevalence of proteinuria and albuminuria was 7.5% (95% CI: 4.3-11.9%) and 19.7% (95% CI: 14.2-26.2%) respectively. Among those without DM but who had HTN, the prevalence of proteinuria and albuminuria was 7.6% (95% CI: 3.4-12.8%) and 19.8% (95% CI: 12.0-28.6%) respectively. The prevalence of proteinuria of patients with neither DM nor HTN, 3% (95% CI: 0.6-11%) and 11% (95% CI: 5.1-17%) had proteinuria and albuminuria respectively. Diabetics had more proteinuria and albuminuria than the non-diabetic groups. The non-diabetic groups did not differ significantly from each other in terms of prevalence of proteinuria and albuminuria. The BMI for diabetic patients did not differ from non-diabetics. On multivariate analysis, only the presence of DM was associated with proteinuria and albuminuria.

Conclusions: In conclusion, we found a relatively high prevalence of microalbuminuria and proteinuria in an urban, obese population. When diabetics were excluded, there was a much lower prevalence. Patients who did not have either DM or HTN had a much lower prevalence than those with hypertension, but still had much more than seen in the general US population, likely reflecting an adverse effect of obesity itself on renal physiology.
Conclusions: eGFR cannot be used in evaluation of glomerular hyperfiltration in IFG and/or IGT subjects. Hematropic abnormalities, possibly caused by increased Rv, associated with poor glycemic control are present even in IFG and/or IGT subjects.

SA-PO728
Diabetes and Hypertension Synergistically Exacerbates Glomerular Hypertrophy. Takaya Sasaki, Kentaro Koike, Kotaro Haruhara, Nobuo Tsuoi, Go Kanzaki, Yusuke Okabayashi, Yoichi Miyazaki, Tetsuya Kawamura, Makoto Ogura, Takashi Yokoo. Nephrology and Hypertension, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.

Background: Glomerular hypertrophy is an early histopathological finding in diabetic nephropathy that precedes the development of diabetes-specific glomerular lesions. Although hypertension is a major clinical feature associated with a poor renal outcome in diabetes, no previous study has analyzed diabetic glomerular hypertrophy in relation to hypertension in humans.

Methods: Autopsied kidneys without renal dysfunction (eGFR >60 ml/min/1.73 m²) were analyzed to estimate the glomerular volume (GV) in different parts of the renal cortex. The mean GV was calculated from a formula involving the glomerular surface area (approximately 50 glomeruli measured per cortex).

Results: We analyzed a series of 80 Japanese autopsy specimens. The average values were age of 70 years and estimated glomerular filtration rate (eGFR) of 98 ml/min/1.73 m². The autopsied specimens were obtained from normotensive non-diabetes patients (n=31), hypertensive non-diabetes patients (n=28), normotensive diabetes patients (n=13), and hypertensive diabetes patients (n=8). The mean GV in the diabetic hypertensive patients was markedly higher than in the other groups in both superficial (SF) and juxtamedullary (JM) cortices (figure).

The factors independently associated with the mean GV were a low glomerular density, diabetes and hypertension in the SF cortex, and diabetes and hypertension in the JM cortex. In contrast, neither age nor renal function nor degree of glomerulosclerosis were found to be related to the mean GV in either cortex in multivariate analyses.

Conclusions: These results suggest that diabetes and hypertension may synergistically exacerbate glomerular hypertrophy across all layers of the human renal cortex.

SA-PO729
Predictors of Resolution of Glomerular Hyperfiltration in Obese Patients following Bariatric Surgery. Sinje Lee,1 Suyeon Park,2 Hye Ran Kang,1 Jin Seok Jeon,1 Hyunjin Noh,1 Dong Cheol Han,1 Soon Hye Kwon,1 1Div of Nephrology, Dept of Internal Medicine, Soochunhyang Univ Seoul Hospital, Seoul, Korea; 2Dept of Biostatistics, Soochunhyang Univ Seoul Hospital, Seoul, Korea.

Background: Obesity is associated with increased glomerular filtration rates (GFR). Bariatric surgery is efficient to improve glomerular hyperfiltration. The aim of this study was to elucidate the predictors of resolution in glomerular hyperfiltration.

Methods: We prospectively enrolled obese patients who underwent bariatric surgery and had follow-up more than one-year. Glomerular hyperfiltration was defined as estimated GFR (eGFR) above 95 percentile of GFR values in age, sex-matched cohorts extracted from the Korea National Health and Nutrition Examination Survey (KNHANES) Database. eGFR was estimated using a body surface area (BSA)-adjusted Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (mL/min) at the time of surgery and annually during follow-up period.

Results: Among total 136 of eligible patients, ninety-nine patients with glomerular hyperfiltration (age range, 14-58; 16 men; 83 women) were analyzed. Median follow-up period was 2 years (range, 1 to 4 years). 44 Diabetic (32%) and 45 hypertensive (33%) patients were included. Bariatric surgery decreased eGFR (150.0:18.5 vs. 126.5:16.7 ml/ min; p<0.001). Among them, eGFR of 49 (50%) patients returned to the normofiltration range (5-95 percentile of eGFR in KNHANES). Multivariate analysis identified pre-operation BMI (p=0.001, OR=0.80; 95% CI= 0.70-0.92) and age (p=0.01, OR=1.12; 95% CI=1.02-1.21) as independent factors of resolution of glomerular hyperfiltration at surgery.

Conclusions: The predictive factors for resolution of increased GFR following bariatric surgery include BMI and age at surgery time.

SA-PO730
Urinary Angiotensinogen (AOG) Is Increased in Type I Diabetes with Macroalbuminuria. Minghao Ye, Jan A. Wysocki, Ahmed Mohamed Khattab, Hasan Issa, Matthew Adam Gutterman, Mark E. Molitch, Daniel Battle. Nephrology/Endocrinology, Feinberg School of Medicine, Chicago, IL.

Background: An increase in urinary AOG, a key component of the RAS, has been reported in CKD patients including some with type 1 and 2 diabetes. These patients usually had macroalbuminuria and were receiving RAS blockers which may alter AOG. At the stage of macroalbuminuria AOG, like albumin, can be filtered as alterations in glomerular permeability have developed since both proteins have a similar molecular weight. We evaluated urinary AOG in biosamples from patients with mild elevations in albumin excretion rate (AER) from a cohort where hypertension was an exclusion criteria and RAS blockers were not used.

Methods: Biosamples were obtained from NIDDK repositories from participants in the Diabetes Control and Complications Trial (DCCT). AOG in patients with microalbuminuria was compared to a group of normoalbuminuric participants matched for the following: GFR, SBP, DBP, HbA1C, age, gender, diabetes duration and allocation to intensive or moderate therapy (Table).

Results: Urinary AOG was increased in biosamples from patients with microalbuminuria as compared to those with normoalbuminuria and similar GFR, HbA1C, blood pressure and disease duration (Table). There was no significant correlation between AOG and UAE (R=0.2) within the low range of UAE examined. This suggests that the source of increased AOG is not only filtered AOG from the circulation but also AOG formed intrarenally.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Urinary Progenin Is Increased in Patients with Type 1 Diabetes and Nephropathy
Jan A. Wysocki,1 Johannes Rein,1 Maryam Akbarian,2 Daniel Battie.1 Northwestern Univ, Chicago, IL; 1Univ of Washington.

Background: Progenin is increased in patients with T1D and T2D with complications, whereas plasma renin activity is not. Recent studies have shown that the soluble progenin receptor can activate renin enzymatically thereby potentiating active renin and therefore activating RAS. This information on urinary progenin from patients with diabetes, and the levels are very low in subjects without diabetes. Proteolytic and non-proteolytic activation of progenin may be important in kidney RAS overactivity in DN. We evaluated urinary progenin as well as active renin in biosamples from subjects with T1D who developed DKD and controls who had not, despite longstanding diabetes (>25 years).

Methods: Biosamples and clinical data from people with T1D were obtained from the Kidney Research Institute DKD Repository of the University of Washington. DKD was defined as either a urine ACR ≥300 mg/g or an eGFR ≤60 mL/min per 1.73 m² and ACR ≥20 mg/g. People with longstanding diabetes but no evidence of DKD had: 30 years of T1D, estimated eGFR > 90 mL/min per 1.73 m², and ACR < 300 mg/g. Samples for active renin were first concentrated before applying to ELISA. Urinary progenin was measured using ELISA detecting progenin only.

Results: Progenin was detectable in 81% (30/37) of samples from the cases but only in 51% of the urines (22/43) from the controls who did not have diabetic kidney disease. Median urine Progenin/Cr (IQR) was significantly higher in DKD biosamples 99 (33.203) pg/mg than in biosamples from those without DKD 39 (21.84) pg/mg, p<0.005. Median urinary active renin/Cr was also increased in subjects with DKD 2.92 pg/mg (1.87.5) as compared to what it without 1.4 pg/mg (0.9, 3.6), p<0.05. There was a significant positive correlation between urinary progenin and active renin protein (0.676, p<0.001).

Conclusions: Urinary progenin could be a source of increased urinary active renin in persons with type 1 diabetes. Both progenin and active renin are increased in patients with DKD as compared to those who have escaped this complication after longstanding diabetes. Prospective studies are needed to examine the potential predictive value of urinary progenin and active renin for the development of DKD.

Funding: NIDDK Support

SA-PO732
Urinary Excretion of Podocyte mRNA Is an Early Diabetic Biomarker in Diabetic Nephropathy
Akiko Fukuda, Akiko Minakawa, Yuji Sato, Kazuo Kitamura, Shouichi Fujimoto. First Dept of Internal Medicine, Univ of Miyazaki, Miyazaki, Japan.

Background: Albuminuria is used for early diagnostic assessment of diabetic nephropathy but does not always reflect disease activity. Recent studies suggest that podocyte injury has already begun at the early stage of diabetic nephropathy. Podocyte cell lineage-specific mRNA can be recovered from urine pellets. The study examined whether urinary excretion of podocyte mRNA can be used as an early diagnostic biomarker in diabetic nephropathy.

Methods: We examined both animal models of diabetic nephropathy and human samples. The leptin-deficient Zucker diabetic fatty (ZDF-fatty) rat model of type 2 diabetes was compared with heterozygous ZDF rats as a control. From January 2015 to June 2015, spot urine samples from out-patients at various stages of diabetes (normoalbuminuria group: n=99, microalbuminuria group: n=38, macroalbuminuria group: n=37) and healthy controls (n=41) without diabetes or hypertension, were taken. We examined urinary excretion of podocyte mRNA and urine albumin/creatinine ratio, and measured glomerular volume, and podocyte number and density in the rat model. Results: ZDF-fatty rats became diabetic with increased blood glucose and glycosuria by 10 weeks. Albuminuria significantly increased by 10 weeks, however, urinary excretion of podocyte mRNA increased by 3 weeks in ZDF-fatty rats. At 6 weeks, podocyte numbers had not decreased, while glomerular volume significantly increased and podocyte density significantly decreased compared to controls, suggesting that podocyte stress had begun at the early stage of diabetes. Similar results were observed in human participants. Urinary excretion of podocyte mRNA increased dependent on albuminuria level in diabetes patients vs. controls (normoalbuminuria: 4.3-fold; microalbuminuria: 4.2-fold; macroalbuminuria: 16.7-fold). Urinary excretion of podocyte mRNA in the normalalbuminuria group at the interquartile range of the control level of albuminuria significantly increased vs. controls (6.7-fold).

Conclusions: Urinary excretion of podocyte mRNA begins to increase much faster than albuminuria in both animal models and humans, and could be an early diagnostic biomarker in diabetic nephropathy.

Funding: Government Support - Non-U.S.

SA-PO734
Impaired Leukocyte Glucose 6-Phosphate Dehydrogenase (G6PD) Response to Hyperglycemia Is Associated with Rapidly Progressive Kidney Disease in Individuals with Diabetes
Matthew R. Lynch,1 Robert C. Stanton.2 1Div of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; 2Kidney and Hypertension Section, Joslin Diabetes Center, Boston, MA.

Background: Mechanisms of diabetic kidney disease (DKD) progression are unclear. An appropriate response to oxidative stress is an increase in G6PD activity, the source of the essential antioxidant NADPH. Impaired G6PD activity occurs in animal models of DKD and in leukocytes from animals and persons with diabetes, suggesting that leukocyte G6PD activity correlates with kidney G6PD activity. We hypothesized that leukocyte G6PD activity response would be impaired in patients with progressive DKD.

Methods: 45 patients with DKD were recruited; those with at least a 3.3 ml/min/year loss in eGFR since establishing care were deemed to be rapid progressors. Rapid progressors with an uninterrupted decline in eGFR were judged linear rapid progressors (LRP), while the rapid progressors with at least one period of at least one year of stable eGFR were called non-linear rapid progressors (NLRP). Non-rapid progressors (NRP) included all remaining patients. The change in leukocyte G6PD activity to high glucose stress was measured. Leukocytes were isolated from whole blood and incubated in normal (5.5 mM glucose) or high glucose (25 mM) conditions for one hour at 37°C. Serum glucose, hemoglobin A1C, creatinine, hemoglobin, albuminuria and medications were abstracted from medical records.

Results: Compared to baseline, leukocyte G6PD activity changes to high glucose stress were decreased in LRP (-19.52;13.85%), unchanged in NLRP (1.9;10.3%), and increased in NRP (18.216.7;47%), p=0.035 versus LRP. There was no difference between the groups’ baseline leukocyte or erythrocyte G6PD activity. Albuminuria was higher in LRP than in the other groups (LRP: 38151310 mg/mL; NLRP: 724.9569 mg/mL and NRP: 454.5±16.5 mg/mL, p<0.01 and p<0.001, respectively).

Conclusions: Leukocyte G6PD activity response to high glucose stress was significantly impaired in patients with linear rapidly progressive DKD. Leukocyte G6PD response may act as a surrogate for renal G6PD activity, suggesting that G6PD may be both a biomarker and potential therapeutic target in human DKD.

SA-PO735
Proteomic Analysis Suggests Role of TGF-B Regulatory Proteins in Development of Diabetic Kidney Disease
Elwaleed Elnagar,1 Christian Herzog,2 Maria Lopes-Virella,3 Kelly J. Hunt,3 Michael G. Janecz,3 Ricky Edmondson,1 John M. Arthur.1 1Univ of Arkansas for Medical Sciences; 2Medical Univ of South Carolina.

Background: Diabetic nephropathy is the leading cause of ESRD in the US but a relatively small percentage of patients with type 2 diabetes have reduced renal function after 15 years. Albuminuria is used to predict decline in renal function but it is neither sensitive nor specific. The goal of this study is to identify novel predictive biomarkers and pathways involved in development of diabetic kidney disease.

Methods: Urine from 10 subjects enrolled in the VA Diabetes Trial who had normal serum creatinine (SCr) and normoalbuminuria at enrollment, but doubled their SCr during follow up, were matched to 10 that had no increase in SCr. Urine proteins were digested with trypsin and analyzed by liquid chromatography/tandem mass spectrometry. Identified proteins were quantified using spectral counting and differences between progressors and nonprogressors were identified using a t-test with Benjamini-Hochberg correction for multiple comparisons.

Results: We identified 888 proteins with a decoy false discovery rate of 0.08%. After removing proteins primarily expressed in bladder or skin, 20 had p values <0.05. Vasorin had the smallest p value (0.001) and was lower in progressors. Vasorin binds TGF-B preventing its stimulation of the receptor. Among the 20 proteins with p<0.05, 7 (vasorin, plasma serum protease inhibitor, gamma-glutamylcysteine transferase, oxidized low-density lipoprotein receptor 1, angiotsensinogen, kallikrein-1 and L-selectin) were involved in TGF-B signaling and the directional changes in five are consistent with increased TGF-B signaling. Observed changes in other mediators with slightly higher p values also would result in an increase in TGF-B (MMF-9, latent TGF binding protein 2, activin receptor).

Conclusions: A high percentage of differentially abundant urine proteins in patients that will develop diabetic kidney disease are involved in regulation of TGF-B signaling and most of the differentially abundant proteins in the pathway should lead to an increase in TGF-B. This is an intrarenal pro-fibrotic signal that can potentially be used to predict patients that will develop CKD.

Funding: NIDDK Support, VA Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO736
Classification Tree Model Analysis on Related Factors of the Incidence and Degree of Albuminuria of Diabetic Kidney Disease Wenbo Zhao,1 Meijun Li,1 Hui-Qun Li,1 Zhoqing Gan,2 Weiming Han,1 Tan-Qi Lou,1 Dept of Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; Zhongshan School of Medicine, Sun Yat-sen Univ, Guangzhou, Guangdong, China.

Background: To analyze the impact factors for the degree of albuminuria of diabetic kidney disease by the classification tree analysis.

Methods: A total of 2068 hospitalized patients with type 2 diabetes were enrolled. According to glomerular filtration rates and urine albumin quantification, the patients were divided into type 2 diabetes group (1329 cases), early diabetic renal damage group (529 cases) and macroalbuminuria group (210 cases). The clinical data of the patients were recorded to analyze the main influential factors for the microalbuminuria of type 2 diabetic patients using the Exhustive CHAID classification tree algorithm.

Results: Eight important explanatory variables were screened out by the classification tree model from the 30 candidate variables related to microalbuminuria and macroalbuminuria, including Cys C levels, fibrinogen, SBP, retinopathy, sex, diabetes peripheral vascular disease, diabetes duration, serum albumin. CysC was the main factor of DKD, CysC > 1.58 mg/L and diabetes duration of 1.50 years or less appear macroalbuminuria is a 53.6% chance, CysC > 1.58 mg/L, diabetes duration > 1.50 years and SBP > 147 mmHg have 83.3% chance of macroalbuminuria.

Conclusions: Classification tree model can effectively analyze the different levels of albuminuria related influencing factors, and identify people at high risk characteristics, is conducive to early prevention and treatment.

SA-PO737
Fibrinogen May Be an Independent Predictor of Diabetic Kidney Disease Wenbo Zhao,1 Hui-Qun Li,1 Zengchun Li,1 Meijun Li,1 Hui-Qun Li,1 Zhoqing Gan,2 Weiming Han,2 Tan-Qi Lou.1 Dept of Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; Zhongshan School of Medicine, Sun Yat-sen Univ, Guangzhou, Guangdong, China.

Background: Analysis of the correlation of fibrinogen and different stages albuminuria in diabetic kidney disease.

Methods: As a Cross-sectional study, we collected hospital clinical data of 1152 cases for type 2 diabetes, without albuminuria group (785 cases), microalbuminuria group (285 cases) and macroalbuminuria group (112 cases), analyzing albuminuria progress related influence factors for multiple factors regression.

Results: The levels of fibrinogen was in the three groups respectively for (3.46±1.33) g/L, (4.16±1.32) g/L, and (4.85±1.28) g/L (P=0.000). In the without albuminuria group and microalbuminuria group, the multi-factor Logistic regression analysis showed fibrinogen (Fib) (β=0.463, P=0.000, OR=1.589), and retinopathy, CysC, systolic blood pressure into the model. In microalbuminuria group and macroalbuminuria group, the multi-factors Logistic regression analysis showed fibrinogen (Fib) (β=0.463, P=0.000, OR=1.589), and retinopathy, CysC, Waist-to-hip ratio into the model.

Conclusions: Fibrinogen associated with different stages albuminuria, that could be independent predictors of diabetic kidney disease.

SA-PO738
Non-Alcoholic Fatty Liver Disease Is Not Related to the Incidence and Degree of Albuminuria of Diabetic Kidney Disease Wenbo Zhao, Zengchun Li, Meijun Li, Hui-Qun Li, Tan-Qi Lou, Dept of Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.

Background: To analyze the association between non-alcoholic fatty liver disease (NAFLD) and the incidence and degree of albuminuria of diabetic kidney disease in patients with type 2 diabetes.

Methods: The incidence of diabetic nephropathy was assessed in 2008 type 2 diabetic patients, NAFLD was diagnosed based on liver ultrasonography. The difference in diabetic nephropathy incidence between patients with and without NAFLD was tested by y2. Multinomial logistic regression analysis was used to assess the factors associated with degree of albuminuria of diabetic kidney disease.

Results: The incidences of NAFLD and diabetic nephropathy in participants were approximately 44% (910/2068) and 35.7% (739/2068) respectively, microalbuminuria and macroalbuminuria in participants were approximately 25.6% (529/2068) and 10.1% (210/2068) respectively, and there were difference in the prevalence of degrees of albuminuria between patients with and without NAFLD (p<0.05). The incidences of NAFLD was highest in Patients without albuminuria (64.3%, 628/1329), in Patients with microalbuminuria (25.6%, 225/529), in Patients with macroalbuminuria (10.2%, 57/210). In multinomial logistic regression analysis, Fasting blood-glucose, BMI, Waist-to-hip ratio, fibrinogen, systolic blood pressure, CysC, history of hypertension were significantly associated with Patients with microalbuminuria, whereas age of onset, high blood pressure, fibrinogen, diabetic retinopathy, CysC, triglyceride (TG), high-density lipoprotein, low density lipoprotein were significantly associated with were significantly associated with Patients with macroalbuminuria. NAFLD were not associated with the degree of albuminuria of diabetic kidney disease.

Conclusions: The present results suggest that NAFLD is not related to the the incidence and degree of albuminuria of diabetic kidney disease.

SA-PO739
Glomerular IgM Deposition Predicts Renal Outcome in Patients with Type 2 Diabetes Xi Tang, Li Li, Yu Han Li, Fang Liu. Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China.

Background: Immunofluorescent staining reveals IgG, IgM, C3 deposits in renal tissue of some patients with type 2 diabetes. However, the clinical implication of such immune complex deposition is unclear.

Methods: A retrospective study was carried out in the west china hospital, Sichuan university, China. Among the 347 patients with diabetes who underwent renal biopsy from 2001 to 2015, 190 cases had pure diabetic nephropathy. According to the classification of Tervaert et al, 108 patients (glomerular class I to III) with at least 12-month follow-up were enrolled in this study. Clinical and pathological data were collected. Immunofluorescent staining was classified into three categories according to the intensity (0=none, 1=weekly positive, and 2=positive). Renal survival was estimated by the Kaplan-Meier method. The Cox proportional hazards model was employed to identify the risk parameters associated with renal survival.

Results: The number of cases with positive glomerular IgG, IgM and C3 staining were 29, 40, and 28, respectively. Over a median follow-up of 32 months, 38 cases developed into ESRD, 19 cases died. The Median time of renal survival 50(47.40, 72.60) months. The renal survival rates more than 12 years after biopsy were 41.7%. By univariate Cox proportional analysis, smoking [HR, 2.775(1.281, 6.010), P=0.010], eGFR [HR, 0.981(0.962, 0.999), P=0.045], and positive glomerular IgM deposit [1.997(1.095, 4.269), P=0.039] were independent predictors of ESRD. According to the intensity of IgM deposits, patients were divided into three groups. Compared with those with none renal IgM deposits, patients with positive staining of glomerular IgM had significant lower baseline eGFR (45.78±18.08 vs. 66.9±30ml/min/1.73m2). Age, gender, duration, hypertension, BMI, diabetic retinopathy, diabetic peripheral neuropathy, 24 hour proteinuria, serum IgG, IgM and C3 albuminuria, glomerular class were similar among the groups.

Conclusions: Glomerular IgM deposits as well as smoking and eGFR at the baseline of renal biopsy were the independent risk factors of ESRD in the patients with type 2 diabetic nephropathy.

SA-PO740
Impact of Anti-Erythropoietin Receptor Antibodies in Diabetic Patients with Chronic Kidney Disease Akinori Haragaki Koshino, Yasunori Iwata, Norihiko Sakai, Miyu Shimizu, Kengo Furuiuchi, Takashi Wada. Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan.

Background: To examine the clinical significance of autoantibodies to the erythropoietin receptor (EPOR) in diabetic patients with chronic kidney disease (CKD).

Methods: One hundred and twelve type 2 diabetic patients with CKD who have been followed up until 2014 (mean age, 62.9±12.5 years) were enrolled in this study. Anti-EPOR antibodies in sera from these patients were measured using enzyme-linked immunosorbent assay.

Results: Anti-EPOR antibodies were detected in 26 (23%) of the 112 diabetic patients enrolled. Patients with anti-EPOR antibodies were older and had lower estimated GFR (eGFR) than those without. In addition, in patients with anti-EPOR antibodies, hemoglobin concentration was lower than those without. During follow-up period, end-stage renal failure (ESRF) requiring dialysis therapy was more frequently observed in patients with anti-EPOR antibodies than in those without, and presence of the antibodies were significant risk factors for progression of ESRF. In 52 patients who had undergone renal biopsy, positivity for anti-EPOR antibodies was associated with the extent of interstitial inflammation.

Conclusions: These results suggest that anti-EPOR antibodies might be involved in the progression of CKD through interstitial inflammation, and the presence of the antibodies may be a predictor for renal dysfunction in type 2 diabetic patients.

Funding: Government Support - Non-U.S.
SA-PO741
Novel Tubular Biomarkers PredictRenal Progression in Type 2 Diabetes Mellitus: A Prospective Cohort Study
Kaseman Aramsonawak, Bancha Satirapoj, Thersarak Tangwonglert, Naowanit Nata, Amnat Chaiprasert, Prajej Ruangkanchanaset, Ouppatham Supasanydh. Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand.

Background: Estimated glomerular filtration rate (GFR) and albuminuria are routinely used for assessing renal progression. Tubulointerstitial injury is both a key feature of diabetic nephropathy and an important predictor of renal dysfunction. Novel tubular biomarkers that relate to renal injury in diabetic nephropathy could improve risk stratification and prediction.

Methods: A prospective cohort study, a total of 303 type 2 diabetes patients were followed up. The baseline values of urine Cystatin-C to creatinine ratio (UCCr), urine angiotensinogen to creatinine ratio (UANG), urine NGAL to creatinine ratio (UNGAL) and urine KIM-1 to creatinine ratio (UKIM-1) were measured. The primary outcome was a decline in estimated GFR of ≥25% per year from baseline.

Results: The median follow-up period was 12.5 months, and the primary outcome was noted in 13.5%. Urine tubular biomarkers of UCCr, UANG, UNGAL and UKIM-1 were significantly higher according to the degree of albuminuria and all of them had significant higher in patients with the rapid decline in estimated GFR of ≥25% per year from baseline. All biomarkers predicted primary outcome with ROC for UCCr = 0.72; 95% CI 0.64-0.79, UANG = 0.71; 95% CI 0.63-0.79, UNGAL = 0.64; 95% CI 0.55-0.76, UKIM-1 = 0.64; 95% CI 0.55-0.76. In multivariate Cox regression analysis, the number of patients with rapid renal progression was higher in those in the upper quartiles of all biomarkers than in those in the lower quartiles.

Conclusions: The study supported that type 2 diabetic patients with high levels of urine tubular biomarkers (Cystatin-C, angiotensinogen, KIM-1 and NGAL) had a more rapid decline in renal function. These tubular biomarkers may be independent predictors of the progression of type 2 diabetic nephropathy.

SA-PO742
p66Shc: A Novel Biomarker of Tubular Oxidative Injury in Patients with Diabetic Nephropathy
Xiaoxuan Xu,1,2 Xuejing Zhu,1 Yuchun Han,1 Chun Hu,1 Chang Wang,1 Shuguang Yuan,1 Yuan Yang,1 Li Xiao,1 Fu-You Liu,1 Yashpal S. Kanwar,2 Lin Sun.3,2 Second Xiangya Hospital, China; ‘Depts of Pathology & Medicine, Northwestern Univ, Chicago; ‘Health Management Center, Xiangya Hospital.

Background: Increased p66Shc expression has been associated with diabetic nephropathy (DN). However, whether p66Shc can serve as a potential biomarker for tubular oxidative injury in DN is unknown.

Methods: We measured the expression of p66Shc in peripheral blood monocytes (PBMs) and renal biopsy tissues from DN patients and then analysed the relationship between p66Shc expression and the clinical characteristics of patients with DN. Patients were divided into 4 groups (class Ia, class Ib, class III and the control group). qPCR, Western blotting and immunohistochemistry were performed.

Results: The results showed that both p66Shc and p-p66Shc expression significantly increased in PBMs and kidney tissues of DN patients. Moreover, Spearman’s correlation and multiple regression analyses were carried out. A positive relationship between the expression of p66Shc and the clinical characteristics of patients with DN. Patients in the upper quartiles of all biomarkers than in those in the lower quartiles.

Conclusions: These data indicated that increased expression of p66Shc may serve as a therapeutic target and a novel biomarker of DN.

Funding: Government Support - Non-U.S.

SA-PO743
APX-501 Protein as a Novel Biomarker for Diabetic Nephropathy in Type 2 Diabetes
Jin Joo Cha,1,2 Young Sun Kang,1 Gyu Sik Choi,1 Hye Sook Min,1 Ji Eun Lee,1 Hyeewoon Kim,1 Jungyeon Ghee,1 Ji Ae You,1 Kitea Kim,1 Sang Youn Han,1 Kym Hyun Han,1 Sewon Oh,1 Dae R. Cha.1,3 Korea Univ; 1Wonsung Univ; 2Yonsei Univ; 3Dong-A Univ; 4Inje Univ, Republic of Korea.

Background: Excess production of reactive oxygen species in many tissues leads to tissue injuries through inflammation and fibrosis. Recently, we identified that APX-501 protein was synthesized from endothelial cells and is involved in oxidative stress in the kidney. Therefore, we investigated the role of APX-501 as a new biomarker for diabetic nephropathy in type 2 diabetic patients.

Methods: Preliminary animal and in vitro experiments were performed to identify the expression of APX-501 protein in renal tissues and cells in diabetic condition. For human study, 171 type 2 diabetic patients and 65 healthy control subjects participated in the study. Plasma levels of APX-501 were measured in 4 groups (n=52) and 4 overt proteinuria group (n=53). Plasma levels of APX-501 were measured by ELISA.

Results: In type 2 diabetic db/db mice, plasma level and renal expressions of APX-501 were increased and secreted in a glomerular filtration rate (GFR) dependent manner compared with those in nondiabetic db/m mice. In cultured murine podocytes and mesangial cells, high glucose condition markedly increased APX-501 synthesis and secretion. In type 2 diabetic patients, plasma APX-501 concentrations were significantly higher compared to healthy controls. Plasma APX-501 levels were the highest in patients with overt proteinuria. APX-501 levels were inversely correlated with body mass index (BMI) and positively correlated with systolic blood pressure, postprandial glucose levels, HOMA-IR, plasma retinol binding protein 4 (RBP-4) and urinary albumin(UAE) excretion. UAE, RBP-4 and BMI were independent determinants of plasma APX-501 concentration. APX-501 levels were not correlated with estimated glomerular filtration rate and we could not detect urinary excretion of APX-501 even in the overt proteinuria group.

Conclusions: These findings suggest that APX-501 synthesis may be activated in early stage of diabetic environment, may be a new biomarker for diabetic nephropathy in type 2 diabetic patients.

SA-PO744
Longitudinal Associations of Urinary Sodium and Potassium Excretion with eGFR and Albuminuria in Type 1 Diabetes
Jessica B. Kendrick,1 Leila R. Zehnic,1 Michael Steffes,2 Michel Chonchol,1 Ian H. De Boer.3 1Univ of Colorado; 2Univ of Washington; 3Univ of Minnesota.

Background: Patients with type 1 diabetes are at high risk of renal complications. While dietary sodium or potassium intake affects the development of kidney disease remains unclear.

Methods: We performed a cohort study of 1391 participants with type 1 diabetes in the Diabetes Control and Complications Trial and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications Study. We measured urinary sodium and potassium excretion in 4-hour timed urine samples collected between 1986-1996. Up to 3 measurements were made per participant and averaged. Over the subsequent 14 years, we ascertained the development of incident reduced eGFR (sustained eGFR <60 ml/min/1.73m2), ≥30% decline in eGFR and incident albuminuria (sustained increase in urine albumin:creatinine ratio (AER) ≥30 mg/d). Cox proportional hazards models were used to examine associations of tertiles of urinary sodium and potassium excretion with each outcome, excluding participants who had developed the outcome of interest prior to follow-up.

Results: Baseline mean (SD) age and eGFR were 38 (7) years and 109 (17) ml/min/1.73m2. Afterward adjustment for demographics, BMI, smoking, SBP, DBP, baseline eGFR and AER, duration of diabetes, HbA1c and use of ACEi/ARBs, lower urinary excretion of sodium and potassium tended to be associated with lower and higher estimated risks of renal outcomes, respectively, but none of these associations was statistically significant (Table).

Conclusions: Urinary sodium and potassium excretion were not significantly associated with incident kidney disease in type 1 diabetes.

Funding: NIDDK Support.

SA-PO745
Fetuin-A and Insulin Resistance Measured by Hyperinsulinemic Euglycemic Clamp Are Independent Determinants of Aortic Stiffness in Patients with CKD Stages 3 and 4
Sadipa Sarkar,1 Serpil Muge Defer,1 Leon Hsueh,2 Ian H. De Boer,3 Brijesh Patel,1,3 Edward D. Siew,1,2 Talat Alp Ikizler,1,2 Adriana Hung,1,2,3 1Vanderbilt Univ, TN; 2Vanderbilt Hospital; 3Oregon Health & Science Univ, Portland, OR.

Background: Both increased arterial stiffness and insulin resistance (IR) are highly prevalent and closely associated with cardiovascular disease in chronic kidney disease (CKD). Fetuin-A is a hepatic protein that inhibits arterial calcification and insulin action. In this study, we evaluated whether IR and fetuin-A are important determinants of arterial stiffness.

Methods: In this cross-sectional study, we enrolled 33 individuals with nondiabetic CKD stages 3 and 4 from the Nashville VA Hospital and Vanderbilt. Insulin sensitivity was measured by hyperinsulinemic euglycemic clamp (HEGC). Arterial stiffness was assessed by aortic pulse wave velocity (aPWV). Fetuin-A was measured by ELISA. Pearson correlation was used for univariate analysis and linear regression was used for both univariate and multivariate analyses.

Results: The mean age was 65±11 years, 74% were male, and 27% were African Americans. The mean BMI was 31±5 kg/m2. Both fetuin-A and insulin sensitivity index (ISI) were negatively correlated with aPWV (r=-0.42, p=0.03 and r=-0.50 p=0.02, respectively). In the multivariate analysis, ISI (β=−3.34 cm/sec per ln insulin) was a significant predictor of aPWV, but aPWV and BMI were independent determinants of arterial stiffness.

Conclusions: These data indicated that increased expression of p66Shc may serve as a therapeutic target and a novel biomarker of DN.

SA-PO746
Funding: NIDDK Support.

SA-PO745
Fetuin-A and Insulin Resistance Measured by Hyperinsulinemic Euglycemic Clamp Are Independent Determinants of Aortic Stiffness in Patients with CKD Stages 3 and 4
Sa
SA-PO746

NGAL and C-Cystatin Association with Albumin-Creatinine Relation in Type 1 Diabetes Patients
Marcelo Rodrigues Baci, Priscila Fernandes Allieri, Francisco Winter dos Santos Figueiredo, Fernando Luiz Affonso Fonseca, General Practice, ABC Medical School, Santo Andre, Sao Paulo, Brazil.

Background: Type 1 diabetes (T1DM) renal disease is well known because of its histological findings and established timeline since the beginning. Early injury kidney biomarkers are well studied in acute states however in chronic conditions as diabetes their relationship with albuminuria is not known. The aim of the study was analyse early kidney injury biomarkers between patients with T1DM and type 2 diabetes (T2DM) with the same pattern of glycemic control.

Methods: It is a cross-sectional study. Patients with the diagnosis of diabetes (type 1 and type 2) were recruited in order to compare the following kidney injury biomarkers: NGAL, C-cystatin, HbA1c, urinary beta trace protein and albumin/creatinine relation (ACR). Exclusion criteria included patients with end stage renal disease in dialysis, cancer and hospitalized for any reason in the previous 30 days of blood collection. The modified diet of renal disease equation was used in adults to estimate glomerular filtration rate and the modified Schwartz equation to estimate eGFR in children.

Results: A total of 77 patients were included. Of them, 56 with T2DM and 21 with T1DM. T1DM had 56.7% of females and a mean age of 23.8 years. T2DM were composed by 69.6% of females and a mean age of 63.5 years. The mean eTFG was 89.76 ml/min/1.73m2 for T1DM patients and 76.8 ml/min/1.73m2 for T2DM. Adjusting the analysis for the same HbA1c level for both groups they did differ with the following parameters: ACR, NGAL, C-cystatin, creatinine, HbA1C, urinary beta trace protein and albumin/creatinine relation (ACR). Exclusion criteria included patients with end stage renal disease in dialysis, cancer and hospitalized for any reason in the previous 30 days of blood collection. The modified diet of renal disease equation was used in adults to estimate glomerular filtration rate and the modified Schwartz equation to estimate eGFR in children.

Conclusions: For a same glycemic level, patients with T1DM and T2DM had different patterns of biomarkers of renal dysfunction ese3n with a normal eGFR. NGAL was associated with worse ACR and eGFR in T2DM. C Cystatin was associated inversely with ACR in T1DM. Despite same glycemic control, T2DM had worse ACR than T1DM.

Funding: Private Foundation Support

SA-PO747

Examination of Glycemic Control Index in Diabetic Dialysis Patients under On-Line Hemodiafiltration
Yukie Kitajima,1 Toru Hyodo,1 Tokyo Healthcare Unit, Setagaya, Tokyo, Japan; 2Eizin Clinic and Kurata Hospital Dialysis Center, Hiratsuka, Kanagawa, Japan.

Background: Glycosemoglobin (HbA1c) of diabetic dialysis patients has been reported to underestimate diurnal blood sugar fluctuations as it is affected by red cell survival, erythropoietin, etc. Therefore, it is recommended in Japan that glycoalbumin (GA) should be used for glycemic control index of diabetic dialysis patients. However, recently in Japan, on-line hemodiafiltration (o-HDF) with high albumin (Alb) leakage has been widely used in dialysis treatment methods due to the reimbursement in the national insurance system since 2012. As GA is affected by albumin metabolism, evaluation of GA values needs to be reexamined for diabetic dialysis patients under HDF. In this study, we examined GA values for different dialysis treatment methods.

Methods: The subjects were 156 diabetic dialysis patients (99 males and 57 females) with an average age of 69.2 ± 12.7 years. Those with Hb of less than 8.0 g/dL, diabetic dysfunction, and transfusion history, were excluded. [Methods] The subjects were divided according to treatment types: a hemodialysis (HD) group (23 patients) and an o-HDF group (13 patients). We examined the correlation of GA and HbA1c in comparison with known correlation, and the amount of Alb removed in the HDF group.

Conclusions: Lower fetuin-A and decreased insulin sensitivity are associated with increased aPWV and may contribute to increased CV risk in patients with CKD. Larger studies are needed to further evaluate the beneficial effect of higher levels of fetuin A in arterial stiffness in CV outcomes in CKD.

Funding: VA Support

SA-PO748

Don’t Hang Your Hat on Retinopathy in Diabetic Kidney Disease
Ambarkish Athavale, Amit J. Joshi, Radhika Jivsival, Albert M. Osei, Peter D. Hart, Nephrology, Stroger Hosp of Cook County, Chicago, IL.

Background: In ethnic minorities with type II Diabetes (DM) and “atypical” kidney disease, the frequency of non-diabetic glomerular disease is unknown and whether retinopathy correlates with Diabetic nephropathy (DN) is undetermined. Aim: 1. To describe prevalence of non-diabetic glomerular disease in patients with DM. 2. Correlate retinopathy with Diabetic nephropathy in patients with DM with atypical features.

Methods: Retrospective review of the medical records of 94 patients with DM who had kidney biopsy at our hospital between 01/2010 and 12/2015.

Results:

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>Diabetic nephropathy</th>
<th>Non diabetic glomerular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>Male</td>
<td>African American</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>Female</td>
<td>Hispanic</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>African American</td>
<td>White</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>African American</td>
<td>Asian/Pacific Islander</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>African American</td>
<td>Other</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>African American</td>
<td>Hematuria</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>African American</td>
<td>Proteinuria</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>African American</td>
<td>Low complements</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>African American</td>
<td>Hepatitis C</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>African American</td>
<td>+ ANCA</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
<tr>
<td>54.5 ± 9.5 yrs</td>
<td>African American</td>
<td>Monoclonal band</td>
<td>24/25 (25.53%)</td>
<td>24/25 (25.53%)</td>
</tr>
</tbody>
</table>

60% had non-diabetic glomerular disease and the most common were IgAN (14%) and FSGS (13%), 31% had Diabetic nephropathy and 9% had Diabetic nephropathy and another primary glomerular disease (most commonly arterioles nephrosclerosis). Retinopathy information was available in 81/94 patients. 33/81 had retinopathy and 48/81 had no retinopathy. Presence of retinopathy did not accurately predict Diabetic nephropathy. Of 33 patients with retinopathy, 14/33 (42.42%) had a non-diabetic glomerular disease while 12/48 (25%) patients with no retinopathy also had Diabetic nephropathy.

Conclusions: Non-diabetic kidney disease is very common in Diabetic ethnic minorities with atypical features. Retinopathy did not reliably predict Diabetic nephropathy. Thus, atypical features, with or without retinopathy warrants kidney biopsy.

SA-PO749

Incidence of Peripheral Arterial Disease in Hemodialysis Patients in 2 Separate Dialysis Units
David H. King,1 Philip Davis,2 Viyasaan Mahalingasivam,3 Amrita Rammarine,3 Sumith C. Abeygunasekara,1 Abdelgalil Abdelrahman Ali,1 Iain C. MacDougal,2 1Renal Unit, Broomfield Hospital, Chelmsford, Essex, United Kingdom; 2Renal Dept, Kings College Hospital, London, United Kingdom.

Background: The true incidence of Peripheral Arterial Disease (PAD) in Chronic Kidney Disease (CKD) is unknown. Conventional Ankle/Brachial (ABI) screening is inaccurate in the presence of severe medial artery wall calcification as seen in CKD and diabetic patients. We have used a new instrument BlueDop™, capable of achieving accurate PAD triaging in the presence of calcification.

Results: A significant positive correlation was observed between GA and HbA1c in the HD group (R² = 0.809 and p < 0.0001). Inaba et al. reported a similar result (r = 0.777 and p < 0.001: J Am Soc Nephrol, 2007). However, the correlation in the o-HDF group was lower than in the HD group (R² = 0.316 and p < 0.0001). In the o-HDF group, average of GA, HbA1c and HB was 20.4 ± 4.7%, 6.0 ± 0.9% and 10.6 ± 1.0g/dl. The mean amount of Alb removed in the effluent in the o-HDF group (24 diabetic dialysis patients) was 2.5 ± 2.17 g per a session. [Discussions] It is possible that GA value is underestimated in the o-HDF group due to the effect of Alb leakage. If Hb value is stable by the therapy, HbA1c may be the golden standard of the diabetic estimation even also in dialysis patients.

Conclusions: For glycemic control index of diabetic dialysis patients, GA and HbA1c need to be used along with the dialysis treatment method.

Funding: VA Support
Methods: BlueDop™ Vascular Expert Technology was employed in the PAD screening role. This system does not require external compression of the calf arteries as used in conventional ABI systems. Dialysis patients were screened in two units A (City) and B (Urban), some 50 miles apart. Patients underwent a 4 minute test involving application of non-invasive Doppler Ultrasound to each leg with automatic PAD recognition by BlueDop™.

Results:

<table>
<thead>
<tr>
<th>Number Pts/</th>
<th>Female Gender</th>
<th>Caucasian Ethnicity</th>
<th>Mean Age yrs</th>
<th>% diabetic</th>
<th>% PAD</th>
<th>%diabetic+PAD</th>
<th>% non-diabetic+PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 53/103</td>
<td>64</td>
<td>62</td>
<td>65</td>
<td>24</td>
<td>65</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>B 45/90</td>
<td>18</td>
<td>91</td>
<td>70</td>
<td>20</td>
<td>31</td>
<td>39</td>
<td>11</td>
</tr>
</tbody>
</table>

Conclusions: Incidence of PAD in the diabetic group in this study was 3.3 to 3.5 times that in the non-diabetic group. This was remarkably consistent between the 2 dialysis units despite large differences in gender mix, ethnicity and PAD incidence. Interestingly, although much has been published on the incidence of PAD in hospitalized diabetic patients, the data are subject to selection bias since, by definition, these patients have been referred as a result of ischemic symptoms. The strength of this study is that the findings are ‘incidental’ and not related to the reason for hospital attendance. Further work should be aimed at ascertaining whether early detection of PAD in this high-risk population may allow earlier intervention and treatment of this devastating condition.

Funding: Pharmaceutical Company Support - BlueDop Medical Ltd

SA-PO750 Cross-Sectional Study of Chronic Kidney Disease Prevalence in Association with Monoinfected Patients Hepatitis C Virus in ANRS CO-22 Hepather Cohort Eric Theret,1,2 Vincent Bonnenmann,1 Laurent Alric,1,4 Jean-Jacques Boiffia,1 Philippe Mathurin,1 Benedicte Stengel,1 Fabrice Carrat,1 Stéphane Fradet,1 Carole Cognet,1 Linda Withkop,1 Nephrology, HEGP, Paris 05, France; 1UMR976, U1223, UMR1136, UMR152, U1219, INSERM, France; 2Hepatology, Cochin, Paris 05, France; 3Internal Med-Dig, CHUTooulouse3, France; 4Nephrology, Tenon, Paris6, France; 5Hepatology, CHU Liège, France; ANRS, France; 6ISPED, France.

Background: Patients with chronic HCV infection have an increased risk of CKD. HCV is also more common in CKD patients than in the general population. The purpose of this study was to estimate the prevalence of ≥ stage3CKD in HCV patients and to look for correlation with the liver disease severity.

Methods: We analyzed the eGFR using CKDEPI formula in patients with a positive virus C serology in a multicenter observational prospective national cohort Hepatitis CO-22 (n = 20082). Exclusion criteria was kidney transplant recipients.

Results: The analysis included 8571 patients and the characteristics were: 56% men, 57 ± 20 years; 30% hypertensive; 10.0% diabetic. Patients with (vs. without) constipation had a higher multivariable adjusted risk of incident CKD: Risk Factors for Incidence and Progression – IIIPoster/Saturday

SA-PO751 Constipation and Incident Chronic Kidney Disease Keichi Sumida,1,2,3 Miklos Zsolt Molnar,1 Praveen Kumar Potukuchi,1 Fridjof Thomas,1 Jun Ling Lu,1 Elami Striga,1 Kunihiro Matsushita,1 Kunhiro Yamagata,1 Kamyar Kalantar-Zadeh,1 Csaba P. Kovesda,1,3 1Univ of Tennessee Health Science Center, Memphis, TN; 2Johns Hopkins School of Public Health, Baltimore, MD; 3Univ of Tsukuba, Ibaraki, Japan; 4Univ of California, Irvine, CA; 5VA Medical Center, Memphis, TN.

Background: Constipation is one of the most prevalent conditions in primary care settings, and it increases the risk of cardiovascular disease, potentially through inflammation triggered by altered gut microbiota. Little is known about its association with incident CKD.

Methods: In a cohort of 3,504,732 U.S. veterans with eGFR ≥60 ml/min/1.73 m² between 2004 and 2006 and follow-up through 2013, we examined the association of constipation status and its severity (absent, mild, or moderate/severe), defined using ECD9 codes and laxative use, with incident CKD and ESRD, and change in eGFR in Cox regression (for time-to-event analyses) and multinomial logistic (for eGFR slope) regressions, with adjustment for sociodemographics, comorbidities and medications.

Results: The mean (SD) age was 60.0 (14.1) years, 93% were male; and 25% were diabetic. Patients with (vs. without) constipation had a higher multivariable adjusted risk of CKD (HR, 1.25; 95% CI, 1.24-1.27) and ESRD (HR, 1.17; 95% CI, 1.08-1.26), and experienced faster eGFR decline (multinomial ORs [95% CI] for eGFR slope < −10 to < −5, and > −5 to < −1, vs. −1 to < −0.9 ml/min/1.73 m²/year, 1.12 [1.01-1.15], 1.07 [1.05-1.09], and 1.03 [1.02-1.05], respectively). More severe constipation was associated with incremental risk for all renal outcomes.

Conclusions: Constipation status and its severity are independently associated with higher risk of incident CKD and ESRD, and with progressive eGFR decline. Further studies are needed to elucidate the underlying mechanisms and to determine whether the amelioration of constipation can prevent adverse renal outcomes.

Funding: NIDDK Support, VA Support

SA-PO752 External Validation of the Framingham Risk Score for Incident Chronic Kidney Disease at 10 Years in a Thai General Population Chayapa Khivathanak,1 Konthong, N., Sukhoom, Prin Vithea,1 Vathoutakoti,1 Naksong Thongthong,1 Piyanitr Sritara.1 1Dept of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand; 2Research Center, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand.

Background: A risk score for incident CKD has been developed for the general population using the Framingham Heart Study (FHS) Offspring cohort. This score has been validated in Caucasians, African-Americans, but has not in an Asian population. Thailand has among the highest rise in ESRD in the world. The ability to identify patients at high risk of CKD may be essential to reduce ESRD rates. We aim to assess the performance of the FHS CKD risk predictors for incident CKD at 10 years follow-up in a Thai general population cohort.

Methods: Employees of EGAT (The Electric Generating Authority of Thailand) were studied prospectively in 2002 and followed up in 2012 (n=2588). Incident CKD refers to subjects without CKD at baseline who develop CKD (GFR <60) at follow up. CKD was defined alternatively by MDRD or CKD-EPI. The performance of the FHS simplified risk score (developed using MDRD) and the FHS 5 variable algorithms (separate algorithms for MDRD and CKD-EPI) for predicting incident CKD were assessed. Differences between predicted and observed rate were compared using Hosmer-Lemeshow test. Discrimination was quantified by c statistic. Calibration was performed to correct for differences in CKD and risk factors prevalence.

Results: After excluding CKD at baseline, 10.4% of subjects developed incident CKD by MDRD, and 10.0% developed incident CKD by CKD-EPI. For the original simplified risk score, the agreement between predicted and observed rates were not high (MDRD: c2 =20, P<0.001; CKD-EPI: c2 =256, P<0.0001) and the discrimination were moderate (MDRD: AUC=0.69, CKD-EPI: AUC=0.63). The observed versus predicted probability of CKD by the recalibrated FHS algorithm were fair: (MDRD c2 =19, p=0.015; CKD-EPI c2 =20, p=0.01) with CKD-EPI having better discrimination (AUC: MDRD, 0.67; CKD-EPI, 0.75).

Conclusions: The CKD-EPI FHS algorithm performs well in estimating a Thai individual’s 10-year probability of developing chronic kidney disease using clinical factors readily accessible in primary care.

Funding: Government Support - Non-U.S.

SA-PO753 Association of Urine Sulfate with Death and Kidney Outcomes in Hypertensive Chronic Kidney Disease Kalani L. Raphael,1 Jennifer L. Murray,2 David J. Carroll,1 Srini Beddhu.1 1Univ of Utah; 2Colorado College.

Background: The type of dietary protein, plant or animal, might be an important determinant of outcomes in chronic kidney disease (CKD) patients. We examined the association between urine sulfate excretion, an indicator of animal protein intake, with CKD progression and death in the African American Study of Kidney Disease and Hypertension (AASK).

Methods: Baseline urine [sulfate] ([mg/L] was measured by the barium precipitation method (n=1057). Daily sulfate excretion was calculated from 24-hour urine volumes. Participants were divided into tertiles of urine sulfate excretion ([mg/day], Cox and stage regression models related baseline urine sulfate excretion to the AASK primary composite outcome (death, dialysis or GFR reduction by 50%). Models were adjusted for demographics, randomized group, protein intake, urine potassium excretion, body mass index, measured GFR (mgFR), proteinuria, and serum bicarbonate at baseline. The lowest tertile was the reference group in the Cox model. The median sulfate excretion value was the reference in the spline model.

Results: Baseline characteristics were: age 54 years, 61% male, mgFR 47 ml/min per 1.73m², median proteinuria 81 mg/gm, and median urine sulfate excretion rate 26.3 (95%
and diastolic (DBP) blood pressure (age-gender-height z-scores). AKI C-eGFR (age-adjusted percentile), urine albumin to creatinine ratio (ACR), systolic (SBP) followed postop and 3, 12, 24, 36m post-discharge. AKI definition: ≥50% or ≥0.3 mg/dL baseline or dialysis. Follow-up included blood pressure (BP), SCr and Cystatin C-glomerular filtration rate (eGFR), urine albumin to creatinine ratio (ACR). HTN definition: systolic blood pressure, heart disease, and smoking status in the model. Adjusted spline regression model showed higher risk of the composite outcome with lower urine sulfate excretion.

Conclusions: Lower urine sulfate excretion was associated with a higher risk of death and CKD progression in African Americans with hypertensive CKD independent of mGFR, proteinuria, protein intake, and other factors.

Funding: VA Support, Private Foundation Support

SA-PO754

High Prevalence of Chronic Kidney Disease and Hypertension in the First 3 Years after Pediatric Cardiac Surgery

Michael Zappitelli,1 Chirag R. Parikh,2 Steven G. Coca,3 James S. Kaufman,4 Paul L. Kimmel,6 Marva M. Moxey-Mims,7 Vernon M. Chinchilli,8 Alan S. Go,9 Prasad Devarajan.3

Background: Late chronic kidney disease (CKD) and hypertension (HTN) outcomes after pediatric cardiac surgery (CS) are unclear. We determined CKD and HTN prevalence in the 3 years post-pediatric CS.

Methods: The Assessment, Serial Evaluation and Subsequent Sequela in AKI study includes a prospective cohort of children having CS at Montreal and Cincinnati Hospitals. Children were recruited pre-CS, followed postoperatively (postop) and at 3, 12, 24 and 36 m post-discharge. AKI definition: ≥50% or ≥0.3 mg/dL serum creatinine (Scr) rise from baseline or dialysis. Follow-up included blood pressure (BP), Scr and Cystatin C-glomerular filtration rate (eGFR), urine albumin to creatinine ratio (ACR). HTN definition: systolic (Sys) or diastolic (Dia) BP>95th percentile for height, gender, age. CKD definition: eGFR< or ACR> normal for age. HTN and CKD prevalence was calculated in the whole cohort and in AKI vs non-AKI groups.

Results: 124 children (52% boys, 46% AKI) were enrolled (11% loss/death over 3 years). In the whole cohort, CKD prevalence was 3, 12, 24, 36 m was 22, 32, 33, 34%, respectively. Similarly-defined CKD prevalence in the US general child population ranges from <2-12%. Follow-up HTN prevalence was 31, 18, 26, 22%, respectively, compared to general child population HTN prevalence of 1-4% (US/Canada population data). CKD or HTN prevalence did not significantly differ between AKI groups at any visit (p<0.05).

Conclusions: Within 3 years of pediatric CS, about one-third and one-fifth patients have CKD and HTN, respectively. This warrants close follow-up of children after CS, for renal and cardiovascular risk reduction.

Funding: NIDDK Support

SA-PO755

Renal Function and Blood Pressure Recovery 3 Years after Pediatric Cardiac Surgery-Associated Acute Kidney Injury: A Two-Center Study

Michael Zappitelli,1 Chirag R. Parikh,2 Steven G. Coca,3 James S. Kaufman,4 Paul L. Kimmel,6 Marva M. Moxey-Mims,7 Vernon M. Chinchilli,8 Alan S. Go,9 Prasad Devarajan.3

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Results: 124 children (52% boys, 46% AKI) were enrolled (11% loss/death over 3 years). In the whole cohort, CKD prevalence was 3, 12, 24, 36 m was 22, 32, 33, 34%, respectively. Similarly-defined CKD prevalence in the US general child population ranges from <2-12%. Follow-up HTN prevalence was 31, 28, 16, 22%, respectively, compared to general child population HTN prevalence of 1-4% (US/Canada population data). CKD or HTN prevalence did not significantly differ between AKI groups at any visit (p<0.05).

Conclusions: Within 3 years of pediatric CS, about one-third and one-fifth patients have CKD and HTN, respectively. This warrants close follow-up of children after CS, for renal and cardiovascular risk reduction.

Funding: NIDDK Support

SA-PO756

Charles Comorbid Index and the Progression of Renal Disease

Filipa B. Mendes,1 João Santos,2 Luisa H. Pereira,1 Ana Paula Silva,1,2 Ana Marreiros,3 Pedro Neves.3 1Nephrology Dept, Algarve Hospital Centre; 2Dept of Biomedical Science, Algarve Univ; 3Algarve Univ.

Background: With the worldwide ageing of population, associated with the consequent comorbidities, chronic kidney disease (CKD) prevalence is progressively increasing. These conditions multiply the dependence on health care units and increase costs. Because comorbidities could be expected to worsen the kidney function, the Charlson Comorbidity index (CCI) may have a role in the prediction of renal survival. In this study we evaluated the degree of comorbidities in a pre-dialysis population and investigated the relationships between the CCI and the renal progression disease.

Methods: A retrospective observational study included 693 patients, with an eGFR< 30 ml/min/1.73m2 followed in a pre-dialysis clinic during a four-year period (2008-2012). The population was divided into four groups according to the CCI: G1 (n=172); CCI ≤ 5.2; G2 (n=162); CCI 5.4-6.4; G3 (n=177) CCI 6.5-7.4 and G4 (n=182) CCI ≥ 7.5. Descriptive statistics, the ANOVA and the chi-square tests were used for comparison between groups. Bonferroni test was used as a post-hoc test. Multivariate and univariate logistic regressions for relationship between CCI and the other variables.

Results: The mean age of patients was 70.09 years, 54% (371) male gender and the mean eGFR (MDRD) was 20.17 ± 9.16 ml/min. When compared with the other groups, G1 showed lower age (p<0.001) and higher hemoglobin (p<0.001), eGFR (p<0.025), calcium (p<0.033) and albumin (p<0.001). In a multivariate logistic regression model adjusted to gender, phosphorus, eGFR, albumin and blood pressure, we found that CCI (OR= 1.002–2.623 p=0.049). female gender (OR= 2.046, 95% CI, 1.272-3.292, p<0.003), phosphorus (OR=2.212; 95% CI, 1.576-3.105 p<0.001) and eGFR (OR=0.868 95% CI, 0.823-0.915 p<0.001) were independent risk factors for renal disease progression and renal replacement therapy. By univariate logistic regression, G4 was a predictive factor for the progression of renal disease, when compared with G1 (OR: 1.622; 95% CI: 1.002-2.623 p<0.049).

Conclusions: In our study CCI was a strong predictor of renal disease progression in patients with chronic kidney disease stages IV-V.

SA-PO757

Oral Medicinal Charcoal Adsorbent Ameliorates Uremic Serum-Induced Intestinal Epithelial Barrier Disruption

Shanshan Jiang, Hongli Jiang, Dialysis Dept of Nephrology Hospital, First Affiliated Hospital of Medicine School, Xi’an Jiaotong Univ.

Background: Chronic kidney disease (CKD) causes intestinal barrier dysfunction which by allowing influx of endotoxin and other noxious products. Oral activated charcoal has been shown to markedly reduce plasma concentration of uremic toxins like indoxyl sulfate and p-cresol sulfate which are produced by the gut microbial flora. This study determined whether CKD-associated disruption of intestinal tight junction is mediated by activated charcoal adsorptive removal retained uremic toxins/metabolites.
The role of oestrogen in gender difference of CIN.

Medicine, Hospital Juan A Fernandez Univ de Buenos Aires, Buenos Aires, Argentina.

Background: Gender difference is reported in various diseases, in general, women seems have less common and less severe acute kidney injury and chronic kidney disease compared to men. However, female animals have more susceptibility of cisplatin induced nephropathy(CIN) were reported.

Methods: The National Health Insurance Research Database in Taiwan was used to identify patients received cisplatin treatment for cancer therapy. Patients have any history of acute or chronic kidney disease before using cisplatin, have multiple cancer or sex organ cancer and younger than 20 years old were excluded. Outcome is defined as diagnosis of either acute or chronic kidney disease within 3 months after first cisplatin administration. Age, non-steroid anti-inflammatory disease, treatment with aminoglycoside or exposure of contrast media were regarded as confounding factors and adjusted. Subgroups according to age of childbearing, perimenopause and post menopause in women were further analysed.

Results: A total of 3973 male and 1154 female patients with cisplatin treatment were analysed. The age was 56.15±12.85 and 56.31±12.40 in male and female separately without significant difference. Overall, 37.4% of patients who treated cisplatin has CIN without significant difference between men and women. Age older than 55 years old, history of diabetes mellitus, higher Charlson comorbidity score and treated with aminoglycoside after cisplatin were risk factors of CIN. In different age groups, women in perimenopause stage have a 1.28 times higher risk of CIN compared with men in the same age.

Conclusions: Women in perimenopause stage have a greater risk of CIN compared with men. Estrogen level is higher in the stage of perimenopause, which might imply the the role of oestrogen in gender difference of CIN.
SA-PO762
Association between GSTM1 Copy Number and Incident End-Stage Renal Disease in the Atherosclerosis Risk in Communities (ARIC) Study
Adrienne Cozzolino,1 Biagio Raffaele Di Micco,2 Domenico Galassi,1 Matthew Astor,1 Michelle B. Estrada,3 Megan Grove,4 Dan Arking,1 Eric Boerwinkle,3 Josef Coresh,1 1Johns Hopkins Univ; 2The Univ of Texas Health Science Center at Houston.
Background: Glutathione S-transferase mu 1 (GSTM1) catalyzes the conjugation of glutathione with a range of electrophiles. Having 0 copies of GSTM1 (GSTM1-0) has been associated with chronic kidney disease (CKD) progression in African American patients in the AASK trial. Whether GSTM1-0 is associated with ESRD in the general population independent of hypertension and diabetes is unknown.
Methods: In the African American cohort of the ARIC study, we estimated GSTM1 copy number using whole exome sequencing reads and ascertained ESRD events using linkage to the US Renal Data System (USRDS). We evaluated the association between GSTM1 copy number and the use of Cox regression controlling for age, sex, baseline eGFR, prevalent diabetes and hypertension. We estimated the association between GSTM1 copy number and ESRD in participants with and without 2 APOL1 renal risk alleles.
Results: Of the 1924 African Americans in this study, 52% had hypertension and 16% had diabetes. The mean baseline eGFR was 112 ml/min/1.73 m². The median follow-up time was 23 years. GSTM1-0 was significantly associated with a 1.72-fold higher risk of ESRD compared with those with 2 copies of GSTM1 (table, p-trend=0.04). When stratified by APOL1 risk, GSTM1-0 vs. 2 copies was associated with 2.45-fold higher risk of ESRD in those with 2 APOL1 risk alleles and a 1.6-fold high risk in those with 0/1 copy of the APOL1 risk allele (for interaction 0.70).
Conclusions: GSTM1 was significantly associated with ESRD independent of traditional risk factors. These results are consistent with those reported from the AASK trial and extend the association between GSTM1 copy number and ESRD in participants with and without 2 APOL1 renal risk alleles.
Summary: GSTM1-0 may be used to triage these patients to prepare for renal replacement therapy.

SA-PO763
Phosphate Balance and Outcome in Advanced CKD
Antonio Bellasi,1 Lucia Di Micco,2 Domenico Russo,2 Luca Di Lullo,3 Andrea Galassi,4 Mario Cozzolino,6 Biagio Raffaele Di Iorio,7 1ASST-Lariana; 2ASST-Lariana; 3PO Landolfi; 4Federico II Univ, Naples; 5Ospedale Parodi Delfino; 6ASST Monza - Desio; 7Univ of Milan.
Background: Perturbation of phosphate homeostasis portends unfavorable outcome in CKD. Although some lines of evidence suggest an association with mortality, serum levels of phosphate poorly reflect phosphate balance. A considerable effort is devoted to define new markers of phosphate homeostasis. We investigated the association of fraction excretion of phosphate (FeP) with relevant outcome in advanced CKD.
Methods: Retrospective, longitudinal study of 407 CKD subjects (age 66 years, 43% female, mean creatinine clearance 32 ml/min) receiving Nephrology care in Italy. Demographic and clinical characteristics were obtained at the time of referral. Routine laboratory and 24-urine collection were used. Risk of CKD progression to ESRD, all-cause mortality as well as the composite of the 2 were regarded as outcome of interest. ANOVA, logistic regression and survival analysis were used to compare patients’ characteristics across quartiles of FeP, detect predictors of FeP and the association of FeP with the outcome of interest.
Results: Higher FeP was associated with older age, higher azotemia and PTH levels as well as lower creatinine clearance, serum phosphate and 24-hour potassium excretion (all p-values<0.01). After adjustment for confounders, abnormal FeP (≥20%) was inversely associated with creatinine clearance (B=-0.03, p=0.060), diastolic blood pressure (B=-0.04, p=0.01) and serum phosphate (B=-0.43, p=0.008). Independent of multiple adjustments, a graded and independent association between quartiles of FeP and ESRD but not all-cause mortality was detected.
Conclusions: FeP is associated with ESRD but not all-cause mortality risk in a large cohort of advanced CKD patients. Future efforts are required to validate FeP as a marker of phosphate balance and if CKD progression explains the risk burden of phosphate imbalances in this high-risk population.
Funding: Government Support – Non-U.S.

SA-PO764
Acute Kidney Injury, Proteinuria, Glucocorticoid Control, and Kidney Disease Progression in Diabetes Mellitus
Mollie Y. Sands, Anthony C. Leonard, Charuvas Thakar. Univ of Cincinnati, Cincinnati, OH.
Background: Acute kidney injury (AKI), proteinuria (PU), and glucocorticoid control (A1c), are each known to influence the risk of chronic kidney disease (CKD) in diabetics. The relationship between these risk factors and CKD progression is not well studied.
Methods: In a de-identified Veterans Affairs cohort of 3,679 type 2 diabetics (T2D) with baseline glomerular filtration rate (eGFR) >30 ml/min (followed between 1999 and 2008, inpatient and outpatient), we examined relationships between PU, AKI (during hospitalizations), and mean A1c > 7 (averaged for study period) as major predictors. CKD progression outcomes were: annualized mean glomerular filtration rate (eGFR) decline; rapid decline (eGFR decline > 5 ml/min/year); and reaching Stage IV CKD. Logistic regression and Cox models (adjusted for demographics, co-morbidities and baseline eGFR) generated risk estimates expressed as odds and hazard ratios (OR, HR) with 95% confidence intervals (CI). The sample was 97.7% male (mean age of 61.7 yr), with mean baseline eGFR of 79.7 ml/min.
Results: Linear rates of eGFR decline across 3 risk groups [High (N = 421) mean A1c > 7, PU, and AKI; Medium (N=2,134) 1-2 of these risk factors present; Low (N=1,124) 0 present] showed a mean annual rate of decline of 4.33, 2.88 and 2.29 ml/min respectively (ANOVA p = 0.005; adjusted ANOVA p = 0.002). Overall, 14% (N=503) reached Stage IV CKD; compared to low-risk, the high-risk group was more likely to do so (adjusted OR, 7.2, 95% CI 5.1 – 10.1). For the rapid decline outcome (N=903) logistic regression models showed significant positive interactions between PU and mean A1c >7 (p = .005), and between PU and AKI (p = .007). The crude mortality rate was higher in rapid decliners (27.2% vs others 20.1%; p<.0001); as well as in those reaching Stage IV CKD (36.2% vs 19.8% in others; p<.0001).
Conclusions: Diabetics with AKI, PU, and mean A1c > 7 experience faster rates of linear eGFR decline, and are 7-fold more likely to reach Stage IV CKD than those without these risk factors. The effect of two risk factors at once (AKI and PU, or PU and mean A1c > 7) imparts more than respective additive effects on the rapid decline outcome.
Funding: VA Support

SA-PO765
Protein Composition of High Density Lipoprotein Varies with Progression of Chronic Kidney Disease
Background: High density lipoprotein (HDL) particles contain a heterogeneous composition of proteins of humoral and cellular origin and serve important anti-atherosclerotic functions. HDL particles from chronic dialysis patients are enriched in several proteins involved in inflammation, vitamin binding, and lipoprotein metabolism.
We used novel mass spectrometric methods to characterize the protein composition of HDL particles across the spectrum of kidney function.
Methods: We analyzed plasma samples of 507 participants from the Seattle Kidney Study, a clinic-based prospective study of chronic kidney disease (CKD). We used sequential density gradient ultracentrifugation to isolate the HDL fraction. HDL proteins were quantified using tryptic digestion and liquid chromatography-tandem mass spectrometry. We used linear regression to estimate associations of each 15 ml/min/1.73m² lower estimated glomerular filtration rate (eGFR) with the log transformed concentration of each HDL protein after adjustment for age, race, sex, diabetes, body mass index, smoking, and statin use.
Results: Mean participant age was 58 ±14 years, 24% were African American, 33% were female, and 50% had diabetes. The mean estimated GFR was 45 ±26 ml/min/1.73m² and the mean plasma HDL cholesterol concentration was 42 ±17 mg/dL. Lower estimated GFR was associated with significant differences in the concentration (per g total HDL protein) of multiple proteins within HDL. After full adjustment and accounting for multiple comparisons, lower estimated GFR was significantly associated with higher HDL concentrations of retinol binding protein 4, apolI-III, apolI, and lower HDL concentrations of vitronectin and apoL1.
SA-PO766

Metabolic Components and Chronic Kidney Disease (CKD) Prevalence in the United States

Background: Obesity is thought to affect CKD risk. We examined the association between the metabolic components (MC) related to obesity and CKD in a national sample.

Methods: This included participants ≥20 years old in the National Health and Nutrition Examination Survey 2007-14. CKD was defined as eGFR<60 ml/min/1.73 m² between the metabolic components (MC) related to obesity and CKD in a national sample.

Results: The number of MCs resulted in little association between BMI and CKD prevalence (Fig 1.b). Without BMI adjustment and 1.6 (1.4, 1.7) with BMI adjustment. A higher number of MCs with subjects with <3 MCs, in those with ≥3 MCs the adjusted PR of CKD was 1.6 (1.5, 1.8) without BMI adjustment and 1.6 (1.4, 1.7) with BMI adjustment. A higher number of MCs was associated with higher prevalence of CKD (Fig 1.a). Additionally, adjustment for the number of MCs resulted in little association between BMI and CKD prevalence (Fig 1.b).

Conclusions: In this cross-sectional analysis our findings suggest that MCs may incrementally increase the risk of CKD and that there may be little or no effect of BMI on CKD beyond these MCs.

Funding: Other U.S. Government Support

SA-PO767

ErbB4 Deletion Induced Metabolic Syndrome in Mice on a High Energy Diet

Background: Patients with obesity and diabetes have a higher risk to develop chronic kidney diseases. Although reports have indicated a possible relationship between decreased ErbB4 expression and diabetic nephropathy, its role in the development of diabetes has not been previously examined.

Methods: Heart rescued ErbB4 deletion (ErbB4Δht) and wild-type (WT) mice were fed a high energy diet (HED) that contains 11% fat. Body weight, body mass index, and lipid profile were measured. Insulin sensitivity was studied using IPGTT and IPITT. In the ErbB4Δht and WT mice were fed the HED after weaning and they had similar body weight. At 20-week of age compared to WT mice, ErbB4Δht mice developed metabolic syndrome manifested by increased body weight and fat weight; hyperglycemia; abnormal IPGTT, IPITT, and increased HOMA-IR index; and dyslipidemia shown by elevated levels of free fatty acid, cholesterol, triglycerides, and LDL cholesterol. Even though serum leptin levels were significantly increased in ErbB4Δht mice, there were no differences in food intake from controls. Serum adiponectin tended to be reduced in ErbB4Δht mice. Pathologically, ErbB4Δht mice developed severe liver steatosis, and larger adipocytes with large lipodroplets. Severe inflammation was predominantly detected in epidydimal white adipose tissue (eWAT) demonstrated by increased F4/80 immunoactivity and widely spread crown-like structures, with increased mRNA levels of iNOS, an M1 macrophage marker, with no significant changes of Arg1 expression, a marker for M2 macrophage. The mRNA levels of proinflammatory cytokines, TNF-α, MCP1/CC2, and CXCL1, were significantly increased in the eWAT of ErbB4Δht mice. There was no significant changes in the mRNA levels of IL-10 and IL-4, the antiinflammatory cytokines.

Conclusions: Our findings suggest ErbB4 is involved in energy homeostasis possibly through regulating insulin sensitivity and inflammation in adipose tissues, and may constitute a novel therapeutic target for the treatment of obesity and diabetes.

Funding: NIDDK Support, VA Support

SA-PO768

Obesity Predicts Steeper Measured Glomerular Filtration Rate Decline in a Non-Diabetic General Population

Background: Obesity is associated with an increased risk of end-stage renal disease. Obesity and diabetes are established mediators of the effect of obesity on kidney function. Whether obesity also contributes directly to the wide variation in age-related decline in the glomerular filtration rate (GFR) seen in healthy persons, is unknown. Previous studies of obesity and GFR decline have shown mixed results, depending on whether creatinine or cystatin C was used to estimate GFR. These estimates are confounded by non-GFR-related factors, and are inaccurate in the normal and high ranges of GFR. We aimed to explore the relationship between obesity and the measured GFR (mGFR) decline rate.

Methods: GFR was measured using iohexol clearance in 1594 non-diabetic middle-aged subjects without cardiovascular or renal disease from the general population. The study was repeated after a median observation time of 5.6 years in 1324 (83%) subjects in aged subjects without cardiovascular or renal disease from the general population. The mean (SD) mGFR decline rate was -0.95 (2.23) ml/min/year. The obesity variables were not linearly associated with a change in the mGFR decline rate in the multivariable adjusted linear mixed models. However, statistically significant non-linear relationships were found between the mGFR decline rate and both BMI and estimated BFP. The mGFR decline rate was analyzed using multivariable adjusted linear mixed models, and non-linear relationships were explored using fractional polynomial transformations.

Results: The mean (SD) mGFR decline rate was -0.95 (2.33) ml/min/year. The obesity variables were not linearly associated with a change in the mGFR decline rate in the multivariable adjusted linear mixed models. However, statistically significant non-linear relationships were found between the mGFR decline rate and both BMI and estimated BFP.

Conclusions: Severe obesity contributes to a steeper age-related mGFR decline in the non-diabetic general population.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim, Government Support - Non-U.S.

SA-PO769

Overweight Is Associated with Chronic Kidney Disease Progression

Background: Obesity and overweight are frequent in patients suffering from chronic kidney disease (CKD). Previous studies are discordant about the link between CKD progression and body mass index (BMI). We examined the database of our renal care network to study CKD course according to BMI.

Methods: We analyzed patients followed in the renal care network. All patients with two serum creatinine (Scr) values at an interval of 6 months or more were included. Patients with glomerular filtration rate (eGFR, MDRD equation) below 15 ml/min were excluded.

Conclusions: In this cross-sectional analysis our findings suggest that MCs may incrementally increase the risk of CKD and that there may be little or no effect of BMI on CKD beyond these MCs.
that ERβ can delay the progress of a variety of tissue fibrosis, but the role of ERβ in renal fibrosis is still unknown. The purpose of this study is to investigate the effect of ERβ in renal fibrosis and its underlying mechanism.

Methods: 40 biopsy-proven CKD patients were collected. The model of unilateral ureteral obstruction (UUO) was used in vivo, and mouse primary renal tubular epithelial cells (PTECs) were treated with TGFβ1 in vitro.

Results: 1) The expression of ERβ and snail 1 were significantly down-regulated in fibrotic renal tissues among the 40 biopsy-proven CKD patients. Besides, both ERβ mRNA and protein were decreased in UUO mice, compared with the sham group. 2) ERβ was widely expressed in mouse kidney, highest in the cortex, followed by the outer medulla and inner medulla. Moreover, ERβ was also expressed in mouse primary renal tubular epithelial cells. 3) UUO mice exhibited marked interstitial inflammation and fibrosis in renal tissue stained with hematoxylin and eosin and Masson’s trichrome. However, treatment with DPN, a specific agonist of ERβ, 5 days after UUO operation, significantly reduced inflammatory cell infiltration and interstitial fibrosis score. What’s more, UO-induced renal fibrosis was aggravated in ERβ knockout mice, compared with the WT mice. 4) DPN can significantly decrease collagen production in PTECs and reduce TGFβ1-induced PTECs’ EMT. Consistent with this, treated with ERβ-siRNA, collagen production and cell migration were increased in PTECs. 5) Over expression of snail 1 by plasmid can increase collagen production in PTECs and reduce TGFβ1-induced PTECs’ EMT.

Conclusions: ERβ hinders renal fibrosis in obstructive nephropathy by selectively inhibiting snail 1-induced renal tubular epithelial cell Epithelial to Mesenchymal Transition.

Funding: Government Support - Non-U.S.

SA-PO772
Chorioretinal Thinning in Chronic Kidney Disease Links to Inflammation and Endothelial Dysfunction Neeraj Dhaum. Centre for Cardiovascular Sciences, Univ of Edinburgh.

Background: Chronic kidney disease (CKD) is strongly associated with cardiovascular disease (CVD) and there is an established association between vasculopathy affecting the kidney and eye. Optical coherence tomography (OCT) is a novel, rapid method for high-definition imaging of the retina and choroid. Its use in patients at high CVD risk remains unexplored.

Methods: We used the new SPECTRALIS OCT machine to examine retinal and retinal nerve fibre layer (RNFL) thickness, macular volume and choroidal thickness in a prospective cross-sectional study in 150 subjects – 50 patients with hypertension, 50 with CKD and 50 matched healthy controls. The same, masked ophthalmologist carried out each study. Plasma IL-6, TNFα, ADMA, and ET-1, as measures of inflammation and endothelial function, were also assessed.

Results: Retinal thickness, macular volume and choroidal thickness were all reduced in CKD patients compared to hypertension and health (p<0.001 for CKD vs. both hypertension and health for each). RNFL thickness did not differ between groups. Interestingly, a thinner choroid was associated with a lower eGFR (p<0.0001) and, in CKD, with greater proteinuria as well as increased plasma concentrations of CRP, IL-6, ADMA and ET-1 (all p<0.05).

Finally, choroidal thickness associated inversely with renal histological inflammation and arterial stiffness. In a model of hypertension, choroidal thinning was seen only in the presence of renal injury.

Conclusions: The decreases in chorioretinal thicknesses in CKD are associated with lower eGFR and higher proteinuria but not blood pressure. Larger studies, in more diverse groups of CKD patients, are now warranted to clarify whether these eye changes reflect kidney pathology and the natural history of CKD. Similarly, the associations with measures of arterial stiffness, inflammation and endothelial dysfunction should be examined further.
Nuclear Phosphatase, SCP4 Interacts with the FOXOs Transcriptional Factors Contributing to Muscle Wasting in Chronic Kidney Disease

**Xinyan Liu,1 Yanlin Wang,2 William E. Mitch,2 Zhaoxiong Hu;1 Nephrology Div, The 2nd Hospital of Shanxi Medical Univ, Tianyuan, Shanxi, China; 1Nephrology Div, Baylor College of Medicine, Houston, TX.**

**Background:** Chronic kidney disease (CKD) and related inflammatory cytokines stimulate protein-energy wasting (PEW), a complication which manifests sustainably loss of muscle mass. The mechanisms leading to muscle wasting are complex but primarily resulting from accelerated protein degradation and activation of autophagic/lysosomal and proteasomal pathways. However, the regulation of these proteolysis pathways during muscle wasting remains unclear. We examined how a novel nuclear phosphatase, SCP4 (Small C-terminal Phosphatase 4) influences muscle protein metabolism by regulating FoxO transcription factors.

**Methods:** We measured protein synthesis and degradation in C2C12 cells with knockdown or forced-expression of SCP4 and examined the signaling pathway by which SCP4 regulates muscle protein metabolism. In muscles of CKD mice, we tested if knockdown of SCP4 ameliorates the loss of muscle protein.

**Results:** In muscle cell cultures, overexpression of SCP4 stimulates muscle proteolysis; conversely, knockdown SCP4 prevents cytokines and serum starvation induced muscle protein loss. SCP4 overexpression causes FOXO1a accumulation in nuclei and this response is accompanied by induction of atrogin-1/MuRF1 and activation of autophagic pathway. Treatment of myotubes with proinflammatory cytokines stimulates SCP4 expression and NF-kB mediates this response. In muscle of CKD mice, SCP4 is up-regulated and observed in muscles of patients with CKD. Mice with SCP4 knockout or knocking down SCP4 by electroporation of SCP4 shRNA in muscle decrease FoxO1a nuclear accumulation and transcription activities despite of CKD. These led to suppression of protein degradation and maintain muscle mass.

**Conclusions:** SCP4 expression stimulates muscles proteolysis in CKD. Targeting SCP4 may prevent muscle wasting in CKD and perhaps other catabolic conditions.

**Funding:** NIDDK Support

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Magnetic Resonance Imaging Sensitive to Hypoxia and Fibrosis in a Multi-Center Study of Chronic Kidney Disease

**Pottumarthi V. Prasad, Wei Li, Eugene Dunkle, Ying Zhou, Stuart M. Sprague, Combine Investigators. NorthShore Univ HealthSystem, Evanston, IL.**

**Background:** Renal hypoxia and interstitial fibrosis are key contributors to CKD progression according to chronic hypoxia theory [PMID: 9551436]. Phosphate and FGF23 excess have been linked to accelerated CKD progression. COMBINE (CKD Optimal Management with Binders and Nicotinamide) is a multicenter trial to test whether nicotinamide and lanthanum carbonate will safely lower serum phosphate and FGF23 levels in an attempt to prevent cardiovascular and progressive renal disease compared to placebo. In this study, we evaluated both renal cortical oxygenation and diffusion coefficients using blood oxygenation level dependent (BOLD) and diffusion MRI at baseline in subjects participating in COMBINE and compared them to measures in a cohort of healthy subjects with no known renal disease.

**Methods:** To date data was available for a total of 98 subjects with CKD (age=65.8±11.9 years; 53% male; 73% eGFR<60 ml/min/1.73m²) and 29 healthy controls (age=41.3±18.9 years; 61% male). Both BOLD and Diffusion MRI data was acquired on a 3.0 T scanner. BOLD MRI measurements were repeated following administration of 20 mg i.v. of furosamide. Large cortical and whole kidney regions of interest (ROIs) were used for analysis [PMID: 26193455]. Lower oxygenation should result in higher R2* values and presence of fibrosis should result in lower apparent diffusion coefficient (ADC).

**Results:** Both cortical R2* (20.6±3.4 vs. 18.0±1.6 ±10-4 s-1; p=0.0001) and ADC (1460.0±165.5 vs. 1715.5±92.0 mm²/s; p<0.0001) were significantly different in CKD compared to controls. Further the response to furosamide was significantly reduced in CKD (1.0±0.9 vs. 2.3±1.1 ±10-4 s-1; p<0.0001). All the three MRI measures showed significant correlation with eGFR (R2*=-0.34 (p=0.0003); p=0.0001). ADC (R2*)= 0.41 (p<0.0001); p<0.0001) were significantly different in CKD vs. controls. Further the response to furosemide was significantly reduced in CKD compared to controls. We found a significant correlation between the degree of tubular loss on chronic phase after AKI.

**Conclusions:** SCP4 knockout or knocking down SCP4 by electroporation of SCP4 shRNA in muscle may prevent muscle wasting in CKD and perhaps other catabolic conditions.

**Mikako Urinary Human L-Type Fatty Acid Binding Protein on Chronic Phase of Chronic Kidney Disease**

**Zhaoyong Liu,1 Yung Ma,2 Ha Yeon Kim,1 Chang Seong Kim,1 Eun Hui Bae,1 Seong Kwon Ma,1 Kook-Hwan Oh,2 Soo Wan Kim,1 Curie Ahn.2 1Chonnam National Univ Medical School; 2Seoul National Univ Hospital.**

**Background:** We investigated the relationships of dietary phosphate intake and serum phosphate with chronic kidney disease (CKD) stages 3-5. We collected 24-h non-dialysis patients from a prospective cohort study (NIDK-COCK). A renal event is defined by a >50% decrease in estimated glomerular filtration rate (eGFR) from the baseline values, doubling of serum creatinine, or end stage renal disease. CV event is defined myocardial infarction (fatal and nonfatal), coronary revascularization, stroke and new or aggravation of congestive heart failure. We used multivariate logistic regression models to assess associations of baseline 24-h urine phosphate excretion and serum phosphate with clinical outcomes (renal and CV event).

**Results:** Among the 849 participants in this study, the mean age ± SD was 56.5 ± 11.2 years (range: 20-75); 61.7% were male. 24-h urine phosphate excretion was not correlated with serum phosphate concentrations after eGFR adjustment (r=−0.073, P=0.034). Models were adjusted for age, sex, primary renal disease (glomerulonephritis, diabetes, hypertension, polycystic kidney disease and others), eGFR, 24-h urine protein and an oxygenation, body mass index, smoking, use of phosphate binder and coronary artery disease. There was no association of 24-h urine phosphate excretion with renal event, CV event and total event. Whereas, higher serum phosphate concentrations were not associated with renal event (odds ratio [OR] 1.839, 95% confidence interval [CI] 0.839-4.028, P=0.128) and CV event (OR 1.491, 95% CI 0.565-3.925, P=0.419). But, strongly associated with total event (OR 1.957, 95% CI 1.008-3.800, P=0.047).

**Conclusions:** There was no evidence that dietary phosphate intake assessed by 24-h urine phosphate excretion is associated with clinical outcomes. On the other hand, higher serum phosphate was associated with clinical outcomes in CKD stages 3-5.

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

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Patient Awareness of Target Blood Pressure and Hypertension Control in Chronic Kidney Disease

**Natalia Alencar de Pinho,1 Celine Lange,1,2 Luc Frimat,1 Denis Fouque,2 Maurice Laville,6 Christian Jacquelinet,1 Bruce M. Robinson,1 Christian Combe,1 Ziad Massy,1,2 Benedicte Stengel,1 1CESP Inserm U1018, Villejuif; 2Agence Biomédecine; 3CHU Nancy; 4CHU Lyon; 5Arbor Research Collaborative for Health, Ann Arbor; 6CHU Bordeaux; 1CHU A.Paré –APHP, France.**

**Background:** Patient awareness of treatment goals may help improving risk factor control in CKD. We assessed awareness of target blood pressure (BP) among CKD patients and its associations with BP control.

**Methods:** We used baseline data from the CKD-REIN/CKDOPPS study, a prospective cohort study of patients enrolled with CKD stage 3 and 4 in a nationally representative sample of 40 nephrology clinics in France. We compared patients who reported target BP ≤140/90 mmHg (BP ≤140/90 mmHg) to patients who did not. We performed separate analyses with achieved BP ≤140/90 or <130/80 mmHg as dependent variable.

**Results:** Of 2850 patients, 86% had a diagnosis of hypertension registered in medical records. Median age was 69 [QR 62-77] years, 66% were men, 41% had stage 4 CKD, 38% were smokers and 35% of their hypertension was treated. Awareness of target BP “to have been told about target BP”, “94% reported target SBP ≤140 (including 67% reporting target SBP value ≤130), 5% reported target SBP ≥140, and 1% did not remember their target. Fewer patients (75%) reported a diastolic BP target value. Overall, 40% of the patients had BP ≤140/90, and 17%, office BP ≤130/80. Awareness of target SBP was associated with younger age, higher education level, CKD awareness, and self-BP monitoring. After adjusting for potential confounders, patients reporting target SBP values ≤140 did not have...
better BP control, whatever the threshold. Those who reported target SBP <130 were more likely to have BP <140/90 (OR 1.34 95% CI 1.09-1.65, p =0.006), but not <130/80 (OR 1.16 95% CI 0.90-1.51, p =0.26).

Conclusions: Both awareness of BP target and achievement of BP <140/90 mm Hg are low among CKD patients. Given the importance of hypertension control in preventing CKD progression and cardiovascular complications, setting lower SBP targets (<130) may be a strategy to achieve minimally acceptable BP control (<140/90).

Funding: Pharmaceutical Company Support - AMGEN, Baxter, Fresenius Medical Care, MSD, Lilly, Otsuka, Government Support - Non-U.S.

SA-PO778

Geographic Variation in Rapid Kidney Function Decline

Benjamin Charles Bowe,1 Yan Xie,1 Hong Xian,2 Ziyad Al-Aly,3,4 1Clinical Epidemiology Center, Research and Education Service, VA St. Louis Health Care System, St. Louis, MO; 2Dept of Biostatistics, St. Louis Univ. St. Louis, MO; 3Dept of Medicine, Washington Univ School of Medicine, St. Louis, MO; 4Div of Nephrology, VA St. Louis Health Care System, St. Louis, MO.

Background: Geographic variation in the prevalence of CKD and incidence of ESRD has been previously reported. However, the geographic epidemiology of rapid eGFR decline has not been examined. We aimed to characterize the spatial epidemiology of rapid eGFR decline using a national longitudinal cohort of United States Veterans.

Methods: We built a cohort of 2,107,570 US veterans and investigated the prevalence of rapid eGFR decline (defined as eGFR slope < -5 ml/min/1.73 m^2/year) and potential ecologic risk factors using mixed effect logistic regression models. To examine possibility of clustering, cluster analysis was performed.

Results: 1. Prevalence of rapid eGFR slope adjusted for age, race, gender, diabetes, and hypertension varied by county from 4.10-6.72% in the lowest prevalence quintile to 8.41-22.04% in the highest prevalence quintile (p for heterogeneity <0.001). Examination of adjusted prevalence by diabetes and hypertension status showed that while these conditions were major drivers of rapid eGFR decline, substantial geographical variation was present in those with and without diabetes and those with and without hypertension. Compared to rural areas, living in metropolitan neighborhoods was associated with increased odds of rapid eGFR decline (OR: 1.09; CI: 1.03-1.14). Residents of counties with higher proportion of people living in poverty, and higher percentage of African Americans exhibited highest odds of rapid eGFR decline (OR: 1.05; CI: 1.01-1.10; and OR: 1.20; CI: 1.16-1.27, respectively). Spatial analyses suggest the presence of cluster of counties with high prevalence of rapid eGFR decline.

Conclusions: In conclusion, our findings show substantial geographic variation in rapid eGFR decline among United States veterans; the variation persists in analyses stratified by presence of diabetes and hypertension; results also suggest ecologic factors associated with rapid eGFR decline.

Funding: VA Support

SA-PO779

Optimizing Timing of Pre-Emptive AV Access Creation: Results from the CRIC Study


Background: Scant data exist to guide clinicians regarding optimal timing of pre-emptive AV access surgery (surgery) in preparation for chronic dialysis. We hypothesized that using a trigger based on predicted likelihood of developing ESRD within the next year had appropriately undergoing/correctly triggering surgery among those who actually developed ESRD. We calculated sensitivity as the probability of a priori Equation (KFRE)(Tangri JAMA 2011) estimated likelihood of developing ESRD within 1-yr >20%

Methods: We studied Chronic Renal Insufficiency Cohort (CRIC) enrollees with eGFR <30 ml/min/1.73m^2 after 8/2010 (N=608). We compared 3 potential strategies: i) current practice, captured by patient self-report of surgery; ii) hypothetically triggering surgery when eGFR <20 ml/min/1.73m^2; iii) hypothetically triggering surgery when Kidney Failure Risk Equation (KFRE)/Tangri JAMA 2011 estimated likelihood of developing ESRD within 1-yr >20% (thresholds chosen a priori). We calculated sensitivity as the probability of appropriately undergoing/correctly triggering surgery among those who actually developed ESRD within a year. Specificity is the probability of correctly not undergoing/not triggering surgery among those who did not develop ESRD within a year.

Results: Mean age of the study population was 66 years, 49% were female, 40% non-Hispanic whites and 41% non-Hispanic blacks. 118 cases of chronic hemodialysis were observed. A strategy guided by likelihood of developing ESRD within the next year had the best disease odds ratio (DOR) at 2.79 (Table 1).

Current practice (patient self-report of AV access surgery)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (CR)</td>
<td>0.987 (0.980, 0.992)</td>
<td>0.986 (0.985, 0.987)</td>
</tr>
<tr>
<td>DOR (95% CI)</td>
<td>24.0 (21.7, 25.2)</td>
<td>2.88 (2.80, 2.96)</td>
</tr>
</tbody>
</table>

Scenario if AV access surgery triggered by eGFR <20 ml/min/1.73m^2

<table>
<thead>
<tr>
<th>Scenario</th>
<th>OR (CR)</th>
<th>p-value</th>
<th>DOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.831 (0.806, 0.855)</td>
<td>0.001</td>
<td>2.20 (2.16, 2.25)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.787 (0.659, 0.876)</td>
<td>0.001</td>
<td>1.28 (1.25, 1.31)</td>
</tr>
<tr>
<td>DOR (95% CI)</td>
<td>18.1 (9.2, 35.4)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Scenario if AV access surgery triggered by likelihood of ESRD within 1-yr >20%

<table>
<thead>
<tr>
<th>Scenario</th>
<th>OR (CR)</th>
<th>p-value</th>
<th>DOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.932 (0.913, 0.941)</td>
<td>0.001</td>
<td>2.20 (2.16, 2.25)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.672 (0.548, 0.776)</td>
<td>0.001</td>
<td>1.28 (1.25, 1.31)</td>
</tr>
<tr>
<td>DOR (95% CI)</td>
<td>27.9 (15.5, 50.3)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Using predicted likelihood of ESRD to guide pre-emptive AV access surgery may be a promising strategy.

Funding: NIDDK Support

SA-PO780

The Expression of VDR in Renal Tissue of Lupus Nephritis and Its Association with Renal Injury Activity

Jian Sun,1 Shuang Zhang,1 Youzhou Tang,1 Ming Gui,1 Wei Zhang,1 Hao Zhang,1 1Dept of Nephrology, The Third Xiangya Hospital, Central South Univ, Changsha, Hunan, China; 2Dept of Medicine, Div of Biological Sciences, Univ of Chicago, Chicago.

Background: The incidence of systemic lupus erythematosus is closely related to the polymorphism of vitamin D receptor (VDR). To further explore the role of VDR in lupus nephritis (LN), we observed the expression of VDR in renal tissue of LN and evaluated the renal pathological index.

Methods: 20 renal biopsy specimens were collected from 35 patients with LN according to ISN/RPS2003 lupus nephritis type standards pathological type and carrying out the activity index (AI), chronic index (CI). 5 tissue specimens over 2cm far from kidney tumor of renal cancer patients were used as normal control. The expression of VDR were detected by immunohistochemistry in renal tissue of two groups. The relationship between VDR expression and histological injury index, proteinuria and SLICC renal activity scores were analyzed.

Results: 1. Compared with the control group, the expression of VDR in the lupus nephritits were lower(P<0.05). 2. The expression of VDR were negatively correlated with AI (r=-0.548, P =0.012), and no correlation were observed between VDR level and CI (r >0.05). 3. The expression of VDR in renal tissue is negatively correlated with SLICC renal activity scores. (r=-0.470, P =0.037).

Conclusions: Down-regulation of VDR in renal tissue of lupus nephritis was associated with renal activity injury severity.

SA-PO781

Renal Outcomes in Patients with Colorectal Cancer and Repeated Intravenous Contrast Contrast Exposure

Jennifer Heinen, Meier Hsu, Roman A. Shingarev. Medicine, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Renal function in cancer patients is affected by exposure to various nephrotoxins. Its preservation is important for effective cancer treatment and surveillance. Contrast-induced nephropathy is a well-recognized acute complication in this population, but the long-term effects of repeated contrast exposure are unknown. We analyzed the association of the number of contrasted computed tomographies (cCT) and other clinical factors with the reduction of eGFR in colorectal cancer (CRC) survivors after CRC resection.

Methods: We retrospectively queried a prospective surgical CRC database to identify 592 patients with stage I or II CRC who underwent resection in 2007-2012 and were alive for at least 3 years. CKD-EPI equation was used to calculate eGFR relative to baseline was defined as significant and used as the primary outcome. The association of clinical factors with the primary outcome at 1 and 3 years was analyzed using logistic regression.

Results: At 1 year, 313 patients had creatinine (Cr) available for eGFR calculation. Significant eGFR decline was observed in 51 (16%) of these patients. In multivariable analysis, cardiovascular disease (CVD) was independently associated with significant eGFR decline [OR=2.4, 95%CI(1.18-4.89), p=0.02]. At 3 years, 208 patients with measured Cr were available with 34 (16%) demonstrating significant eGFR decline that was associated with comorbid hypertension, CVD and operation time. Exposure to ≥24 cCTs was marginally associated with significant eGFR decline.

Figure 1. Univariate analysis of eGFR decline

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

810A
SA-P0783
The Tissue Expressions of Tubular Injury Marker, NGAL and KIM-1, Are Associated with Renal Function Decline in Diabetic Nephropathy
Subin Hwang, Eun Jeong Lee, Jae Shin Choi, Hee Jin Kwon, Hye Ryoun Jang, Woosong Huh, Youn-Goo Kim, Da Jeon Kim, Ha Young Oh, Jung Eun Lee.
Div of Nephrology, Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Korea.

Background: The tubular injury may be involved in the pathogenesis and progression of renal dysfunction in addition to glomerular damage in diabetic nephropathy (DN). This study was conducted to examine whether tubular expressions of neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) predict the subsequent decline of renal function in human DN.

Methods: We identified 126 patients with diabetes who underwent renal biopsy from 2000 to 2014 and confirmed to have DN. After exclusion of patients with coexisting other renal disease, estimated glomerular filtration rate (eGFR) > 30 ml/min/1.73m², 35 subjects were included in the analyses. Annual decline of eGFR (GFR slope) was calculated by linear regression analysis. We assessed tissue tubular expressions of NGAL and KIM-1 by immunohistochemistry.

Results: Overall, GFR slopes were linear. The median baseline urinary protein to creatinine ratio (PCR) was 6.76 (2.18 - 7.61) mg/mgCr, the median baseline eGFR was 50.4 (42.6 - 64.4) ml/min per 1.73m², and median GFR slope was -15.6 (-32.3 - 0.7) ml/min per 1.73m² per year. In linear regression analyses, tubular expressions of NGAL were correlated with GFR slope and interstitial fibrosis and tubular atrophy score (P = 0.012, P = 0.088, respectively). Those of KIM-1 were correlated with GFR slope and PCR (P = 0.002, P = 0.003, respectively). In multivariate analyses, tubular expressions of NGAL remained as an independent predictor of GFR slope (P = 0.011). However, the association between KIM-1 expressions and GFR slope was dependent on PCR.

Conclusions: Tissue expressions of tubular injury marker, NGAL were closely associated with GFR decline, independently of PCR. These findings suggest that tubular injury might play an independent role in the pathogenesis of DN.

SA-P0784
Associations of Blood Pressure with End Stage Renal Disease in Chronic Kidney Disease
Matthew F. Blum,1 Jesse D. Schold,1 Stacey Jolly,1 Susana Arrigain,1 Joseph V. Nally,1 Sankar D. Navaneethan.2 1Cleveland Clinic; 2Baylor College of Medicine.

Background: Hypertension is a risk factor for kidney disease progression, but the optimal blood pressure for CKD patients is undetermined. We studied the associations of systolic and diastolic blood pressure with ESRD among non-dialysis dependent CKD patients.

Methods: We included 31850 patients with eGFR < 60 ml/min/1.73m² (twice 90 days apart) and on at least one antihypertensive agent. ESRD details were ascertained from the US Renal Data System. We fitted competing risk regression models for ESRD to evaluate various SBP (<110, 110-119, 120-129, 130-139, 140-149, and ≥150 mmHg) and DBP (<50, 50-59, 60-69, 70-79, 80-89 mgHg) targets. The competing event was all-cause mortality.

Results: During a median follow-up of 2.2 years, 915 patients developed ESRD. In multivariate models, SBP <110 and 110-119 mmHg were associated with lower risk of ESRD, while SBP ≥150 mmHg was associated with higher risk of ESRD. DBP ≥90 mmHg was associated with higher risk of ESRD.

Conclusions: In a non-dialysis dependent CKD population, SBP <120 mmHg was associated with a lower risk of ESRD. SBP ≥150 mmHg and DBP ≥90 mmHg were associated with a higher risk of progression to ESRD.

Funding: Pharmaceutical Company Support - Development of CCF CKD registry is supported by an unrestricted grant to the Department of Nephrology and Hypertension, Cleveland Clinic from Amgen.

SA-P0785
The Effect of Calcitriol and Cholecalciferol Supplementation on Proteinuria in CKD Stage 3-4
Jessica B. Kendrick,1 Emily Decker,2 Zhiying You,1 Michel Chonchol.1 1Univ of Colorado Denver; 2Denver Health & Hospital.

Background: Vitamin D deficiency is associated with an increased risk of proteinuria and kidney disease progression in patients with chronic kidney disease (CKD). The effect of vitamin D supplementation on proteinuria has not been well studied. We examined the effect of calcitriol vs. cholecalciferol supplementation on proteinuria in a randomized double-blind, direct head-to-head comparison.

Methods: In a randomized trial to evaluate the effect of calcitriol vs. cholecalciferol on vascular endothelial function, 128 patients with CKD stage 3-4 (estimated GFR 15-44 ml/min/1.73m²) with vitamin D deficiency, defined as serum 25-hydroxyvitamin D level < 30 ng/ml, and proteinuria < 3.5 g/day, were randomly assigned to receive either cholecalciferol (4000 IU daily x 4 weeks then 2000 IU daily x 20 weeks) or calcitriol (0.25 mg/day x 4 weeks then 0.5 mg/day x 20 weeks). Urinary albumin to creatinine ratio (ACR) was measured at baseline and end of study. We examined the change in ACR from baseline to end of study in the calcitriol group vs. cholecalciferol group.

Results: 115 patients completed the study. The mean (SD) age and eGFR was 58.1 ± 12.5 years and 33.2 ± 10.0 ml/min/1.73m², respectively. The use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) was similar between the two groups (69.6% in the calcitriol group vs. 68.5% in the cholecalciferol group). The baseline median (IQR) ACR was 222.0 (39.7-846.8) mg/g in the calcitriol group and 158.8 (29.2-585.6) mg/g in the cholecalciferol group. Over the 6 month time period, the ACR decreased from baseline in the calcitriol group by 14.6%, p<0.02 and increased in the cholecalciferol group by 5.8%, p=0.35. The change in ACR during the follow-up period between the two groups was significant (+1.36, 95% CI -7.25 to 6.62, p=0.02). The between-group difference in IQR remained after adjustment for age, gender, race, systolic blood pressure and use of ACEI/ARB. Incidence of hypercalcemia and adverse events was similar between the two groups.

Conclusions: Treatment with calcitriol but not cholecalciferol results in a significant decrease in albuminuria in patients with CKD stage 3-4.

Funding: NIDDK Support.
SA-PO786

Increasing Climate Temperature Is Associated with Earlier Age of Onset of End Stage Renal Disease


Background: Global temperature is increasing, and there has been a rising concern that high climate temperatures may be associated with chronic kidney disease such as Meso-American Nephropathy. To explore the relationship between climate temperature and age of ESRD, we evaluated data from the United States Renal Data System (USRDS). US data is particularly useful because of a relatively standard approach to when dialysis is started and because of a broad range in climate temperature in the US.

Methods: We obtained data for all patients with new onset ESRD between ages 30 and 90 in the continental United States. We were particularly interested in where individuals were likely to have spent most of their life rather than where they lived when dialysis was initiated. We therefore obtained from the USRDS the state where each patient obtained his social security number. In the US, social security numbers are usually obtained before or at the age of 18 years. We obtained median annual state temperature data from the US National Oceanographic and Atmospheric Association. A multivariate linear regression model was developed with age of ESRD as the outcome variable, and gender, race, median income, and median annual state temperature as independent variables.

Results: 2.3 million individuals were included in the analysis. There was an inverse linear relationship between age of onset of ESRD and climate temperature.

Conclusions: Higher climate temperatures are associated with a younger age of onset of ESRD. This could significantly contribute to ESRD incidence in developing countries, and could be affected by climate change.

Funding: Clinical Research Support

SA-PO787

Estimation of Nephron Number of Japanese CKD Patients

Toshiyuki Imasawa,1 Takelko Kawaguchi,2 Kensei Yahata,3 Takashi Nakazato,4 ‘Kidney Center, National Hospital Organization Chiba-East Hospital, Chiba-city, Chiba, Japan; 1Dept of Nephrology, National Hospital Organization Kyoto Medical Center, Kyoto-city, Kyoto, Japan; 2Dept of Medical Information Management, National Hospital Organization Chiba Medical Center, Chiba-city, Chiba, Japan.

Background: Previous studies showed that nephron number is a good predictor of CKD progression. However, all these results were based on animal studies or on autopsied human kidneys (retrospective studies). Because nephrologists cannot count nephron number of CKD patients, this knowledge is unavailable at a real clinical place. Recently, we established an estimation formula for nephron number in CKD patients who were received kidney biopsies (BMC Nephrol 2012, 13:11).

Methods: Patients were from PRONEP (Predicting the Outcome of Chronic Kidney Disease by the Estimated Nephron Number) study (protocol: BMC Nephrol 2012). In this analysis, 573 Japanese patients were included. By the estimation formula, we calculated nephron numbers of Japanese CKD patients. In addition, nephron numbers of IgA nephropathy, diabetic nephropathy, and FSGS (focal segmental glomerulosclerosis) due to hemodynamic factor were individually calculated. Because sclerosed glomeruli might be absorbed, we also calculated nephron numbers of cases whose eGFR were over 45 ml/min/1.73m².

Results: All results are in Table.

SA-PO788

The Association of Sleep Duration and Quality with Chronic Kidney Disease Progression


Background: Although there is increasing evidence that sleep disorders are common in individuals with chronic kidney disease (CKD), its association with CKD progression is not known. We examined the association of sleep duration and quality with CKD progression and all-cause death.

Methods: We conducted a prospective longitudinal study of 432 adults (mean age 60 years, 48% women, 48% and mean estimated glomerular filtration rate [eGFR] 38 ml/min/1.73m²) enrolled at two participating sites of the CRIC Study. Participants wore a wrist actigraph for 5-7 days to measure sleep duration and quality. Subjective sleep quality, apnea risk and daytime sleepiness were self-reported using validated questionnaires. We used Cox proportional hazards models to evaluate the association of sleep measures with incident end stage renal disease (ESRD) and all-cause death, and linear mixed-effects models to assess differences in eGFR slope.

Results: Participants slept an average of 7.4 hours/night, and the mean sleep fragmentation was 21%. Over median follow-up of 5 years, we observed 70 ESRD events and 48 deaths. In analyses adjusted for sociodemographic factors, body mass index, blood pressure, diabetes, cardiovascular disease and baseline kidney function, longer sleep duration was associated with 19% lower risk of ESRD (HR 0.81, 95% CI 0.67-0.99 per hour increase in sleep duration), and higher sleep fragmentation was associated with 4% increased ESRD risk (HR 1.04, 95% CI 1.01-1.07 per 1% increase in fragmentation). In adjusted mixed effects regression models, higher sleep fragmentation was associated with significant eGFR decline (-0.17 ml/min/1.73m²/year, p = .016). Self-reported daytime sleepiness was associated with 10% increased risk for all-cause death in the fully adjusted model (HR 1.10, 95% CI 1.02-1.18, per 1 unit increase). We found no significant association between sleep start time, self-reported sleep quality or apnea risk with outcomes.

Conclusions: These findings suggest that short and poor quality sleep are unapprreciated risk factors for CKD progression.

Funding: NIDDK Support

SA-PO789

The Association of Histopathological Lesions with Renal Function Decline and Mortality in Biopsy-Confirmed Kidney Disease

Anand Srivastava,1 Arnaud Djou Kaze,1 Isaac Ely Stillman,2 Helmut G. Remm,2 Sushrut S. Waikar,1 1Renal Div, Brigham & Women's Hospital, Boston, MA; 2Pathology Dept, Brigham & Women's Hospital, Boston, MA; 3Pathology Dept, Beth Israel Deaconess Medical Center, Boston, MA.

Background: Kidney biopsy is the gold standard for diagnosing many kidney diseases, and may also provide prognostic information. No study to our knowledge has tested whether histopathologic lesions independently predict outcomes across a variety of kidney diseases.

Methods: We enrolled 654 patients undergoing kidney biopsy at three tertiary care hospitals in Boston, MA into a prospective observational cohort study. We fit multivariable-adjusted Cox proportional hazards models to test the association of histopathological lesions involving the mesangium, vessels, and tubulointerstitium with the composite endpoint of renal function decline (doubling of serum creatinine or need for renal replacement therapy) or mortality.

Results: The most common diagnoses were lupus nephritis (13.6%), IgA nephropathy (11%), and diabetic nephropathy (10.4%). 38.3% had other primary glomerular diseases and 37.1% had non-glomerular diseases. 127 patients reached the primary endpoint over a median follow-up time of 21.9 [IQR 10.9–42.8] months. Table shows the associations of histopathological findings with the composite endpoint, adjusted for age, race, sex, log(proteinuria), and estimated glomerular filtration rate (eGFR).
This review identifies a potentially important correlation whereby change in albuminuria and clinical outcomes, we determined the treatment effect ratio characteristics and outcome data independently. To determine the association between albuminuria progression and adverse clinical outcomes (all-cause death, cardiovascular disease [CVD], and end-stage renal disease [ESRD]) in adults based on a systematic review of the literature.

Methods: CENTRAL, EMBASE, and MEDLINE were systematically searched for randomized controlled trials (1946-January 2015) that reported change in albuminuria and treatment effect on the change in albuminuria. Two reviewers abstracted trial characteristics and outcome data independently. This review identified a potentially important correlation whereby change in albuminuria and clinical outcomes, we determined the treatment effect ratio characteristics and outcome data independently. To determine the association between albuminuria progression and adverse clinical outcomes (all-cause death, cardiovascular disease [CVD], and end-stage renal disease [ESRD]) in adults based on a systematic review of the literature.

Results: We identified 27 trials (50,300 patients) that met the inclusion criteria. Reported data on ESRD, 13 on CVD, and 19 on all-cause death. Treatment effects on the change in albuminuria and clinical outcomes, we determined the treatment effect ratio (TER), defined as the ratio of the treatment effects on clinical outcomes and the effects on the change in albuminuria.

Conclusions: Across a diverse group of kidney diseases, histopathological lesions on kidney biopsy provide independent prognostic information even after adjusting for known risk factors including proteinuria and eGFR.

Funding: NIDDK Support

SA-PO790

Assessing the Association between Change in Albuminuria and Clinical Outcomes: A Systematic Review and Meta-Analysis Tyrone Harrison, Helen Tam-Tham, Brenda Hemmelgarn, Min Jun. Univ of Calgary, Calgary, AB, Canada.

Background: Albuminuria is a significant predictor of kidney disease progression, cardiovascular morbidity, and mortality among patients with diabetes and/or established chronic kidney disease. However, there is limited information on the prognostic value of albuminuria change on clinically important outcomes. We aimed to assess the association between albuminuria progression and adverse clinical outcomes (all-cause death, cardiovascular disease [CVD], and end-stage renal disease [ESRD]) in adults based on a systematic review of the literature.

Methods: CENTRAL, EMBASE, and MEDLINE were systematically searched for randomized controlled trials (1946-January 2015) that reported change in albuminuria and at least 1 of the 3 clinically important outcomes. Two reviewers abstracted trial characteristics and outcome data independently. To determine the association between albuminuria change in albuminuria and clinical outcomes, we determined the treatment effect ratio (TER), defined as the ratio of the treatment effects on clinical outcomes and the effects on the change in albuminuria.

Results: We identified 27 trials (50,300 patients) that met the inclusion criteria. Reported data on ESRD, 13 on CVD, and 19 on all-cause death. Treatment effects on the change in albuminuria and clinical outcomes were consistent with minimal heterogeneity (TER 0.95 [0.80-1.13]). There was greater heterogeneity (I² 1.13), while relatively similar levels of consistency were observed for the outcomes of albuminuria and ESRD and relatively similar levels of consistency were observed for the outcomes of CVD and all-cause death. Assessment of the surrogacy of albuminuria in large prospective trials is needed.

Conclusions: This review identifies a potentially important correlation whereby progression of albuminuria may be a valid surrogate for ESRD. However, greater heterogeneity was observed for the outcomes of CVD and death. Assessment of the surrogacy of albuminuria in large prospective trials is needed.
Methods: We investigated this association in stage 3-5 NDD-CKD patients with anemia using 2011-2013 Medicare data. A baseline period was used to define CKD, anemia, and comorbidities from diagnosis codes, and ESA use from drug codes. A 1-year follow-up period was used to define HRU and adverse events. HDE as a measure of ESA resistance was defined by an average monthly ESA dose >90th percentile of monthly doses. Analyses were adjusted for patient characteristics, IV iron use, RBC transfusion, and CKD stage.

Results: A total of 12,901 stage 3-5 NDD-CKD patients with anemia receiving ESAs were included. HDE cut-points were ≥75,630 units for erythropoietin and ≥351 mcg for darbepoetin. HDE use was associated with a significantly increased burden of cardiovascular and thromboembolic events. Furthermore, the risk of death was 60% higher among HDE patients (HR 1.60, [1.43-1.79]), and the risk of major adverse cardiac event (MACE) was 46% higher (1.46, [1.31-1.62]) (Table). Medicare payments were 52% higher for HDE patients (1.52, [1.41-1.63]).

Conclusions: Anemia requiring HDE use in stage 3-5 NDD-CKD patients is associated with increased death, MACE, cardiovascular events, thromboembolic events and HRU. Further research is needed to confirm these associations in other cohorts that include more precise data on hemoglobin measurement and ESA dose.

Funding: Pharmaceutical Company Support - AstraZeneca

SA-PO795

Unexpected Medical Consequences of Revised ESA Label in Non-Dialysis-Dependent Chronic Kidney Disease Patients with Anemia

Suying Li,1 Haifeng Guo,2 Shaun Kabadi,2 Sean Zhao,2 Trudy Pendergraft,2 Louise Janice Sargent Heuer,2 Yi Peng,2 Wendy L. St. Peter,2 David T. Gilbertson,1 Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN; 2AstraZeneca, Wilmington, DE.

Background: In 2011, the US Food and Drug Administration (FDA) revised labeling for erythropoiesis-stimulating agent (ESA) treatment in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients, and a Hb target of 10-12 g/dL was replaced by guidance to initiate therapy when Hb fell to <10 g/dL. This study aimed to examine changes in anemia treatment, comorbidities, and outcomes after the ESA label change.

Methods: Stage 3-5 NDD-CKD patients with anemia were selected from a 20% Medicare random sample. Two study cohorts were created: the “2008 cohort,” consisting of patients identified from the 2007-2009 claims, and the “2012 cohort,” based on the 2011-2013 claims. Use of ESAs, intravenous (IV) iron, red blood cell (RBC) transfusions and cardiovascular (CV) comorbidities were defined in a 1-year baseline period, and outcomes (major adverse cardiac events [MACE] including all-cause death, hypertensive emergency [HE], deep vein thrombosis [DVT], and pulmonary embolism [PE]) were defined in a 1-year follow-up period for each study cohort. Results were unadjusted.

Results: ESA use in NDD-CKD patients with anemia declined from a 2012 relative to 2008, while use of IV iron and transfusions remained stable (Table). Although the prevalence of baseline comorbidities was similar between the two cohorts, rates of HE, DVT, and PE increased in the 2012 cohort by 100%, 31%, and 45%, respectively. In addition, all-cause death and MACE incidence did not decline.

Conclusions: After the 2011 ESA label change, a reduction in all-cause death and MACE was not observed, while HE, DVT and PE rates increased. Adjusted risk of these unexpected medical outcomes warrants further investigation.

Funding: Pharmaceutical Company Support - AstraZeneca
Hyperkalemia and Prescription of Antihypertensive Medications: Early Findings from the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) Francesca Tentori,1,2 Charlotte Tu,1 Lindsay Zepel,1 Brian Bieber,1 Michelle M.Y. Wong,1 Friedrich K. Port,1 Christian von Tengel,3 Danilo Fliesser,4 Ricardo Sesso,5 Ichiei Narita,6 Bruce M. Robinson,1 Arbor Research 7Vanderbilt U,8CHU de Bordeaux,9U Bordeaux,10Inserm U1018,11Saarland U. Med. Cte,12UNIFESP,13Niigata U. Grad School of Med. and Dental Sci,14CKDOPPS and CKD REIN Investigators.

Background: Current guidelines identify renin angiotensin system inhibitors (RAASI) as a key element in the treatment of patients with chronic kidney disease (CKD). However, these drugs may be limited in the presence of hyperkalemia. We postulated that prescription of antihypertensive drugs depends on serum potassium (SK) levels, and that these practices vary across countries.

Methods: We leveraged early data from the CKDopps (2013-2016), a prospective cohort study of patients (pts) with eGFR <60 ml/min/1.73m2 from national samples of nephrology clinics in Brazil (BR), France (FR), Germany (GER) and the US to provide descriptive analyses of prescription of antihypertensives and K-binding resins by country and SK.

Results: Among 5,104 pts, mean age by country was 66 to 73 yrs; 35-48% were female; 41-58% had diabetes; 46-67% had eGFR < 30. RASI use was less common in the US and BR than GER and FR; no large differences were seen between diabetes and non-diabetics. RAASI use in the US was less common at SK>5 than SK<5: Prescription of K-binding resins in pts with SK<5 was common in FR and GER, and almost absent in BR and US (Table 1).

Conclusions: Among pts with advanced CKD, prescription patterns vary across countries. Pharmacological treatment of hyperkalemia, especially in FR and GER, may allow for more liberal prescription of RASI. There is a substantial opportunity for improvement in management of diabetic pts, especially in the US where only half were prescribed a RASI and use of K-binding resins was exceedingly rare.

Funding: Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsia, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain. All grants are made to Arbor Research Collaborative for Health and not to Dr. Tentori directly.

SA-P0797

Asymmetric Dimethyl Arginine Modifies the Relationship between High Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR) and the Risk of Death and Cardiovascular (CV) Events in Stage 2-5 CKD Patients Carmine Zoccali, Patrizia Pizzini, Graziella D'arrigo, Daniela Leonardis, Claudia Torino, Maurizio Postorino, Giovanni Tropepi, Francesca Mallamaci, CNR-IFC, Nephrol Dial Transplant, Reggio Calabria, Reggio Calabria, Italy.

Background: suPAR is an innate immunity/inflammation biomarker strongly related with cardiovascular mortality and atherosclerotic events in patients with cardiovascular disease and in chronic kidney disease (CKD). Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide (NO), is substantially raised in CKD patients and predicts mortality and cardiovascular events (CV) in CKD. Inflammation powerfully activates NO synthesis and there may be a biological interplay between suPAR and ADMA in CKD.

Methods: We measured serum suPAR levels (R&D ELISA) and ADMA (ELISA (DLD Diagnostika GMBH, Hamburg, Germany) in 753 stage G2-5 CKD patients with a 31 ± 10 months follow-up.

Results: suPAR was strongly and independently related with ADMA (r=0.22, P<0.001) as well as with major biomarkers of inflammation (IL-6 r=0.27, P<0.001; Procalcitonin r=0.21 P<0.001; CRP r=0.137, all P<0.001). During follow-up 130 patients developed the combined end point death-CV events and in an adjusted model suPAR predicted this end-point (HR 1.33; 95% CI: 1.08-1.64, p=0.006) while no risk excess by ADMA was registered in the second and third suPAR tertiles.

Conclusions: suPAR robustly associates with ADMA and biomarkers of innate immunity in CKD and shares a pathogenic pathway whereby ADMA competitively interacts with suPAR for the risk of death and cardiovascular events. ADMA and suPAR should be jointly considered in mechanistic and in clinical studies.

Funding: Government Support - Non-U.S.

SA-P0798

APOL1 Risk Variants and Subclinical Cardiovascular Disease (CVD) in HIV+ and HIV- Men Tessa Kimberly Novick,1 Ruizang Wang,2 Sudhir Penugonda,2 Michael Shlipak,3 Carl Grundfleth,4 Adrienne Tin,5 Jeremy J. Martinson,6 Matthew Jay Budoff,7 Rulan S. Parikh,8 Wendy S. Post,9 Michelle M. Estrella,10 Johns Hopkins,11UCSF,12Northwestern Univ,13Univ of Pittsburgh,14UCLA,15Univ of Toronto.

Background: HIV is associated with increased CVD risk and augments adverse effects of risk variants. We assessed whether the APOL1 variants are associated with subclinical CVD in HIV+ and HIV- blacks in the Multicenter AIDS Cohort Study (MACS).

Methods: We conducted a cross-sectional analysis of men who were genotyped for the APOL1 G1 and G2 variants and took part in the CVD substudy which enrolled men aged 40-70, weighed <130kg and had no prior coronary revascularization, or progression in comparison to compare associations of high-risk (2 variants) vs. low variant (0-1 variant) genotypes with prevalence of coronary artery calcium (CAC), coronary artery plaque and if present, type of coronary artery plaque (non-calcified, mixed and calcified) on CT imaging. Mean age and eGFR were 52 and 93 ml/min/1.73m2, respectively, and were similar by APOL1 genotype. Of 214 HIV+ and 95 HIV- men, 15% had 2 risk variants, 39% had CAC and 69% had coronary artery plaque present. Overall, high- vs. low-risk genotypes were associated with lower prevalence of CAC, but there was little difference in the presence of coronary artery plaque or its subtypes (Table). Stratified analyses showed a stronger association of APOL1 variants with less CAC and greater non-calcified plaque presence in HIV+ than in HIV- men, though the interactions did not reach statistical significance.

Table. Associations of APOL1 high- vs. low-risk genotypes with prevalence of subclinical CVD in HIV+ and HIV- black men

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Prevalence (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>CAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any coronary plaque</td>
<td>1.09 (0.87-1.37)</td>
<td>0.46</td>
</tr>
<tr>
<td>Non-calcified plaque</td>
<td>1.10 (0.88-1.41)</td>
<td>0.33</td>
</tr>
<tr>
<td>Mixed plaque</td>
<td>1.21 (0.62-2.41)</td>
<td>0.56</td>
</tr>
<tr>
<td>Calcified plaque</td>
<td>1.03 (0.54-1.94)</td>
<td>0.94</td>
</tr>
<tr>
<td>HIV+ black men**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any coronary plaque</td>
<td>0.37 (0.15-0.92)</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-calcified plaque</td>
<td>1.12 (0.70-1.72)</td>
<td>0.44</td>
</tr>
<tr>
<td>Mixed plaque</td>
<td>1.32 (0.98-1.78)</td>
<td>0.07</td>
</tr>
<tr>
<td>Calcified plaque</td>
<td>0.71 (0.26-1.97)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

**Adjusted as above except for HIV status. P-interactions for HIV x APOL1 R005 for all models.

Conclusions: APOL1 risk variants are associated with lower CAC burden in blacks. This association is particularly robust and may be driven by presence of non-calcified plaque in HIV+ men. Studies are needed to delineate underlying mechanisms and further evaluate if associations of APOL1 variants with subclinical CVD indicators differ by HIV serostatus.

Funding: NIDDK Support, Other NIH Support - NIAID, NCI, NIBA, NIHBI, NIDCD, JHU-ICTR

SA-P0799

Serum Magnesium and Mortality Risk in Patients with and without CKD in the Dallas Heart Study Silvia Ferré, Xiliang Li, Beverly Adams-Huet, Nain M. Maalouf, Robert D. Toto, Orson W. Moe, Javier A. Neyra. UT Southwestern, Dallas, TX.

Background: Low serum magnesium (Smg) has been linked to increased mortality in hemodialysis patients and cardiovascular disease (CVD) in the general population. We examined whether similar associations exist in patients with prevalent CKD in the multiethnic population-based Dallas Heart Study (DHS) cohort.

Methods: The whole cohort, CKD and non-CKD subgroups were analyzed. The independent variable was Smg as a continuous variable and divided into tertiles. Study outcomes were all-cause and CV death evaluated using multivariable Cox regression hazards models adjusted for demographics; comorbidity; anthropometric and biochemical parameters including albumin, phosphorus, and PTH; use of diuretics; and their interactions. Median follow-up=12.3 yrs.

Results: Among 3550 participants, 404 (11.4%) had prevalent CKD. Mean Smg (mg/dl) was 2.07 (SD=0.18) in the whole cohort, 2.08 (0.19) in the CKD and 2.07 (0.18) in the non-CKD subgroups. All-cause and CV death occurred in 135 (4.5%) and 52 (1.7%) participants, respectively. Smg was independently associated with all-cause death in the whole cohort (adjusted HR, 1.9, 95% CI, 1.3-2.6; for low vs high tertile). Every 0.2 mg/dl increase in Smg reduced the adjusted hazard for all-cause death by 80% of these.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
observations were observed in both CKD and non-CKD subgroups. In contrast, SMg was only associated with CV death in the CKD subgroup (adjusted HR, 8.4; 95% CI, 1.6–43.6; for low vs high tertile).

**Conclusions:** Low SMg was independently associated with all-cause death in both CKD and non-CKD participants, and with CV death only in CKD participants. The pathophysiologic mechanisms of the effect of Mg on CVD and whether Mg supplementation may impact the CVD burden in CKD patients warrants further investigation.

**Funding:** Other NIH Support - U1I TR001105; P30 DK079328-06

**SA-PO800**

Subclinical Atheromatosis Detection by Arterial Ultrasound Predicts the Time Free from Cardiovascular Events in Chronic Kidney Disease. Results of the NEFRONA Study

José M. Valdivielso, Montserrat Martínez-Alonso, Angeles Betriu, David Arroyo, María Abajo, Elvira Fernandez. IRBlleida, Lleida, Spain.

**Background:** Cardiovascular disease remains the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD).

**Methods:** The NEFRONA study enrolled 2445 CKD patients without previous cardiovascular disease and 559 subjects with normal renal function. The aim of the study was to assess the value of ultrasound detection of subclinical atheromatosis in the prediction of cardiovascular risk. This study shows the competing risk regression analysis of cardiovascular events (CVE) at the end of the study.

**Results:**

There have been 216 CVE (48 fatal and 168 nonfatal), 110 non-cardiovascular deaths and 588 renal transplants (both considered competing events). The number of missing patients is 99. The cumulative incidence of CVE is of 7.19% (69.4% men and 30.6% women) with a median of follow-up of 48.09 months. Kaplan Meier curves of survival free from CVE show that it decreases gradually and progressively with increases in the number of territories with plaque. The competing event regression analysis of the whole population shows that the factors significantly predicting CVE incidence are age in non-diabetic subjects, the number of territories with plaque, being a CKD patient in any stage, diabetes and low 25OH vitamin D in CKD stage 3. The stratified analysis showed that factors affecting survival in CKD stages 3-4 were age in non-diabetics, the number of territories with plaque, the levels of 25OH vitamin D, potassium levels over 5 and cholesterol over 240. In dialysis the number of territories, the dialysis vintage, the levels of phosphate, sex and diabetes significantly affected survival.

**Conclusions:** The severity of arterial atheromatosis estimated by ultrasound predicts the time free from CVE in CKD. Arterial ultrasound is a useful tool to predict cardiovascular risk in CKD patients.

**Funding:** Pharmaceutical Company Support - Abbott

**SA-PO801**

Osteopontin and Cardiovascular Outcomes in Patients with Stable Coronary Disease

Meeyoon Park, Debbie Huang, Rakesh Mishra, Michael Shlipak, Mary Whooley. UCSF.

**Background:** Osteopontin (OPN) is an adhesion molecule upregulated by cardiac myofibroblasts and synthesized by endothelial cells in atherosclerotic plaques. OPN promotes hypoxia-induced proliferation of kidney mesangial cells and is stimulated by angiotensin II. We investigated the association between OPN and cardiovascular outcomes in patients with stable ischemic heart disease and variable levels of kidney function assessed by eGFR and ACR.

**Methods:** OPN was measured in 985 patients with stable coronary disease enrolled in the Heart and Soul Study between 9/2000-12/2002. Poisson regression models were used to examine the relationship between baseline OPN and myocardial infarction (MI), heart failure hospitalization (HF), and all-cause death. Five-year mortality rates were stratified by quartile of OPN.

**Results:** Spearman correlations between OPN and eGFR and ACR were -0.40 and 0.23. In unadjusted models, risks of MI and HF were significantly higher for participants in Q4 OPN compared to the lower 3 quartiles [incident rate ratio (IRR) 2.48 (95% CI 1.71, 3.60) and 2.96 (2.17, 4.03)] (Fig. 1). Adjusting for demographics and clinical risk factors, participants in Q4 OPN had a higher risk of HF [IRR 1.56 (1.08, 2.25)], while risk of MI was not different between OPN quartiles after adjustment [IRR 1.39 (0.90, 2.16)]. The association between OPN and HF was no longer significant after adjusting for eGFR and ACR [IRR 1.35 (0.90, 2.03)]. Risk of death was highly significant in unadjusted models [IRR 3.59 (2.61, 4.94)] and remained so even after adjustment for eGFR and ACR [IRR 1.83 (1.23, 2.71)].

**Conclusions:** Higher levels of OPN were associated with risk of HF after adjusting for demographic/clinical factors, but eGFR and ACR attenuated these associations. Higher levels of OPN were nevertheless associated with risk of death independent of eGFR and ACR. OPN may mediate CV risk via angiotensin II-dependent pathways in both kidneys and heart.

**Funding:** NIDDK Support

**SA-PO802**

Plasma Diphosphorylated Uncarboxylated Matrix Gla Protein Associate with Vascular Calcification and Vascular Stiffness in Chronic Kidney Disease

Paweena Susantiphong, Sipanan Thamratnopkoon, Psut Katavetin, Nattachai Srisawat, Khajohn Tiranhathaeng, Kearkriet Praditpornsilpa, Somchad Eiam-Ong. Div of Nephrology, Dept of Medicine, Chulalongkorn Univ, Bangkok, Thailand.

**Background:** Vascular calcification causes cardiovascular morbidity and mortality in chronic kidney disease (CKD) patients. Matrix Gla protein (MGP) is a potent inhibitor of vascular calcification and needs vitamin K-dependent phosphorylation and carboxylation for its activity. Therefore, the plasma level of “inactive” diphosphorylated uncarboxylated MGP (dp-ucMGP) which would reflect vitamin K status might associate with vascular calcification. This study was conducted to investigate the association between plasma dp-ucMGP and vascular calcification as well as vascular stiffness in CKD patients.

**Methods:** Eighty-three CKD stage 3-5 patients were enrolled in this study. Vascular calcification was determined using abdominal aorta calcification (AAC) score from lateral lumbar film, vascular stiffness was assessed by carotid-ankle vascular index (CAVI), and plasma dp-ucMGP levels were measured using ELISA method, Maastricht, The Netherlands.

**Results:** The mean age was 62.9±13.9 years. The plasma dp-ucMGP levels in CKD stage 3, and CKD stage 4&5 were 604.0 (457.5-925.0) and 1,056 (523.3-1,663.5 pmol/L, respectively (normal <500 pmol/L). The prevalence of vascular calcification (AAC score) was 63.4% and that of vascular stiffness (CAVI>9) was 46.3%. Multivariate logistic regression analysis to predict vascular calcification showed that age and plasma dp-ucMGP were significantly associated with vascular calcification (OR 1.23, 95%CI 1.09-1.37; p=0.001 and OR 1.03 95%CI 1.01-1.05; p=0.002, respectively). In contrast, there was no association between plasma dp-ucMGP and vascular stiffness.

**Conclusions:** Plasma dp-ucMGP levels increase progressively with more advanced stage of CKD. Plasma dp-ucMGP associated with vascular calcification could be the marker for vascular calcification in CKD patients. Since vitamin K supplement is the readily available treatment to reduce of dp-ucMGP, the effect of vitamin K supplement on vascular calcification in CKD patients should be further explored with the long-term randomized clinical trial.

**SA-PO803**

Need for Insulin Is Associated with Increased Risk of All-Cause Mortality (ACM) in Various CKD Stages in Type 2 Diabetes Mellitus (T2DM)

Rabia Nadeem Kiani,1 R. E. Boucher,2 Guo Wei,1 Debra Lynn Simmons,1 T. S. Bjordahl,1 Linda F. Fried,1 Tom Greene,1 Sriini Beddhu.2 1Univ of Utah, SLC, UT; 2VA, Pittsburgh, PA.

**Background:** In more advanced CKD, insulin use might reflect insulin resistance and/or co-intandization to oral hypoglycemic agents. Therefore, we examined the relationship between the need of insulin and ACM at various stages of CKD in a national cohort of 1,561,876 veterans with serum creatinine and serum HDL-cholesterol measured within 3 months of each other from Jan 1, 2000 to Dec 31, 2008.

**Methods:** There were 158,544 veterans with T2DM (defined by ICD9 codes). Data on filled medications were obtained from outpatient pharmacy database. Laboratory data were
obtained from routine clinical labs. Mortality data were from vitals files. Within each eGFR subgroup, the risk for ACM in those on insulin vs. those not on insulin were examined in separate Cox regression models.

**Results:** Mean age was 65±11 yrs. 97.4% were males and 18.4% were black. 20.4% were using insulin. The mean eGFR was 73 ± 23 ml/min/1.73 m².

**SA-PO804**

**Brain Deep and Subcortical White Matter Hyperintensity in Predialysis CKD Patients Hideaki Shimada,1 Tatsuhiko Mori,2 Hajime Hiroi,1 Mika Sonoda,2 Mikio Okamura,3 Tetsuo Shoji,2 Eiji Ishimura,4 Masaaki Inaba,2 *Nephrology, Osaka Medical College, Takatsuki, Japan; 2Internal Medicine 2, Osaka City Univ, Osaka, Japan; 3Nephrology, Kayasuyama-Kuno Hospital, Kadoma, Japan.**

**Background:** CKD patients have higher risk for stroke than the general population. Magnetic resonance imaging (MRI) of brain is highly sensitive for detecting ischemic lesions such as deep and subcortical white matter hyperintensity (DSWMH). DSWMH reported to be a risk factor for future stroke and dementia in non-CKD population. In this study, we investigated the prevalence of DSWMH and its relation to clinical severity in predialysis CKD patients without prior stroke.

**Conclusions:** DSWMH was more prevalent and severer in more advanced stages of CKD. A lower eGFR, rather than proteinuria, was the factor associated with the presence of DSWMH independent of age, sex, diabetes mellitus, and blood pressure. DSWMH may explain the higher risk of stroke in this population.

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

817A
SA-PO087

Kidney Dysfunction and Left Ventricular Hypertrophy in Population-Based Autopsy Samples: The Hisayama Study. Ken-ichou Izumida,1 Jun Hata,2 Yutaka Nakashima,1 Toshiaki Nakano,3 Kazuhiko Tsuruya,4 Yoshio Oda,3 Takami Kitazono,2 Yutaka Kiyohara,3 Toshinari Ninomiya,1 Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan; 1Dept of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 2Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 3Dept of Anatomical Pathology, Pathological Sciences, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 4Hisayama Research Inst For Lifestyle Diseases, Fukuoka, Japan.

Background: Growing evidence has suggested that subjects with kidney dysfunction develop left ventricular hypertrophy (LVH) with the progression of renal disease. However, there are limited studies addressing pathologically the association between kidney dysfunction and LVH.

Methods: In 334 population-based autopsy samples, we investigated the thickness of left ventricular wall according to estimated glomerular filtration rate (eGFR) levels. In 95 sample selected randomly from these samples, the sizes of cardiac cell and the percentages of fibrosis in left ventricular wall were also estimated.

Results: The thickness of left ventricular wall increased significantly with eGFR levels of ≥60, 45-59, and <30 (<p value < 0.05). Lower eGFR levels were associated significantly with greater mean values of cardiac cell size in left ventricular wall after adjusting for confounding factors: 15.3, 16.1, 16.4, and 17.4 (µm) in eGFR levels of ≥60, 45-59, and <30 (p < 0.001). Likewise, subjects with lower eGFR had significantly higher multi-variable-adjusted mean values of percentage of fibrosis in left ventricular wall, being 3.2%, 3.3%, 3.3%, and 6.1% (p < 0.001). In eGFR levels of ≥60, 45-59, and <30 (p < 0.001).

Conclusions: Our findings suggest that renal dysfunction is associated with the cardiac hypertrophy and fibrosis of left ventricle via cardiac cell enlargement and cardiac fibrosis.

SA-PO088

Utility of High-Sensitivity Troponin I in Patients with Impaired Renal Function. Eve Victoria Miller-Hodges,1 Centre for Cardiovascular Science, Univ of Edinburgh, United Kingdom.

Background: Cardiorenal disease remains the cause of death in Chronic Kidney Disease. The optimal diagnosis and exclusion of acute myocardial infarction is limited in these patients by the uncertain role of cardiac biomarkers such as Troponin. We investigated whether low serum High-Sensitivity Troponin I (hsTnI) continued to identify those at low risk of cardiac events in the presence impaired renal function (eGFR<60).

Methods: Patients with impaired renal function (eGFR<60) were identified from two prospective cohorts of patients presenting to emergency departments with suspected acute coronary syndrome (Shah AS, Lancet 2015 & Shah AS, BMJ 2015). Serum hsTnI was measured at presentation. The negative predictive values for a range of hsTnI concentrations were established for a composite outcome of myocardial infarction or cardiovascular death at 30 days and 1 year, compared to the normal population (eGFR >60).

Results: 1160/5050 (23%) patients had an eGFR<60. 302 (26%) had a diagnosis of myocardial infarction or cardiovascular death at 30 days and at 1 year (302 [26%] vs. 55 [1.4%]) and at 1 year (302 [26%] vs. 55 [1.4%]) and at 1 year (302 [26%] vs. 55 [1.4%]). Serum hsTnI concentration at admission was higher in patients with impaired renal function (median 15.5ng/L (IQR 6–53) vs. 4.00ng/L (IQR 2–10)) but the majority of patients were below the 99th centile threshold (702 [61%]). As in health, a low hsTnI threshold of <5ng/L continued to identify those patients with impaired renal function at very low risk of myocardial infarction or death within 30 days (negative predictive value 99.4% [98.4-99.9]).

Conclusions: In this large representative cohort of patients presenting with suspected acute coronary syndrome patients with impaired renal function were at the highest risk of myocardial infarction and cardiac death. A low serum hsTnI concentration identified those at very low risk of myocardial infarction and cardiac death.

SA-PO089

Evaluation of Clinical Outcomes among Nonvalvular Atrial Fibrillation Patients Treated with Warfarin or Rivaroxaban Stratified by Renal Function. Matthew R. Weir,1 Lloyd P. Haskell,2 Jeffrey S. Berger,2 Veronica Ashton,2 Francois Laliberte,4 Concetta Crivera,2 Kip Brown,2 Patrick Lefebvre,2 Jeff R. Schein,3 Univ of Maryland School of Medicine, Baltimore, MD; 1Janssen Scientific Affairs, LLC, Raritan, NJ; 2New York Univ School of Medicine, NY, NY; 3Groupe d’Analyse, Lille, Montréal, QC, Canada.

Background: Renal impairment is linked to increased risk of thromboembolic and bleeding events in NVAF patients. This study compares these events for patients treated with warfarin or rivaroxaban stratified by renal function.

Methods: Patients with first dispensing of warfarin or rivaroxaban after 11/2011 from IMS PharMetrics Plus data (05/2011-6/2015) were included. Ischemic stroke, major bleeding, and MACE rates were calculated and adjusted HRs were provided. Results of Cox regression models were adjusted for confounding factors: 15.3, 16.1, 16.4, and 17.4 (µm) in eGFR levels of ≥60, 45-59, and <30 (p<0.05). Lower eGFR levels were associated significantly with greater mean values of cardiac cell size in left ventricular wall after adjusting for confounding factors: 15.3, 16.1, 16.4, and 17.4 (µm) in eGFR levels of ≥60, 45-59, and <30 (p<0.001). Likewise, subjects with lower eGFR had significantly higher multi-variable-adjusted mean values of percentage of fibrosis in left ventricular wall, being 3.2%, 3.3%, 3.3%, and 6.1% (p<0.001). In eGFR levels of ≥60, 45-59, and <30 (p<0.001).

Conclusions: Our findings suggest that renal dysfunction is associated with the cardiac hypertrophy and fibrosis of left ventricle via cardiac cell enlargement and cardiac fibrosis.

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

818A
SA-PO811
Role of TCF7L2 Gene and PPARG2 Gene Polymorphism on Renal and Cardiovascular Complications in Patients with Type 2 Diabetes: A Cohort Study
Pamela Tanasawiprap, Bancha Satirapoj, Amnae Chairaprasert, Naowanit Nata, Theerasak Tangwongler, Prajej Ruangkanchanasetr, Opapath Supasanyak. Medicine, Phramongkukklao Hospital and College of Medicine, Bangkok, Thailand.

Background: The emergence renal and cardiovascular complications of type 2 diabetes genetics involves differently assembled gene variants including transcription factor-7-like-2 (TCF7L2) and peroxisome proliferated activated receptor gamma 2 (PPARG 2) polymorphism. However, the relevance of these genes for complications prediction has not been extensively tested.

Methods: We analyzed the SNPs rs7903146 in TCF7L2 and PPARG2 gene polymorphism for their contribution to incidence of CKD and CVD complications in the prospective cohort study. All type 2 diabetes patients were followed the estimated glomerular filtration rate (eGFR) and CV outcomes. Cox proportional hazards regression models were used to estimate the genotype effect on the incidence of CKD and CV complications.

Results: A total of 422 patients with mean age of 62±11.8 years and eGFR of 72.8±31.8 mL/min/1.73 m² were included. SNPs rs7903146 in TCF7L2 gene were classified into 3 groups: C/C 385 patients (91.2%), C/T 37 patients (7.6%) and T/T 5 patients (1.2%) and PPARG2 gene were classified into 2 groups. Pro12Pro 404 patients (95.7%) and Pro12Ala 18 patients (4.3%). The prevalence of CKD, CV disease and death at the end of the 5-year follow-up was 16.8%, 29% and 7.9%, respectively. The Pro12Ala variant of PPARG2 gene was significantly associated with increased CKD risk at the end of the study (adjusted HR 3.45 [95% CI 1.01–11.77, p = 0.046], it did show significant association with increase stroke risk, but not CV diseases and mortality. Whereas, no genotype effect of rs7903146 in TCF7L2 gene was apparent on renal and CV complications in type 2 diabetes over time except that it increased coronary artery disease risk.

Conclusions: The findings of our study are that Pro12Ala variant in PPARG2 gene is associated with risk of developing CKD in Asian type 2 diabetes in the prospective cohort. Further investigations are warranted to understand the pathway-based functional implications of the important loci in PPARG2 gene.

SA-PO812
Cardiac Stress Testing in U.S. Patients with Chronic Kidney Disease: Is the Epoch of Nihilism and Renalism Ancient History? Charles A. Herzog, Tanya Natwick, Shuling Li, David M. Charytan. 1MMRF, Chronic Disease Research Group, Mpls, MN; 2HCMC, Univ of MN; 3Brigham & Women's Hospital, Boston, MA.

Background: A "nihilistic approach" to coronary artery disease (CAD) in pts with chronic kidney disease (CKD) has previously been reported. We have revisited this "truisim" in the context of cardiac stress testing in the modern era (2008-12).

Methods: The 20% Medicare sample was searched by single cohort yrs (2008-12) to identify pts age 65+ with no CKD (n = 4,232,080 in 2012) and Stages 1-5D CKD (n= 332,058 in 2012). Incidence rates of non-invasive CAD testing (Stress: Echo, Nuclear, MRI, and ECG and CT. angiography or Calcium score) were estimated within each cohort by yr.

Results: Demographics of pts receiving tests (2012): non-CKD: 35% age 75-84, 6% age 85+; 88% white, 7% black, 54% male, 7% CKD stages 1 & 2, 67% 3,4,5ND, 8% ESRD and 17% age 85+, 88% white, 7% black, 48% male; non-CKD: 35% age 75-84, 6% age 85+; 88% white, 7% black, 48% male, 7% CKD stages 1 & 2, 67% 3,4,5ND, 8% ESRD and 17% age 85+, 88% white, 7% black, 54% male, 7% CKD stages 1 & 2, 67% 3,4,5ND, 8% ESRD and 17% age 85+, 88% white, 7% black, 48% male.

Conclusions: The findings of our study are that Pro12Ala variant in PPARG2 gene is associated with risk of developing CKD in Asian type 2 diabetes in the prospective cohort. Further investigations are warranted to understand the pathway-based functional implications of the important loci in PPARG2 gene.

SA-PO813
Efficacy of Statin Therapy in Early-Stage Chronic Kidney Disease
Han Ro,1 Sun Moon Kim,2 Yun Jung Oh,3 Ae Jin Kim,1 Jae Hyun Chang,1 Hyun Hee Lee,1 Woo Kyung Chung,1 Ji Yong Jung,1 1Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea; 2Dept of Internal Medicine, Chungbuk National Univ Hospital, Cheongju, Republic of Korea; 3Dept of Internal Medicine, Chua Halifax General Hospital, Jeju, Republic of Korea.

Background: Chronic kidney disease (CKD) is a major risk factor for the development of cardiovascular disease (CVD), and statin treatment can reduce the risk of CVD. However, whether statin treatment affects renal progression and outcomes in CKD patients remains unclear.

Methods: We retrospectively reviewed CKD patients who visited to Gachon University Gil Medical Center with renal problems from 2003 to 2013. From a total 14497 CKD patients, 858 statin users were paired with 1:1 with non-users for analysis using propensity score matching. The outcomes of this study were creatinine doubling, renal death, all-cause mortality, and interactive factors for composite outcomes.

Results: Statins were prescribed to 13.5% of the study subjects. Statin treatment-associated hazard ratios (HRs) (95% confidence intervals (CIs) for the doubling of serum creatinine levels were significant only in patients with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m², and were 0.744 (0.635–0.873) in the unmatched cohort and 0.767 (0.696–0.856) in the matched cohort. In analyses of secondary outcomes, the HRs (95% CIs) for all-cause mortality were 0.655 (0.502–0.855) in the unmatched cohort and 0.537 (0.297–0.973) in the matched cohort. The HRs (95% CIs) for composite outcomes among patients with and without eGFR ≥30 mL/min/1.73 m² were 0.764 (0.613–0.952) and 1.232 (0.894–1.697), respectively (p for interaction, 0.017).

Conclusions: Statin treatment in the early stages of CKD may be related to renal progression and the all-cause mortality rate.

SA-PO814
Low Systolic Blood Pressure during the Follow-Up Period Is Associated with Increased Risk of Cardiovascular Disease in Patients with Type 2 Diabetes and Renal Impairment with and without Heart Failure - The Swedish National Diabetes Register (NDR) Hanri Afgah,1 Maria K. Svensson,2 1Nephrology, Skaraborg Hospital, Södertalje, Sweden; 2Medical Sciences, Uppsala Univ, Uppsala, Sweden.

Background: Current guidelines recommend a SBP target of <140 mmHg in patients with diabetes and renal impairment (RI) and <130 mmHg when albuminuria is present. The aim of this study was to further evaluate the relationship between SBP and risk of cardiovascular events (CVEs) in patients with type 2 diabetes (T2D) and (RI), with or without a history of chronic heart failure (CHF) using time-updated mean SBP.

Methods: 27,732 patients with T2D and RI (eGFR <60ml/min/1.73m²) were followed for mean 4.7 years. The relationships between SBP and CVEs were examined by time-dependent Cox models, to estimate hazard ratios (HR), adjusting for cardiovascular risk factors and medications.

Results: The patients were mean age of 75±9 years, their diabetes duration was 10±8 years. 42% were male, mean SBP at baseline was 138±18 mmHg and 15% had a history of CHF. Patients were classified into 4 groups by time-updated mean SBP (<130, 130-140, 141-160 and >160 mmHg). A time updated mean SBP between 130 and 140 mmHg was used as a reference group. All patients with a time updated mean SBP >130 mmHg had a higher risk of CVEs (HR 1.23, 95% CI 1.19-1.34). In patients without a history of CHF a time-updated mean SBP <130 mmHg was also associated to a higher risk of CVEs (HR 1.23 95% CI 1.14-1.32).

Conclusions: In patients with type 2 diabetes and renal impairment a systolic blood pressure <130 mmHg over the time was associated with a higher risk of cardiovascular events. This association was also found in patients without a history of CHF.
SA-PO815
Triglycermine-N-oxyde (TMAO) Accumulates in Patients with Chronic Kidney Disease (CKD): Correlation with the Measured Glomerular Filtration Rate (mGFR)  Caroline C. Pelletier,1,2  Mikael Croyal,3  Michel Krempf,2  Laurent Juillert,2  Christophe O. Soulage,2  ‘Nephrology, Hospices Civils de Lyon, France; ‘Univ Lyon, INSA-Lyon, INSERM U1060, CarMeN Lab, France; ‘INRA, UMR 1280, CRNH, Mass Spectrometry Area, Nantes, France.

Background: TMAO is associated with poor cardiovascular outcomes in the general population. Significant higher TMAO levels has been ever been reported in patients with CKD. However, these observations were only based on estimated GFR. We wanted to further confirm plasma TMAO accumulation and its relationship with kidney function in a cohort of CKD patients characterized by measured GFR.

Methods: Control and CKD patients were recruited in the E.Herriot university hospital, in Lyon (France) to perform a measurement of GFR by an inulin clearance and plasmatic TMAO determination by LC-MS/MS.

Results: TMAO was measured in 75 patients and was strongly associated with the level of mGFR.

### Characteristics of healthy volunteers and CKD patients.

<table>
<thead>
<tr>
<th>Characteristics of healthy volunteers and CKD patients</th>
<th>Healthy volunteers</th>
<th>CKD patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1-2</td>
<td>12</td>
<td>23</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stage 3 and 4-5</td>
<td>22</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Effective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>41.2±10.5</td>
<td>47.3±14.8</td>
<td>51.5±21.0***</td>
</tr>
<tr>
<td>Creatinin, µM</td>
<td>64.3±14.7</td>
<td>83.1±17.6</td>
<td>275.3±14.6***</td>
</tr>
<tr>
<td>Log (U/Creat, mg/mmol)</td>
<td>1.2±1.0</td>
<td>1.26±0.281</td>
<td>59.5±19.7 52.7±6.7***</td>
</tr>
<tr>
<td>mGFR, ml/min/1.73 m²</td>
<td>102±8.2</td>
<td>76.1±10.6</td>
<td>74.3±8.9 18.4±5.3***</td>
</tr>
<tr>
<td>TMAO, µg/L</td>
<td>2.4±2.1</td>
<td>3.3±4.1</td>
<td>7.3±4.5 21.5±17.7***</td>
</tr>
</tbody>
</table>

Means were compared with ANOVA test with a significant p<0.05.

We observed a significant differences between the stages 4-5 and the stage 3 as well as between the stage 3 and all the other patients with better renal function.

Conclusions: Plasma TMAO is increased in patient with CKD and negatively associated with the stages of CKD, defined by mGFR. We confirmed that TMAO accumulates in CKD as a result of the decreased GFR suggesting that TMAO could be considered as a novel uremic toxin.

Funding: Clinical Revenue Support

SA-PO816
The Predictive Value of Serum Triglyceride to High-Density Lipoprotein Cholesterol Ratio According to Renal Function in Patients with Acute Myocardial Infarction (From the Korea Acute Myocardial Infarction Registry)  Jin Sug Kim, Yu Ho Lee, Da Rae Kim, Chun-Gyoo Ihm, Tae Won Lee, Kyung-Hwan Jeong. Kyung Hee Univ Hospital.

Background: Serum triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio has been reported as an independent predictor for cardiovascular events in general population. However, the prognostic value of this ratio is unclear in patients with renal dysfunction. We examined the association of TG/HDL-C ratio and major adverse cardiovascular events (MACEs) according to renal function in patients with acute myocardial infarction (AMI). The final model 2 was significantly (P<0.001) more accurate than the model 1.

Conclusions: Plasma TMAO is increased in patient with CKD and negatively associated with the stages of CKD, defined by mGFR. We confirmed that TMAO accumulates in CKD as a result of the decreased GFR suggesting that TMAO could be considered as a novel uremic toxin.

Funding: Clinical Revenue Support

SA-PO817

Background: Patients with chronic kidney disease (CKD) have an increased risk of peripheral artery disease (PAD). A predictive model may help evaluate risk before significant changes in ankle-brachial index (ABI) to provide early detection, prevention, and treatment.

Methods: A total of 3,146 adult CKD patients in the Chronic Renal Insufficiency Cohort Study without PAD at the baseline visit were included in this analysis. Incident PAD was defined as a new onset ABI of <0.9 or clinical PAD confirmed by an endpoint assessment committee. Models were developed using Cox proportional hazards regression methods and evaluated using C-statistics. The LASSO approach was used to select predictors, where the best fitting model is the one that minimizes the deviance in cross-validation.

Results: 635 individuals developed PAD over 6 years of follow-up. The hazard ratios for selected risk factors in the predictive models are presented in the table.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1 (HR (95% CI))</th>
<th>Model 2 (HR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log ABI</td>
<td>0.60 (0.54, 0.66)</td>
<td>0.61 (0.55, 0.68)</td>
</tr>
<tr>
<td>Log age</td>
<td>1.27 (1.16, 1.39)</td>
<td>1.21 (1.09, 1.34)</td>
</tr>
<tr>
<td>Female</td>
<td>1.37 (1.17, 1.61)</td>
<td>1.28 (1.08, 1.52)</td>
</tr>
<tr>
<td>Black</td>
<td>1.53 (1.31, 1.79)</td>
<td>1.19 (1.01, 1.42)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.01 (1.63, 2.48)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.28 (1.02, 1.59)</td>
<td></td>
</tr>
<tr>
<td>Log pulse pressure</td>
<td>1.16 (1.05, 1.28)</td>
<td></td>
</tr>
<tr>
<td>Log alkaline phosphatase</td>
<td>1.10 (1.01, 1.20)</td>
<td></td>
</tr>
<tr>
<td>Log C-reactive protein</td>
<td>1.12 (1.05, 1.22)</td>
<td></td>
</tr>
<tr>
<td>Log fibrinogen</td>
<td>1.08 (0.97, 1.19)</td>
<td></td>
</tr>
<tr>
<td>Log hemoglobin</td>
<td>0.99 (0.90, 1.09)</td>
<td></td>
</tr>
<tr>
<td>Log Hemoglobin A1c</td>
<td>1.11 (1.01, 1.23)</td>
<td></td>
</tr>
<tr>
<td>Log eGFR</td>
<td>0.90 (0.82, 0.99)</td>
<td></td>
</tr>
<tr>
<td>C-Statistics</td>
<td>0.67 (0.49, 0.94)</td>
<td>0.72 (0.58-0.70)</td>
</tr>
</tbody>
</table>

The final model 2 was significantly (P<0.001) more accurate than the model 1.

Conclusions: A model using readily available clinical and laboratory tests can improve the risk prediction over ABI for development of PAD in CKD patients. Further studies should validate this predictive model.

Funding: NIDDK Support

SA-PO818
Efficacy and Safety of Warfarin Therapy in Chronic Kidney Disease Patients with Atrial Fibrillation  Priscilla P. How,1,6  Timothy Koh,1  Xin Yi Wong,1  Doreen Tan,1  Ying-Ying Seow,1  Hemanshar Sran,1 2  ‘Dept of Pharmacy, National Univ of Singapore; 1Dept of Pharmacy, Khoo Teck Puat Hospital; 3Dept of Medicine (Nephrology), National Univ Hospital.

Background: While anticoagulation of atrial fibrillation (AF) patients without chronic kidney disease (CKD) to reduce stroke risk is well-established, it is less straightforward in patients with both conditions due to their increased bleeding and stroke risk. This study aimed to determine warfarin’s efficacy and safety in local AF patients with varying degrees of renal impairment.

Methods: Patients who filled warfarin prescriptions at two acute care hospitals in Singapore between June 2010 and May 2012 were included if they were ≥ 21 years old, received warfarin for AF for ≥ 3 months prior to study entry (target INR 2-3), and for 2 continuous years or until discontinuation due to an event or death. The patients were classified by CKD stages into 4 groups. Risk of major adverse cardiovascular events (MACE) and major bleeding were estimated using time-dependent Cox regression analyses.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Of the 250 patients recruited, 81 (32.4%) had stage 3 CKD, 32 (12.8%) had stage 4 CKD, and 56 (22.4%) had end-stage renal disease (ESRD) and were receiving dialysis. Compared to patients with no CKD (eGFR > 60 ml/min/1.73m², reference group), risk of MACE was similar among stage 3 CKD (hazard ratio [HR] 0.95; 95% CI 0.86–1.05), stage 4-5 CKD (HR 0.91; 95% CI 0.82–1.01) and stage 4-5 CKD (HR 0.93; 95% CI 0.10–0.75), while a trend of increased bleeding risk was observed among ESRD patients (HR 9.21; 95% CI 1.00–84.71). Proportion of patients with labile INR was also highest among ESRD patients (68.8% vs. 47.1-53.1%, P=0.407).

Conclusions: Similar risk of MACE and major bleeding was observed among our local AF patients with varying degrees of renal impairment receiving warfarin. However, ESRD patients may be at increased risk of major bleeding.

SA-PO819
Impact of Updated Recommendations for Aspirin Use for the Primary Prevention of Cardiovascular Disease Fanny Lepeyre, Myriam Khalili, Stephan Troyanov, Josee Bouchard, Francois Madore. Nephrology, Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada.

Background: Newly updated guidelines of the U.S. Preventive Services Task Force (USPSTF) recommend initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) in adults aged 50-59 yrs who have a ≥ 10% 10-yr CVD risk. In adults aged 60-69 yrs or at increased risk of bleeding, the decision to initiate aspirin use should be individualized. The impact of these new recommendations remains largely unknown especially for patients with CKD.

Methods: We studied 20,004 randomly selected individuals from the general population aged 40-69 yrs to estimate the number and the characteristics of individuals with and without aspirin therapy. We evaluated CVD history and risk factors, Framingham score, medication use and kidney function.

Results: Among participants aged 50- 59 yrs with no history of CVD and a ≥10% 10-yr CVD risk, 15.5% (n=462) were currently taking aspirin or another platelet aggregation inhibitor. For individuals aged 60-69 yrs, this proportion was higher (28.3%). Factors independently associated with current aspirin use in patients with no history of CVD and increased risk are shown below.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OR</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.05, 1.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.37</td>
<td>1.16, 1.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (BMI kg/m²)</td>
<td>1.20</td>
<td>1.10, 1.40</td>
<td>0.02</td>
</tr>
<tr>
<td>Regular medical visits *</td>
<td>1.92</td>
<td>1.28, 2.88</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes *</td>
<td>1.60</td>
<td>1.07, 2.41</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes treatment</td>
<td>2.84</td>
<td>1.87, 4.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia *</td>
<td>1.29</td>
<td>1.08, 1.54</td>
<td>0.01</td>
</tr>
<tr>
<td>Statin use</td>
<td>3.30</td>
<td>2.73, 3.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-hypertensive treatment</td>
<td>3.36</td>
<td>2.83, 3.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD EPI &lt; 60/min</td>
<td>0.71</td>
<td>0.54, 0.95</td>
<td>0.02</td>
</tr>
</tbody>
</table>

No association was found with hypertension*, income, education, ethnicity, tobacco use. *: self reported.

Conclusions: Current aspirin use for primary CVD prevention is low (15.5%) and is associated with CVD risk factors and corresponding treatments. Patients with chronic kidney disease are less likely to receive aspirin. Implementation of updated USPSTF guidelines will require significant practice changes.

Funding: Clinical Revenue Support

SA-PO820
Quantitative Evaluation of Antihypertensive Adherence in Chronic Kidney Disease Lee Lee Zhu, Thuy Hoang, Linda Awadishu. Skaggs School of Pharmacy and Pharmaceutical Sciences, Univ of California, San Diego, La Jolla, CA.

Background: Adherence to ACEI and ARB therapy is important to reduce blood pressure (BP) and proteinuria in patients with chronic kidney disease (CKD). No studies to date has reported measurements of antihypertensive concentrations in biological fluids to assess medication adherence.

Methods: This is a prospective medication reconciliation and adherence study of 492 adults aged 60-69 yrs or at increased risk of bleeding, the decision to initiate aspirin use should be individualized. The impact of these new recommendations remains largely unknown especially for patients with CKD.

Methods: We studied 20,004 randomly selected individuals from the general population aged 40-69 yrs to estimate the number and the characteristics of individuals with and without aspirin therapy. We evaluated CVD history and risk factors, Framingham score, medication use and kidney function.

Results: Among participants aged 50- 59 yrs with no history of CVD and a ≥10% 10-yr CVD risk, 15.5% (n=462) were currently taking aspirin or another platelet aggregation inhibitor. For individuals aged 60-69 yrs, this proportion was higher (28.3%). Factors independently associated with current aspirin use in patients with no history of CVD and increased risk are shown below.

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<td>Male gender</td>
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<td>1.16, 1.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (BMI kg/m²)</td>
<td>1.20</td>
<td>1.10, 1.40</td>
<td>0.02</td>
</tr>
<tr>
<td>Regular medical visits *</td>
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<td>1.28, 2.88</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes *</td>
<td>1.60</td>
<td>1.07, 2.41</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes treatment</td>
<td>2.84</td>
<td>1.87, 4.33</td>
<td>&lt;0.001</td>
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<tr>
<td>Dyslipidemia *</td>
<td>1.29</td>
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</tr>
<tr>
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<td>0.54, 0.95</td>
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</tr>
</tbody>
</table>

No association was found with hypertension*, income, education, ethnicity, tobacco use. *: self reported.

Conclusions: Current aspirin use for primary CVD prevention is low (15.5%) and is associated with CVD risk factors and corresponding treatments. Patients with chronic kidney disease are less likely to receive aspirin. Implementation of updated USPSTF guidelines will require significant practice changes.

Funding: Clinical Revenue Support

SA-PO821
Circulating ACE2 as a Biomarker of Cardiovascular Outcomes Lidia Anguiano,1 Marta Riera,2 Julio Pascual,2 Sergi Clotet-Freixas,3 Angels Betriu,2 Jose M. Valdivielso,4 Clara Barrios,5 Elvira Fernandez,5 Maria Jose Soler,5 1Nephrology, Hospital del Mar-Inst Hospital del Mar d’Investigacions Mediques, Barcelona, Spain; 2Nephrology, Hospital Arnau de Vilanova, Lleida, Spain.

Background: ACE2 activity from human EDTA-plasma samples directly correlated with the classical CV risk factors namely older age, diabetes and male gender and with atherosclerosis progression at 2 years of follow-up. In a CKD population without previous history of CV disease. Aim: To study circulating ACE2 activity as a biomarker of CV outcomes in CKD stages 3-5(KD-3) patients at 4 years of follow-up.

Methods: Prospective study of 1237 CKD3-5 patients. Circulating ACE2 activity was analyzed. Variables assessed: non-fatal and fatal CV event, non-CV mortality, all-cause mortality (CV and non-CV), and the composite all-cause mortality + non-fatal CV event. For the overall survival analysis, stratified baseline circulating ACE2 activity (low-level ACE2: <24.9 RFU/L and high-level ACE2: ≥24.9 RFU/L) was used.

Results: Non-fatal and fatal CV events was higher in the high-level ACE2 group (9.4%) as compared to the low-level group (5.1%, p<0.008). Estimated mortality was also assessed in patients with the composite all-cause mortality and non-fatal CV event in patients with all-cause mortality. In both cases, estimated mortality was higher in the high-level ACE2 group (14.1% and 8.5%, respectively) as compared to the low-level ACE2 group (8.7% and 4.8%, respectively; p=0.008 and p=0.024, respectively). Multivariate logistic regression was adjusted for 10 variables (see Table).

Conclusions: Circulating ACE2 may help to detect patients at risk for CV event and non-CV mortality at 4 years of follow-up.

SA-PO822
Effects of CKD on Survival Who Were Screened for Sleep Apnea Syndrome Kunioishi Iseki,1 1Clinical Research Support Center, Tomishiro Central Hospital, Tomigusuku, Okinawa, Japan; *Internal Medicine, Nakamura Clinic, Urasoe, Okinawa, Japan.

Effects of CKD on survival who were screened for sleep apnea syndrome (SAS) may be at increased risk of major bleeding.

Funding: Pharmaceutical Company Support - Millennium Research Institute
SA-PO823
Prognostic Value of Reverse Dipper Blood Pressure Pattern in Patients with Non-Dialysis Chronic Kidney Disease: A Prospective Cohort Study
Zengchun Ye, Cheng Wang, Ming Li, Mejjin Si, Wenbo Zhao, Tan-Qi Lou. Div of Nephrology, Dept of Medicine, The Third Affiliated Hospital of Sun Yat-Sen Univ, Guangzhou, China.

Background: Reverse dipper blood pressure (BP) pattern has been studied among the general and hypertensive population. However, the prognosis of reverse dipper BP pattern in chronic kidney disease (CKD) patients remains unknown.

Methods: We monitored BP throughout the day and followed health outcomes in 588 CKD patients admitted to our hospital. Time to all-cause mortality, to cardiovascular mortality, to renal and to cardiovascular events was recorded. Multivariate-adjusted Cox regressions were carried out to detect the prognostic value of reverse BP pattern for total mortality, cardiovascular mortality, renal events and cardiovascular events.

Results: The prevalence of dippers, non-dippers and reverse dippers was 34.69%, 43.54% and 18.03% respectively. Patients with reverse dippers had higher incidence of total mortality, cardiovascular mortality, renal and cardiovascular events than patients with dippers (P<0.05), and also had higher incidence of total mortality, cardiovascular mortality and events than patients with non-dippers (P=0.05). Multivariate-adjusted Cox regression analyses showed that reverse dippers (versus dippers) was associated with a higher risk of total mortality (HR=5.085, P=0.002), cardiovascular mortality (HR=4.437, P=0.013), renal events (HR=3.291, P=0.001) and cardiovascular events (HR=4.259, P=0.006) even adjusted by 24h systolic BP (SBP).

Conclusions: In conclusion, we have provided the first evidence that reverse dipper BP pattern, independent of 24-hour SBP levels, had prognostic value in Chinese patients with non-dialysis chronic kidney disease. Further prospective randomized clinical trials are needed to clarify whether correcting blood pressure pattern by administration of antihypertensive drugs at night has a beneficial effect in improving the prognosis and attenuating the progression of cardiovascular and renal disease in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO824
Testosterone Replacement Therapy (TRT) to Normalize Serum Total Testosterone (T) Levels Is Associated with Delayed Progression of CKD and Lower All-Cause Mortality
Archana Goel,1 Mukut Sharma,2 Peter Sigurd Wiegmann,1 Ulirunde Oni,1 Rajat S. Barua,1 Ram Sharma,1 Rishi Sharma,1 Virginia J. Savin,2 Thomas Wiegmann,2 Nephrology, Kansas City VA Medical Center, Kansas City, MO; 2Research, Midwest Biomedical Research Foundation (MBRF), KVMC Medical Center, Kansas City, MO.

Background: The effect of TRT on the progression of CKD is not known. We used data from a large cohort to retrospectively determine whether TRT has adverse effects on patients with CKD.

Methods: The Veterans Administration Informatics and Computing Infrastructure (VINCI) data were extracted using SAS Enterprise Guide 7.1 and analyzed using SPSS. Serum creatinine (mg/dL) as a measure of renal function was compared between groups of Veterans with low total testosterone (T) levels (Gp1) who were untreated or treated with TRT (N=33879) and (Gp2) untreated subjects who maintained low T levels (Gp2, N=9755, creatinine 1.11 ± 0.004, FU 5.1 years). Change was defined by time to various plasma creatinine concentration thresholds and all-cause mortality.

Results: Table 1A shows that increase in serum creatinine levels from <1.5 to ≥1.5, <3 to ≥3 and <6 to ≥6 was significantly (P<0.001) delayed in Gp1. Table 1B shows that all-cause mortality in individuals <50 years and those ≥50 years was significantly lowered in Gp1 (P<0.001).

<table>
<thead>
<tr>
<th>TABLE 1A</th>
<th>N</th>
<th>Final Creatinine (mg/dL±SEM)</th>
<th>Days to event±SEM (P, Normalized vs. untreated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine from &lt;1.5 to ≥1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized</td>
<td>8042</td>
<td>1.72±0.01</td>
<td>899:10 (P=0.001)</td>
</tr>
<tr>
<td>Untreated</td>
<td>1815</td>
<td>1.70±0.01</td>
<td>757:19</td>
</tr>
<tr>
<td>Creatinine from &lt;3 to ≥3 (ESRD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized</td>
<td>1146</td>
<td>3.92±0.04</td>
<td>131±52 (P=0.001)</td>
</tr>
<tr>
<td>Untreated</td>
<td>335</td>
<td>3.76±0.08</td>
<td>105±34</td>
</tr>
<tr>
<td>Creatinine from &lt;6 to ≥6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized</td>
<td>280</td>
<td>7.19±0.09</td>
<td>131±64 (P=0.001)</td>
</tr>
<tr>
<td>Untreated</td>
<td>66</td>
<td>7.40±0.22</td>
<td>109±10</td>
</tr>
</tbody>
</table>

Conclusions: Normalization of T levels does not hasten decline in renal function and may lower all-cause mortality.

Funding: VA Support, Private Foundation Support

SA-PO825
Thyroid Hormone Replacement May Decrease the Risk of Cardiovascular Events in Diabetic Nephropathy Patients with Subclinical Hypothyroidism
Changhwan Seo, Hyoungmin Kim, Min-Uk Cha, Seoghun Kim, Dae-Suk Han. Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Recent studies have revealed that subclinical hypothyroidism is associated with several adverse cardiovascular outcomes in diabetic nephropathy. Although thyroid hormone replacement therapy (THRT) could restore these conditions in general population, the effectiveness of THRT in diabetic nephropathy combined with subclinical hypothyroidism is not investigated.

Methods: From 2000 to 2014, we identified 257 patients who diagnosed with diabetic nephropathy combined with subclinical hypothyroidism. Subclinical hypothyroidism was defined as normal free thyroxine (fT4) with elevated thyroid stimulating hormone (TSH). THRT was defined as the replacement of thyroid hormone at least 60 days. The primary outcomes are defined as all-cause mortality and incident major cardiovascular events.

Results: The mean age was 65.6±12.5 years. Among 257 diabetic nephropathy combined with subclinical hypothyroidism patients, 83 (32.3%) were classified as the THRT group. THRT group showed significantly high TSH level (7.10±1.53 vs 6.16±1.21, P=0.028) even after adjustment for age, sex, TSH, HbA1c and estimated glomerular filtration rate.

Conclusions: These findings suggest that THRT in patients with diabetic nephropathy combined subclinical hypothyroidism might be considered the therapeutic options.

SA-PO826
The Subclinical Fluid Overload Is Significantly Associated with Coronary Artery Calcification in Patients with Chronic Kidney Disease
Changhwan Seo,1 Seohyun Park,1 Hae-Ryong Yun,1 Boyoung Nam,2 Ji Min Park,2 Tae-Hyun Yoo,1 1Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Republic of Korea; 2Dept of Internal Medicine, College of Medicine, Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ, Seoul, Republic of Korea.

Background: The aim of this study is to identify the relationship between fluid status and underlying renal function, and to elucidate the association between fluid overload and coronary artery calcification in patients with chronic kidney disease (CKD).
Methods: The data was retrieved from the prospective observational cohort for Cardiovascular and Metabolic Disease Etiology Research Center-High Risk (CMERC-HR NCT02003781). Fluid status was measured by bioimpedance analysis and extracellular water was adjusted by total body water (ECW/TBW). The subjects were excluded from the study if they had severe overhydration (ECW/TBW > 0.4). Finally, 1,148 CKD patients were eligible in present analysis.

Results: The mean age of the study subjects was 60.0±10.9 years, and 656 (57.1%) patients were male. The fluid overload value by ECW/TBW was gradually intensifying according to CKD stages. The participating individuals were divided into four groups according to the quartiles of ECW/TBW. Age 1 prevalence of diabetes, peripheral and central pulse pressure, and coronary calcium score (CCS) increased in accordance with increasing quartiles of ECW/TBW. In multiple linear regression analysis, age, diabetes, serum albumin, C-reactive protein, and eGFR were independently associated with ECW/ TBW. In addition, ECW/TBW was found to be independency associated with CCS after adjustment for multiple confounding factors (per 0.001 increase in ECW/TBW; odds ratio=1.06, 95% confidence interval=1.02-1.10, P<0.003) in multiple logistic regression analysis. Subgroup analysis in patients with CKD stage I-3a also demonstrated the significant association between ECW/TBW and CCS.

Conclusions: Extracellular volume status is significantly associated with coronary artery calcification in patients with CKD throughout all stages.

SA-PO827
High-Normal Albuminuria Is Associated with Subclinical Atherosclerosis in a Nondiabetic Population without Chronic Kidney Disease
Toshinori Ueno, Ayumu Nakashima, Shigehiro Doi, Aki Sanada, Takao Masaki. Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.

Background: Low-grade albuminuria is considered to be a predictor of cardiovascular mortality, while little is known about the relationship between high-normal albuminuria and subclinical atherosclerosis in the general population without diabetes mellitus.

Methods: In this cross-sectional study, 2137 non-diabetic Japanese middle-aged men (mean age, 53 years), who attended general health checkups between April 2012 and March 2015, underwent blood sampling, urinalysis, and carotid ultrasonography. Presence of chronic kidney disease (CKD) was diagnosed by the clinical criteria, estimated glomerular filtration rate <60 ml/min per 1.73 m² or urine albumin to creatinine ratio (UACR) ≥30 mg/g. Carotid intima-media thickness (IMT) and the number of focal atheroma plaques were used as indicators of subclinical atherosclerosis. To assess independent predictors of IMT and carotid plaque formation in the non-CKD subgroup, multivariate stepwise analysis was used.

Results: Among 2137 participants, 324 (15.2%) had CKD. Both IMT (0.68±0.13 vs. 0.64±0.13 mm, P=0.01) and the presence of plaques (71.0% vs. 59.0%, P=0.01) were significantly higher in the CKD than in the non-CKD subjects. In subjects without CKD (n=1813), mean UACR was 5.1 (range 0.0–29.8) mg/g, and a significant positive trend across UACR quartiles was observed for IMT and the number of carotid plaques. Age, body mass index, and hypertension were independently associated with thickened IMT, whereas UACR did not show a significant correlation. In contrast to IMT, UACR was independently associated with the number of carotid plaques.

Conclusions: Our data indicate that high-normal albuminuria is associated with carotid plaque formation in a nondiabetic population without CKD.

SA-PO828
Endogenous Ouabain as a Biomarker of Heart Failure and a Predictor of Mortality After Cardiac Surgery in CKD Patients
Marco Simonini, Simona Pozzoli, Nunzia Casamassima, Chiara Lanzani, Lorena Citterio, Simona Delli Carpini, Elisabetta Messaggio, Stefano Tentori, Elena Bignami, Paolo Manunta. San Raffaele Scientific Inst, Milan, Italy.

Background: Cardiovascular diseases remain the main cause of mortality and morbidity worldwide and, in particular, in patients with Chronic Kidney Disease (CKD). The identification of subjects with increased risk of developing new cardiovascular events remains a priority in order to guide treatments and determine individual prognosis. Biomarkers are useful tools that are able to help physicians in decision-making. Our aim is to investigate Endogenous Ouabain (EO), an adrenal stress hormone with hemodynamic effects, as a valuable biomarker of heart failure in patients with impaired renal function.

Methods: Among 2137 participants (mean age 60±13yrs; eGFR 44±13ml/min/1.73 m²), 324 (15.2%) had CKD (stages 1-5). Both IMT (0.68±0.13 vs. 0.64±0.13 mm, P=0.01) and the presence of plaques (71.0% vs. 59.0%, P=0.01) were significantly higher in the CKD than in the non-CKD subjects. In subjects without CKD (n=1813), mean UACR was 5.1 (range 0.0–29.8) mg/g, and a significant positive trend across UACR quartiles was observed for IMT and the number of carotid plaques. Age, body mass index, and hypertension were independently associated with thickened IMT, whereas UACR did not show a significant correlation. In contrast to IMT, UACR was independently associated with the number of carotid plaques.

Results: Among 2137 participants, 324 (15.2%) had CKD. Both IMT (0.68±0.13 vs. 0.64±0.13 mm, P=0.01) and the presence of plaques (71.0% vs. 59.0%, P=0.01) were significantly higher in the CKD than in the non-CKD subjects. In subjects without CKD (n=1813), mean UACR was 5.1 (range 0.0–29.8) mg/g, and a significant positive trend across UACR quartiles was observed for IMT and the number of carotid plaques. Age, body mass index, and hypertension were independently associated with thickened IMT, whereas UACR did not show a significant correlation. In contrast to IMT, UACR was independently associated with the number of carotid plaques.

Conclusions: Our data indicate that high-normal albuminuria is associated with carotid plaque formation in a nondiabetic population without CKD.

SA-PO829
Red Cell Distribution Width as a Biomarker of Cardiovascular Disease in Patients with Chronic Kidney Disease
Nissreen Elfadawy, Chang H. Kim, Sadeer Al-Kindi. Internal Medicine, Case Medical Center - Univ Hospitals - Case Western Reserve Univ, Cleveland, OH.

Background: Cardiovascular risk stratification in patients with CKD is required to direct prevention and intervention strategies. Anisocytosis, as measured by Red Cell Distribution Width (RDW) has been linked to adverse cardiovascular outcomes in patients with heart failure. It is unknown whether higher RDW is associated with increased prevalence of cardiovascular disease (CVD) in CKD population. The aim of the study is to evaluate the association between high RDW and prevalence of CVD in patients with CKD.

Methods: Using Explorys database, we identified patients with CKD (age 18-65 years) and had live active records between 1999 and 2016. Patients were stratified into normal RDW (<14.5%) and high RDW (>14.5%). We studied the frequency of CVD, namely: coronary artery disease (CAD), heart failure (HF), myocardial infarction (MI), atrial fibrillation (AFib), and cerebrovascular accident (CVA), based on the ICD diagnoses, in the 2 groups. Statistical comparison between the normal and high group was performed with chi-square test, and risk ratio (RR) of the CV adverse events was calculated.

Results: A total of 231,390 CKD patients (stages I- V) were included. The proportion of the CKD patients with CVD was significantly higher in the RDW high group compared to the RDW normal group. The RR was greater in the HF (3.1 [1.0-3.1]) and A fib (3 [2.9- 3.1]). When patients were stratified by CKD stage, the RR was highest in the early CKD stages and decreased with advancing stage.

Conclusions: In this large cohort of CKD patients, elevated RDW was associated with significantly increased CVD prevalence specially in early CKD stages I-II. RDW could identify patients for CVD prevention trials in this high risk population.

SA-PO830
Arterial Wave Reflection and Cardiorespiratory Fitness in Mild to Moderate CKD
Danielle L. Kirkman, Bryce J. Muth, Raymond R. Townsend, David G. Edwards. 1Univ of Delaware; 2Univ of Pennsylvania.

Background: Cardiorespiratory fitness levels are reduced in Chronic Kidney Disease (CKD) patients and are associated with a poor quality of life, increased cardiovascular disease (CVD) risk and premature death. Disease related structural and functional cardiac and vascular changes provide central limitations to exercise tolerance. Increased arterial wave reflection amplitude may contribute to increased left ventricular pulsatile load and thus hamper oxygen delivery during activity. The relationship between arterial wave reflection and cardiorespiratory fitness in CKD is unknown.

Methods: Cardiopulmonary exercise testing (CPX) and assessment of central aortic pressure with wave separation analysis were carried out in 27 stage 3-5 CKD patients (Mean±SD, age 60±13yrs; eGFR 44±11ml/min/1.73 m²) and 20 healthy controls (57±5yrs). VO₂peak was measured by expired respiratory gas analysis during graded CPX. Aortic pressure waves were synthesized from radial artery waveforms acquired by applanation tonometry and use of a generalized transfer function. Augmentation Index (AI) was calculated and the central pressure waveform was separated into forward and reflected waves using a physiologic flow waveform.

Results: VO₂peak was reduced in CKD patients (27±7 vs. 18±5ml/kg/min, P=0.01). Central aortic systolic pressure was increased in CKD patients (134±21 vs. 119±14mmHg, P=0.01). AI was similar between groups (29±11 vs. 27±14%, P=0.5), however both forward and reflected wave amplitudes were higher in CKD.

Conclusions: In this large cohort of CKD patients, elevated RDW was associated with significantly increased CVD prevalence specially in early CKD stages I-II. RDW could identify patients for CVD prevention trials in this high risk population.

Poster/Saturday
In CKD patients, moderate to strong inverse relationships were shown between VO2peak and NT-proBNP, and both forward (r=-0.68, p<0.01) and reflected (r=-0.55, p<0.01) wave amplitudes.

Conclusions: Forward and reflected wave amplitudes are increased in CKD, which may contribute to the high CVD risk in these patients. Increased arterial wave amplitudes may pose a central limitation to exercise tolerance in CKD.

Funding: Other NIH Support - NIH National Heart Lung and Blood Institute: HL1151401

SA-PO831
Clinical Value of Natriuretic Peptides in Predicting Short- and Long-Term Dialysis in Stage 4 and 5 Chronic Kidney Disease Patients Dominique Guerrot, Sofia Anna Sundqvist, Frank Le Roy, Michel R. Godin. Nephrology, Rouen Univ Hospital, Rouen, France.

Background: Anticipating the time to renal replacement therapy (RRT) in chronic kidney disease (CKD) patients is an important but challenging issue. Natriuretic peptides are biomarkers of ventricular dysfunction related to poor outcome in CKD. We comparatively investigated the value of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) as prognostic markers for the risk of RRT in stage 4 and 5 CKD patients within a 5-year follow-up period.

Methods: Baseline plasma BNP (Triage, Biosite) and NT-proBNP (Eliicyos, Roche) were measured at inclusion. Forty-three patients were followed-up during 5 years. Kaplan-Meier analysis, with log-rank testing and hazard ratios (HR), were calculated to evaluate survival without RRT.

Results: During the first 12-month follow-up period, 16 patients started RRT. NT-proBNP concentration was higher in patients who reached endpoint (3221 ng/L vs 777 ng/L, p=0.02). NT-proBNP concentration > 1345 ng/L proved significant predictive value on survival analysis for cardiovascular events (p=0.004) and dialysis within 60 months follow-up (p=0.008; Figure). BNP concentration > 140 ng/L was an independent predictor of RRT after 12 months follow-up (p=0.005), and of significant predictive value for initiation of dialysis within 60 months follow-up.

Conclusions: Our results indicate a prognostic value for BNP and NT-proBNP in predicting RRT in stage 4 and 5 CKD patients, regarding both short- and long-term periods. NT-proBNP also proved a value in predicting cardiovascular events. Natriuretic peptides could be useful predictive biomarkers for therapeutic guidance in CKD.

SA-PO832
Sodium/Urea Nitrogen in Second Urine Is the Best Tool in Predicting 24-Hour Urinary Sodium Sang Youb Han,1 Hyecong Cheon Park,2 Sang-Woong Han.1 1Internal Medicine, Inje Univ Ilsan-Paik Hosp.; 2Yonsei Univ.; 1Hanyang Univ.

Background: Determining daily salt intake is important in predicting public health. Sodium intake has been calculated based on using spot urine to estimate sodium intake instead of 24-hour urine due to inadequate collection. However, it is still unclear what is best to estimate daily sodium intake. We measured sodium and other electrolytes for each samples collected as every episode of urination during 24 hours, and examined any correlation to represent 24-hour urinary sodium.

Methods: Fifteen male adults (age: 33.7 ± 6.43) were participated. They had only 3 meals per day which includes total of 2.0 g of sodium and no restriction to water intake. The 24-hour urine was collected starting from second urine of the first day to first urine of the second day. The 24-hour sodium intake was estimated using Tanaka’s equation. Urine sodium had significantly (r=0.66, p<0.01) and reflected (r=0.54, p<0.01) correlation to serum aldosterone in the spot urine. We used ratio of Na to other parameters to analyze any correlation to total 24-hour urinary sodium. Each urine sample was compared in three sets; first morning urine of the second day, and every 8 collected urine samples of 15 enrolled participants.

Results: The 24-hour urinary sodium (24UNa) was 143.9 ± 42.1 mg. The 24UNa was significantly correlated with Na/urea nitrogen (r=0.56, Na/Osm (r=0.51), age (r=0.54), Na/Cr (r=0.392) and estimated sodium using Tanaka’s equation (Tanaka’s Na, r=-0.403). Most significant correlation was seen in second urine of the first day. 24UNa was correlated with Na/urea nitrogen (r=0.710), Na/Osm (r=0.680), Na/Cr (r=-0.58), age (r=0.54), Na/Cr (r=-0.58), and Tanaka’s Na (r=0.666). However, first morning urine of the second day showed unexpected poor correlation: Na/urea nitrogen (r=0.322), Na/Osm (r=0.308), age (r=0.308), and Tanaka’s Na (r=0.375).

Conclusions: In conclusion, second urine sample is more suitable than first morning urine to estimate 24UNa. The Na/urea nitrogen had significant correlation with 24UNa in second urine in all participants. Further studies are necessary to validate valuable index and optimal time for urine sample in predicting 24-hour urinary sodium.

SA-PO833
Association of Serum Aldosterone Levels with Clinical Outcomes in the Elderly Amanda K. Leonberg-Yoo,1 Ronit Katz,2 Linda F. Fried,3 Stephen Kritchevsky,4 Michael Shlipak,2 Joachim H. Ix,5 Mark J. Sarnak.1 1Div of Nephrology, Tufts Medical Center; 2Div of Nephrology, Univ of Washington; 3Renal-Electrolyte Div, Univ of Pittsburgh; 4Stitch Center on Aging, Wake Forest School of Medicine; 5Div of Nephrology, Univ of California, San Diego; 6Div of Nephrology, Univ of California, San Francisco.

Background: Elevated serum aldosterone levels have been associated with adverse outcomes in persons with hyperaldosteronism and cardiac disease. We investigated the relationship between serum aldosterone and clinically important outcomes in a healthy elderly cohort.

Methods: Serum aldosterone was measured at baseline in the Health ABC Study, a cohort of well-functioning adults aged 70-79 years. Using a case-cohort study design, cases were selected for kidney disease progression (30% reduction in eGFR), incident heart failure (HF), incident cardiovascular disease (CVD), and all-cause mortality. Weighted Cox proportional hazards models, sequentially adjusted for cardiovascular and kidney factors, were used to examine the associations of serum aldosterone with each clinical outcome.

Results: Mean (SD) age was 73.6 (2.8) years; 49% were women, and 61% were white. Median (25%, 75%) serum aldosterone was 5.12 (3.15, 8.85) ng/dL. There was no association between serum aldosterone with kidney disease progression, incident HF, or all-cause mortality. After adjustment for cardiovascular and kidney factors, medication use and urine sodium, there were significant lower atherosclerotic CVD events with high serum aldosterone levels.

Conclusions: There was no relationship between high serum aldosterone and kidney disease progression, incident HF, or all-cause mortality. Higher aldosterone levels were associated with lower CVD risk after adjustment for urine sodium excretion and medications. Additional studies are needed to confirm these relationships in healthy, younger people.

SA-PO834
Association of Urine Sodium with Clinical Outcomes in the Elderly Amanda K. Leonberg-Yoo,1 Ronit Katz,2 Linda F. Fried,3 Stephen Kritchevsky,4 Michael Shlipak,2 Joachim H. Ix,5 Mark J. Sarnak.1 1Div of Nephrology, Tufts Medical Center; 2Div of Nephrology, Univ of Washington; 3Renal-Electrolyte Div, Univ of Pittsburgh; 4Stitch Center on Aging, Wake Forest School of Medicine; 5Div of Nephrology, UCSF; 6Div of Nephrology, UCSF.

Background: Recent studies in persons at high cardiovascular risk suggest a U-shaped relationship between sodium intake and cardiovascular outcomes. We assessed the relationship of urine sodium, as a proxy for sodium intake, to clinical outcomes in healthy older adults. Because aldosterone levels may increase with low sodium intake, we evaluated whether aldosterone is an important confounding variable.

Methods: Baseline spot sodium urine and serum aldosterone were measured in the Health ABC Study, a cohort of well-functioning adults aged 70-79 years. 24-hr urine sodium excretion was estimated by the Kawasaki formula. Using weighted cox proportional hazards models in a case cohort study design, we evaluated the association of urine sodium with kidney disease progression (30% decrease in eGFR), incident heart failure, incident atherosclerotic cardiovascular disease (CVD), and all-cause mortality. Sequential adjustments for cardiovascular and kidney factors as well as aldosterone were performed.

Results: Mean (SD) 24-hr urine sodium excretion was 4174 (1546) mg. Lower levels of urine sodium were associated with CVD but not kidney disease progression, heart failure, or all-cause mortality. Aldosterone did not attenuate the relationship of low urine sodium with CVD. There was no interaction between aldosterone and urine sodium for CVD (p-interaction=0.6).

Conclusions: There was no relationship between high serum aldosterone and kidney disease progression, incident HF, or all-cause mortality. Higher aldosterone levels were associated with lower CVD risk after adjustment for urine sodium excretion and medications. Additional studies are needed to confirm these relationships in healthy, younger people.
Conclusions: Lower levels of urine sodium were associated with higher risk of CVD in healthy adults, but not with heart failure, kidney disease progression, or mortality. Aldosterone did not attenuate the relationship between low urine sodium excretion and CVD.

SA-PO835
Growth Arrest-Specific Gene 6 May Be a Biomarker of Non-Complicated Atherosclerotic Plaque Burden

Background: Growth arrest-specific gene 6 (Gas6) belongs to the family of vitamin K-dependent proteins. Gas6 is not detected in normal vessels but is expressed by vascular smooth muscle cells at all stages of human atherosclerosis and is markedly higher in non-complicated plaques than in complicated (i.e., vulnerable) plaques. Gas6 may act as a protective factor, in part, by reducing the pro-inflammatory phenotype of VSMCs. The objective of this study was to determine the association of Gas6 with measures of atheroma burden quantified by carotid ultrasound.

Methods: In 204 participants referred for coronary angiography, blood was collected and maximum plaque height and carotid intima media thickness (CIMT) was assessed in the internal carotid arteries (ICA) and carotid bulbs by ultrasound. Gas6 and FGF-23 were measured in plasma via ELISA (Immunotopics Inc). Multi-variable models evaluated independent predictors of maximum plaque height, CIMT and the difference between maximal plaque height and CIMT (PH-CIMT).

Results: In bivariate analysis, Gas6 was significantly higher in females (p=0.019), diabetics (p=0.010) and those with BMI > 30 kg/m² (p=0.004). There was a significant correlation between gas6 and FGF-23 (r=0.262, p<0.001). There was no association between gas6 and CIMT. In multivariable models adjusted for age, sex, and diabetes, a higher level of gas6 was associated with lower plaque height and lower PH-CIMT. This significant relationship remained robust after adjustment for smoking, hypertension, hyperlipidemia, phosphate and FGF-23.

Conclusions: Although Gas6 levels were higher in diabetics and obese subjects, there was a significant and inverse association between Gas6 and plaque height. Gas6 is an atheroprotective factor and its expression is markedly higher in non-complicated plaques. Therefore, gas6 could be a biomarker reflecting the presence of less vulnerable plaques in humans. Whether vitamin K is a significant mediator of this process is not known.

SA-PO836
Social Support and Health Outcomes in Hispanics with Chronic Kidney Disease

Background: The present study aims to study the spectrum and severity of peripheral neuropathy in CKD patients and correlate electrophysiological findings with estimated GFR and to establish electrophysiological and pathological correlation in assessment of the severity of peripheral neuropathy with progression of CKD.

Methods: A prospective cross-sectional observation study where 60 consecutive patients with CKD (eGFR <60 ml/min) were enrolled excluding patients with neuropathy due to any other causes except diabetes. Detailed history and clinical examination including neurology symptom score (NNS) score and electrophysiological examinations were done. Sural nerve biopsy was done and correlated with severity and progression of CKD using suitable statistical tool.

Results: Out of 60 CKD patients, 29 were diabetic CKD. About 81.66% of subject had distal symmetric polyneuropathy and NNS Score was 1.75±1.36. In 25% mononeuropathy, 3.33% (CTS), Cranial Neuropathy and 11.6% autonomic involvement were found. Among 89 neuropathy positive patients, 48.97% had sensory motor polyneuropathy while 51.02% had pure sensory polyneuropathy.Neurophatic group were more symptomatic and had higher sensory latency (p<0.012) compared to non-neuropathy group. Hypokalemia was more in neuropathic group with mean serum K+ level of 5.33 compared to non-neuropathy group (mean x K+ 4.93) (p<0.17). Diabetes patients were at higher risk of neuropathy with odds ratio of 6.89 compared to non-diabetic in CKD subjects. Paraesthesia and/or dysesthesia were the most common symptoms in 40(66.66%),while most common complaint was burning in vibration sensitivity in 37(61.66%) subjects. Nerve conduction study revealed sural sensory action potential (81.66% abnormal) was the most common abnormal parameter, while tibial motor action potential and peroneal distal latency were second most common findings. Sural nerve biopsy revealed mostly axonopathy in advanced CKD and in few cases demyelination which closely correlated with EP study.

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

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Conclusions: Peripheral neuropathy is common and linearly correlated with severity of CKD. 2. Atopy is common in advanced CKD and there is a clear relationship between electrophysiological – pathological study.

SA-PO839
Factors Predicting Renal Events among Chronic Kidney Disease Patients Including Post-Kidney Transplantation Cases
Satoshi Tandai, Ryo Yamada, Ken Matsuo, Yoko Matsuo, Masaaki Murakami, Kikihiro Sonoda, Kiyoshi Mori, Noriko Mori, Dept of Nephrology, Shizuoka General Hospital, Shizuoka, Japan; Dept of Laboratory Medicine, Shizuoka General Hospital, Shizuoka, Japan; School of Pharmaceutical Sciences, Univ of Shizuoka, Shizuoka, Japan.

Background: Increase in urinary biomarkers of tubular injury is associated with poor renal outcome among patients with chronic kidney disease (CKD) but relative significance of each biomarker remains elusive. Much less is known about utility of those biomarkers in post-kidney transplantation (KT) cases. We carried out single-center, prospective, observational study among 250 out-patient CKD subjects including KT cases.

Methods: Urine albumin, alpha-1 microglobulin (a1MG), liver-type fatty acid binding protein (L-FABP) and N-acetyl glucosaminidase were measured in 250 CKD subjects. Cox proportional hazards models were used to examine association of creatinine (Cr)-normalized urinary biomarker levels with renal events defined by serum Cr doubling, end-stage renal disease (ESRD) or death. Decline rate of renal function was also studied by comparing serum Cr changes after 2 years.

Results: Ages of participants were 59.0±16.1 (mean± SD) years, 61% were men, 11% had diabetes mellitus and 20% were KT cases. Median follow-up period was 4.5 years. Among patients who did not develop renal events within 2 years, relative serum Cr values after 2 years were 129±73% (diabetic nephropathy, n=14), 111±29% (nephrosclerosis, n=36), 96±60% (diabetic nephropathy, n=37), 87±10% (hypertensive nephropathy, n=15) and 104±28% (KT, n=48), reflecting response to treatment. After post hoc analysis using stepwise method, independent variables predicting renal events were male gender [hazard ratio (HR) 2.2, P<0.01], serum Cr (0.678 and 0.798, respectively), suggesting that stored sFlt-1 had more predictive accuracy in renal deterioration than other sFlt-1.

Conclusions: In addition to classical risk factors for ESRD, urinary a1MG was independently associated with increased risk of renal events in individuals including KT cases.

SA-PO840
Understanding Pharmaceutical Care Needs of Living Kidney Donors Through Linked Transplant Registry and Pharmacy Claims Data
Krista L. Lenting, Sally K. Gustafson, Mark Schnitzler, Gregory P. Hess, Dorry L. Segev, Amit X. Garg, Bertram L. Kasiske, Saint Louis Univ; Chronic Disease Research Group; Symphony Health; Johns Hopkins; Western Univ.

Background: Limited data are available on pharmaceutical care needs of living kidney donors (LKD).

Methods: We integrated 1 national US Scientific Registry of Transplant Recipients data for LKD (1987-2012) with 2 pharmacy fill records from a nationwide pharmacy clearinghouse to examine utilization patterns of diabetes treatments, antihypertensive medications, and antidepressants as measures of these conditions before and after donation.

Results: The linked data captured 32,065 LKD actively filling in the first year before, and 36,597 actively filling in the first year after donation (Table). A very small but surprising fraction of LKD were treated with insulin or an oral hypoglycemic agent in the 3 years prior to donation. In year 10 after donation, 0.4% received insulin and 2.3% received an oral glucose-lowering agent. Angiotensin converting enzyme inhibitors comprised the most common class of antihypertensive agent used in the year after donation, with use in 11.3% by year 10. Among the sample, 8.6% received a diuretic by year 10. The fraction of LKD were treated with insulin or an oral hypoglycemic agent in the 3 years after donation was 8.6% (n=2070), reflecting response to treatment. After post hoc analysis using stepwise method, independent variables predicting renal events were male gender [hazard ratio (HR) 2.2, P<0.01], serum Cr (0.678 and 0.798, respectively), suggesting that stored sFlt-1 had more predictive accuracy in renal deterioration than other sFlt-1.

Conclusions: Decreased stored sFlt-1 is significantly associated with renal events.

SA-PO841
Diagnostic Utility of Stored sFlt-1 for Future Renal Deterioration
Hideo Tsuchima, Masaru Matsui, Miho Tagawa, Ken-Ichi Samejima, Yasuhiro Akai, Yoshihiro Saito, First Dept of Internal Medicine, Nara Medical Univ, Kashihara, Japan.

Background: Soluble fms-like tyrosine kinase-1 (sFlt-1), produced by alternative splicing of Flt-1 pre-mRNA is an endogenous antagonist as VEGF and placental growth factor signaling. We have already demonstrated that in the baseline condition, the majority of sFlt-1 is stored in the endothelial cell surface, with an extremely small amount in the circulation, and that stored sFlt-1 is significantly decreased in patients with advanced CKD, as verified by heparin-stimulation; however the relationship between stored sFlt-1 and renal deterioration clinically remains unknown.

Methods: We recruited 104 participants undergoing heparin-loading test, defined as blood collection before and 5 minutes after intravenous heparin injection at a dose of 0.4 IU/kg. The linked data captured 32,065 LKD actively filling in the first year before, and 36,597 actively filling in the first year after donation (Table). Among patients who did not develop renal events within 2 years, relative serum Cr values after 2 years were 129±73% (diabetic nephropathy, n=14), 111±29% (nephrosclerosis, n=36), 96±60% (diabetic nephropathy, n=37), 87±10% (hypertensive nephropathy, n=15) and 104±28% (KT, n=48), reflecting response to treatment. After post hoc analysis using stepwise method, independent variables predicting renal events were male gender [hazard ratio (HR) 2.2, P<0.01], serum Cr (0.678 and 0.798, respectively), suggesting that stored sFlt-1 had more predictive accuracy in renal deterioration than other sFlt-1.

Conclusions: Decreased stored sFlt-1 is significantly associated with renal events.

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Conclusions: CKD stage and anemia at first visit were risk factors for RRT during pregnancy. Urgent pregnancy cessation due to eclampsia, preeclampsia and polyhydramnios was more frequent in the HD group. As expected, babies from the HD group had lower gestational age and lower weight at birth when compared to babies of CKD mothers that did not need HD. Renal recovery after delivery remains low, but perinatal and maternal outcomes are improving.

SA-PO843
Pregnancy in Mexican, Low-Income, Chronic Kidney Disease Patients

María de la Luz Alcántar-Vallín, Angela María Soto-Cruz, Karina Renoirte, Guillermo García-Garcia. Nephrology, Hospital Civil Guadalajara, Guadalajara, Jalisco, Mexico.

Background: Chronic Kidney Disease (CKD) affects up to 6% of women of childbearing age & women with more advanced CKD are now rarely advised to avoid pregnancy. There are variable data on the effect of pregnancy on CKD & this observational study is the largest to our knowledge to look at both renal & obstetric outcomes in women with CKD 3-5.

Methods: Women with an MDRD eGFR below 60ml/min/1.73m² either to pregnancy or by 12 weeks of gestation, from 2 tertiary centres were included. Women already on dialysis or with early fetal loss were excluded. Outcomes analysed included a renal transplant, and t-test were used when appropriate. Multivariate logistic regression analysis was used to estimate odds ratios and 95% CI. Significance was assessed at p <0.05.

Results: 88 women (2003-2012) were identified & followed up for a median 1408 days. 12 had a renal transplant, 3 of whom had pancreas transplants. Median age: 32.2yrs & gestation at delivery. 47/88 women showed 100% live births. Mode of delivery (13 (28%) emergency caesarean section, 18 (38%) elective caesarean section, 16 (34%) vaginal delivery) was not affected by baseline renal function. Women with CKD 3-5 were more likely to have a low-birth weight (43%), low-birth weight (<2500g (51%) & gestation at delivery. The worse the renal function & gestation at delivery.

Conclusions: Women with CKD 3-5 are at risk of adverse renal and obstetric outcomes, with renal decline most commonly occurring in the 3rd trimester. The worse the renal function at conception the greater the risk of requiring RRT and preterm delivery.
Results: A total of 63 (5.0%) developed ESRD. The age–adjusted incidence of ESRD decreased significantly over time, from 12.5 to 1000 person-years (95% confidence interval [CI], 2.5–24.6) in 1979–1989, to 6.5 per 1000 person-years (95% CI, 1.7–25.2) in 1990–1999; to 4.2 per 1000 person-years (95% CI, 1.8–17.5) in 2000–2010. The proportions of patients with preserved renal function and acute inflammatory histologic changes (i.e., endocapillary hypercellularity, capillaritis proliferation, and acute crescentic lesion) at the timing of biopsy increased over time, as did the rates of prescriptions of renin–angiotensin system inhibitors and corticosteroids (all P<0.001). The impacts of acute inflammatory histologic lesions on renal prognosis were drastically reduced with the times.

Conclusions: These findings suggest that early diagnosis in the acute inflammatory phase and subsequent aggressive treatment may have contributed to the significant downward trends over three decades in the incidence of ESRD in Japanese patients with IgAN.

SA-PO846 Hospitalization Burden of Chronic Renal Insufficiency Cohort (CRIC) Study Participants Amanda Hyre Anderson,1 Jason Roy,1 Eugene Lin,2 Michael J. Fischer,2 L. Lee Hamm,3 James P. Lash,2 Eva Lustigova,2 Emile Mohler,1 Akinlolu O. Ojo,1 Mahboob Rahman,4 Julia J. Siclla,4 Susan P. Steigerwalt,5 Harold I. Feldman,1 ‘Univ of Pennsylvania; The CRIC Study.

Background: Patients with chronic kidney disease (CKD) experience a substantial burden of morbidity requiring hospitalization. However, hospitalizations prior to development of end-stage renal disease (ESRD) are not well characterized.

Methods: Participants of the multi-center prospective observational CRIC Study (N=5,939, mean estimated glomerular filtration rate (eGFR): 45 ml/min/1.73m²; age range: 21–75 years; 48% white, with diabetes). Over a median of 6.9 years, hospitalizations were ascertained by patient reports, confirmed by queries of local hospitals, and categorized by ICD-9 codes. Hospitalization rates (unadjusted and adjusted for age, gender, race/ethnicity, clinical center, education, eGFR, and proteinuria in Poisson regression models) were compared across subgroups.

Results: Through mid-2013, 14,794 hospital stays were confirmed pre-ESRD with a mean duration of 2.8 days. Prior to ESRD, the mean time spent in the hospital per participant per year was 2.6 days, with 50% and 10% of participants spending 0.5 days and nearly one hospital stay annually, respectively. Unadjusted hospitalization rates (95% CI) were 61.5 (60.5–62.5), 49.3 (48.2–50.5), and 77.3 (75.6–79.0) per 100 person-years among those overall, without and with diabetes, respectively. Unadjusted rates were highest among older participants, non-Hispanic blacks, and those with lower levels of education, higher levels of proteinuria, higher SBP, history of CVD, and lower eGFR. Multivariable-adjusted rates were equal to or higher than for baseline eGFR, higher proteinuria, diabetes, and higher systolic blood pressure. The top three primary ICD-9 codes included those for congestive heart failure, chest pain, and acute kidney injury.

Conclusions: The burden of pre-ESRD hospitalizations among individuals with CKD is substantial and varies by sociodemographic and clinical factors.

Funding: NIDDK Support

SA-PO847 Chronic Kidney Disease and All-Cause Mortality: The Influence of Selection Bias in a National Health Survey Seth P. Kurranz, Decision Resources Group, Burlington, MA.

Background: The National Health and Nutrition Examination Survey (NHANES) collects biologic measures to assess CKD among participants who travel to mobile examination centers. NHANES likely underascerts severe cases of CKD due to issues of patient mobility. We assess the influence of potential selection bias due to under-ascertainment of severe cases on the association between CKD and all-cause mortality.

Methods: NHANES data (cycles 2005-06, 2007-08, and 2009-10) linked to NCHS mortality files were assessed the association between CKD (GFR < 60 ml/min, calculated by Cockroft-Gault equation) and other health outcomes. Although NHANES is a well conducted nationally representative survey, this particular form of selection bias should be considered in studies that use NHANES data to assess associations between CKD and other health outcomes.

Funding: Pharmaceutical Company Support - Decision Resources Group

SA-PO848 Prolonged Conservative Therapy in End Stage Renal Disease: A Therapeutic Option? The Verona Experience Vincenzo De Biase, Alfredo Petrosino, Alessandra Dalla Gassa, Giuseppina Pessolano, Isabella Squarzoni, Chiara Branco, Antonio Lupo. Renal Unit, Univ Hospital of Verona, Verona, FR, Italy.

Background: The prolonged conservative therapy (CT) of End Stage Renal Disease (ESRD) ameliorates uremic symptoms and postpones the initiation of renal replacement therapies (RRTs). There is no evidence of survival advantage from early initiation of dialysis, thus CT could be considered as a common path for ESRD patients, both in “palliative care” as well as in those intended to RRTs.

Methods: We observed 144 ESRD patients in CT in our low-clearance clinic, followed up in the period 01/2013–05/2016 and enrolled as they reached a eGFR (CKD-EPI)=15±1 ml/min/1,73m². The observation ended at the initiation of RRTs (haemo [HD] or peritoneal [PD] dialysis or kidney transplant [T]) or in case of death. RRTs when started indicated, in according to KDIGO 2012 guidelines. The duration of follow up [FU] was the main end point. We further evaluated serum albumin [A] and azo-taenia [N], as indexes of dietary adequacy, and eGFR variations.

Results: The mean FU at the end point was 20.2±0.8 months (CI 16.0-23.8) with no differences between those who initiated RRTs and those who did not. 37 patients (60.7%) started HD, 4 (6.6%) PD, 3 (4.9%) received a T. 12 patients (19.7%) died without RRTs. 88 patients continued the FU. Mean eGFR at the endpoint was 10.4±3/ml/min/1,73m². [A] did not change within 21 months (p=0.027, quadratic regression) and [N] showed a similar but opposite trend (p=0.066, quadratic regression); eGFR slightly declined (p=0.0001).

Conclusions: CT in ESRD patients seems to confer a stable nutritional status, as assessed by [A] and [N], within 21 months of treatment. Moreover, it allows postponing the beginning of RRTs of nearly 2 years, proving RRTs to be avoidable in many cases.

SA-PO849 Factors Affecting Secondary Care Referral of Older People with Advanced Chronic Kidney Disease and Their Outcomes: An Observational Cohort Study Amalrudi Rago,1 Stephanie J. MacNeill,1 Yeav Ben-Shlomo,2 Fergus J. Caskey,12 ‘UK Renal Registry, Bristol, United Kingdom; ’Univ of Bristol, Bristol, United Kingdom.

Background: Aim of this study was to identify patient characteristics and outcomes associated with advanced chronic kidney disease (CKD) being managed solely in primary care rather than co-managed in primary and secondary care as current evidence is limited.

Methods: The Health Improvement Network (THIN) primary care database was used to identify patients aged ≥65 years with new advanced CKD (eGFR ≤20mls/min/1.73m²) managed solely by a general practitioner(GP/Primary care cohort) or co-managed with a nephrologist(Secondary care cohort). Multivariable regression models were used to explore cohort differences in baseline demographics, clinical & laboratory markers, and survival in the 12 months following the index eGFR. Cohort differences in GP consultations and proportion having ≥4 hospitalisations was assessed using Mann Whitney and Chi-square tests respectively.

Results: There were 632 and 2,464 patients in the Primary and Secondary care cohorts respectively. In a multivariable logistic model, older patients (65-69yrs (ref; 70-74yrs: OR 0.5, 95% CI 0.2–1.8; 75-79yrs: 2.2, 0.8-6.0; ≥80yrs: 3.3, 1.3-8.7; ≥85 yrs 10.6, 4.1-27.1), women(OR 2.2, 95% CI 1.6-3.1), those living in rural areas(OR 2.1, 95% CI 1.5-3.1), cardiovascular disease(OR 1.7, 95% CI 1.2-2.4) and cancer(OR 1.6, 95% CI 1.1-2.4) were more likely in the Primary care cohort. Patients in this cohort had fewer GP consultations(median(IQR) 7(3-13) vs 9(5-15), p<0.001) and a lower proportion reported ≥4 hospitalisations(3.6% vs 9%, p<0.001) in the first year when compared to those in secondary care. Mortality remained higher in primary care cohort despite adjustment for sociodemographic, clinical measures and Charlson IndexHR 1.6, 95% CI 1.1-2.2, p=0.08).

Conclusions: People with advanced CKD are more likely to be managed solely in primary care if they are older, female and have a co-existing diagnosis of cardiovascular disease or cancer. They have a higher mortality rate, but are less likely to consult their GP or be admitted to hospital. Further study is required to understand the reasons for and appropriateness of these referral decisions.

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SA-PO850

Chronic Kidney Disease Is Associated with Mortality in Stage IV Cancer Patients Taisuke Ishii,1,2 Takuya Fujimura,1 Gautham A. Deshpande,3 Eriko Nakano,1 Yasuhiro Komatsu,1 Nephrology, St. Luke's International Hospital, Chuo-ku, Tokyo, Japan; 2Medical Oncology, St. Luke's International Hospital, Chuo-ku, Japan; 3Center for Clinical Epidemiology, St. Luke's International Univ, Chuo-ku, Tokyo, Japan.

Background: The prevalence of chronic kidney disease (CKD) is increasing among cancer patients. However, the impact of CKD on the prognosis of patients with advanced cancer is unknown. The aim of this study is to examine the association between CKD and mortality in stage IV cancer patients.

Methods: In this single-center, retrospective cohort study, we collected data from all patients with newly diagnosed stage IV solid cancer from April 2009 to December 2014, with follow-up through December 2015. CKD was defined as eGFR ≤ 60 ml/min/1.73m² at the time of diagnosis. The primary endpoint was all-cause mortality. The secondary endpoint was cancer-specific mortality. Log-rank test and Cox proportional hazard analysis were used for analysis.

Results: Of 962 patients (age 69±10, 51.8% of males) meeting inclusion criteria, 150 patients (16%) had CKD. During follow-up (median 293 days, IQR 79-751 days), 639 patients (66.4%) died. On Kaplan-Meier survival analysis, patients with CKD showed significantly poorer survival compared to those without CKD (log-rank test, p = 0.001). After adjusting for age, gender, BMI, type of cancer, antineoplastic therapy, baseline serum sodium, glucose, WBC, hemoglobin, CRP, and ECOG Performance Status, CKD showed significantly poorer survival compared to those without CKD (log-rank test, p < 0.001) and was identified as an independent risk factor in multivariate analysis (HR 1.63, 95% CI 1.26-2.10).

For cancer-specific mortality, CKD was also correlated with poorer survival (log-rank test, p = 0.001) and remained significantly associated with all-cause mortality (HR 1.63, 95% CI 1.26-2.10).

Conclusions: This study is the first to report CKD as an independent predictor of mortality in patients with advanced cancer.

SA-PO851

Canadian Child Multi-Centre ABLE Study: Long-Term Renal Outcomes 3 Months Post-Cisplatin Kelly McMahon,1 Tom D. Blydt-Hansen,2 Maury N. Pinsk,1 Cherry Mannmen,3 Shahrad Rod Rassekh,2 Ross T. Tsuyuki,3 Prasad Devarajan,3 Michael Zappitelli,1 ‘McGill U, Montreal; ’U British Columbia, Vancouver; ’U Alberta, Edmonton, Canada; ‘Cincinnati Children’s Hosp, Cincinnati.

Background: Acute kidney injury (AKI) during cisplatin therapy is common in pediatric patients. The prevalence of chronic kidney disease (CKD) or hypertension [HTN]) in the long-term renal outcome phenotype remains unclear. ABLE is a pan-Canadian study on biomarkers of late child cancer treatment effects, including nephrotoxicity. Aim: Describe CKD and HTN 3 months post-child cisplatin therapy.

Methods: Ongoing 12-site prospective study of cisplatin-treated children. Exclusion: GFR<30 ml/min/1.73m². Protocol: 2 acute visits (AV) at an early (1st or 2nd) and late (≥2+4, AVL) cisplatin infusion; 3 follow-ups (FU): 3, 12, 36 months post-cisplatin with urine/blood, blood pressure(BP) collection. AKI: serum creatinine rise≥50% from baseline (≥3 fold change) at AV or AVL FU outcomes: CKD: eGFR<90ml/min/1.73m² [by 1) serum creatinine, 2) cystatin C] or albumin-to-creatinine ratio (ACR)>30 mg/g; HTN: BP>90 percentile for age, gender, height. We calculated % with low eGFR, albuminuria or HTN at 3 months.

We compared AKI vs. non-AKI groups (chi-square or non-parametric tests).

Results: Of 56/110 with 3-month data (median[IQR] age 6[3-12] years; 53% male), HTN (7%) and albuminuria (39%) were very common (Table, “All”). Albuminuria was more common in AKI patients (though not significant); eGFR was higher in AKI (non significant, Table). 3-month HTN was more common in AKI patients (p=0.05) due to higher diastolic BP (Table).

Conclusions: ABLE will be the largest renal follow-up of cisplatin-treated children. 3-month post-cisplatin CKD and HTN prevalence is high overall. HTN is more common in patients with cisplatin-AKI. Patients with AKI may have relative hyperfiltration 3 months post-cisplat.
Evidence of Chronic Kidney Disease in Veterans with Diabetes prior to Treatment

Justin Gatwood,1,3 Marie Chisholm-Burns,1 Robert L. Davis,2 Fridjof Thomas,2 Praveen Kumar Potukuchi,2,3 Adriana Huang,4 Csaba P. Kovésy,2,3 1College of Pharmacy, University of Tennessee Health Science Center, Memphis, TN; 2College of Medicine, University of Tennessee Health Science Center, Memphis, TN; 3Pathology, Memphis VA Medical Center, Memphis, TN; 4Nephrology, Vanderbilt Univ School of Medicine, Nashville, TN.

Background: Diabetes mellitus (DM) is a growing public health threat, and its impact on chronic kidney disease (CKD) remains of paramount importance. This study evaluated the extent of CKD in a national cohort of US veterans prior to initiating oral antidiabetic (OAD) therapy for cases of diabetes.

Methods: The VA Corporate Data Warehouse was used to identify the first prescription for uncomplicated DM and the presence of disease was confirmed by an accompanying prescription for an OAD agent during 2002-2014. CKD was measured using estimated glomerular filtration rates (eGFR) and urine albumin-to-creatinine ratios as recorded nearest to the initial DM diagnosis and up to the date of the first OAD prescription fill.

Results: A total of 41,658 patients were analyzed, and most were White (77.7%) and male (96%). At DM diagnosis, mean (SD) age and hemoglobin A1C were 61.4 (10.18) and 7.4% (1.37), respectively, and 69.9% exhibited normal kidney function (UACR <30 and eGFR >60). However, 30.1% had CKD and 16.2% exhibited at least moderately reduced eGFR (CKD Stages 3a-5, Figure). The odds of any CKD stage (vs. no CKD) increased with age and hemoglobin A1C (p<0.0001 for both). Self-identified Asian (OR = 1.45, CI: 1.12-1.88) or African American race (OR = 1.12, CI: 1.05-1.20) was associated with a higher risk of CKD compared to White race.

Conclusions: CKD is common in veterans with incident DM, especially among older patients and certain minorities. Efforts to diagnose CKD should be made in conjunction with attempts to lower blood sugar early in the treatment process.

Evaluation of Non-Prescribed Opioid and Illicit Drug Use in Chronic Kidney Disease Patients

Thuy Huang, Linda Awdishu, Lee Lee Zhu Pharmacy, Univ of California, San Diego Skaggs School of Pharmacy & Pharmaceutical Sciences, La Jolla, CA.

Background: Over 58% of CKD patients experience pain and 49% of patients report their intensity of pain to be moderate to severe. Neuropathic and musculoskeletal pain are among the most common types of pain experienced by this population. The objective of this study was to determine the prevalence of non-prescribed pain medication or illicit drug use in patients with and without CKD using urinary and saliva samples.

Methods: This was a sub-study from a larger prospective medication reconciliation and adherence study of 493 patients at UCSHD Health System and ambulatory care clinics. Medication reconciliation was conducted by a pharmacist or student pharmacist for each patient. Urine and saliva specimens were collected at the time of medication reconciliation and analyzed using triple quadrupole chromatography with tandem mass spectrometry (LC-MS/MS) for the presence of opioids and illicit drugs. Patients with a GFR <60mL/min/1.73m² (by MDRD equation) were defined as CKD. We hypothesized that patients with CKD were more likely to use non-prescribed pain medications and illicit drugs than patients without CKD. A Fisher's exact test was used to compare the occurrence of non-prescribed pain medications and illicit drug use detected in biological samples between CKD and non-CKD groups.

Conclusions: As of this date, 260 patients were included in this study, 145 in non-CKD group and 106 in the CKD group. The detection of a prescribed pain medications were similar between CKD and non-CKD patients (p=0.60) indicating similar rates of adherence. Illicit drug use in CKD and non-CKD patients were overall low. No difference was found between the two groups (6.2% vs. 2.9%, p=0.37) regarding illicit drug use. Patients without CKD were more likely to use non-prescribed pain medications, mostly consisting of opioids than CKD patients (40% vs 10.6%, p=0.0001).

Conclusions: Urine and saliva testing provides an objective measurement of medication reconciliation and adherence. Despite current knowledge that CKD patients are under-treated for pain, we found that CKD patients are less likely to use non-prescribed pain medications compared to non-CKD patients.

Funding: Pharmaceutical Company Support - Millennium Research Institute

Renoprotective Effect of Dipyridamole in Pre-Dialysis Advanced Chronic Kidney Disease -A Nationwide Database Analysis

Ke-Lin Kuo,1 Szu-Chun Hung,1 Jia-Sin Liu,2 Chi-Heng Hsu,2 Der-Cheng Tang,3 1Taipei Tzu Chi Hospital, Taiwan; 2National Health Research Insts, Taiwan; 3Taipei Veterans General Hospital, Taiwan.

Background: Dipyridamole decreases proteinuria and improves renal function progression in patients with glomerular disease through its inhibition of platelet activation and enhanced nitric oxide expression. Whether the effects of dipyridamole on renal outcome or survival is unclear in CKD stage 5 patients who have not yet received dialysis (CKD 5 ND).

Methods: A prospective cohort study was conducted based on the Taiwan National Health Insurance Research Database. From January 1, 2000 to June 30, 2009, we enrolled 28497 CKD 5 ND patients with serum creatinine levels >6 mg/dL and hematocrit levels >28% and who were treated with cyclophosphamide-stimulating agents (ESA’s) but not yet received renal replacement therapy. All patients were further divided into two groups and dipyridamole within 90 days after starting ESA therapy (index date). Patient follow-up took place until long-term dialysis, death before initiation of dialysis or December 31, 2009.

Results: With a mean follow-up of 12 months, 20,152 patients (70.7 %) required long-term dialysis and 5,697 (20.0%) died before progression to end-stage renal disease requiring dialysis. After propensity score-matching, use of dipyridamole was associated with a lower risk for long-term dialysis (HR, 0.96; 95% CI, 0.93-0.99) and pre-dialysis death (HR, 0.89; 95% CI, 0.84-0.95) as compared with nonusers.

Conclusions: Dipyridamole exhibited a protective effect in reducing the risk for long-term dialysis and pre-dialysis death in CKD 5 ND patients. Randomized studies are needed to validate this association.

Effect of Rituximab on Malignancy Risk in Patients with ANCA-Associated Vasculitis

Emma Van Daalen,1 Raffaela Rizzo,2 Andreas Kronbichler,3 Ron Wolberbeck,1 Jan A. Brujin,1 David R.W. Jayne,2 Ingeborg M. Bajema,3 Chinar Rahmatulla.1 1Pathology, Leiden Univ Medical Center; 2Nephrology, Dialysis and Hypertension Unit, St. Orsola-Malpighi Univ Hospital; 3Vasculitis and Lupus Clinic, Addenbrooke’s Hospital, Cambridge Univ Hospitals; Internal Medicine IV (Nephrology and Hypertension), Medical Univ of Innsbruck; Medical Statistics and Bioinformatics, Leiden Univ Medical Center.

Methods: We looked for the association of malignancy and ANCA in a cohort of 201 MN treated patients. Malignancies included cancer diagnosis between 2000 and 2014. The malignancy incidence in these patients was compared to the incidence in the general population by calculating standardized incidence ratios (SIRs). Malignancy incidence was compared between rituximab- and cyclophosphamide-treated patients.

Results: Of the 323 included patients, 33 developed a total of 45 malignancies during a mean follow-up of 5.6 years. This represented a 1.89-fold increased (95% confidence interval [CI], 1.38 to 2.53) malignancy risk compared to the general population. Cyclophosphamide-treated patients had an increased malignancy risk compared to the general population (SIR, 3.10; 95% CI, 2.06 to 4.48). In contrast, rituximab-treated patients had a malignancy risk similar to the general population (SIR, 0.67; 95% CI, 0.08 to 2.43). The malignancy risk in patients treated with cyclophosphamide was 4.61-fold higher (95% CI, 1.16 to 39.98) than the risk in patients treated with rituximab.

Conclusions: The malignancy risk in patients with AAV was lower in patients treated with rituximab than in patients treated with cyclophosphamide. Notably, rituximab treatment was not associated with an increased malignancy risk compared to the general population. Rituximab may therefore be a preferable alternative therapy to cyclophosphamide.

Malignancy in Membranous Nephropathy: Evaluation of Incidence

Basil Alnasrallah. 1Nephrology, Auckland City Hospital, Auckland, New Zealand.

Background: Membranous Nephropathy (MN) is known to be associated with malignancy. However, the exact risk remains unclear. In addition, the number of inflammatory cells in the glomeruli has been reported to be associated with malignancy in MN and has been suggested to direct screening; this has not been further validated.

Methods: We looked for the association of malignancy and MN in a cohort of 210 MN patients in Auckland region; we systemically reviewed the clinical records and linked them to the New Zealand Cancer Registry. We calculated the expected risk of a matched population by using age and stage to account the annual change of risk. We also examined the pathology of renal biopsies of 17 MN patients with malignancies and compared to number of inflammatory cells per glomerulus with matched controls.

Results: 40 malignancies were identified. 28 after the MN diagnosis, the standardized incidence ratio (SIR) was 2.1 (95%CI, 1.3 - 2.8). The 17 malignancies after MN were compared to a cohort of 160 patients with MN in a mean 15 years. The SIR was higher in the first 5 years at 2.3 (95%CI, 1.29 - 3.4) but diminished and lost significance after that. The median number of inflammatory cells per glomerulus didn’t differ between MN patients with and without malignancies at 1.86 (IQR, 1.17-2.7) and 2.07 (IQR, 1.17-3.65), respectively (p-value 0.56).

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

Underline represents presenting author.

830A
Conclusions: The relative risk of malignancy in MN patients was similar across different age groups at 2.1; this risk was most prominent in the first 5 years. The number of inflammatory cells per glomerulus did not differentiate between MN patients with and without malignancies.

SA-PO858
Risk of Renal Progression Is Higher in Upper Tract Urothelial Carcinoma Than in Renal Cell Carcinoma after Unilateral Nephrectomy - A Population-Based Study
Huei-Lan Lee, Ming-Yen Lin, Wei-Ming Li, Sheng-Wen Niu, Chun-Nung Huang, Wen-Jeng Wu, Li-Tzong Chen, Shang-Jyh Hwang. Baylor College of Medicine, Houston, TX.

Background: Impairment of renal function in patients with carcinoma at diagnosis as upper tract urothelial carcinoma (UTC) seems more frequent than in renal cell carcinoma (RCC), which influenced renal outcome and also resulted in a worse clinical outcome. Limited information is available to compare the risk of progression of preexisting renal impairment to end-stage renal disease (ESRD) in patients of UTC and RCC, respectively. The aim of study was to compare risk of renal progression in patients with UTC and RCC after receiving unilateral nephrectomy.

Methods: We conducted a population-based cohort study through Taiwan National Health Insurance Research Dataset. Incident UTC and RCC patient who underwent nephrectomy from 2002 to 2007 was identified from Taiwan Cancer Registry Dataset and linked to claim data. Primary endpoint was defined asaposteoperative dialysis 3 months after surgery. Differences of characteristics between UTC and RCC patients were described as mean ± standard deviation or percentage and tested by independent t test and chi-square test. Competing risk approach was used for estimating cause-specific hazard ratio (CSHR) and 95% confidence interval (CI).

Results: Totally, 1571 UTC and 1910 RCC patients were included and traced until dialysis or end of the 3-years follow-up. Similar prevalence of CSHR stages in UTC (48.7%) and RCC (45.8%) patients was represented at the baseline. UTC patients were significantly older, more female, and had more diabetes and stroke than RCC patients. After adjusting factors of age, sex, tumor grade, and co-morbidities, patient with UTC was significantly associated with excessive risk of postoperative dialysis (CSHR: 2.09, 95%CI: 1.61-2.69, p<0.01) than that of patient with RCC.

Conclusions: UTC is associated with increased risk of dialysis than RCC. Base on this finding, the strategy of renal function screen after nephrectomy should depend on the type of urinary tract cancer.

Funding: Government Support - Non-U.S.

SA-PO859
Prevalence and Outcomes of Chronic Lung Disease in Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis
Chung-Juh Justin Chen, Sreedhar A. Mandyam, Wolfgang C. Winkelmayr, Sankar D. Navaneethan. Baylor College of Medicine, Houston, TX.

Background: Chronic lung diseases and CKD are both major public health issues. The burden and impact of chronic lung diseases in the CKD population has not been systematically studied. Hence, we conducted a systematic review and meta-analysis to study the prevalence of chronic lung disease and its impact on all-cause mortality in those with CKD.

Methods: We searched MEDLINE (1966-May 2016) using appropriate MESH terms to identify relevant observational studies reporting obstructive or restrictive lung disease prevalence in CKD patients and mortality outcomes in CKD patients with lung disease. Prevalence rates of chronic lung disease (obstructive and restrictive lung disease separately) and all-cause mortality risk estimates were extracted from individual studies and pooled using a random effects model.

Results: Seven studies were included (n = 839,736). Overall, prevalence of COPD was 18.4% (6 studies, 95% CI: 11.7%, 27.6%) in CKD population. Prevalence was significantly higher among studies that used spirometry to diagnose COPD (3 studies, prevalence rate: 34%, 95% CI: 14.4%, 60.9%) than the prevalence among studies that used chart review (ICD-9 codes, medication use etc.) for diagnosing COPD (3 studies, prevalence rate: 9%, 95% CI: 5%, 13%). There was an increased risk for all-cause mortality in CKD patients with COPD (vs. without COPD) (Hazard ratio: 1.26, 95% CI: 1.09, 1.41). One study reported prevalence rate of 10% for restrictive lung disease in CKD population. Further, restrictive lung disease was inversely associated with albuminuria and eGFR.

Conclusions: Obstructive and restrictive lung diseases are highly prevalent and are significantly associated with higher all-cause mortality in CKD. Prevalence rates of COPD in CKD patients who underwent spirometry are significantly higher than those of CKD patients with COPD identified by medical records, suggesting that chronic lung diseases are probably underdiagnosed in CKD patients. Even though restrictive lung disease appears to be common in CKD population, formal studies are lacking. Further studies are required to characterize pathogenic mechanisms between lung disease and CKD.

SA-PO860
Trends in Self-Reported Communication of Sleep Problems between U.S. Adults with CKD and Their Doctors
Jennifer L. Bragg-Gresham,1 Monica Shieu,1 Hal Morgenstern,1 Neil R. Powe,2 Delphine S. Tuot,2 Sharon Saydah,1 Deborah Rolka,1 Rajiv Saran.1 1University of Michigan, Ann Arbor, MI; 2UCSF, San Francisco, CA; 3CDC, Atlanta, GA.

Background: Given sleep’s importance for health, we explored trends in the prevalence of self-reported communication of sleep problems between US adults with CKD and their doctors.

Methods: A sample of 25,255 adults aged 20+ from the 2005-2014 National Health and Nutrition Examination Survey was used to estimate the prevalence of (1) having ever told a doctor about having trouble sleeping, and (2) having ever been told by a doctor s/ he had a sleep disorder. Prevalence was estimated for each 2-year survey interval. CKD was defined as eGFR <60 ml/min/1.73 m2 or UACR >30 mg/g. Logistic regression was used to assess unadjusted and age-sex-BMI-adjusted trends over time among adults with CKD and all adults.

Results: From 2005 to 2014, the crude and adjusted prevalence of each sleep outcome increased in both adults with CKD and all adults (all p for trend <0.02). The crude prevalence of both outcomes was greater in adults with CKD than in all adults throughout the 10-year period. Adults with CKD had a greater absolute increase than all adults in the percentage told by a doctor they had a sleep disorder (8.0% vs. 3.0%). In both groups, age and BMI were positively associated with poor sleep outcomes, women were more likely to tell a doctor of their sleep problems, and men were more likely to be told they had a sleep disorder (all p<0.0001).

Crude Prevalence (%): of each sleep outcome in US adults with CKD and all adults, by 2-year Interval

<table>
<thead>
<tr>
<th>Year</th>
<th>Sleep Problems Communicated</th>
<th>CKD</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-06</td>
<td>Told a Doctor</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>2007-08</td>
<td>Told by a Doctor</td>
<td>25%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Conclusions: The frequency of sleep problems communicated between adults with CKD and their doctors increased in the US in the past decade and were consistently greater in adults with CKD than all adults.

Funding: Other U.S. Government Support

SA-PO861
The Rise of Kidney and Related Chronic Diseases in Remote Living Aboriginal People in the Context of the Epidemiologic and Health Transitions
Wendy E. Hay,1,2 Susan A. Mott,1 Cheryl E. Swanson,1 Suresh Kant Sharma,1,2 Jennifer J. Nicol.1 1CKD.CRE, The Univ of Queensland, Herston, Brisbane, QLD, Australia; 2Menzies School of Health Research, Darwin, Northern Territory, Australia.

Background: The increase in chronic diseases in Aboriginal communities is poorly understood. We describe the emergence of chronic disease and CKD in one remote community since 1960 in the context of epidemiologic and health transition.

Methods: We analysed deaths and renal replacement records (RRT) records (deaths<1.66, RRT<91) for the Tiwi Aboriginal community in the Northern Territory from 1960 to 2010, inspected birthweights since 1956 and used population estimates in 1957 and census data since 1986.

Results: In the early 1960s, <50% of Tiwi deaths were in infants or children: >45% of newborns were low birthweight (LBW, <2.5 kg), and infant mortality rate was about 130/1000 live births, higher in LBW subjects, Deaths in infants and children fell by >95% by the late 1980s, with a greater absolute and relative reduction for LBW persons. Now nearly all babies survive to adult life, with nearly all deaths occurring in adults, and increasingly in adults >45 years old. Most adult natural deaths are from pulmonary, cardiovascular, renal and liver disease, with a >2-fold increase in LBW persons- evidence of the “Barker hypothesis”. As treatment postpones pulmonary and CV deaths, and people are ageing, renal deaths are increasing. However, age at renal failure has risen by 20 years since the 1970s. The Tiwi population has tripled since 1957, and the age-structure is maturing from a third world to an intermediate pattern. A pressing current concern is deaths from misadventure (often suicide) of young adults.

Conclusions: Emergence of chronic disease is a consequence of triumphs in public health and healthcare delivery in the last 5 decades. Such phenomena are more intimately echoed in the developing world, although it is unlikely that many other populations have experienced these events in such a compressed way. As birthweights continue to increase and chronic disease management improves further, longevity will continue to increase.

Funding: Pharmaceutical Company Support - The Colonial Foundation Australia, Amgen Australia, Government Support - Non-U.S.
SA-PO862

Negative Psychosocial Factors and Chronic Kidney Disease (CKD) Outcomes among African Americans

Clarissa Jonas Diamantidis,1 Nrupen Anjan Bhavsar,2 Mario Sims,2 Julia J. Sciolla,2 Clementina A. Davenport,2 Rasheeda K. Hall,3 Crystal C. Tyson,4 Wei Wang,2 Adolfo Correa,2 L. Ebony Boulware2

1Duke University School of Medicine; 2University of Mississippi Medical Center.

Background: Established CKD risk factors do not fully account for the renal outcomes of African Americans. We studied the association between negative psychosocial factors and CKD prevalence, incidence and progression in the Jackson Heart Study (JHS).

Methods: We used factor analysis to identify common domains of 12 psychosocial factors (perceived daily, lifetime, and burden of discrimination; anger in, anger out, hostility, pessimism, stress, John Henryism, spirituality, perceived social status, social support). We stratified the association of identified factor domains with baseline CKD prevalence (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m2 or urine albumin-to-creatinine ratio ≥ 30 mg/g) and CKD progression (annualized rate of eGFR decline), or incident CKD (new eGFR <60 mL/min/1.73m2 at follow-up and 25% eGFR decline from baseline, or new onset albuminuria) in multivariable models adjusted for sociodemographics and comorbidity. Those missing key CKD or psychosocial variables were excluded.

Results: Of 3390 (64%) participants with baseline CKD status available, 656 (19%) had CKD. Those with CKD (vs. no CKD) had lower perceived daily, lifetime and burden of discrimination; lower hostility, stress, and perceived social status; less John Henryism; higher pessimism, all p < 0.05. Factor analysis identified 3 psychosocial domains for CKD prevalence: 1) stressors (perceived discrimination, stress), 2) moods (anger, hostility), and 3) coping strategies (John Henryism, spirituality, social status, social support). After adjustment, those with greater stressors were less likely to have prevalent CKD (OR 0.76 [0.65-0.89]). Psychosocial domains were not associated with CKD incidence or progression. Our study, limited to a single US area, may not be generalizable. Further study should explore the role personal expression of negative attitudes plays in engagement in care among African Americans.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO863

Level of C-Reactive Protein Is Associated with the Progression of Diabetic Nephropathy in African Americans in the Jackson Heart Study Cohort

Satyesh K. Sinha,1 Keith C. Norris,2 Susanne B. Nicholas.3 1Internal Medicine, Charles R Drew Univ of Science and Technology, Los Angeles, CA; 2Davida Geffen School of Medicine, Univ of California Los Angeles, Los Angeles, CA.

Background: The reasons for the disparities in the prevalence and incidence of diabetic nephropathy (DN) and end stage renal disease (ESRD) in African Americans (AA) remain unclear but may involve complex inflammatory mechanisms that contribute significantly to the development and progression of DN. We recently reported a strong association between C-reactive protein (CRP) and urinary albumin excretion (UAE). The level of CRP and UAE both were significantly higher in AA compared to whites, suggesting that inflammatory processes of DN may be influenced by ethnicity. However, the association of CRP with progression of DN in the longitudinal follow-up data has not been examined.

In this study, we tested the hypothesis that circulating inflammatory markers, such as CRP, are associated with the progression of DN in AA.

Methods: We analyzed longitudinal follow-up data from Exam 1 (2000-2004), Exam 2 (2005-2008) and Exam 3 (2009-2012) at the JHS to determine the role of inflammation in the development of DN in AA using the inflammatory marker, high sensitive C-reactive protein (hs-CRP) and kidney function (measured by UAE). We analyzed data using Cox regression to estimate the hazard ratio (HR) for DN according to tertile of hsCRP, controlling for demographics. Data are presented as HR, and 95% confidence interval (CI); p<0.05 was statistically significant.

Results: In the fully adjusted model, the elevated hsCRP (>4.24 mg/L) was associated with DN (HR = 2.34, 95% CI 1.1-5.01, p=0.05) compared to the reference group (hsCRP ≤ 1.46 mg/L). The mean change in estimated GFR was mean 0.031±0.065. The rate of eGFR decline in the 4th quartile of decline of eGFR (annual decline from 0.81 to 21.19 ml/min/1.73m2) was statistically significant.

Conclusions: In conclusion, a rapid decline in eGFR associates with a higher risk for all-cause mortality but not cardiovascular disease. Increases in eGFR among participants don’t associate with similar clinical outcomes.

SA-PO865

HBV and HCV Prevalence and Incidence among ESRD Patients in France

Corinne Liaud-Bagnou,1 Cécile Couchoix,1 Luc Haudebourg,1 Gilbert Deray,2 Patrice Cacoub,3 Sophie Tezenas du Montcel,3 1Nephrology, Hôpital Pité Pitié Salpetrière APHP, Paris, Ile de France, France; 2Biostatistics, Hôpital Pité Pitié Salpetrière APHP, Paris, Ile de France, France; 3UMR_S1136 and INSERM UMR_S1136 Inst Pierre Louis d’Épidémiologie et de Santé Publique, Sorbonne UPMC Univ Paris 06, Paris, Ile de France, France; 4REIN Registry, Agence de la Biomédecine, Saint Denis La Plaine Cedex 93212, Ile de France, France; 5Institut de Medicine-Immunothérapie Dept 12B and UMR S1139, Hôpital Pitié Salpetrière APHP and Sorbonne Univ, Paris, Ile de France, France.

Background: Risk for HBV and HCV is increased in ESRD patients. New HCV treatments have prompted us to generate updated epidemiological data.

Methods: In a multi center cohort study, using the REIN French national prospective registry (ESRD), we extracted data for patients who initiated dialysis/had been put down on the kidney transplant waiting list (Jan, 2005 to Dec, 2013). We extracted records related to “inclusion into REIN”, “annual dialysis follow-up”, “death or graft failure”, “registration on the kidney transplant waiting list” and “kidney transplant”. A positive HbAg and a positive HCV RNA defined HBV and HCV infections.

Results: 72,948 patients started dialysis or were preemptively transplanted, 45,591 men (62.5%), (mean age 66.9±16.1 years),13,609 (18.7%) patients received a kidney graft, (mean age 50.9±15.5 yrs). At inclusion, 615 patients were HBV and 1,026 HCV infected. The prevalence of HBV and HCV infections were 0.84% (95% PI: 0.78 – 0.91) and 1.41% (95% PI: 1.32 – 1.49). Prevalence of HBV and HCV infection by age group increased progressively until a maximum rate of 1.80% (95% PI: 1.46 – 2.20) and 3.14% (95% PI: 2.68 – 3.65) in the 4th decade, then regularly decreased. During follow up, we identified new HBV or HCV infections in 117 and 81 patients, respectively. Overall incidence for HBV and HCV infections between 2005 and 2013 were 0.076% (95% PI: 0.062 – 0.090) and 0.053% (95% PI: 0.041 – 0.065) respectively. During the 1st year of dialysis, the incidence of HBV infection was 0.35% (95% PI: 0.28 – 0.43) and that of HCV 0.22% (95% PI: 0.16 – 0.29).

Conclusions: Our data highlights the need for HCV therapy for over 1000 patients and persistence of nosocomial cases.

SA-PO866

Heterogeneity of Chronic Kidney Disease with Age in a Major Metropolitan Renal Service

Usman Mahmood,1 Wendy E. Hoy,2 Helen G. Healy,2 Andrew John Mallett,2 Adrian Lawrence Kirk,2 Anne Cameron (Salisbury),2 Zainim Wang,2 Rajitha Asangayegeca,1 1Royal Brisbane & Women’s Hospital, Australia; 2University of Queensland, Australia.

Background: Aim of the study is to describe the characteristics of disease and outcomes with increasing age in people with CKD.

Methods: 1,265 patients enrolled into the CKD.QLD registry at Royal Brisbane and Women’s Hospital were grouped according to age into <25, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, 85+ years at consent and followed till start of renal replacement therapy (RRT), death, discharge or November 2015. Characteristics were described as mean (SD), proportions as percentage (%) and outcomes defined as mortality, start of RRT, hospitalization and progression of kidney disease.

Results: 651 of the cohort were male and 614 were female, mean ages of 66.5 and 66.6 years respectively (Renal vascular disease (including diabetic nephropathy) was the leading primary diagnosis in both genders, followed by diabetee nephropathy. Proportions with RVD progressively increased from undetectable in the <25 year to 69.4% in the 85+. A single diagnosis was recorded in 76% of <25 years, compared to 58% in > 85 years, with remaining having two or more etiologies listed. In the youngest and older age group, proportions with CKD stage 3A to 5 were 27% and 98% respectively. Up to 8 comorbidities were documented per patient, with means of 0.5 in <25 and 2.9 in 85+ age groups. All comorbidities were more common in males than females (mean 2.8 (1.7) vs. 2.2 (1.5)). Mortality rates increased from 1.6 to 17.4 per 100 person years, whilst RRT rates decreased from 1.7 to 0.4 per 100 person years in the 35-44 to 85+ age groups. Rates of hospitalization, length of stay and cost progressively increased from the youngest to eldest groups. The proportion of patients who lost more than 5 ml/min of eGFR during follow up increased from 10.5% in the youngest age group to 29.2% in the eldest.
Conclusions: The characteristics of CKD patients differ by age. Older people more likely have vascular and metabolic disease, have less conversion to dialysis, higher death rates, and are more likely to access acute hospital services. There is opportunity to personalize CKD care delivery taking this heterogeneity into account.

Funding: Government Support - Non-U.S.

SA-PO867

The Association of Monocyte Count and eGFR with All-Cause Mortality

Farrukh M. Koraisah,1,2 Benjamin Charles Bowe,3 Yan Xie,4 Hong Xian,1 Ziyad Al-Aly,1,2,3 Div of Nephrology, Veterans Affairs St. Louis Health Care System, St. Louis, MO; 1Clinical Epidemiology Center, Veterans Affairs St. Louis Health Care System, St. Louis, MO; 2Div of Nephrology, St. Louis Univ, St. Louis, MO; 3Dept of Biostatistics, St. Louis Univ, St. Louis, MO; 4Dept of Medicine, Washington Univ, St. Louis, MO.

Background: Chronic kidney disease (CKD) is associated with a high all-cause mortality risk. Elevated monocyte count has been associated with increased risk of death in the general population, however, data in CKD is limited. Whether monocyte count modifies the association of estimated glomerular filtration rate (eGFR) and mortality is not known.

Methods: We built a national cohort of 7,706,589 U.S. veterans and followed them over a median of 9.16 years to examine the association of monocyte count with eGFR categories: 15-30 ml/min/m², 30-45 ml/min/m², 45-60 ml/min/m², 60-90 ml/min/m², 90-105 ml/min/m² (reference) and >105 ml/min/m², and with all-cause mortality risk. Monocyte count was divided into quartiles: 0.00-0.40 k/cumm (reference) 0.40-0.56 k/cumm, 0.56-0.70 k/cumm and >0.70 k/cumm. Interaction analyses were undertaken to test whether monocyte count modifies the risk of mortality associated with eGFR.

Results: A high monocyte count (>0.56 k/cumm) was associated with increased risk of death overall and across each eGFR category. A high monocyte count was associated with high (<90 ml/min/m²) and low (<45 ml/min/m²) eGFR; eGFR levels that were associated with higher mortality risk. The maximum joint mortality risk was noted in the lowest eGFR and highest monocyte category (HR = 2.68, CI = 2.59-2.79). The mortality risk associated with high monocyte count and low eGFR exhibited a significant negative interaction on both additive and multiplicative scales.

Conclusions: To our knowledge this is the first study to investigate the interactions between monocyte count, eGFR and their association with death. Increased monocyte count and both low and very high eGFR were associated with higher all-cause mortality risk. Monocyte count modifies the risk of death associated with eGFR at low eGFR levels and is a valuable parameter in determining the prognosis of patients with CKD.

Funding: VA Support

SA-PO868

Infection as a Major Cause of Death in Japanese Elderly Chronic Kidney Disease: The G enory Study Tae Yamamoto,1 Gen Yamada,1 Mariko Miyazaki,1 Masaki Nakayama,1 Toshinobu Sato,1 Hiroshi Sato,1 Sadyo T.1,3 Tohoku Univ, Sendai, Japan; 2Fukushima Medical Univ School of Medicine, Fukushima, Japan; 3Japan Community Health care Organization Sendai Hospital, Sendai, Japan.

Background: Chronic kidney disease (CKD) is increasing in Japan, based on the rapidly growing ageing-population. Infection is a major complication by ageing, and the second cause of death after cardiovascular disease. In those, increased the risk of infection-related mortality was as frequent as CVD (24.3%). In elderly population, the survival risk before developing ESKD associated significantly with high age, low body mass index (BMI), and history of cardiovascular disease. In those, increased the risk of infection-related mortality was associated with the lower BMI. In elderly population, the survival risk before developing ESKD associated significantly with high age, low body mass index (BMI), and history of cardiovascular disease.

Conclusions: Infection is the second leading the cause of death in our CKD population, especially is that in elderly.

SA-PO869

The Interplay between Clostridium difficile Infection (CDI) and Renal Disease: Epidemiology, Treatment Management and Outcomes Anjay Rastogi,1 Ravina Kullar,2 Setareh Alipourfetraei,3 Farid Arman,1 Helen S. Hama,1 Saif Faiek,1 Laura Puzniak.1 Div of Nephrology, Dept of Medicine, Univ of California, Los Angeles, Los Angeles, CA; 2Center of Observational and Real World Evidence, Merck & Co, Inc; 3Kenilworth, NJ.

Background: Despite increased risk of CDI among patients (pts) with renal impairment, there is limited data evaluating treatment and outcomes in these pts. We evaluate the impact of CDI among the continuum of renal impairment.

Methods: Retrospective, observational study of consecutive cases of CDI, verified by positive PCR at UCLA (12/2013-12/2014). Pts were stratified into two groups: renally impaired (acute kidney injury, chronic kidney disease, end stage renal disease) (renal) and no renal impairment (non). Charts were reviewed for demographics, comorbidities, CDI therapy and clinical outcomes.

Results: Overall, 222 pts had CDI, 90% were considered first CDI episode. 89 (40%) pts were female (64.7% on dialysis) and 133 (60%) pts were non. Baseline demographics displayed in mean (standard deviation) or n (%); age: 67 years (16) vs. 60 years (20); admitted from community: 60 (67.4) vs. 99 (74.4); private insurance: 16 (18) vs. 48 (36); medicare: 50 (56); 64 (48.1). Most common comorbidities included chronic pulmonary disease (36 vs. 27.1%), acute coronary syndrome (37 vs. 25.6%), and diabetes mellitus (19.3 vs. 23.3%). CDI-related shock was most common in renal (15.7 vs. 3.8%). Most pts were initially treated with metronidazole (metro) (75.2 renal and 76.8% non). Renal pts were more likely to receive both metro then vancomycin than non (38.2 vs. 24.8%). Hospitalists were the most common prescribers of CDI therapy. Length of hospital and ICU stay was longer in renal, 24 (33) vs. 22 days (24), and 9 (24) vs. 3 days (8), respectively. Readmission and CDI recurrence were more frequent in renal: 36.9% vs. 27% and 20.2% vs. 16.7%, respectively.

Conclusions: 40% of pts with CDI were renal and almost all of these received various CDI treatments with most pts initially treated with metrom. Recurrence and readmission rates were frequent in these pts. Pts are at high risk for CDI and poor outcomes and require aggressive treatment management.

Funding: Pharmaceutical Company Support - Merck & Co, INC

SA-PO870

Increased Serum Alkaline Phosphatase Predicts Rapid Decrease of Glomerular Filtration Rate in Patients with Normal Renal Function/Early Chronic Kidney Disease Sunhwa Lee,1 Eunjeong Kang,1 Jung Nam An,2 Meng Xian Hyung Ah Yoon,1 Minjeong Kim,1 Chun Jo,1,2 Kang,1 Soo Lim,2 Jung Pyo Lee.2 Internal Medicine, Nephrology, Seoul National Univ Hospital, Republic of Korea; 2Internal Medicine, Nephrology, Seoul National Univ Boramea Medical Center, Republic of Korea.

Background: High alkaline phosphatase has been associated with increased mortality and coronary calcification in many subgroups, but the impact of alkaline phosphatase on decline in glomerular filtration rate (GFR) is unknown.

Methods: We retrospectively included patients with normal renal function or early chronic kidney disease who underwent cardiac CT angiography (CCTA) from March 2008 to June 2013 in a single medical center. We gathered available medical records of patients as follows; demographics, baseline laboratory findings at the time of CCTA scan, serum creatinine data of 0, 3, 6, 12, and 24 month (±3 weeks). The latest serum creatinine level, any major cardiovascular events and major cardiovascular events were retrieved till February 2016.

Results: Of 2,132 patients, there were 110 (5.2%) patients who showed decreases in GFR above 30% within a median 3.1 years. In multivariable Cox regression analysis, high alkaline phosphatase (>120 IU/L) was a definite predictor for GFR decrease even after adjusting for following variables; age, sex, history of hypertension, diabetes mellitus, hyperlipidemia, smoking status, use of anti-hypertensive agents, use of statins, history of myocardial infarction, the presence of calcification score (CCS) and GFR at the time of CT scan (HR 2.20, 95% CI 1.08-4.51, P=0.031). For subgroup analysis, subjects with lower arterial calcification (CCS<100), non-diabetes, male, high-GFR (>60ml/min/1.73m²), and lesser age (age<70 years) revealed significant increased risk of GFR decline by high alkaline phosphatase level, while the opponents did not. On the other hand, high alkaline phosphatase (>120 IU/L) had little influence on major cardiovascular events (OR 1.106, 95% CI 0.516-2.373, P=0.795), and CCS was not related to elevation of serum alkaline phosphatase (P=0.367).

Conclusions: We found that elevated serum alkaline phosphatase in normal renal function/early chronic kidney disease can predict more decrease in GFR, which mechanism may not related to arterial calcification.

SA-PO871

Associations of Liver Histopathology with Inflammatory Markers in Non-Uremic and Uremic Hepatitis C Positive Patients Sukran Kose,1 Bengu Tatar,1 Sabri Atalay,1 Eran Tatar.2 Infectious Diseases and Clinical Microbiology, Tepcek Education and Research Hospital, Izmir, Turkey; 2Dept of Nephrology, Izmir Education and Research Hospital, Izmir, Turkey.

Background: The aim of this study is to investigate the association between hepatic activity index (HAI) and fibrosis score (FS) with inflammation in non-uremic hepatitis C positive patients.

Methods: Fifty chronic hepatitis C (CHC) positive patients, 15 with end-stage renal disease (ESRD), having a liver biopsy were included in this study. 25 patients with similar age and gender were also enrolled as control group. Liver biopsies were scored according to

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 833A
Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Cystatin C as Predictors of Undiagnosed Kidney Injury in Diabetic African American Men

Goji Premadasa, 1 Hirofumi Maruyama, 1 Shoichi Fukagawa, 1 Enyu Sakata, 1 Shoichi Hishida. 1

1Hyogo Prefectural Nishinomiya Hospital, Japan; 2Osaka Univ, Japan; 3Showa Univ, Japan; 4Eastern Regional Comprehensive Metabolomics Resource Core, RTI International, Research Triangle Park, NC.

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD). Ethnic minorities disproportionately bear the burden of complications of diabetes, yet minorities, especially African American men, are underrepresented in research studies that serve to develop biomarkers for diagnosis and therapies. Traditional tests for DN lack sensitivity and are often inaccurate. As a result, DN is underdiagnosed in patients in the early stages of the disease, making it difficult to implement interventions to slow progression to ESRD. Assays for recently developed protein-based biomarkers, such as NGAL, Cystatin C, and kidney injury molecule-1 (KIM-1) are more sensitive and thus suitable for early diagnosis of kidney injury. However these assays are not widely available in clinical settings.

Methods: Enzyme-linked immunosorbent assays (ELISA) were used to determine the levels of creatinine, NGAL, Cystatin C, and KIM-1 in 67 African American men from three groups: 1) diabetics without diagnosed DN, 2) diabetics with diagnosed DN, and 3) non-diabetic control.

Results: The levels of serum NGAL and Cystatin C were significantly higher (p<0.001) in patients with diagnosed DN compared to non-diabetic controls. However, there was no significant difference in the levels of urine KIM-1. Importantly, a substantial proportion (17%) of the diabetic patients without diagnosed DN exhibited both NGAL and Cystatin C levels that were ≥2 SD above the mean levels found in non-diabetic controls.

Conclusions: A combination of NGAL and Cystatin C could be used to predict early stage DN in African American men. The data will serve as a basis for the development of educational material to engage African American men in community participatory research to prevent and/or manage diabetes and slow progression to DN and to encourage collection of biological samples for biomarker development.

Funding: Other NIH Support - NHMD, Center Award # U54MD008621 (CFDA 93.307) (NHMD), Sub-Awards # H1U40004 and H1U15006; NIH/NCATS award # UL1TR001111.

SA-PO873

The Effect of Annual Income on the Progression of CKD in Japan

Naohiko Fujii, 1 Takayuki Hamano, 1 Tadao Akizawa, 2 Seiichi Matsuo, 3 Hirofumi Makino, 4 Enyu Imai, 5 Tsuyoshi Watanabe, 6 Kosaku Nitta, 7 Shoichi Maruyama, 8 Masafumi Fukagawa, 9 Akira Hishida. 10

1Hyogo Prefectural Nishinomiya Hospital, Japan; 2Osaka Univ, Japan; 3Showa Univ, Japan; 4Nagoya Univ, Japan; 5Okaya Univ, Japan; 6Nakayamadera Imai Clinic, Japan; 7Fukushima Medical University, Japan; 8Tokyo Women’s Medical University; 9Tokai Univ, Japan; 10Taito City Hospital, Japan.

Background: The effect of socioeconomic status on the disparity in medical treatment and healthcare should not be overlooked as an interventional target. However, such evidence is limited inJ. We assessed the association between income level and eGFR trajectory over time, by using the dataset from the Japanese CKD prospective cohort study (CKD-JAC, N=2977, mean eGFR 28.7 ± 12.2 ml/min/1.73m2).

Methods: We enrolled 1849 (62%) participants that responded to the questionnaire on annual household income at baseline, which were stratified into quartiles. We evaluated eGFR change by using a joint model analysis, incorporating both random-effects and survival models to take into account fewer observations due to worse outcomes. We first adjusted for demographics and renal function at baseline (Model 2), and then for other possible confounders, such as age, sex, race, systolic BP, albuminuria, eGFR at baseline, and at MRS (Model 3).

Results: The income quartiles were defined as Low (Q1, N=456), Medium (Q2, N=506), High (Q3, N=434), and Highest (Q4, N=453) for the subjects with annual household income of <$30,000, $30,000-49,999, $50,000-79,999, and ≥$80,000, respectively. The subjects with lower income were likely to be significantly older, female, diabetic, and hypertensive. They also had a lower renal function, a higher prevalence of CVD, and a higher prevalence of hypertension. When we adjusted for demographic factors and renal function at baseline, the overall time-interaction term of income quartiles became significant (overall P<0.029), and we observed the fastest eGFR decline in income Q3 (-0.43 [0.08, 0.71]; P<0.055), however, the further adjustment for other covariates diminished the significance of time-interaction by income quartiles (Model 3).

Conclusions: The annual household income level was not associated with eGFR decline among CKD patients in Japan.

SA-PO874

Application of Group-Based Trajectory Modeling (GBTM) in Renal Disease

Zhuang You, Jessica B. Kendrick, Michel Chonchol. Medicine, Univ of Colorado Anschutz Medical Campus, Aurora, CO.

Background: In epidemiological studies of chronic kidney disease (CKD) and autosomal dominant polycystic kidney disease (ADPKD), kidney function and total blood volume and other variables are repeatedly or longitudinally measured. The group-based trajectory modeling (GBTM) is a powerful approach that summarizes such data collected across the study period and divides the subjects into groups based on their trajectories and pattern of change over time. The identification of clinical variables associated with trajectories may help identify new risk factor and novel therapeutic targets. In the published renal literature there is a lack of use of GBTM. Here we report two examples of GBTM application.

Methods: We used GBTM to identify five trajectory groups of plasma fibroblast growth factor 23 (FGF23) levels among patients with end stage renal disease (ESRD) in the first example, using data from the Hemodialysis (HEMO) study. In the second example, we identify four trajectory groups of serum calcium levels among patients with CKD of stage IIIB and IV and with vitamin D insufficiency or deficiency, using data from a randomized controlled trial titled “Vitamin D and arterial function in patients with chronic kidney disease” that was funded by NIH/NIDDK (5K23DK087859). All analyses were performed by using SAS procedure TRAJ under SAS version 9.4 (SAS Institute, Cary NC).

Results: Five trajectories of plasma FGF23 were considered reasonable based on consideration of (1) the criterion of the Bayesian information and Akaike information, (2) sample size, and (3) the profiles of the identified trajectory groups and their percent. The five groups were stable lower and higher level, going up from low and stable low level, and going from high level to low level. Similarly, four trajectory groups of calcium were considered appropriate and they were stable low, moderate, and high level, and going up from high level.

Conclusions: The SAS TRAJ procedure is user friendly and is easy to use. Exploratory analysis is necessary because GBTM was developed to empirically examine what trajectory groups present in a target population.

SA-PO875

Slope of Renal Decline as an End-Point for Intervention Trials to Prevent End-Stage Renal Disease

Jan Skupien, 1,2 James Warram, 1 Adam Smiles, 1 Robert C. Stanton, 1 Andrzej S. Krolewski, 1 Joslin Diabetes Center, Boston, MA; 3Jagiellonian Univ Medical College, Krakow, Poland.

Background: Clinical trials of interventions to prevent ESRD enroll high-risk patients with impaired renal function. Recently validated surrogate end-points include a 40% or a 30% decline from baseline eGFR within 1-3 years, predicting ESRD occurrence several years later. However, no end-points have been proposed for early intervention studies, especially towards whose ESRD develops after 10 years of follow-up. We examined data from patients in whom ESRD developed and whose eGFR had been followed since it was normal. Our aim was to investigate the relationship between validated end-points and the slope of eGFR decline.

Methods: We analyzed data from 264 Joslin Clinic patients (49% women) participating in natural history studies of diabetic nephropathy who developed ESRD 2-25 years after their enrolment with normal eGFR. Median duration of follow-up and rate of renal decline were 7 years and 9 ml/min/year, respectively. At entry, median age was 32 years, diabetes duration 18 years, glycated hemoglobin 9.7% and baseline eGFR 84 ml/min.

Results: The frequencies of alternative end-points according to year of follow-up were:

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>ESRD</th>
<th>Doubling serum creatinine</th>
<th>40% loss</th>
<th>30% loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0%</td>
<td>0%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>2%</td>
<td>11%</td>
<td>24%</td>
<td>40%</td>
</tr>
<tr>
<td>3</td>
<td>10%</td>
<td>26%</td>
<td>47%</td>
<td>62%</td>
</tr>
</tbody>
</table>

For 90% of patients with ESRD within 3 years, the slope of renal decline was 21 ml/min/year or more. For 90% of those with a doubling of serum creatinine, a 40% loss or a 30% eGFR loss within 3 years, the slope of decline was ≥14, ≥10 and ≥8 ml/min/year, respectively. Among the 38% who were not detected by any surrogate endpoint, in ~95% the time to ESRD was 8-18 years, and the rate of renal decline 24 ml/min/year.

Conclusions: Currently approved surrogate end-points develop during a clinical trial only in high-risk patients with rapid renal decline or significantly impaired renal function. It limits clinical validity of such trials. Early intervention trials should enroll patients whose renal decline is 4-8 ml/min/year. We urge diligent efforts to validate slope of renal decline as a surrogate end-point for intervention trials to postpone or prevent ESRD.

Funding: Private Foundation Support
SA-PO876

Vitamin D Associates with Higher Physical Activity and Comorbidities in Chronic Kidney Disease: Result from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD)

Eunyong Kang,1 Hyo Jin Kim,2 Hyunjin Ryu,3 Muyeon Han,4 Hyun Suk Kim,5 Curie Ahn,6 Kook-Hwan Oh,7 1 Internal Medicine, Seoul National Univ Hospital, Seoul, Korea; 2 Internal Medicine, Dongguk Univ Gyeongju Hospital, Gyeongju, Korea.

Background: Although vitamin D (Vit D) is known to be related the physical activities and comorbidities, there was a lack of evidence of their relationship in chronic kidney disease (CKD) patients.

Methods: Data were collected from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD, NCT01630486 at http://www.clinicaltrials.gov). Baseline serum 25-OH Vit D concentration was measured using chemiluminescence immunoassays in the central laboratory. Vit D insufficiency was defined by 25-OH Vit D below 20ng/mL. We categorized patients into 3 groups (low, moderate, high physical activity level) according to their physical activity, quantified by the International Physical Activity Questionnaire. We used age-adjusted Charlson comorbidity index (CCI) for assessment of comorbidities, and divided into 2 groups based on ≥ 4 points of CCI or below. The associations were assessed by multivariate linear regression analyses with log-transformed 25-OH Vit D because of skewed distribution of 25-OH Vit D.

Results: 496 vitamin D deficient patients were included (78.6% male, mean age 62.8±12.5 years). Baseline serum 25-OH Vit D was 11.7±7.5ng/mL. The proportion of 25-OH Vit D insufficiency was 33.6%. Physical activity (P = 0.026) and age-adjusted CCI (P = 0.012) was independently associated with log 25-OH Vit D. Factors influencing log 25-OH Vit D were BMI, hemoglobin, and serum Alb levels in each group were <23 kg/m², <110g/L, and <40 g/L, respectively. Serum Ca, ALP, and iPTH levels were different among groups, while serum P wasn’t. Serum iPTH and ALP were lower in elderly patients.

Funding: Government Support - Non-U.S.

SA-PO877

Clinical Characteristics of Age Distribution in 496 Severe Secondary Hyperparathyroidism Patients Undergoing Parathyroidectomy

Ninong Wang, Yao Jiang. Dept of Nephrology, First Affiliated Hospital with Nanjing Medical Univ, Nanjing, China.

Background: Severe secondary hyperparathyroidism(SHPT) patients are characterized by systematic clinical manifestations and parathyroidectomy(PTX) is recommended for treatment, the relationships between age and clinical characteristics of severe SHPT are unknown.

Methods: Clinical baseline data were analyzed according to the stratification of age in retrospective study of 496 PTX patients from single centre.

Results: Clinical characteristics of patients were shown in table 1.

Funding: Government Support - Non-U.S.

SA-PO878

A Real-World Cost-Effective Analysis of Sevelamer versus Calcium-Based Binders for the Treatment of Hyperphosphatemia in Korean Dialysis Patients

Jaein Park1, Inryang Hwang, Min Jung Kim, Wonseok Do, Kyu Yeun Kim, Youngae Yang, Sukyung Lee, Hee-Yeon Jung, Jis-Young Choi, Jang-Hee Cho, Sun-Hee Park, Chae-Duck Kim, Yong-Lim Kim. Dept of Internal Medicine, Kyungpook National Univ Hospital, Daegu, Republic of Korea.

Background: Sevelamer, a non-calcium based phosphate binder, has been shown to attenuate the progression of vascular calcification and improve survival in dialysis patients compared with calcium-based binders (CBBs). We conducted a cost-effectiveness analysis (CEA) comparing sevelamer with calcium acetate in dialysis patients using real-world data from the Health Insurance Review Agency (HIRA) database in Korea.

Methods: Data from 4674 patients enrolled in Korean multicenter prospective cohort study between Sep. 2008 and Dec. 2012 were linked to the HIRA database. After propensity score matching, the final dataset used in the CEA comprised 501 sevelamer-treated and 501 calcium acetate-treated patients. A Markov model was used to estimate costs, life years (LY), quality-adjusted life years (QALYs), and cost effectiveness. Forty-month treatment-specific survival was analyzed.

Results: Patients receiving sevelamer had lower mortality compared with patients receiving calcium acetate (HR, 0.64; 95% CI, 0.45–0.91; p=0.012). In the base case analysis, treatment with sevelamer was associated with a gain of 1.758 in LYs and 1.108 QALYs per patient compared with calcium acetate. The incremental cost effectiveness analysis showed that sevelamer was cost effective compared with calcium acetate across a wide range of alternative assumptions. Probabilistic sensitivity analyses showed that sevelamer was cost effective in 100% of the model iterations, using a willingness-to-pay threshold of $31,355,740 per QALY gained.

Conclusions: Sevelamer was associated with better survival and acceptable cost effectiveness in dialysis patients compared with calcium acetate. Treatment of hyperphosphatemia with sevelamer could serve as a cost-effective alternative treatment option to CBBs in dialysis patients in Korea.

Funding: Government Support - Non-U.S.

SA-PO879

 Shotgun Lipidomics Reveals Alteration of Acyl Chain Carbon Number and Unsaturation with Advancing Chronic Kidney Disease

Farsad Afshinnia, Thekkelnaycke Rajendiran, Tanu Soni, Subramaniam Pennathur, Univ of Michigan.

Background: Alteration in carbon number and double bonds in complex lipids are linked with poor outcome. Impact of chronic kidney disease (CKD) on such alterations has not been studied. We systematically determined abundance of lipids across different stages of CKD using mass spectrometry based shotgun lipidomics.

Methods: In a cross sectional observation, 214 CKD patients from stage 1 to 5 with available baseline clinical characteristics were selected from the Clinical Phenotyping Resource and Biobank Core (CPRBEC). Lipids from plasma was extracted with modified Bligh-Dyer method carrying the extraction in a 2:2:2 volume ratio of water/methanol/dichloromethane, spiked internal standards, reconstituted in Buffer B (10% ACN and 90% IPA in 10mM ammonium acetate) and injected in ABSciex 5600 quadrupole time

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of flight mass spectrometer. MS/MS spectra were obtained in electrospray positive and negative modes with Analyst TF software and processed with MultiQuant 1.1.0.26. Data were normalized, log2 transformed and z-score standardized. Mixed linear models were applied to test independent alteration of lipid abundance by acyl chain carbon number of double bond across various stages of CKD.

Results: The selected patients included 36 (16.8%), 99 (56.3%), 61 (28.5%), and 18 (8.4%) participants from stage 1 to stage 5, respectively. Using shotgun lipidomics we identified 330 compounds from 17 lipids. In stage 2, there was a significant linear increase in abundance of free fatty acids by number of double bonds and carbon numbers in acyl chains (p<0.006), a trend which was reversed in CKD stage 5, independent of any covariates (p<0.002). On the other hand there was a significant linear decrease in abundance of triacylglycerols, phosphotidylcholines, phosphotidylethanolamines (PE), LysoPE, cardiolipins, and cholesteryl esters by number of double bonds and carbon numbers is stage of triacylglycerols, phosphotidylcholines, phosphtidylethanolamines (PE), LysoPE, cardiolipins, and cholesteryl esters by number of double bonds and carbon numbers is stage.

Conclusions: We conclude that CKD stage is associated with dynamic alteration of acyl chain carbon number and double bonds which may have mechanistic implications on outcomes which should be studied in future investigation.

Funding: NIDDK Support

SA-PO880

Diffusion Tensor Imaging Demonstrated White Matter Structural Abnormalities in Hemodialysis Patients

David A. Drew, Bang-Bon Koo, Rafeeqe Bhdelal, Hocine Tighiouart, Sarah M. Duncan, Maria de Los Angeles Mendoza-De la Garza, Tammy Scott, Daniel E. Weiner, Mark J. Sarnak. 1 Tufts Medical Center; 2Boston Medical Center, 3BIDMC.

Background: Patients treated with dialysis have high rates of clinical stroke and structural brain disease. There are limited data regarding the presence of more subtle damage to white matter integrity.

Methods: In the Boston Dialysis Study, we compared brain magnetic resonance imaging (MRI) using a diffusion tensor imaging (DTI) protocol in hemodialysis (HD) patients to community dwelling persons without known kidney disease who underwent the same MRI protocol. Using a tract based spatial statistics (TBSS) software package, significant differences in Fractional Anisotropy (FA) and Mean Diffusivity (MD) between patients and controls were placed on a three dimensional skeleton highlighting white matter fiber tracts. Statistical comparison of each overlaid voxel was age controlled, using a permutation based corrected p value of <0.05.

Results: Thirty HD patients and twenty six controls had adequate imaging for analysis. Mean age was similar (52 vs 49 years for HD vs control). The HD group had fewer women (38% vs 23%), more African Americans (38% vs 23%), and a higher rate of diabetes (29% vs 18%). Hemodialysis patients had significantly lower FA across multiple white matter fiber tracts, with fronto-temporal lobes, genu of the corpus callosum and fornix more significantly affected than posterior parts of the brain.

Similarly, the hemodialysis group had significantly higher mean diffusivity across multiple anterior brain regions.

Conclusions: Hemodialysis patients show loss of white matter integrity on DTI, more anterior than posterior, compared to those without known kidney disease. The pattern of injury may imply accelerating aging as it is most similar to that seen in elderly adults.

Funding: NIDDK Support

SA-PO881

Renal SCAN-ECHO and Renal e-Consults Improve Care and Value for Rural and Highly Rural Veterans Who Live Distant to Veterans Affairs Renal Specialty Care

Raimund H. Pichler, Nancy M. Harris, Maureen Germani, Elizabeth A. Mattox, Lauren Best, Michael F. Chang, Bessie A. Young. 1 Dept of Veterans Affairs, Puget Sound Healthcare System, Seattle, WA; 2Dept of Veterans Affairs, Portland Healthcare System, Portland, OR.

Background: Renal Specialty Care Access Network-Extension for Community Health Outcomes (SCAN-ECHO) is a provider-to-provider telemedicine program linking primary care providers (PCPs) with specialists. In 2010 the VA launched a form of consultations (i.e. non-visit consults or NVC) involving reviews of the electronic medical records by specialists. We evaluated differences in SCAN-ECHO, NVC, and traditional in-clinic consults (ICC) in a geographic area of the Pacific Northwest.

Methods: We reviewed patient demographics and characteristics of patients served through either renal SCAN-ECHO consults (n=105), NVCs (n=350) or ICCs (n=380). Patient rurality and driving distance to specialty clinic were established.

Results: Veterans served by SCAN-ECHO lived the furthest away and were more likely to be highly rural, followed by NVC, and ICC Veterans (see Table). The total number of round trip driving miles saved by SCAN-ECHO was 98,280, which represented $40,786 saved in travel reimbursement compared to 127,824 miles saved NVCs ($53,045).

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

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SA-PO883
Telenephrology: An Effective Strategy for Improving Access and Opportunity of Nephrologist Evaluation of Primary Care Chronic Kidney Disease Patients
Maria Cecilia
School, Univ Andres Bello.

Background: Chronic Kidney Disease (CKD) is a significant public health problem in Chile, leading to a great demand of unsatisfied renal consultations, which is worsened by a workforce shortage of nephrologists. This study assessed the impact of telenephrology (TN) to improve access and opportunity of care by renal specialist in a public health care network.

Methods: A retrospective cohort of TN asynchronous consults between 55 primary care providers (PCPs) and nephrologists in two cities of southern Chile, between Aug 2012 and May 2016 were analyzed. The main analyzed variables were: 1. Average response time versus historical response for in-person consult; 2. Average invested time per consult/nephrologist; 3. Identification of patients in need of advanced care 4. User satisfaction questionnaire among PCPs.

Results: 2256 consults were included, (59 % females), mean age 69 years (15-96), CKD stage III (57%), IV (24%), V (4.5%). Average historical response time for traditional person consult diminished from 195 days to 1 day for electronic consult; Invested time per consult/nephrologist diminished from 20 minutes for in-person to 10 minutes for electronic consult. Following consultation, 1268 patients (56.2%) were sent back by the nephrologist to primary care with treatment advice and 988 patients (43.8%) were sent to renal outpatient evaluation for CKD predialysis stage and complex nephropathy. Additionally, at six month of TN implementation we reach No waiting list of referred renal patients. PCP rated 85% approval of the electronic model, highlighting the decreasing waiting time for consult, health network integration and continuous education.

Conclusions: The tele-consult model is an efficient method for improving access to nephrologist assessment, prompt treatment, selection of patients for specialized and complex care and optimizes the available time of nephrologist in an integrated network with PCP.

Funding: Government Support - Non-U.S.

SA-PO884
Implementation and Evaluation of Electronic Consultation in Nephrology
Malikia L. Mendu, Gearoid M. McMahon, Sushrut S. Waikar. Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Background: The care of kidney disease patients is fragmented and poorly coordinated between referring primary care providers (PCPs) and nephrologists. Nephrology is a specialty that could embrace an electronic consultation (e-consult) model to improve the process of referral by facilitating communication and determining the need and urgency of a referral.

Methods: We conducted a pilot study to examine the impact of an e-consult system for patients with kidney-related conditions over the course of 15 months. Nephrologists (n = 2) reviewed questions submitted by PCPs (n = 49), and provided recommendations within an EHR-based platform. We sought to determine what types of kidney-related conditions PCPs found most helpful to treat as an e-consult, how much time the consults took, and the impact on patient care.

Results: 74 total nephrology e-consults were completed during the study period. The median time required for completion was 10 minutes for both provider groups. The most common kidney conditions leading to an e-consult were stage 3 CKD (16.2%), medication-related questions (13.5%), abnormal imaging findings (10.8%), electrolytes (9.5%), and proteinuria (8.1%). Satisfaction with the e-consult model was high among both nephrologists and PCPs.

Conclusions: The tele-consult model is an effective method for improving access to nephrologist evaluation of primary care chronic kidney disease patients, by decreasing waiting time for consult and optimizing the available time of nephrologist in an integrated network with PCP.

Funding: Pharmaceutical Company Support - AMGEN Australia Research Grant

SA-PO885
iConnect Care - A Web Based Chronic Kidney Disease Virtual Consultation Program
Vishwas Raghunath,1, 2 Ivyon Jonathan Katz,1 2 Renal Medicine, St. George Hospital and Community Services, Sydney, New South Wales, Australia; 2Univ of New South Wales, Sydney, New South Wales, Australia.

Background: Specialist care with chronic kidney disease (CKD) patients, who can be managed in primary care (PC). Opportunity to screen for (HR) CKD patients and follow up in PC is the most feasible model of care. The iConnect Care CKD program provides a virtual consultation (VC) instead of face to face (F2F) consultation.

Methods: A total of 70 patients were recruited from GP sites and Hospital clinics and followed for one year. The HR patients (eGFR<30ml/min/1.73m2 +/- albuminuria >30mg/mmol/L) were randomised to either VC or F2F. Patients were monitored every 6 months by a Clinical Nurse Specialist (CNS). The specialist team providing VC comprised a Nephrologist, Endocrinologist, Cardiologist and a Palliative care Physician.

Results: Sixty one (87%) patients were virtually tracked or consulted with 14 (23%) of these being HR. At 12 months there was no difference in progress or outcomes in VC versus F2F groups nor a difference in low risk (LR) patients followed by CNS or GP. All were successfully followed. Software integration was challenging, especially in regards to the GP. Reported high level of satisfaction and patients found the system attractive. VC consultations occurred within a week and a second specialist opinion within another two.

Conclusions: The program followed safe, quick and efficient consultation from multiple specialists. VC has a role to play in future patient care and ongoing evaluation is necessary.

Funding: Pharmaceutical Company Support - AMGEN Australia Research Grant

SA-PO887
Source and Content of Chronic Kidney Disease Videos on YouTube®: Stream with Caution
Elizabeth Ortiz, Claudia M. Lora. Univ of Illinois at Chicago.

Background: Many individuals with chronic diseases use the internet to obtain health information. Recently, concerns have been raised about the content of this information on YouTube; the second most globally used internet site. YouTube videos related to pre-dialysis chronic kidney disease (CKD) have not been evaluated.

Methods: We identified 362 videos using the following search terms: “chronic kidney disease,” “chronic kidney failure,” “chronic renal failure,” ”chronic renal insufficiency,” “kidney disease” and “kidney failure.” We excluded videos that were not in English, did not relate to CKD in humans or were duplicates. We examined the source, target audience, the number of views and comments, and the content.

Results: We excluded 211 videos. Of the remaining 151, 20% were uploaded by universities and professional societies, 50% by commercial organizations, 7% by individuals without clear credentials, and 23% by individuals with CKD. Target audiences were patients (66%), students (5%), health care personnel (2%), or were unspecified (27%). The mean number of views was 96,323, and the mean number of comments was 20. Table 1 summarizes the content of the videos. A total of 36 (24%) videos contained misleading or incorrect information, and 73 (48%) videos marketed a non-evidenced based treatment for CKD. Specifically, 12 (8%) advertised an herbal supplement for CKD.

Conclusions: Most YouTube videos on CKD are uploaded by commercial organizations and target a patient audience. A large number of videos included misleading information or advertised treatments that could be harmful in CKD. Patients should be cautious about using YouTube as a source of health information. Future studies need to examine YouTube as an intervention aimed at improving knowledge of CKD.

Funding: NIDDK Support

SA-PO888
Tracking Health Behavior Using Google Analytics: A New Clinical Investigative Tool
Stephanie W. Ong,1 Kelly Min,1 Akib Uddin,2 Sarbjeeta Jassal,1 Emily Seto,2 Alexander G. Logan.1 Nephrology, Univ Health Network, Toronto, ON, Canada; 2Centre of Global eHealth Innovation, Univ Health Network, Toronto, ON, Canada.

Background: We have developed and tested an integrated smartphone app system for advanced CKD, which allows patients to track blood pressure (BP), medications, symptoms and lab tests and have access to CKD care resources and provider contact information. Results suggest improved outcomes; however its effect on health behaviors remains unknown. Google Analytics (GA) can track interactions with electronic devices, and thus evaluate health behaviors. In this study we evaluated the app’s features using GA.

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Methods: GA was used to determine the frequency of visits to each feature and the pattern of use over a 6-month period. At exit, participants were interviewed about usability and feasibility of the app, and the results were correlated with GA usage.

Results: Patients (n=45) used the app consistently throughout the study. There were 33,085 unique views with the total time spent per person averaging 8.1 hours. BP was the most utilized feature, followed surprisingly by laboratory results as most participants had tests done at baseline and once or occasionally twice during the study, and then by medications. The use of the symptom feature was infrequent, even though patients were asked to complete the symptom checklist at a minimum month and more often if symptomatic. The CKD resources and contact features were rarely used. Pattern analyses revealed multiple unexplained spikes in use of the BP feature. In exit interviews (n=38) patients stated that BP and labs were most useful features due to their interactive nature and supportive feedback, while many questioned the value of tracking symptoms as it led to few changes in treatment.

Conclusions: GA is a valuable and inexpensive tool that may help clinicians track, and better understand, changes in health behaviors over time. Apart from tracking feature use, GA provides insights into which features patients are most likely to use and which do not provide enough value and may require redesign. It also raises questions about clinical correlates to changes in the pattern of use.

Funding: Government Support - Non-U.S.

SA-PO888

Racial Disparities in Cardiopulmonary Resuscitation Knowledge in Chronic Kidney Disease Patients due to Low Health Literacy

Nwamaka Denise Eneanya, Kabir O. Olaniran, Ravi I. Thadhani, Michael Paasche-Orlow, Massachusetts General Hospital; Boston Medical Center.

Background: Patients (pts) with chronic kidney disease (CKD) experience poor survival after receiving cardiopulmonary resuscitation (CPR). Minority CKD pts also receive CPR more often than other racial groups. Low health literacy (HL) affects one’s ability to understand health information to make appropriate health decisions and disproportionately affects minorities. As low HL affects up to 32% of CKD pts, we investigated whether HL mediates racial disparities in CPR knowledge.

Methods: Cross-sectional study of CKD pts in nephrology clinics affiliated with two academic centers in Boston, MA. Inclusion: age ≥ 45 years, English-speaking, Black or White race and, Stage 4 or 5 CKD (defined by eGFR < 30 ml/min/1.73m²). Exclusion: patients with history of dementia. An 8-item multiple choice CPR knowledge survey was administered. HL was assessed via the Rapid Estimate of Adult Literacy in Medicine (REALM).

Results: 149 pts completed the study. Mean summary percentage score (±SD) was 68 (±11) for Black pts and 66 (±11) for White pts (p=0.02). In adjusted analysis, these associations remained significant [older (OR 0.94 p<0.01), and more advanced CKD (OR 2.42 p=0.02)] to use the portal compared to those of lower income. After adjustment for age, sex, race, income, and education, this association was diminished and only older patients were found less likely to use the portal (OR 0.97 p=0.02). Older patients (OR 0.97 p=0.01) were less likely, and patients with annual income > $50K (OR 3.27 p<0.01) and more advanced CKD (OR 2.42 p=0.02) more likely, to use the Internet to learn about CKD. In adjusted analysis, these associations remained significant [older (OR 0.94 p<0.01), annual income > $50K (OR 6.90 p<0.01) and more advanced CKD (OR 3.54 p<0.02)].

Conclusions: Portals offer benefits to communication and care, but older patients and those of lower income may be less likely to reap these benefits. Future work must ensure health portals are useful and accessible to all patients with CKD.

Funding: NIDDK Support

SA-PO889

Disparities in Patient Reported Barriers to Optimal Self-Management for Chronic Kidney Disease

Julie A. Wright Nunes, Eve Kerr, Akinlolu O. Ojo, Angela Fagerlin, Internal Medicine, Univ of Michigan, Ann Arbor, MI; Veterans Affairs Healthcare System and Ann Arbor Center for Clinical Management Research, Ann Arbor MI; Population Health Sciences, Univ of Utah and Salt Lake City VA, Salt Lake City, UT.

Background: Patient self-care is critical to chronic kidney disease (CKD) management. The study goal was to determine barriers that impact patients’ ability to practice healthy behaviors.

Methods: 202 adults with CKD Stages 1-5 completed a cross-sectional survey between April 2015-May 2016. Patients rated how often barriers got in the way of keeping their kidneys healthy; scale from 0=never to 3=almost all the time. Topics included: lack of psychosocial support, poor communication with providers, lack of resources/motivation for healthy behaviors, and low knowledge. We used linear regression to examine associations between demographics and ratings.

Results: Mean (SD) age was 59 (16) years, 48% were male, 78% Caucasian, 17% African American (AA), 73% had CKD Stage 3-5, 51% had an annual income > $50K, and 95% ≥ H.S. education. Ratings ranged from mean (SD) 0.28 (0.63) [poor communication with doctor] to 1.00 (0.96) [not having motivation to exercise]. 31% rated not having motivation to exercise and 29%, not being healthy enough to exercise as most frequent barriers. In univariate analysis, annual income < $25K was significantly associated with 9 out of 10 barriers and many remained significant after adjusting for age, sex, race, income, CKD stage, and education: lack of social support (β=0.40 p<0.04), insurance situation (β=0.37 p=0.04), poor access to fresh foods (β=0.25 p=0.01), low income (β=0.20 p=0.01), low motivation to exercise (β=0.53 p<0.01). Although most felt poor communication with doctors was not a barrier, AA race (β=0.30 p=0.01) and income < $25K (β=0.21 p<0.04) were associated with perceiving this as a barrier more often, and were significant after adjustment. AA race (β=0.45 p<0.01), income < $25K (β=0.36 p<0.01), low motivation to exercise (β=0.32 p=0.04), and low income (β=0.21 p<0.01) were significantly associated with barriers.

Conclusions: Barriers to healthy behaviors are reported more often in those most vulnerable to CKD progression. Future efforts must focus on more support and improved communication for minority and low income patients.

Funding: NIDDK Support

SA-PO891

Quantitative Analysis: What Patients Want from Kidney Disease Education

Kabir O. Olaniran, Angela Fagerlin, Internal Medicine, Univ of Michigan, Ann Arbor, MI; Veterans Affairs Healthcare System and Ann Arbor Center for Clinical Management Research, Ann Arbor MI; Population Health Sciences, Univ of Utah and Salt Lake City VA, Salt Lake City, UT.

Background: Chronic kidney disease (CKD) patients often lack understanding of their disease, treatment options, and the potential for disease progression. The study purpose was to understand patients’ wants and needs for CKD education.

Methods: 202 adults with CKD Stages 1-5 completed a cross-sectional survey between April 2015-May 2016. Questions focused on: Barriers to using current education materials (10 sub-topics with yes/no response), desired educational content (21 sub-topics rated 0–less important to 4–more important), preferred timing to use materials, and design of materials. Two summary scores were created: (1) a helpfulness score for the current education materials, and (2) a helpfulness score for hypothetical new interventions.

Results: Mean (SD) age was 59 (16) years. 48% were male, 78% Caucasian, 17% African American, 73% had CKD Stage 3-5, 51% had an annual income > $50K, and 95% had > H.S. education. The most common barriers to using current education materials included too little information provided (36%) and content perceived as too general (33%). Topics rated most important to include in future materials were medications that can hurt kidneys [mean (SD) rating 3.7 (0.7)], foods to avoid with advanced CKD [3.6 (0.7)], treatment options for kidney failure [3.6 (0.7)] and explanations about how CKD progresses [3.6 (0.8)].

Conclusions: Descriptions of other patients’ experiences with CKD was ranked
SA-PO894

Gender Disparities in Cardiovascular Outcomes and Mortality in Persons with Chronic Kidney Disease

Background: Data from general populations indicate that cardiovascular events are less common in women than in men, but studies of individuals with chronic kidney disease (CKD) are limited and less conclusive. We evaluated gender-related disparities in cardiovascular events and all-cause mortality in adults with CKD.

Methods: This was a prospective, longitudinal study of 1778 women and 2161 men enrolled in the CRIC Study (mean age 58 years, 42% non-Hispanic white, 42% non-Hispanic black, 13% Hispanic, and mean estimated glomerular filtration rate [eGFR] 45 ml/min/1.73m² at entry). Using Cox-proportional hazards models, we investigated the association of gender (women vs. men) with adjudicated atherosclerotic events (myocardial infarction, stroke or peripheral arterial disease), incident heart failure and all-cause mortality.

Results: Over a median follow-up of about seven years, we observed 585 atherosclerotic, 638 heart failure, and 853 death events. The table below summarizes multivariable analyses results.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)*</th>
<th>P value interaction Gender*Age</th>
<th>P value interaction Gender*Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic events</td>
<td>0.64 (0.52-0.79)</td>
<td>0.11</td>
<td>0.77</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.86 (0.69-1.09)</td>
<td>0.23</td>
<td>0.04</td>
</tr>
<tr>
<td>No Diabetes</td>
<td>0.58 (0.40-0.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.59 (0.48-0.72)</td>
<td>0.19</td>
<td>0.92</td>
</tr>
</tbody>
</table>

*Adjusted for clinical site, age, race/ethnicity, education, marital status, nephropathy care, heart insurance, systolic blood pressure, diabetes history, cardiovascular disease, smoking status, physical activity, body mass index, LDL cholesterol, ACEI/ARB, aspirin and statin use, baseline eGFR, proteinuria, serum FGF23, calcium and phosphorus.

Conclusions: In this large and diverse CKD cohort, women had lower risk of atherosclerotic events and death than men. Among participants without diabetes, women were less likely to experience a heart failure event.

Funding: NIDDK Support

SA-PO895

A Mapping Study of Dialysis Patients’ Perceptions of KidneyTransplantation
Heather Marie Traino, Sarah Bauerle Bass,1 Laurie A. Maurer,1 Avrum Gillespie,2 Dorian R. Schatell,1 1Social & Behavioral Sciences, Temple Univ, Philadelphia, PA; 2Nephrology, Temple Univ Hospitals, Philadelphia, PA; 3Medical Education Inst, Inc, Madison, WI.

Background: Kidney transplantation remains the preferred treatment modality for patients with end stage renal disease, but continues to be underutilized. While previous studies have identified barriers to transplantation, to date no research has explored the relationships between patients’ unique perceptions of transplant-related barriers and facilitators.

Methods: We employed perceptual mapping techniques (multidimensional scaling and vector modeling) to understand and visualize patient-level barriers and facilitators to living and deceased donor kidney transplantation. These methods generate 3-dimensional maps of transplant-related concepts, which can be used to inform message strategies aimed at increasing patients’ interest in transplantation and pursuit of living donors.

Results: Preliminary findings of data collected via an online survey suggest that patients (n=40) perceive themselves well informed and understand the pros, cons and long-term effects of transplantation. However, patients were most concerned by the anticipated pain associated with the transplant surgery and the potential for being placed back on dialysis. With regard to living donation, perceptual maps revealed fears of troubling and feeling indebted to the donor as well as fears of becoming hopeful and having potential donors decline to donate.

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

839A
Conclusions: Although data collection is ongoing, interim findings indicate that certain concepts may prove instrumental to moving patients along the path to kidney transplantation. Specifically, messages highlighting the severity of kidney disease and countering the emotional aspects of making requests for living donation with instruction on how to effectively pursue this treatment option are needed.

SA-PO896
Patient Preferences for End-Stage Renal Disease Management Eric Finkelstein,1 Semra Ozdemir,1 Chetna Malhotra,1 Lina Choong,2 Gan Sheryll Shien Wen,2 Lydia Lim Wei Wei,2 Andy Sim Gim Hiong,2 Tazeen H. Jafar,2 1Duke-NUS Medical School, Singapore; 2Singapore General Hospital, Singapore.

Background: For very elderly (age ≥75) end-stage renal disease (ESRD) patients with multiple comorbidity, there is little expected survival and quality of life (QoL) benefit for dialysis compared to conservative management (CM). Dialysis is also costlier compared to CM. Despite this, dialysis is the most common management option for very elderly ESRD patients including those with co-morbidities in Singapore. To better understand the high dialysis uptake rate, we aimed to investigate the patient level factors influencing decision to choose dialysis or CM.

Methods: We administered a discrete choice experiment survey to 250 Stage 3b-5 chronic kidney disease (CKD) pre-dialysis patients aged ≥65 years visiting outpatient clinics of the Renal Medicine Department of the largest hospital in Singapore. Prior to the DCE, patients were asked to provide their best estimate of survival for a hypothetical patient with similar health problems as themselves, and their expected QoL and cost if they undergo dialysis and CM. They were then asked a series of hypothetical choice tasks that varied by expected survival, QoL, out-of-pocket cost, and treatment type and asked to choose the one that most appealed to them should they be faced with this decision.

Results: Patients were on average aged 74 (SD=6) years, mostly males (65%) and with average CKD-Epi eGFR of 23.7 (SD=10.5) ml/min/1.73m². Over 60% of patients could not provide an estimate of expected survival under any treatment option. Over 40% could not provide an estimate of the expected costs of dialysis or CM, although 66% expected dialysis to be costlier. 60% reported that CM offers better QoL. Expected survival, QoL, cost, and treatment type were significant predictors of patient treatment choices. On average, CM was preferred over a form of dialysis for the management of ESRD.

Conclusions: Findings suggest that most elderly patients with advanced CKD were unaware of key factors that should be considered in the decision making process for dialysis or CM. However, despite this knowledge gap, a majority had a clear preference for CM. Future efforts should be made to inform patients on these factors.

SA-PO897
Identifying Factors That Influence Physicians’ Recommendations for Dialysis and Conservative Management Eric Finkelstein,1 Semra Ozdemir,1 Chetna Malhotra,1 Tazeen H. Jafar,1 Lina Choong,2 1Duke-NUS Medical School, Singapore; 2Singapore General Hospital, Singapore.

Background: For elderly end-stage renal disease (ESRD) patients with multiple comorbidities, dialysis may offer little survival benefits compared to conservative management (CM). Dialysis patients also incur greater costs and greater rates of hospitalization, and lower life satisfaction. Yet, many elderly ESRD patients receive dialysis when it is available. This might be partly due to physician recommendations on treatment choice. Yet the factors that influence these recommendations remain largely unknown.

Methods: We surveyed physicians who attended the 9th Asian Forum of Chronic Kidney Disease Initiative conference to understand factors that influence physicians’ recommendations for managing ESRD. We used vignettes that vary by age and comorbidity status, and asked physicians to predict survival of hypothetical patients undergoing dialysis or CM. We then asked them to choose whether they would recommend dialysis or CM for a hypothetical patient with that profile. We also compared the physician’s recommendations for patients to what they would recommend for themselves if they were diagnosed with ESRD.

Results: On average, physicians believe that dialysis extends life relative to CM. Yet, many believe that CM confers greater survival. Estimates range from 17.3% (for a vignette depicting a 65 year old with diabetes and CHF) to 50% for vignettes depicting patients with advanced cancer. Results further reveal high discordance in treatment recommendations. For a 65 year old, very elderly end stage renal disease patient with diabetes or those with advanced cancer, 25% recommended dialysis. Those who were more optimistic about the ability of dialysis to extend life were far more likely to recommend it to their (hypothetical) patients. Physicians were far more likely to recommend dialysis for themselves than for their patients.

Conclusions: This study suggests that physicians would benefit from a greater understanding of the survival benefits of dialysis and CM for elderly patients with different comorbidity profiles. This information could then be used to better inform patients to ensure that they receive treatment most consistent with their preferences for care.

SA-PO898
Barriers and Facilitators to Chronic Kidney Disease Patient Education as Perceived by Primary Care Physicians: A Qualitative Study Varun Agrawal, Sandeep S. Soman, Clarissa Jonas Diamantidis, Michelle M. Estrella, Kerri L. Cavanaugh, John Sperati, Khaled Abdel-Kader, Bernard G. Jaar, Michael J. Choi, Mark A. Perazella, Yang Liu, Raquel C. Greer. NKF Education Committee, NY.

Background: Education of patients with chronic kidney disease (CKD) in nephrology practice is associated with improved dialysis readiness. Little is known as to how primary care physicians (PCPs) view their role in education of CKD patients.

Methods: We conducted 4 focus group interviews of PCPs in 4 US cities to determine challenges and possible solutions to providing CKD education in primary care. A questionnaire was administered to assess comfort with education of patients with CKD. A trained moderator conducted group discussions using standardized open-ended questions. Two independent abstractors coded the transcribed recorded interviews and identified major themes.

Results: 32 PCPs were interviewed and most (85%) were in private practice. While many PCPs felt comfortable educating patients about CKD (84%), only about half had resources to assist with education on CKD (56%) or hypertension (50%). Even fewer had patient education tools for CKD complications such as anemia (25%), bone disorders (25%), or hyperkalemia (28%). PCPs identified numerous barriers to CKD education at various levels of healthcare, including the patient level (low public awareness of CKD, lack of CKD-specific symptoms and patient’s fear of dialysis) and the provider and healthcare system levels (complexity of CKD educational concepts, lesser emphasis on CKD as compared to other medical conditions at the clinic visit, lack of ancillary support to provide CKD education and limited time). Strategies suggested by the PCPs to facilitate CKD patient education included raising public awareness of CKD, better tools to facilitate patient involvement in CKD care, and nephrology referrals.

Conclusions: While many PCPs felt comfortable educating patients about CKD, they identified numerous barriers to CKD education. Education programs in primary care that enhance patient awareness and knowledge of CKD in the non-dialysis stage, possibly with effective educational tools and nephrologist collaboration, may improve patient’s self-management and outcomes.

Funding: NIDDK Support, Private Foundation Support

SA-PO899
Abstract Withdrawn

SA-PO900

Background: Primary care providers (PCPs) care for the majority of patients with chronic kidney disease (CKD), yet there are missed opportunities for optimal care. This study aims to further identify the causes.

Methods: We conducted 4 PCP focus groups (n=32) (Baltimore, MD, St. Louis, MO, Raleigh, NC, & San Francisco, CA) to identify barriers to PCP management of CKD. A questionnaire was administered to obtain PCPs’ demographics, practice characteristics, and comfort with management of patients with CKD. Standardized, open-ended questions developed by the authors were used to identify PCPs’ perceived barriers to management of CKD (e.g. as tools to facilitate improved CKD care. Groups were audiorecorded and transcribed verbatim. Two investigators independently coded concepts addressed during the discussions, which were categorized into major themes.

Results: 45% (n=14) of PCPs surveyed reported not following CKD guidelines. Most PCPs (n=27, 54%) felt uncomfortable managing patients with CKD, but many were uncomfortable managing specific complications of CKD such as anemia (n=14, 44%), bone disorders (n=16, 50%), and acidosis (n=22, 69%). PCPs cited a lack of tools to manage specific complications of CKD (19-49%) and a lack of educational resources for patients (44-78%). Other significant barriers identified spanned patient (e.g., low awareness of CKD and poor adherence to treatment recommendations), provider (e.g., staying current with CKD guidelines), and system levels (e.g., limited time and reimbursement for complex patients). PCPs desired electronic prompts, lab decision support, medical homes, concise guidelines, PCP education, improved compensation, patient access to self-monitoring tools, and better insurance coverage as tools to facilitate CKD management.

Conclusions: PCPs experience substantial barriers in providing care to patients with CKD. Interventions to address these barriers and increase implementation of facilitative tools may improve PCPs’ effectiveness and capacity for care CKD patients.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO901
Advantages of Nutrition Counseling in CKD Patients by a Professional Dietician on the Physical or Psychological State
Atsushi Ueda, Aki Hirayama, Kunihito Yamagata, Hitachi General Hospital, Japan; \textsuperscript{2}Takusha University of Technology, Japan; \textsuperscript{3}Univ of Tsukuba, Japan.

Background: In Japan, most of chronic kidney disease (CKD) patients go to a clinic. However, it is frequently observed that the patients going to a clinic don’t have access to good nutrition counseling. This lack of opportunity is usually due to the absence of a national registered dietitian the clinic. To solve this problem, we dispatched a national registered dietician to a clinic and subjected CKD patients to nutrition counseling. This study evaluates the advantages of this nutrition counseling method.

Methods: The study groups consisted of 46 (male31, female15) patients with CKD stage I-V, and 54 (male37, female17) matched controls. Nutrition counseling was performed twice within 12 months, and each session lasted 30 minutes. A dispatched a national registered dietician used an iPad including original nutrition counseling software and a textbook. During the session, we first identified the main issues such as obesity, salt restriction, protein restriction or diet restriction according to the patients’ health. We then accurately issued specific nutrition instructions. Finally, we examined the patient’s status, several laboratory data and the behavior modification stage (BMS) by using the transtheoretical model. The previous factors were examined before the first session of counseling and also two months after the second session of counseling. Furthermore, we linked the different BMS to the patient’s status and various laboratory data.

Results: Obesity counseling (34%, 16/46), salt restriction (23%, 10/46), protein restriction (11%) or potassium restriction (5%) counseling were issued. In general after counseling BMI decreased remarkably. Body mass index (BMI) and HbA1c decreased significantly in the group with improved BMS. BMI also decreased significantly in the group with diabetic nephropathy.

Conclusions: This counseling method using an iPad and a textbook by professional dieticians is effective in improving the stage of behavior change, BMI and HbA1c in CKD patients. Therefore, our study demonstrates that the delivering on-demand of nutritional counseling may be useful for preventing the physical or psychological deterioration in CKD patients.

SA-PO902
Utilization of Medical Nutrition Therapy in Patients with Non-Dialysis Chronic Kidney Disease Jennifer K. Bond, Ruth Kafenzik, Kavitha Vellanki, David J. Leehey, Vinod K. Bansal, Amuradha Wadha, Julia Schneider, Benjamin Ling, Holly J. Kramer. Nephrology and Hypertension, Loyola Univ Medical Center, Maywood, IL.

Background: Medical nutrition therapy (MNT) has been associated with slower progression of chronic kidney disease (CKD). As of January, 1 2011 the Patient Protection and Affordable Care Act allows Medicare to fully covered recommended preventive services that were only previously covered through cost-sharing, including MNT. MNT is recommended for diabetes and non-diabetes CKD stage 3-5. CKD: Health Services, Disparities, Prevention and Affordable Care Act funding. A total of 334 adults with CKD, mean age of 69.3 years, were identified. Overall, 56.0% male , 26.7% black, 6.9% Hispanic, 65.3% white. Obesity, diabetes and coronary artery disease were present in 46.7%, 56.6% and 37.4% respectively. Medicare and private insurance was primary insurance for 63.2% and 31.1%, respectively. During 2011-2015 adjusting for the demographics. MNT models were used to assess temporal differences in MNT utilization (years 2009-2010 vs. years 2011-2015) adjusting for the demographics.

Results: A total of 334 adults with CKD, mean age of 69.3 years, were identified. Overall, 56.0% male , 26.7% black, 6.9% Hispanic, 65.3% white. Obesity, diabetes and coronary artery disease were present in 46.7%, 56.6% and 37.4%, respectively. Medicare and private insurance was primary insurance for 63.2% and 31.1%, respectively. During 2011-2015 adjusting for the demographics.

Conclusions: This study demonstrates that the delivering on-demand of nutritional counseling may be useful for preventing the physical or psychological deterioration in CKD patients.

SA-PO903
Diabetes and Kidney Disease Specific Health Literacy in Urban and Rural Resided Based Native Americans Vallabh O. Shah, \textsuperscript{1}Stevens Lancer, \textsuperscript{2}Christopher Aston, Donica M. Ghahate, \textsuperscript{3}Jeanette Bobelu. \textsuperscript{1}Univ of New Mexico; \textsuperscript{2}Univ of Oklahoma.

Background: Health literacy (HL) is a measure of a patients’ ability to read, comprehend, and act on medical information to make appropriate health decisions. Poor HL is disproportionately found on vulnerable populations, such as Native Americans. Little is known about the extent to which HL affects clinical health outcomes including diabetes and kidney disease in reservation based vs non-reservation based Native Americans (NA).

Methods: We conducted a HL survey using validated instrument in Zuni reservation based (n=200) and Oklahoma (n=200) non-reservation based Urban NAs.

Results: HL regarding diabetes and kidney disease was significantly higher in NM (result is significant when compared to OR-Cali based NA). As compared to Arizona residents both native diabetes and non-diabetics. HL varied significantly with age, education and work status both within state and within diabetic status, but not with gender, or with propensity to speak a tribal language. HL was significantly higher in younger participants, those with higher levels of education, and those employing strategies such as using phone book, internet, and text messages to look for information. Also, HL was significantly associated with complications due to diabetes, such as kidney disease, neuropathy or eye disease, tended to have lower HL than those that did not have complications. Among the older, those with one or more family members with complications due to diabetes, HL was significantly lower. Higher HL lead to poorer preventive care. On the other hand, those with one or more family members with complications due to diabetes, HL was significantly lower. Higher HL lead to poorer preventive care. Conclusions: Reservation based NA had significantly higher health literacy regarding diabetes and kidney disease than non-reservation based NA, however, this did not translate into improved (lower) prevalence of diabetes or its associated complications. Higher health literacy appeared to be a consequence rather than a preventative of diabetes or its associated complications.

Funding: Other NIH Support - NIGMS, Other U.S. Government Support

SA-PO904
Veterans Affairs (VA) eKidneyClinic: Addressing Chronic Kidney Disease Health Literacy Gap Devasmita Choudhury, Brooks Robey, Rose Mary M. Pries, Dorian R. Schatell, Susan T. Crowley. \textsuperscript{1}Medicine, Salem Veterans Affairs Medical Center, Salem, VA; \textsuperscript{2}Medicine, White River Junction Veterans Affairs Medical Center, White River Junction, VT; \textsuperscript{3}Veteran Education & Information Program, Veterans Health Administration, Durham, NC; \textsuperscript{4}MEI INC, Madison, WI; \textsuperscript{5}Medicine, Veterans Affairs Connecticut Health Care System, West Haven, CT.

Background: Chronic kidney Disease (CKD) health literacy can be critical in preventing CKD progression. CKD literacy gap is high amongst CKD patients despite clinic education. Well designed, interactive education improves education outcomes. To address CKD literacy gap, VA developed a comprehensive, freely available VA eKidneyClinic (http://edc.va.gov/ckd) web-based tutorial and implementation guide to help the patients’ health. We then, accordingly issued specific nutrition instructions. Finally, we examined the patient’s status, several laboratory data and the behavior modification stage (BMS) by using the transtheoretical model. The previous factors were examined before the first session of counseling and also two months after the second session of counseling. Furthermore, we linked the different BMS to the patient’s status and various laboratory data.

Results: Obesity counseling (34%, 16/46), salt restriction (23%, 10/46), protein restriction (11%) or potassium restriction (5%) counseling were issued. In general after counseling BMI decreased remarkably. Body mass index (BMI) and HbA1c decreased significantly in the group with improved BMS. BMI also decreased significantly in the group with diabetic nephropathy.

Conclusions: This counseling method using an iPad and a textbook by professional dieticians is effective in improving the stage of behavior change, BMI and HbA1c in CKD patients. Therefore, our study demonstrates that the delivering on-demand of nutritional counseling may be useful for preventing the physical or psychological deterioration in CKD patients.

Funding: VA Support

SA-PO905

Background: Hispanics/Latinos are disproportionally affected by chronic kidney disease (CKD). We evaluated the association of physical activity with kidney function in a representative sample of US Hispanic/Latino adults.

Methods: HCHS/SOL is population-based cohort of 16,415 Hispanics/Latinos aged 18-74 yr at baseline (2008-2011) enrolled using a probabilistic sample from 4 US cities. Analyses include individuals with at least 3 days (<10 hours/day) of accelerometer-measured physical activity data, and kidney function (creatinine clearance, cystatin C equation, and urine albumin-to-creatinine ratio (UACR). Complex survey linear regression analyses were conducted adjusting for sociodemographic and clinical variables.

Results: Mean eGFR for Hispanics/Latinos in the high, medium and low activity categories were 111, 109 and 103 ml/min/1.73m^2 respectively. The corresponding UACR was 342, 447 and 542 mg/g respectively. They were also more likely to have diabetes (20% vs 9%), and hypertension (28% vs 15%). After adjustments, low/inactive and medium PA were associated with significantly lower kidney function compared to high activity (CKD-EPI creatinine-cystatin C equation, and urine albumin-to-creatinine ratio (UACR). Complex survey linear regression analyses were conducted adjusting for sociodemographic and clinical variables.

Results: Mean eGFR for Hispanics/Latinos in the high, medium and low activity categories were 111, 109 and 103 ml/min/1.73m^2 respectively. The corresponding UACR was 342, 447 and 542 mg/g respectively. They were also more likely to have diabetes (20% vs 9%), and hypertension (28% vs 15%). After adjustments, low/inactive and medium PA were associated with significantly lower kidney function compared to high activity (CKD-EPI creatinine-cystatin C equation, and urine albumin-to-creatinine ratio (UACR).

Conclusions: Physical activity is an important factor for the prevention and reduction of CKD progression. Physical activity may reduce the risk of CKD progression and improve kidney function.

Funding: Other NIH Support - NIGMS, Other U.S. Government Support

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

841A
Conclusions: US Hispanic/Latino adults not meeting PA recommendations had lower kidney function compared to individuals with high PA. Longitudinal studies are needed to further evaluate the association of PA and incident CKD.

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

SA-PO906

Differences in the National Prevalence of Chronic Kidney Disease (CKD) in Urban versus Rural Veterans within the U.S. Department of Veterans Affairs (VA)

Bessie A. Young,1,2 Jolene A. Borgerding,1 Maureen Germani,1 Raimund H. Pichler,1,2 1Hospital and Specialty Medicine, VA Puget Sound Health Care System, Seattle, WA; 2Center of Innovation, VA Puget Sound Health Care System, Seattle, WA; 3Institute of Public Affairs (VA)

Background: Little is known regarding rural versus urban differences in prevalence of CKD among Veterans. Our objective was to determine the prevalence of CKD from a national sample of rural and highly rural (R/R) compared to urban Veterans, and to further evaluate treatable risk factors for CKD progression and adverse outcomes prior to program implementation.

Methods: We created a 10% stratified sample from over the 5.3 million enrolled Veterans with at least one primary care outpatient (PC) visit from fiscal year (FY) 2011-2015 with proportional allocation by facility from VA's Corporate Data Warehouse (CDW). Rurality status was based on the CDW geospatial information using the patient’s primary address. Standard stages of CKD were determined using estimated glomerular filtration rate (eGFR) by three different methods: 1) CKD-EPI, 2) Modification of Diet in Renal Disease (MDRD), and 3) VA clinical algorithm (MDRD ). Standard stages of CKD were defined, additional comorbid conditions were determined using standard ICD-9 codes.

Results: From FY2011-FY2015, R/R Veterans comprised 35-38% of all Veterans who received PC within VA. Almost 95% of R/R Veterans were male and older as compared to urban Veterans. R/R Veterans had greater prevalence of comorbid conditions vs. urban Veterans, including diabetes (22% vs. 20%), hypertension (48% vs. 43%), congestive heart failure (3.5% vs. 3.7%) respectively. The mean creatinine was similar among R/R and urban Veterans (1.1 (SD=0.49) vs 1.1 (SD=0.61) mg/dl). The estimates of CKD stage showed R/R Veterans had Stage 1CKD (32.9 vs 31.7%), Stage 2 (48.6 vs 45.2%), Stage 3 (16.8 vs 15.7%), Stage 4 (1.3 vs 1.4%), and Stage 5 (0.4 vs 0.6%) CKD, respectively.

Conclusions: Compared to urban Veterans, R/R Veterans had a greater prevalence of lower stage CKD (3-5). Data are needed to determine how risk factor treatment compares in urban and rural settings prior to Nephrology program implementation.

Funding: VA Support

SA-PO907

The Spectrum of Chronic Kidney Disease in Public Renal Services of Queensland, Australia: Data from the CKD.QLD Registry

Wendy E. Hoy,1 Helen G. Healy,1 Zaiming Wang,1 Jianzhen Zhang,2 Rajillia Asanga Abeysekera,1 Ken-Soon Tan,1 Anne Cameron (Salisbury),1 1Centre of Innovation, VA Puget Sound Health Care System, Seattle, WA; 2Institute of Public Affairs (VA)

Background: The spectrum of CKD is wide ranging from mild to severe stages with likely impact on health care utilization and treatment costs. Public renal services in Queensland. Patient enrolment began in May, 2011.

Methods: Differences in the National Prevalence of Chronic Kidney Disease (CKD) in Public Renal Services of Queensland, Australia: Data from the CKD.QLD Registry

Conclusions: Low SES was associated with increased risk of CKD and ESRD, with stronger association for ESRD. Our results suggest that interventions to reduce disparities are at least as important late in CKD as early.

Table: Hazard ratios for CKD and ESRD events by SES categories

<table>
<thead>
<tr>
<th>Household income (N0)</th>
<th>Overall</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD, % (N0)</td>
<td>22.9 (19,958)</td>
<td>25.4 (773)</td>
<td>28.8 (569)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>(95% CI)</td>
<td>(2.14-1.43)</td>
<td>(2.17-1.43)</td>
<td>(2.17-1.43)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>(95% CI)</td>
<td>(0.95-1.14)</td>
<td>(1.09-1.15)</td>
<td>(1.09-1.17)</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>(95% CI)</td>
<td>(0.95-1.15)</td>
<td>(1.04-1.16)</td>
<td>(1.04-1.16)</td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>(95% CI)</td>
<td>(0.95-1.16)</td>
<td>(1.04-1.19)</td>
<td>(1.04-1.19)</td>
<td></td>
</tr>
<tr>
<td>Model 5</td>
<td>(95% CI)</td>
<td>(0.95-1.16)</td>
<td>(1.04-1.19)</td>
<td>(1.04-1.19)</td>
<td></td>
</tr>
<tr>
<td>Model 6</td>
<td>(95% CI)</td>
<td>(0.95-1.16)</td>
<td>(1.04-1.20)</td>
<td>(1.04-1.20)</td>
<td></td>
</tr>
</tbody>
</table>

Income (in 2004 US$): high ($50,000), medium ($25,000-$50,000), low (<$25,000), Education: high (at least 13 years), medium (10-12 years), low (<10 years).

*p<0.05 for ESRD (stronger than CKD).

Conclusions: Socioeconomic Status Shows Stronger Association for Risk of ESRD Than Incidence of CKD in the ARIC Study

Priya Yari,1 Morgan Grams,2 Mark Woodward,2 Shoshana Ballew,1 Josef Coresh,1 Kunhiro Matsushita,1 1Johns Hopkins Univ; 2Univ of Oxford, United Kingdom.

Background: Low socioeconomic status (SES) is strongly associated with ESRD but associations with CKD are less certain and comparing the two will provide insight into whether disparities are wider in early or late in CKD.

Methods: 13,515 participants with eGFR <60 at baseline (1987-1989) in the ARIC Study with household income and educational attainment data were examined for their association with subsequent CKD incidence (eGFR<60 and ≥25% decline in eGFR or CKD hospitalization or ESRD) and ESRD (diagnosis, transplantation or death due to kidney disease). We performed seemingly unrelated regression to compare the association of SES measures with CKD and ESRD.

Results: During a median follow-up of ~23.2 years, 3,300 participants developed CKD and 385 participants developed ESRD. In a demographically adjusted model, with high household income as reference, a higher level income was associated with 24% reduced risk of CKD incidence (HR=1.27, CI: 1.14-1.42) and ESRD (HR=2.31, CI: 1.74-3.07). Table. After additional adjustment for major CKD risk factors, the association across three levels of SES did not reach statistical significance for CKD but did for ESRD (p<0.001; stronger association with ESRD vs. CKD). Similar results were obtained for educational attainment, although its association was attenuated for both both CKD and ESRD when adjusted for risk factors. No significant interaction was observed between SES measures and race or CKD or ESRD.

Conclusions: Socioeconomic Status Shows Stronger Association for Risk of ESRD Than Incidence of CKD in the ARIC Study

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

SA-PO908

The Association between Socioeconomic Status and Risk Factors for Cardiovascular Mortality in Chronic Kidney Disease: Result from the KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD)

Junjeong Kang,1 Hyo Jin Kim,1 Hyunjin Ryu,1 Muyeon Han,1 Curie Ahn,1 Hyun Suk Kim,1 Kook-Hwan Oh,1 Internal Medicine, Seoul National Univ Hospital, Seoul, Korea; 2Internal Medicine, Dongduk Gyu Eungyong Hospital, Gyeongju, Korea.

Background: Although cardiovascular (CV) disease is a major cause of death in chronic kidney disease (CKD) patients, a relationship between socioeconomic status (SES) and risk factors for CV mortality in CKD is less well known.

Methods: Data were collected from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD, NCT01630486 at http://www.clinicaltrials.gov). SES was characterized on the basis of monthly income and education attainment, which were divided into 3 categories, respectively. Left ventricular hypertrophy (LVH) was defined as left ventricular mass index (LVMI) ≥115g/m2 for male, or >95g/m2 for female. Anemia was defined as hemoglobin <13mg/dl for male, or <12mg/dl for female. Mean brachial-to-ankle pulse wave velocity (baPWV) and coronary calcium score (CCS) were divided into higher or lower groups based on their median values. We conducted logistic regression to evaluate the association between SES - categorized into the tertiles of education level or monthly income - and cardiac surrogate markers or anemia. Age, sex, diabetes, CKD stage, body mass index, blood pressure were included as covariates.

Results: Total 1,661 patients were enrolled. The lowest education level was independently associated with LVH (adjusted odds ratio [OR] 1.75, 95% confidence interval [CI] 1.26-2.42, P<0.001), higher baPWV (adjusted OR 1.54, 95% CI 1.09-2.17, P=0.014) and anemia (adjusted OR 1.59, 95% CI 1.11-2.20, P=0.011). The lowest monthly income was independently associated with LVH (adjusted OR 1.48, 95% CI 1.03-2.12, P=0.034), but not with anemia or higher baPWV. Neither education level nor monthly income showed a significant relationship with CCS.

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

842A
Conclusions: In the CKD population, lower SES defined by education attainment exhibited a significant association with LVH, arterial stiffness, and anemia, while monthly income was associated with only LVH. Further efforts are warranted to improve the outcomes for CKD patients in the lower SES.

Funding: Government Support - Non-U.S.

SA-PO910

Association of Comorbidity with Late Nephrology Referral - A Population-Based Study

Ming-Yen Lin, Yiwen Chiu, TengHui Huang, Hueilan Lee, Shang-Jyh Hwang.

Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung Medical Univ, Kaohsiung, NA, Taiwan.

Background: Timely referral to nephrology can ensure adequate care, reduce mortality and medical expenses in patient with chronic kidney disease. However, factors associated with timely nephrology referral are not systematically explored. We hypothesize patients’ comorbidity can contribute to timing of nephrology referral.

Methods: One retrospective population-based cohort study was conducted to include patient newly underwent long-term dialysis from 2000 to 2008 year through Taiwan National Health Insurance Research Databases. The early referral (ER) and late referral group (LR) were defined as patients who were referred to a nephrologist more than or less than half year prior to dialysis initiation, respectively. The suggested 29 comorbidities by previous study for claim data within three years before dialysis were applied for these patients.

Results: A total of 24,846 (38.1%) patients and 40,442 (61.9%) patients were ER and LR group. A proportion of ≥3 comorbidities was higher in ER group than in LR group (57.3% vs 50.8%, p<0.001). In multiple logistic regression adjusting age, sex, insurance amount, urbanization, and various comorbidities demonstrated that patients with alcohol misuse (odds ratio 1.23, 95% confidence interval 1.06-1.43), asthma (1.12, 1.03-1.21), cancer with metastatic (1.26, 1.03-1.54), chronic heart failure (1.19, 1.14-1.23), dementia (1.30, 1.15-1.47), and stroke or transient ischemic attack (1.07, 1.02-1.13) were more likely to have late nephrology referral than those without. However, patients with pain (0.82, 0.73-0.91), chronic viral hepatitis B (0.63, 0.52-0.76), depression (0.78, 0.72-0.86), hypertension (0.53, 0.50-0.55), hypothyroidism (0.71, 0.62-0.81), irritable bowel syndrome (0.80, 0.72-0.88), peptic ulcer disease (0.89, 0.85-0.93), psoriasis (0.77, 0.69-0.95), severe constipation (0.84, 0.80-0.88) were associated negative with late nephrology referral.

Conclusions: Various comorbidity in patient with chronic kidney disease determines the timing of nephrology referral. However, the complex relationship between comorbidity and adequate pre-dialysis care needs further study.

SA-PO911

Healthcare Cost Rises Exponentially by Stage of Chronic Kidney Disease

Ladan Golestanlou, Paula J. Alvarez, Nancy Revena, Susan Funk, Karen J. Mcgaughey, Cristine A. Sproles, Wade Benton, Macaulay A. Onuigbo,

1Albert Einstein College of Medicine; 2Relypsa, Inc; 3Strategic Health Resources; 4County Medical Center, Buffalo, NY; 5Nephrology, Erie County Medical Center, Buffalo, NY.

Background: All-cause health plan costs rise exponentially at each stage of CKD progression. Costs for patients with CKD (stage 4-5) are higher than for patients without CKD (stage 0)

Methods: A large electronic medical record (EMR) database (Humedica) was queried to identify patients (pts) with renin-angiotensin-aldosterone system inhibitor prescription (Rx) history. Pts with 90+ days of ≥1 CKD stage (by GFR or diagnosis), plus CKD-free controls, were studied. Since the EMR database did not contain claims data, mean claims costs to US Commercial (Comm) and Medicare (Medi) plan for specific services and Rx were obtained (OptumInsight) and applied to services and Rx in EMR data of pts ≥65 and ≥65 years of age, respectively. Dialysis in ERSD, rarely reported in EMRs, was excluded. Annualized all-cause cost was computed per pt in each CKD stage, and ERSD, and summed. Payer-specific means were compared between CKD stages (Chi-square).

Results: 93,912 pts ≥65 years (41,737 with CKD/ESRD; 52,175 controls) and 81,829 pts ≥65 years (77,243 with CKD/ESRD; 45,866 controls) were evaluated. Mean annualized and summed. Payer-specific means were compared between CKD stages (Chi-square).

Conclusions: All-cause health plan costs rise exponentially at each stage of CKD progression for both Medi and Comm health plans in the US. ERSD patients costs more even without the burden of dialysis procedure expenses.

SA-PO912

Costs of Chronic Kidney Disease during Transitions between Stages of CKD among U.S. Veterans


1Univ of Michigan; 2VA Healthcare System.

Background: While CKD becomes more expensive with advancing stage, how costs change as individuals transition across stages is unknown. We sought to estimate cost of care for Veterans transitioning the CKD continuum to inform prioritization of VA CKD prevention efforts.

Methods: We analyzed existing data in the VA Renal Information System (VA REINS), an internal national data system that informs the VA about CKD in its population. An operational definition of a VA user (≥1 contact with VA in 3yrs) was used. All users were categorized as CKD stages 3a-5 based on their outpatient eGFR and followed 2010-2011 to determine how the cost of care changed with CKD stage shift. Total annual inpatient, outpatient, and pharmacy costs were aggregated from VA internal cost accounting, external fee-based service, and linked Medicare payments to calculate VA spending on CKD as well as mean annual costs by CKD stage.

Results: In 2011, combined (VA + Medicare) aggregate cost for VA users with ≥1 eGFR <60 (n=845,610) was over $18 billion. Average annual per patient (PP) costs increased by CKD stage: stage3a $17,742; stage3b $23,084; stage4 $33,564; stage5 $85,177. Among users whose CKD stage changed 2010 to 2011, worsening CKD conferred an increased cost; for those with improving CKD status a downward cost. For patients who died in 2011, the change in cost depended on their 2010 stage.

Conclusions: Total cost of caring for US veterans with CKD is high, and change in costs with shift in CKD stage has implications for gauging cost effectiveness of VA CKD prevention strategies.

Funding: VA Support

SA-PO913

Billing Codes Are Not Reliable in the Detection, Staging, and Progression of Chronic Kidney Disease

Kabir Jalal,1 Edwin J. Anand,2 Rocco C. Venuto,2 Pradeep Arona,1 Biostatistics, Univ at Buffalo, Amherst, NY; 2Nephrology, Erie County Medical Center, Buffalo, NY.

Background: Billing codes are not only used for reimbursement, but are also used by administrators and investigators for population health management and therefore need to be reliable. The accuracy of administrative coding was studied, using Chronic Kidney Disease (CKD) as the condition of interest. Clinical progression was compared to progression assessed by coding changes.

Methods: Data from a large third party payer, with an average annual enrollment of 1.3 million, from 2007-14. Patients with eGFR readings less than 60 for 2 months or having proteinuria were identified as CKD cases. ROC analysis examined the sensitivity/specificity of billing codes in capturing CKD. Analysis was stratified based on demographic and comorbidity factors. The correlation of CKD severity data from billing codes with eGFR was analyzed. Longitudinal mixed model analysis identified rapid progressors (eGFR loss >4 per year), and changes in coding were examined for disease progression.

Results: 38,857 CKD cases were identified. 46% were male and 54% were females. CKD stages 3, 4 and 5 were found in respectively 50, 28, and 9%. Billing codes identified...
10,567 patients, giving a sensitivity of 27.19%. The specificity was 97%. With regards to severity, the accuracy of the codes for CKD stage 3 was 69.58%, stage 4, 46.14% and stage 5, 46.77%. Changes in coding alone identified only 11.95% of rapid progressors.

Conclusions: 1. Inaccuracies in billing codes preclude use of this data for identifying patients with a disease of interest. 2. Administrative codes have poor sensitivity in the identification of patients with CKD, but are highly specific. 3. Billing codes inaccurately identify rapid progressors. 4. Physician education on accurate coding is crucial in the EHR era.

SA-PO914
Trends in the Timing of a Second GFR after a First GFR Lower than 60 in a Primary Care Setting Claudine T. Jarkovitz, Richard Caplan, Sarahfaye Heckler, James Thomas Laughergy, Edward Ewen. Christiana Care Health System, Newark, DE.

Background: The KDOQI guidelines recommend 2 measurements of glomerular filtration rate (GFR) <60 mL/min/1.73m² at 3 months intervals or more to establish the diagnosis of chronic kidney disease (CKD). We examined the timing of measurement of a second GFR in an outpatient primary care setting.

Methods: We used the CKD-Epi equation to assess GFR from the serum creatinine records of patients seen in a large network of primary care offices from 2007 to 2015. Our study population was defined as patients 18 or older with at least one GFR<60. We excluded patients whose first GFR was <15. Followup began at the time of the first GFR<60. We calculated the time interval between the first GFR<60 and the second GFR and stratified the patients according to their first GFR into 3 categories (GFR 15<30; 30<45; 45<60). We used Analysis of Variance test for linear contrast to assess the trend of the time interval according to GFR categories and the Cochran-Mantel-Haenszel for linear association for the trend in the proportion of patients who had a second GFR within 3 months, between 3-12 months, and more than 12 months after the first GFR.

Results: A total of 13,320 patients had at least one GFR<60. 1,880 patients who did not have any follow up serum creatinine and 353 with GFR<15 were excluded. Of 11,087 patients, 62% were female, 81% white, 18% black, 6% had a first GFR 15<30, 20% had a first GFR 30<45 and 74% a first GFR 45<60. Mean age was 69. Overall, 39% had a second GFR<60 within 3 months, 44% between 3 and 12 months, and 17% after 12 months. Among patients with first GFR 15<30, 30<45, 45<60 respectively, the median time intervals between GFR measurements were 82, 105, and 140 days (p<0.0001). 52%, 46% and 36% had a second measurement within 3 months, 37%, 40% and 46% had a measurement between 3 and 12 months, and 11%, 14% and 18% had a measurement after 12 months (p<0.0001).

Conclusions: In a primary care setting, the timing of the first GFR depends primarily on the level of the first GFR. It is likely that at low levels of GFR, physicians are concerned about ruling out acute kidney injury and choose to re-measure serum creatinine closer to the first measurement.

Funding: Other NIH Support - Work supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institute of Health under grant number U54-GM104941 (PI: Binder-Macleod).

SA-PO915
Using Primary Care Database to Understand the Generalizability of the European QUALity (EQUAL) Study in the UK Anirdud Rao, Stephanie J. MacNeill, Yoav Ben-Shlomo, Fergus J. Caskey, UK Renal Registry, Bristol, United Kingdom; Univ of Bristol, Bristol, United Kingdom; On Behalf of EQUAL Investigators.

Background: The EQUAL Study is an ERA-EDTA funded cohort study looking at the timing of dialysis start in elderly patients with advanced CKD. Most observational studies are likely to recruit a selected sub-sample of eligible participants which could affect the generalizability. The aims of the study were: 1. Quantify selection biases by identifying factors that were associated with participation/non-participation in EQUAL. 2. Describe differences in outcomes between patients participating & not participating in EQUAL.

Methods: EQUAL data (UK) from first 225 dialysis patients was compared to patients identified from The Health Improvement Network (THIN) database, under a nephrologist meeting EQUAL inclusion criteria(2,464). Descriptive statistics and regression models were used to examine differences in baseline characteristics, clinical & laboratory markers, hospitalization and mortality between the two cohorts.

Results: In a multivariable logistic model, older patients (every 5-year age band, OR 0.7, 95% CI 0.6-0.8), women (OR 0.6, 95% CI 0.5-0.9), those with cardiovascular disease (OR 0.6, 95% CI 0.4-0.9), vascular disease (OR 0.5, 95% CI 0.3-0.9) & rheumatological disease (OR 0.3, 95% CI 0.2-0.7) were less likely to be in EQUAL cohort. Greater proportion of patients started renal replacement therapy in EQUAL in the first year after reaching eGFR ≤20 ml/s/min than when compared to THIN cohort (8% vs 2%, p=0.001). Patients in THIN had worse cardiovascular risk compared to EQUAL as evidenced by >24% having had a myocardial infarction in the first year and relative mortality was increased (HR 1.7, 95% CI 1.2-2.6; p=0.02). This was moderately attenuated after adjustment for various confounders (HR 1.5, 95% CI 0.92.3, p=0.10).

Conclusions: This study provides empirical evidence regarding factors associated with participation in an cohort study of elderly people with advanced CKD: older and sicker patients were less likely to be recruited and this was supported by follow up data on health outcomes. This selection pattern is likely in most observational studies of chronic diseases and needs consideration when generalizing the results to a wider population.

SA-PO916
In Their Own Words: Symptoms and Impacts on the Lives of Patients with Anemia Associated with Chronic Kidney Disease Vanja Sikirica, Susan Mathias, Steven I. Blum, Kirsten L. Johansen. GlaxoSmithKline, Afghanistan; Roivant Sciences; Nossuli Research.

Background: We conducted qualitative interviews with patients with anemia associated with Chronic Kidney Disease (aCKD) to identify and explore the most relevant symptoms and impacts from the patient’s perspective.

Methods: One-on-one interviews were conducted with aCKD patients recruited from dialysis centers in the US. Patients were ≥18 years of age, with a confirmed diagnosis of CKD, and hemoglobin (Hgb) level <12.0 g/dL. Patients receiving dialysis (>3 times/week) also: 1) received an erythropoietin stimulating agent (ESA) for ≥12 weeks; or 2) initiated hemodialysis within the past 4 weeks. Non-dialysis aCKD patients had to either: 1) have been receiving an ESA for ≥12 weeks; or 2) not within the prior 12 weeks. Protocol was IRB approved; all patients provided consent.

Results: Twenty-eight aCKD patients (mean age 60±17.2) were interviewed. Most were female (75%), and receiving treatment with an ESA (82%) or IV Iron (54%). Most were CKD Stage 5 or receiving dialysis (68%). Mean Hgb was 9.6 g/dL (SD=0.9, range: 7.2-11.5 g/dL). Patients with aCKD reported (spontaneously or probed) a range of symptoms and related impacts, which were mostly similar across the different sub-groups (dialysis or ESA status or Hgb level). Frequently mentioned concerns included: difficulty remembering things (n=12 out of the 12 patients that were asked; 100%); feeling weak/lack of strength (n=10/10 patients with Hgb <10g/dL; 100%); feeling tired/exhausted/fatigued (n=27/28; 96%); interference with daily activities (n=19/20; 95%); shortness of breath (n=16/17; 94%); GI symptoms (n=11/15; 73%); difficulty sleeping (n=10/16; 63%); emotional (n=10/16; 63%) and social impacts (n=9/21; 43%); and difficulty concentrating (n=9/24; 38%). Non-dialysis patients were more likely to have difficulty remembering things (n=5/9; 56% vs n=7/15; 47%) or difficulty sleeping (n=5/7; 71% vs n=3/9; 36%).

Conclusions: Regardless of treatment with dialysis and ESAs, aCKD patients experienced a wide range of symptoms and impacts. Some differences were noted between patients based on dialysis status and Hgb level. This study captures the barrier and unmet needs associated with aCKD.

Funding: Pharmaceutical Company Support - This study was funded by GlaxoSmithKline.

SA-PO917
Development of a Patient Reported Outcome Symptoms Measure for Use with Patients with Anemia Associated with Chronic Kidney Disease Susan Mathias, Steven I. Blum, Vanja Sikirica, Kirsten L. Johansen. Health Outcomes Solutions, Winter Park, FL; GlaxoSmithKline, Collegeville, PA; Univ of California, San Francisco, CA.

Background: To develop a new disease-specific patient-reported outcome (PRO) measure to capture relevant symptoms and impacts of anemia associated with Chronic Kidney Disease (aCKD).

Methods: Development included an iterative approach following best practices for PRO development. An initial literature review was conducted to identify the existence of relevant PRO measures and concepts to explore during qualitative research with patients with aCKD. One-on-one interviews were conducted using an Interview Guide developed specifically for this study to identify symptoms and impacts associated with aCKD reported with high frequency. Based on analyses of these transcripts, draft measures were developed, further evaluated and refined based on clinical input and cognitive debriefing (CD) interviews with patients. The study received IRB approval; all patients provided informed consent.

Results: Eight dialysis [5 hemodialysis (HD); 3 peritoneal dialysis (PD)] and 6 non-dialysis (ND) patients (71% female; mean age 65±18) completed the initial CE interview. Interview transcripts were coded and analyzed which led to the development of draft questions to assess the most relevant symptoms and impacts. Draft questions were subsequently revised in an iterative fashion, based on CD interviews with an additional 22 aCKD patients (9 HD, 3 PD and 10 ND; 68% female; mean age 61±17), and clinician input. The final questionnaire, the Chronic Kidney Disease and Anemia Questionnaire (CKD-AQ), containing 23 items, assesses severity and frequency of the most relevant
Adherence to Anemia Management Guidelines among Kidney Transplant Candidates

Meteb M. Albugami,1,2 Fahad Eid Aaltoabi,1,2 Khalid Bel’eed-Akkaïri.1 1Multi-Organ Transplant Center, King Fahad Specialist Hospital, Damman, Saudi Arabia; 2Department of Internal Medicine, College of Medicine, Univ of Damman, Damman, Saudi Arabia.

Background: Anemia is one of the major comorbidities of chronic kidney disease (CKD). It is linked to cardiovascular disease (CVD), and low quality of life.Achieving target levels of hemoglobin requires replenishing iron stores and supplemental erythropoietin stimulating agents. Overshooting could happen and is associated with unwanted complications. This study aimed to measure the extent to which kidney transplant (KT) candidates complied with the National Saudi Anemia Guidelines.

Methods: All potential KT recipients evaluated at the Kidney and Pancreas Transplant Department at King Fahad Specialist Hospital-Damman, between January 2009 and December 2012 were reviewed. Data were collected from electronic database. Blood samples were obtained during patients’ initial visit to the pre-transplant evaluation clinic. For patients on hemodialysis, pre-dialysis samples were obtained.

Results: A total of 678 candidates were evaluated, with a mean age of 43±13.7 years, and 396 (58%) of the subjects were males. Data were missing in 81 (12%) of the cases. Mean hemoglobin level was 11.7±1.8 g/dL, and 20% achieved the guideline target. Median ferritin level was 260 ng/mL (IQR 111 – 519), and 26% had level more than 500 ng/mL. Mean transferrin saturation 30±19%, and 30% had level less than 20%. 347 (58%) subjects had hemoglobin 11.5 g/dL and above.

Conclusions: Substantial proportion of KT candidates referred for pre-transplant evaluation failed to meet the national Saudi guideline targets of anaemia management. Moreover, overshooting target hemoglobin is common. This should prompt us to place greater and more rigorous emphasis on adherence measures to the guidelines in order to improve the cardiovascular risk and quality of life.

SA-P0919

Geographic Variation in Access among Adults with Kidney Disease: Evidence from Medical Expenditure Panel Survey, 2002-2011

Muksuo N. Ozieh,1 Kinfe Gebregziabher Bishu,2 Rebekah J. Walker,2 Jennifer A. Campbell,2 Leonard Egede.2 1Nephrology, MUSC, Charleston, SC; 2Center for Health Disparities Research, Internal Medicine, MUSC, Charleston, SC.

Background: To understand geographic variation in access to care over time in patients with kidney disease.

Methods: We analyzed N = 6,404 (weighted sample of 4,251,129) adults with kidney disease from the Medical Expenditure Panel Survey over 10 years. Three dependent variables were created to investigate variation in access: usual source of care (USC), overall medical access to care, which took into account usual source of care, ability to get care, and delay in care, and prescription access, which took into account ability to get prescriptions and delay in getting prescriptions. Multiple logistic regression was used with geographic region as the main independent variable, adjusting for relevant covariates.

Results: Compared to the Northeast region, adults living in the Midwest (OR=0.56; 95% CI 0.35–0.89), South (OR=0.48; 95% CI 0.32–0.72) and West (OR=0.53; 95% CI 0.34–0.84) had significantly lower odds of reporting a USC. For the combined access measure, compared to Northeast, adults in Midwest (OR=0.60; 95% CI 0.40–0.88), South (OR=0.62; 95% CI 0.44–0.88) and West (OR=0.50; 95% CI 0.34–0.72) had significantly lower odds of medical access to care. Region was not significantly associated with the measure, compared to Northeast, adults in Midwest (OR=0.60; 95% CI 0.40–0.88), South (OR=0.56; 95% CI 0.35–0.89) and West (OR=0.56; 95% CI 0.35–0.89) had significantly lower odds of prescription access, though a significant increase in prescription access was observed over time.

Conclusions: Geographic variation in access to care among adults with kidney disease exists. Further research should investigate the necessary contextual factors, with those in the South least likely to have a USC and those in the West least likely to have overall access to care.

SA-P0920

Factors Shaping the CKD Awareness among the University Nephrology Patients

Emma Rebecca Segal,1 Colin A. Hinkamp,1 Xueron Wen,1 Ashutosh M. Shukla.1,2 1Medicine, Univ of Florida; 2NF/SG VHS, Gainesville, FL.

Background: CKD awareness is known to be poor among patients with CKD. Factors influencing this are not well understood and are a major hindrance to interventional approaches.

Methods: We conducted a cross-sectional study in a university nephrology practice, aimed to assess the effects of patient related factors on their CKD awareness. After consent, subjects were administered a survey packet that included assessment of demographics, health literacy (REALM-SF), KD-QoL, and Charlston Comorbidity Index. A novel 45-item survey was developed for a grade 5 literacy was developed after initial checks for reproducibility, to assess CKD knowledge.

Results: Preliminary findings of an ongoing study with the first 108 enrollees is presented. Participants were 67% Caucasians, 44% women, 60±17 years, had eGFR of 36±20 m/1.73m2 and renal care for 5.3±5.9 years. Majority lived in a two-person household (48%) with household income (57.7%) below the median for general population. Subjects displayed poor matricules of CKD awareness (19.6± 9.2, Range: 0-36). Univariate analyses showed CKD awareness had significant zero phase correlations with age (r=0.33, p=0.0004), eGFR (r=-0.17, p=0.04), duration of renal care (p=0.02), and AKI (r=0.19, p=0.03), but is negatively influenced by age and severity of renal dysfunction.
Results: Nearly 60% of PCPs completed the survey (n=61/105). Most (93.8%) PCPs believed the point-of-care notifications were helpful to order undue diagnostic studies (i.e. microalbuminuria) and noted that better communication among health team members would enhance the registry’s uptake. Patient focus groups suggested the ATSM system was impersonal, though easy to use; that frequent (i.e., weekly) automated calls were preferred to reinforce self-management behaviors; that content should include more dietary advice; and that the convenience of telephone (vs. in-person) health coaching was a preferred alternative. PCPs believed private contexts allow discussing mobile text messages to the program but no desire to include Skype functionality.

Conclusions: A registry is acceptable to healthcare provider teams and has the potential to enhance identification and management of CKD in safety-net primary care clinics. A telephone based CKD-SMS program is appreciated by low-income patients. Funding: NIDDK Support.

SA-PO923
Assessing Literacy Skills Related to NSAID Medication Labeling in Primary Care
Amy Barton Pai,1 Nelson Polanco,2 Mara Garfinkel,2 Verina Hansouw,2 1Univ of Michigan College of Pharmacy, Ann Arbor, MI; 2Albany College of Pharmacy and Health Sciences, Albany, NY.

Background: In primary care, NSAID prescriptions account for up to 20% of prescriptions. Both prescription (Rx) and OTC NSAIDs have medication guides and/or labeling that vaguely describe kidney risks of these products. The purpose of this study was to evaluate the performance of a medication label health literacy tool focused on NSAIDs (MedLit-NSAID).

Methods: The study recruited patients from a large primary care practice in upstate NY. The MedLit NSAID questions assess locating, calculating integrating literacy. Two MedLit-NSAID questions query participants regarding kidney risks using the FDA medication guide (for Rx) and the OTC label to answer the questions. The Newest Vital Sign (NVS) health literacy assessment tool was also administered for comparison. Participants scores were analyzed in the following strata: male/female, age <65 year, age >65 years, eGFR > or < 60 mL/min.73m2. Data on age, ethnicity, education, number and management of medications was collected.

Results: The study enrolled 145 patients (mean SDI) age 56 (15) with the majority being white and self-reporting they manage their own medications. Analysis of total MedLit-NSAID scores in the gender, age and eGFR strata showed that male participants and those with eGFR < 60 had significantly lower scores (p<0.05 for all comparisons). There was no difference in total MedLit-NSAID scores between participants aged < or > 65 years. A higher proportion of participants with eGFR < 60 vs. eGFR > 60 had some or completed high school (47% vs. 24%, respectively). Participants with eGFR < 60 scored similarly on the Rx question related to NSAIDs, however 61% incorrectly answered the OTC question compared to only 11% with eGFR >60 (p=0.01). The total NVS score was positively correlated with total MedLit-NSAID score (r=0.52).

Conclusions: There is variability in literacy related to NSAID medication labeling in the primary care setting. Literacy among those with eGFR < 60 regarding NSAIDs appears to be poor compared to people with intact kidney function. Labeling for NSAIDs should be re-evaluated and better educational initiatives should be developed. Funding: Other U.S. Government Support.

SA-PO924
Factors Affecting Medication Management among Patients with Chronic Kidney Disease
Katie E. Cardone,1 Sabrina Daoui,2 Rachid Daoui,2 Kirsten M. Donato,1 Wendy M. Parker,1 1Albany College of Pharmacy and Health Sciences, Albany, NY; 2Div of Nephrology, Saratoga Hospital, Saratoga Springs, NY.

Background: Patients with chronic kidney disease (CKD) have complex medication regimens and are at high risk for medication-related problems including non-adherence. Effective medication management strategies are required to optimize outpatient treatment of CKD and/or its underlying conditions. Few data exist regarding medication management in patients with CKD. The primary objective of this study was to identify factors affecting medication management skills and strategies in CKD.

Methods: 207 patient nephrology office were surveyed during regularly-scheduled appointments. Patients completed a series of validated survey tools, including the Short Test of Functional Health Literacy in Adults (S-TOFHLA), the Medication Adherence Rating Scale (MARS), and the Self-Efficacy for Appropriate Medication Use Scale (SEAMS). Additional questions about medication management strategies and demographic factors were also included. Correlations between demographic, health literacy and performance on medication management scales were performed using SAS.

Results: Twenty-nine patients participated. Most participants had “adequate” health literacy (S-TOFHLA). N=26 (90%) participants were adherent based on MARS and most were highly confident in their abilities to manage medications (SEAMS). Despite indicating they were organized and managing their care appropriately, nearly half (48%) indicated they forget to take their medications at times and only half (56%) indicated they ask a pharmacist questions on their medications. Aging and female gender were positively associated with use of a pill box.

Conclusions: Lessons learned from this highly literate patient population highlight opportunities to improve medication management and adherence. Medication management strategies should be explored in more diverse cohorts of patients with CKD.

Funding: Private Foundation Support.

SA-PO925
Environmental and Individual Predictors of Medication Adherence among Elderly Patients with Hypertension and Chronic Kidney Disease (CKD): A Geospatial Approach
Yun Han,1 Steven Erickson,1 R. Hirth,2 Rajiv Saran,1 Rajesh Balkrishnan.2 1U of Michigan; 2U of Virginia.

Background: Few studies have assessed geographical variation in medication adherence across different regions. This study aimed to explore local variations in medication adherence and examine environmental and individual influences on adherence to ACEIs and ARBs among elderly hypertensive CKD patients in the United States.

Methods: This retrospective cohort study utilized a linked dataset from Medicare 5% sample claim data (2006-2013), American Community Survey 5-Year Data (2005-2009) and the Primary Care Service Area (PCSA) data (2007). We included hypertensive CKD patients who were aged 67 and above, continuously enrolled in Medicare Part D and had at least one ACEIs/ARBs prescription claim. Patients’ 1-year adherence to ACEIs/ARBs was measured using Proportion of Days Covered (PDC), and then aggregated at county level. The geographically weighted regression and the linear mixed-effects models were applied to investigate the relationship between environmental, individual factors and medication adherence.

Results: Significant spatial autocorrelation was observed in ACEIs/ARBs adherence, as the West North Central and New England region had higher adherence rate than the East South Central and West South Central regions. Residing in medically underserved areas (MUAs) and a higher deprivation score were related with lower average PDC. Patients, who were female, white, enrolled in Part D Low-income-Subsidy program, having diabetes and atrial fibrillation were associated with better adherence.

Conclusions: Medication adherence is geographically differentiated across the United States. Residing in MUAs, county deprivation score, and having Part D LIS are potentially modifiable factors that could improve medication adherence. Such factors may be helpful in the design of interventions focused on improving patient outcomes. Funding: NIDDK Support.

SA-PO926
Receipt of Nephrology Care and Clinical Outcomes among Veterans with Advanced Chronic Kidney Disease
Enrica Fung,1 Tara I. Chang,1 Glenn Matthew Chertow,1 L-Chun Thomas,1 Steven M. Asch,1,2 Manjula Kurella Tamura,1,2 1Stanford Univ; 2Palo Alto VA.

Background: Clinical practice guidelines recommend referral to nephrology once estimated glomerular filtration rate falls (eGFR) below 30 mL/min/1.73m2; however evidence for benefits of nephrology care remains conflicting.

Methods: We assembled a national cohort of veterans with advanced CKD, defined by at least one eGFR <60 mL/min/1.73m2 between January 1, 2010 to December 31, 2010 and a prior eGFR <60 mL/min/1.73m2, using administrative and laboratory data from the Department of Veterans Health Affairs and the United States Renal Data System. We used landmark analysis to determine the associations among the receipt of outpatient nephrology care over a 12-month period, survival and progression to ESRD, defined as receipt of dialysis or kidney transplantation.

Results: Of 11,489 patients included in the cohort, 37.2% received nephrology care. Older age, prior hospitalization, more than 4 outpatient visits to non-nephrology providers, heart failure, dementia, cancer, depression, post-traumatic stress disorder, and rapidly declining kidney function were independently associated with the absence of nephrology care. Over a mean follow up of 1.8 years, 17.0% of patients died and 10.1% progressed to ESRD. In models adjusting for demographics, comorbidities, and trajectory of kidney function, nephrology care was associated with a lower risk for death (HR 0.85, 95% CI 0.78-0.95) but a higher risk for ESRD (HR 1.21, 95% CI 1.05-1.40). Patients who received nephrology care were more likely to have serum phosphate within recommended ranges, but less likely to have blood pressure within recommended ranges.

Conclusions: Among patients with advanced CKD, nephrology care was associated with lower mortality but did not dampen the risk for progression to ESRD. Funding: NIDDK Support, VA Support.
International Variations in the Frequency of the Types of Patient-Physician Contact for CKD Patients: Early Findings from CKDPops

Eloise Speyer,1 Benedicte Stengel,2 Koichi Asahi,3 Brian Bieber,1 Antonio Alberto Lopes,4 Ronald L. Pisoni,1 Nidhi Sukul,1 Francesca Tentori,1* Arbor Research, Ann Arbor, MI; 2UMRS 1018, Paris Sud Univ, Villejuif, France; 3Fukushima Medical University, Fukushima, Japan; 4Faculdade de Medicina da Bahia, Univ Federal da Bahia, Salvador, Brazil; 5Dept of Nephrology, Univ of Michigan, Ann Arbor, MI; 6Vanderbilt Univ, Nashville, TN.

Background: Regular patient-physician contact by multiple caregivers is recommended in CKD to manage complications and improve outcomes.

Methods: CKDPops is an ongoing prospective cohort study of patients with stage 3-5 CKD from national samples of nephrology clinics. The frequency of visits to different health care providers during the year prior the enrollment was self-reported by patients and described by country (Brazil [BR], France [FR], the United States [US]), CKD stage, and patient’s characteristics.

Results: As of May 2016, 3496 patients (mean age=67.1 [SD 12.9]; 61% male; 41% diabetics) completed a questionnaire (67% of enrolled patients). 31% of patients in BR reported that they had not seen a general practitioner in the year prior the enrollment (vs. 2-3%), while not seeing a cardiologist was more common in the US (49% vs. 32-37%). Although the proportion of patients having not seen a dietician or social worker decreased with CKD progression, it still remained high in CKD Stage 5 (59-75%, and 77-94%, respectively). Among diabetics, 32-46% according to the country, reported having not seen a diabetes doctor, and 43% in BR had not seen an ophthalmologist (vs 13-17%). Practices were similar among men and women and across age groups.

Conclusions: These early findings based on patient self-report suggest an underuse of specialist care for advanced CKD patients internationally. Additional work is needed to gain further understanding of specialist use, integration of care, and association with outcomes, which may eventually inform optimal practice.

Funding: Pharmaceutical Company Support - Abbvie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Invega, Merck, Protenum, Relypsa, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japan Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain

Family History of Kidney Disease and Diabetic Nephropathy among Remote Canadian Indigenous Peoples - Results from the FINISHED Screen/Triage/Treat Project

Stephanie Ophey,1 Paul Komenda,1 Thomas W. Ferguson,1 Navdeep Tangri,1 Caroline D. Chartrand,2 Lorraine L. McLeod,1 Audrey Gordon,1 Allison Dart,1 Claudio Rigatto,3 Barry Ad Lavallee,1* Max Rady College of Medicine, Univ of Manitoba, Winnipeg, MB, Canada; 2Diabetes Integration Project, Winnipeg, MB, Canada.

Background: Indigenous Canadians have a high prevalence of Chronic Kidney Disease (CKD). We aimed to determine the relationship between family history of kidney disease and current kidney disease status among remote Canadian Indigenous. We accomplished this using a subset of data from The First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) project, a CKD screening initiative in remote First Nations communities in Manitoba, Canada between 2012 and 2015.

Methods: An interdisciplinary team screened for CKD using both 24-hour urine albumin-to-creatinine ratio (ACR) and eGFR in 630 adults from 4 remote First Nations communities. Our primary outcome of interest was the association between reported family history of kidney disease and current diabetic nephropathy (defined as hemoglobin A1C > 6.5% and urine ACR ≥ 3mg/mmol or eGFR < 60ml/min/1.73m2) or non-diabetic nephropathy (defined as elevated urine ACR or low eGFR without elevated hemoglobin A1C).

Results: 402 of the 587 respondents provided information on family history of kidney disease (first degree relatives and grandparents). Of those with a reported family history of CKD (n = 156), 31.4% were found to have diabetic nephropathy, in comparison to 21.1% in those with no family history (p = 0.02). No statistically significant relationship was observed between family history and presence of non-diabetic nephropathy (13.5 vs. 14.2%; p=0.83).

Conclusions: Remote dwelling Indigenous Canadians have a high prevalence of CKD. Family history is a risk factor for diabetic CKD, but not for non-diabetic CKD. The high incidence of non-diabetic CKD requires further study to establish etiology and improve outcomes.

Family History of Kidney Disease in New South Wales – A Cohort Study 2000-2010

Srdjana S. Kotwal,1 Martin P. Gallagher,1 Alan Cass,2* Angela C. Webster,1* The George Inst for Global Health, Univ of Sydney, Sydney, NSW, Australia; 1Menzies School of Health Research, Darwin, NT; 2Sydney School of Public Health, The Univ of Sydney, Sydney, NSW, Australia; 1Centre for Transplant and Renal Research, Westmead Hospital, NSW, Australia.

Background: Patients with CKD have a higher mortality, but there is limited local data on how this effect differs with the use of renal replacement therapy (RRT – dialysis or transplant) and geographical remoteness. This study compares chronic kidney disease (CKD) progression and survival for hospitalised patients in NSW.

Methods: The NSW Admitted Patient Data Collection identified all patients with an ICD-10 AM code for CKD on any admission between 1/7/2000 and 30/7/2010. Patients were linked to the death registry and ANZDATA. We defined RRT using the ANZDATA Registry and rural status using residential postcode and by ARIA scores. Competitive risk regression was conducted comparing rural versus urban populations.

Results: 165,901 people with CKD were admitted to hospital in NSW (982,887 patient years) and had a median follow up of 6.3 years. 16.0% (n=26,412) of patients lived rurally. During the study follow up period, 6285 (4.2%) people received RRT and 85163 (51.3%) died. Of those that received RRT, 1027 (3.9%) were rural and 5868 (4.2%; p=0.02) were urban. Of those that received RRT, 2979 (43.1%) died by the end of the study compared to 82,190 (51.7%) of those that did not receive RRT (p=0.001). Competitive risk regression showed minimal difference in the risk of receiving RRT between rural and urban residents (HR 0.9395%CI 0.837-1.0; p=0.04).

Conclusions: The presence of ICD-10 codes for CKD in administrative data is associated with very high mortality, greater than that seen in dialysis patients. The frequency of CKD codes and the subsequent mortality far outstrips the burden of requirement for RRT. Further exploration of stages of CKD, differences in baseline characteristics will enhance understanding further.
SA-PO931

Engaging Kidney Disease Patients and Family Members as Co-Investigators in Patient Centered Outcomes Research

Tori Brown,1 Gary Green,2 Katrina Lang-Lindsay,1 Patti Ephraim,1 Patty Danielson,3 Suzanne Ruff,1 Holly St. Clair,1 Lana Schmidt,1 Amy Swoboda,1 Peter Woods,1 Tara Smith Strigo,1 L. Ebony Boulware.1 1College of Social Work, Univ of South Carolina, Columbia, SC; 2American Association of Kidney Patients, Tampa, FL; 3Univ of Mississippi, Jackson, MS; 4Johns Hopkins Univ, Baltimore, MD; 5Patient with Kidney Disease; 6Family Member; 7School of Medicine, Duke Univ.

Background: While often patients and family members are engaged peripherally in patient centered outcomes research (PCOR), our novel model includes them as fully engaged co-Investigators in a currently funded Patient-Centered Outcomes Research Institute (PCORI) kidney disease clinical trial.

Methods: Patients and family members partnered with researchers to develop an intervention, establish outcomes and write a PCORI proposal. We transcribed our meeting discussions, identified common themes, and refined our ideas prior to funding.

Results: Patients and family members were leading participants in all pre-award discussions and contributed to more than 5 major study design revisions. The study intervention evolved from a simple education program into a comprehensive health system intervention including provider tools and educational, behavioral, and psychosocial support for patients to improve kidney care. Patients and family members identified their most important research outcomes as: control, empowerment, acceptance, grief, anxiety, depression and CKD knowledge. Patients and family members are active and full co-Investigators on this project. They meet at least monthly with all investigators, provide feedback on all components of the study protocol, revise all recruitment and communications materials, and ensure all aspects of the intervention respond to patient and family members' needs.

Conclusions: Patients and family members can be fully engaged in research projects, thereby substantially improving the relevance and quality of PCOR studies. Our example could serve as a model to improve kidney disease PCOR studies and outcomes.

Funding: Other U.S. Government Support

SA-PO932

Can-SOLVE CKD: A Pan-Canadian Patient-Oriented Research Network

Adriana Lev simplified,1 Braden J. Manns,2 Mila Tang,3 Helen Chiu,2 Heather A. Harris.4 1Dept of Medicine, UBC; 2PHCRI, BC; 3Dept of Medicine & Community Health Sciences, U of Calgary, AB.

Background: The optimal conduct of patient-oriented research (POR), a priority for many research funding agencies, is uncertain. The Canadian nephrology community has been working for 4 years to develop an integrated POR network—Canadians Seeking Solutions and Innovations to Overcome (Can-SOLVE) CKD. The network’s vision: By 2020, every Canadian with, or at high risk for CKD will receive the best recommended care, experience optimal outcomes and have the opportunity to participate in studies with novel therapies, regardless of age, sex, gender, location or ethnicity.

Methods: Using James Lind Alliance methodology and workgroups including patients and policy-makers, we identified the top research questions for early and advanced CKD.

Results: A research program with 3 themes and 19 projects spanning basic science, clinical and population health research was formed. National core infrastructure resources were developed.

Conclusions: Can-SOLVE CKD is a novel POR network, aimed at overcoming challenges and obliterating the translation of discoveries and clinical trials and uptake of evidence into practice. Lessons learned can be shared with researchers from other countries seeking to partner with patients in research.

Funding: Government Support - Non-U.S.

SA-PO933

Multi-Disciplinary Care Is Cost-Effective in Chronic Kidney Disease

Eugene Lin1, Glenn Matthew Cherton,2 Jeremy D. Goldhaber-Fiebert.2 1Internal Medicine - Nephrology, Stanford Univ; 2Centers for Health Policy and Primary Care and Outcomes Research, Stanford Univ.

Background: End-stage renal disease (ESRD) accounts for 5.6% of total Medicare expenditures, though patients on dialysis make up 1.6% of its beneficiaries. Multi-disciplinary care (MDC) has been proposed as a way to mitigate the morbidity and costs associated with the transition from chronic kidney disease (CKD) to ESRD.

Methods: To evaluate the cost-effectiveness of MDC relative to usual care, we developed a Markov model of progression from CKD to ESRD. Unlike previous models, ours recognizes patient heterogeneity. We assumed that CKD progression depended on age, gender, CKD stage, and level of albuminuria. We calibrated progression probabilities to published data on risks of death and of developing ESRD. The cost-effectiveness analysis adopted the Medicare payer perspective. Using data from a recent systematic review, the model assumes that MDC decreased mortality rates by 15% and progression rates to ESRD by 55%. We modeled a typical MDC program which involved four nurse practitioner (NP) visits per year. We obtained ESRD mortality rates and costs from the United States Renal Data System (USRDS). Sensitivity analyses focused on potentially lower efficiency and higher costs of MDC and on clinical characteristics of the target CKD population.

Results: Compared to usual care, MDC costs $24,613 per QALY gained. MDC remained below $35,000 per QALY gained over a wide range of severities of CKD (from stage 3 to 5), ages (25 to 75 years), and albuminuria (100 mg/g to 1000 mg/g). Cost-effectiveness estimates were robust to changes in the efficiency of MDC. An MDC program that decreased mortality and progression rates by only 2% cost $84,916 per QALY gained. Likewise, an expensive MDC program of 12 NP visits a year cost $44,285 per QALY gained.

Conclusions: Even if deployed inefficiently, MDC programs would likely be cost-effective in CKD patients in the United States.

Funding: NIDDK Support

SA-PO934

The Cost-Effectiveness of Community Health Workers: A Chronic Kidney Disease Markov Model

David N. van der Goes,2 John P. Ney,2 Rajan I. Parmara,3 Kristine Nichol,4 P.P. Mark L. Unruh.2 2Dept of Economics, Univ of New Mexico, Albuquerque, NM; 3Dept of Neurology, Boston Univ, Boston, MA; 4Dept of Internal Medicine, Univ of New Mexico, Albuquerque, NM.

Background: Given the rise in rate of CKD and the increase in number of Americans over 60, there is a clear need to improve outcomes for patients with CKD earlier in the disease; early intervention may be the answer. We explore the use of community health workers (CHW) as an add-on intervention for patients with Stage 3 CKD and Stage 4 CKD to reduce costs and enhance quality of life by slowing the rate of progression and increasing the interval between diagnosis of CKD and ESRD. CHWs and care coordinators have been shown to be effective in educating patients about both their health state and the health care system.

Methods: We constructed a six health state cost-utility Markov model: 1) CKD 3a, 2) CKD 3b, 3) CKD4, 4) ESRD, 5) Transplant, and 6) Death to compare the current standard of care to CHWs. We use payer (Medicare) perspective and lifetime time horizon. We estimate transition probabilities and costs from publicly available data. Our CHW program is theoretical and its impacts are based on the current literature. We ran a baseline model and evaluate uncertainty through probabilistic sensitivity analysis.

Results: The model shows that CHWs reduce costs and improve quality of life. CHWs reduce lifetime costs by about 1 percent and increase quality adjusted life years (QALY) by about 1% compared to current standard of care. The model is most sensitive to, in order, the cost of dialysis, the cost of Stage 4 CKD, and CHW program costs.

Conclusions: Adding CHWs to standard care would reduce costs and improve quality of life for patients with CKD. CHWs should be considered as part of the CKD care team.

Funding: Private Foundation Support

SA-PO935

Posttraumatic Stress Disorder and Mortality in Veterans with Advanced CKD: A Transition of Care in CKD Study

Eliana Streja1, Melissa Soochoo1, Jolene L. Chen1, Daniel L. Gillen1, K. K. Kovesdy2, Kamyar Kalantar-Zadeh1,1 UC Irvine; 2Univ of Tenn.; 3VA Long Beach.

Background: End stage renal disease (ESRD) patients with long dialysis treatment often experience worse mental health and quality of life. It is not known whether posttraumatic stress disorder (PTSD) has any impact on outcomes in these patients. A previous study in veterans showed that late-life PTSD was associated with increased cardiovascular (CV) disease, yet the association of PTSD and outcomes remains unknown in veterans who transition to ESRD.

Methods: We investigated a cohort of 34,681 US veterans who initiated dialysis between 10/2007-9/2011 and utilized the VA healthcare system. We used Cox proportional

Conclusions: PTSD increases mortality risk in veterans with advanced CKD. Future studies should explore the impact of PTSD on health outcomes and the reasons for this association.

Funding: Other U.S. Government Support
Methods: We conducted a prospective multinational, cross-sectional study involving 1309 women followed at 8 centers. Individual domains of sexual dysfunction were assessed using the self-reported Female Sexual Function Index (FSFI). Women provided responses anonymously with lower scores in each domain representing greater sexual dysfunction. The individual domain scores were then totaled and multiplied by a predetermined factor to weigh each domain equally. Correlates of each domain were identified using stepwise multivariable linear regression analysis. Sensitivity analyses considered women who reported being sexually active.

Results: Of 1309 enrolled women, 659 (50.3%) provided complete response to FSFI scale. Thirty and 35% responded sexually and actively, respectively. Most respondents reported either no sexual activity or high sexual dysfunction in all measured domains (organism 75.1%; arousal 64.6%; lubrication 63.3%; pain 60.7%; satisfaction 60.1%; and sexual desire 58.0%). Respondents who were waitlisted for a kidney transplant reported scores consistent with less sexual dysfunction, while respondents who considered older respondents reported scores consistent with greater dysfunction. The presence of depression was associated with worse lubrication and pain scores [mean difference for depressed versus non-depressed women (95% CI) -0.42 (±0.73 to -0.11), -0.53 (±0.89 to -0.16), respectively] while women who had experienced a previous cardiovascular event reported higher pain scores [0.77 (±1.40 to -0.13)].

Conclusions: Women with ESKD report marked sexual dysfunction across a range of domains, which appear to be associated with medical comorbidity.

SA-PO938
The Association of Albuminuria and Kidney Dysfunction with the Risk of the Major Dementia Subtypes in a Japanese Community-Based Population
The Hisayama Study
Keita Takahashi,1 Jun Hatada,1 Tomoyuki Ohara,1 Masaharu Nagata,2 Kazuhiro Tsunyui,3 Takakase Kitaizono,4 Yutaka Kiyohara,2 Toshikazu Ninomiya.1 1Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 2Skin-ekiai Hospital, Kitakyushu, Fukuoka, Japan; 3Hisayama Research Inst for Lifestyle Diseases, Fukuoka, Japan.

Background: Several prospective studies have reported that albuminuria and kidney dysfunction are both risk factors for cognitive impairment and dementia. However, few studies have assessed this issue among patients undergoing hemodialysis (HD). Therefore, we investigate the association of albuminuria with dementia and the subtypes of dementia in HD patients.

Methods: A total of 1,651 community-dwelling Japanese subjects aged ≥60 years without dementia were followed for 10 years. The hazard ratios (HRs) for the development of all-cause dementia and its subtypes, namely, Alzheimer’s disease (AD), and vascular dementia (VaD), were estimated according to the levels of urine albumin-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) using a Cox proportional hazards model.

Results: During the follow-up, 358 subjects developed all-cause dementia (238 ADs and 120 Vadas). Compared with those with UACR ≤6.9 mg/g, multivariable-adjusted HRs (95% confidence intervals [CI]) for the development of all-cause dementia were 1.12 (0.78-1.61), 1.64 (1.17-2.30), and 1.5 (1.02-2.17) in subjects with UACR of 7.0-12.7, 12.8-29.9, and ≥30.0 mg/g, respectively, after adjustment for age, sex, educational level, history of stroke, systolic blood pressure, anti-hypertensive treatment, diabetes, total cholesterol, body mass index, eGFR, smoking habits, alcohol intake, and regular exercise. Likewise, higher albuminuria levels were associated with greater adjusted risks of AD [HR [95% CI]: 1.22 (0.79-1.89), 1.74 (1.15-2.63), and 1.57 (1.03-2.40), respectively] and VaD [HR [95% CI]: 1.03 (0.46-2.29), 1.94 (0.96-3.95), and 2.19 (1.10-4.38), respectively]. However, kidney dysfunction (eGFR ≤60 mL/min/1.73 m2) was not associated with the development of AD or VaD after adjustment for confounding factors.

Conclusions: Albuminuria is a significant risk factor for the development of both AD and VaD, but kidney dysfunction was not in a Japanese community-based population.

SA-PO939
Renal Metabolic Factors and MRI Findings in CKD: The BRain IN Kidney Disease Study
Anne Murray,1 Yelena Sinlin,1 Cynthia S. Davey,2 Prachanthi Venmuri,3 Hennepin County Medical Center, Minneapolis, MN; 2Mayo Clinic, Rochester, MN; 3Univ of Minnesota, Minneapolis, MN.

Background: The extent that renal metabolic factors beyond eGFR contribute to the recognized increased risk of MRI pathology in CKD patients has not been adequately measured. We previously identified elevated phosphorus, anemia, and low cholesterol as factors associated with cognitive impairment in our BRain IN Kidney Disease (BRINK) study cohort.

Methods: We included non- dialysis BRINK CKD participants with eGFR <60 mL/min/1.73 m2. We assessed the cross- sectional relation between baseline hemoglobin, serum phosphorus, and cholesterol and baseline brain MRI outcomes using linear regression models adjusted for age, gender, race, education, eGFR, stroke and diabetes. All MRI scans were acquired on a 1.5 T Philips Ingenia scanner. We used structural MRI (MPRAGE), to measure gray matter regional cortical thickness, FLAIR to measure cerebrovascular disease, T2* GRE imaging for microhemorrhage, and diffusion tensor imaging (DTI) for microstructural changes.

Conclusions: Men 166 CKD BRINK patients with baseline MRI were included in analyses: mean age = 70, mean eGFR = 32.4 (± 10.4), 8.4% Black race, mean education 14.2 years, 48% with diabetes, 15% previous stroke, mean phosphorous 3.6 (± 0.7) mg/dL, mean hemoglobin 12.9 (±1.8) g/dL, and mean cholesterol 176 (± 44) mg/dL. Lower hemoglobin (<1 mg/dL) was associated with a lower occipital thickness (± 0.04 [0.02], P = 0.025), parietal thickness (± 0.08 [0.04], P = 0.027), and mean whole brain cortical thickness (± 0.014 [0.01], P = 0.045) and with (b) higher DTI medial diffusivity in the gray matter temporal lobe (5.5 [2.3], P = 0.021) and white matter occipital lobe (3.5 [1.7], P = 0.043). Higher phosphorus (1 mg/ dL) was associated with increased subcortical infarcts (0.21 [0.09], P = 0.025).

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

849A
Conclusions: We identified anemia and elevated phosphorus as potential mechanisms of GFR pathology in CKD, but 3 year follow up MRIs are needed to confirm these results and their association with cognitive impairment.

SA-PO940

Association between Brain Magnetic Resonance Imaging Pathology and Cognitive Performance in Patients Receiving Maintenance Hemodialysis

David A. Drew, 1 Rafeeqe Bhadelia, 2 Hocine Tighiouart, 1 Tammy Scott, 1 Sarah M. Duncan, 1 Daniel E. Weiner, 1 Mark J. Sarnak, 1 Tufis; 2BDMC.

Background: Although hemodialysis (HD) patients have high rates of clinical stroke and cognitive impairment, there are limited data on the association between subclinical structural brain pathology and cognitive function.

Methods: In the Boston Dialysis Study, we obtained brain magnetic resonance imaging (MRI) in 45 HD patients hospitalized in the clinical history of stroke. We assessed the severity of white matter disease and cerebral atrophy and presence of subclinical infarcts using a semi-quantitative scale (0 to 9) and determined hippocampal size (0 to 3) as well as prevalence of small and large vessel infarcts. A comprehensive battery of cognitive tests was administered, with individual test results reduced into two summary scores, representing memory and executive function. Summary scores have a mean of zero and standard deviation of one. Using multiple linear regression, we determined the association between each MRI finding and summary scores, adjusting for demographics, education, vascular access type, and history of cardiovascular disease.

Results: Mean age (SD) was 55 (17) years, with 50% women, 43% African American, 49% with at least some college education, and median dialysis vintage (25% – 75% ) of 20 months (7 – 39). Both greater ventricular and hippocampal atrophy were associated with worse memory and executive function, whereas white matter lesions were non-significant in fully adjusted analyses. More severe white matter disease, cerebral atrophy and presence of subclinical infarcts were all associated with worse executive function. After adjustment, sulcal prominence remained significant, while ventricular prominence showed a trend.

Conclusions: Structural brain pathology in patients treated with hemodialysis is associated with worse cognitive function. Demographics, including age and cardiovascular disease may in part explain these associations.

Funding: NIDDK Support, VA Foundation Support

SA-PO941

Chronic Kidney Disease in Patients with Alzheimer Disease

Wiesława Janczak, Jolanta Malszykso. 2nd Dept Nephrology, Medical Univ, Białystok, Poland.

Background: Elderly people suffer from physiological or pathological ageing. The prevalence of both dementia and CKD increases in age above 65 years. It is important to assess CKD prevalence in elderly patients with dementia.

Methods: We analyzed retrospectively a group of n=188 elderly (aged 80.6 years) persons, with Alzheimer disease hospitalized in Geriatric Department, Medical University of Bialystok, Poland. Renal function was evaluated using three different formulas: CKD-EPI, MDRD and CKD-EPI. MDRD. All of the patients have normal creatinine according to the hospital central laboratory (IDMS validated Jaffie method). Neurocognitive functions had been tested with use of Mini-Mental State Examination (MMSE). For all of selected patients MMSE score was less than 24.

Results: For analyzed group with Alzheimer disease obtained mean value of eGFR/ creatinine was different depending on evaluation method.

<table>
<thead>
<tr>
<th>Method</th>
<th>eGFR ml/min/1.73m²</th>
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<tbody>
<tr>
<td>CKD-EPI</td>
<td>60.38</td>
</tr>
<tr>
<td>MDRD</td>
<td>62.38</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>56.39</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>59.39</td>
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Mean serum creatinine in the studied group was 1.01 mg/dl. CKD was defined when level of eGFR was less than 60ml/min/1.73m² and it was diagnosed in 81.38% of the group according to CG, in 43.62% according to MDRD and in 54.79% according to CKD-EPI.

Conclusions: CKD frequently occurs among group of elderly people with Alzheimer disease. However it is determined for different percentage of the group depending on estimation method (CKD-EPI, C-G, MDRD). This may lead to uncertainty of diagnosis for some patients. As patient with Alzheimer disease hardly cooperates, it is important to emphasize the presence of impaired kidney function on patient’s and caregiver’s education on renal function and its consequences. The difference between CG and other two formulas may be due to nutrition status and body mass. Assessment of kidney function is of utmost importance for drug dosing, as they are subjected for polypharmacy.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.

850A

SA-PO942

Depressive Symptoms and Cognitive Impairment in Adults with Chronic Kidney Disease

Michael J. Fischel, 1 Dawei Xie, 2 Melissa Lamar, 1 Qiang Pan, 2 Lydia Buzzano, 4 Alan S. Go, 1 Edward J. Horwitz, 8 Manjula Kurella Tamura, 2 Eva Lustigova, 6 Akiniolu O. Ojo, 1 Ana C. Ricardo, 1 Stephen L. Seliger, 4 Jonathan J. Tallierco, 2 Kristine Yaffe, 1 James P. Lash, 1 U. Illinois; 2 Penn; 3UC Irvine; 4Kaiser Permanente; 5MetroHealth; 6 U. Michigan; 7 U. Maryland; 8 Cleveland Clinic.

Background: Depression and cognitive impairment are common in adults with chronic kidney disease (CKD), and are associated with worse health outcomes. While the relationship between depression and cognitive impairment has been studied in end-stage renal disease, it has not been examined in earlier stages of CKD.

Methods: We conducted cross-sectional and longitudinal analyses of depressive symptoms and cognitive function among adult participants with CKD in the prospective multicenter Chronic Kidney Insufficiency Cohort (CRIC) Study. Elevated DS were defined by a Beck Depression Inventory (BDI) score > 11. Global cognitive function was assessed by the Modified Mini-Mental State Exam (3MS) where scores range 1-100. At baseline, linear regression was used to examine the relationship between elevated DS and 3MS scores. During follow up, mixed linear models were used to evaluate the relationship between baseline elevated DS and change in 3MS scores over time. All analyses were adjusted for center, sociodemographic, comorbidity, laboratory, kidney function, and proteinuria covariates.

Results: Among 3863 adults with CKD, 27% had elevated DS at baseline. Mean (SD) 3MS score was 89.4 (0.3) and 92.3 (0.2) in those with and without elevated DS, respectively (p < 0.0001). In fully adjusted analyses, mean 3MS score was significantly lower among those with elevated DS [beta coefficient = -0.81 (-1.34 to -0.29) at baseline. During a median follow up of 5.9 years, the overall mean annual change in 3MS score was -0.03. In fully adjusted analyses, the relation between elevated DS and change in 3MS score over time was not significant (p=0.92).

Conclusions: In a large adult cohort with CKD, elevated depressive symptoms are independently associated with worse cognitive function at baseline but not with changes in cognitive function over time. Whether treatment of depression leads to improvement in cognitive function warrants further study.

Funding: NIDDK Support, VA Support

SA-PO943

Depression and Suicidal Ideation Is Associated with Renal Function in Predialysis Chronic Kidney Disease Patients

Hae-Ryeong Yoon, Jong Hyun Bae, Min-Uk Cha, Hyoun-Seung Kim, Seung-Hyun Han. Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Depression including suicidal ideation is prevalent mental health problems in patients with end-stage renal disease (ESRD). Uremia related factors have been suggested as causes of this increased prevalence in ESRD patients. Although uremic toxicity is known to be increased even in early chronic kidney disease (CKD) patients, the relationship between depression and renal function is not well elucidated. Therefore, the association between renal function and depressive symptoms including suicidal ideation was investigated in predialysis patients with CKD.

Methods: Subjects who participated in the Korean National Health and Nutritional Examination Survey (KNHANES) from 2010 to 2014 were evaluated. Subjects younger than 18 years old or older than 75 years and CKD stage 5 patients were excluded. Depression was screened using the Korean version questionnaire. Suicidal ideation was assessed by a positive answer to the question ‘In the last 12 months, have you ever thought about committing suicide?’.

Results: In a large diverse adult cohort with CKD, elevated depressive symptoms were independently associated with worse cognitive function at baseline but not with changes in cognitive function over time. Whether treatment of depression leads to improvement in cognitive function warrants further study.

Funding: NIDDK Support, VA Support

SA-PO944

Qualitative Study of Coping Strategies Used by Patients with Advanced Kidney Disease

Lalita Subramanian, 1 Martha Quinn, 1 Junhui Zhao, 1 Jarcy Zee, 1 Laurie Lachance, 2 Francesca Tentori, 1, 3 "Arbor Research Collaborative for Health, Ann Arbor, MI; 4 "The Center for Managing Chronic Disease, Univ of Michigan, Ann Arbor, MI; 5 "Vanderbilt Univ Medical Center.

Background: Chronic kidney disease (CKD) and its treatments impact patients’ physical and mental health, as well as identity, lifestyle and relationships. Strategies used by patients to cope with these are not well elucidated. Data from the Empowering Patients on Choices for Renal Replacement Therapy (EPOCH-RRT) Study were used to explore coping strategies.

Methods: CKD patients with eGFR <25 ml/min/1.73 m² were interviewed in 2013, using a protocol developed in collaboration with patients, caregivers and healthcare

Funding: Government Support - Non-U.S.

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

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Conclusions: CKD patients use a variety of coping strategies to deal with their disease. Some strategies were more commonly reported according to the stage of disease and treatment type. Overall, engagement strategies were more diverse and more frequently cited than disengagement strategies. Awareness of effective coping strategies used by others could improve coping and result in better health outcomes for CKD patients.

Funding: Private Foundation Support

SA-PO945

Physical Activity Level Impacts Quality of Life in Patients with CKD

Mai Ot-s-Rosenberg, Jana Uhlinova, Ulle Pechter.

Background: The aim was to investigate the relationship between the main lifestyle-related factor, physical activity (PA) and health-related quality of life (HRQoL) in a samples of patients (pts) with chronic kidney disease (CKD), with chronic conditions (CC) and controls. This is, we analyzed differences in PA levels between CKD and CC pts (p = 0.1642); CKD pts and controls (p = 0.5494); CKD pts and patients using Renadyl™; a Pro/Prebiotic dietary supplement

Methods: A cross-sectional study was conducted on 1006 pts (322 male and 684 female pts, age range 18.9–89.1 years) recruited at primary health care centers and the university hospital. The patient’s age, self-reported smoking status and BMI were used as independent variables to predict PA level. The study was approved by the Ethics Committee. The main outcome measure was HRQoL, assessed with the KDQOL-SF TM1.3 (modified by removing dialysis questions and adding symptoms related factor, physical activity and health-related quality of life (HRQoL). Reduced internal (resilience) and external (emotional support) resources were significantly predicted, adjusting for temporal and patient level factors.

Results:

Conclusions: Physical Activity Level Impacts Life Quality in Patients with CKD.

Funding: Private Foundation Support

SA-PO946

Membranous Nephropathy (MN): Baseline Health Related Quality of Life (HRQOL) in Patients with Severe Nephrotic Syndrome (SNS) in the Membranous Nephropathy Trial of Rituximab (MENTOR) Trial Group.

Background: HRQOL is an important patient reported outcome compromised in people with kidney failure. MN with SNS has potential physical and emotional consequences for patients but its impact on HRQOL has not been studied.

Methods: Baseline HRQOL data were collected from 130 patients (77% male; age 52 ± 12.5 years) with MN and SNS (Uroporin 10.4 g/m² ± 4.7; CrCl 89.6 ± 32.7 mL/min/1.73 m²; BSA 26.4 ± 5.0g/dL) participating in MENTOR. HRQOL was measured with the KDQOL-SF™1.3 (modified by removing dialysis questions and adding symptoms related factor, physical activity and treatment type. Overall, engagement strategies were more diverse and more frequently cited than disengagement strategies. Awareness of effective coping strategies used by others could improve coping and result in better health outcomes for CKD patients.

Conclusions: Kidney disease and overall health. Women and those with worsening kidney function are at particular risk for poor physical functioning. Given the association between HRQOL and clinical outcomes (e.g. morbidity and mortality), it is essential for clinicians to assess the impact of MN on HRQOL and to develop strategies to help patients minimize the burden of their disease.

Funding: Pharmaceutical Company Support - Genentech, Private Foundation Support

SA-PO947

Quality of Life Progression during Dialysis Initiation

Harley Meirovich, Daniel Herz, Garvil Hercz.

Background: Dialysis initiation is associated with emotional distress and poorer quality of life (QOL). Reduced internal (resilience) and external (emotional support) resources may predict which patients are at greater risk of QOL decline.

Methods: This prospective enrolment study assessed QOL parameters (see below) in relation to Connor-Davidson Resilience Scale and Emotional Support scores at 3 time points: 12 weeks before dialysis initiation, ± 183 days prior to dialysis initiation, and 18 ± 13 days after dialysis initiation. The repeated QOL measurements were analyzed using a longitudinal mixed effects model with either resiliency or emotional support, at enrolment, included as independent predictors, adjusting for temporal and patient level factors.

Results: In the 49 patients who successfully completed the three QOL assessments, the resiliency and emotional support scores were 84.7 ± 9.2 (score range 0-100), and 44.7 ± 21.0 (score range 0-60), respectively. All QOL parameters tended to drop significantly with the initiation of dialysis, and then rising towards baseline at the last assessment. Resiliency and emotional support had a strong positive association with nearly all the QOL parameters included in this study before, during, and after dialysis initiation.

Funding: Private Foundation Support

SA-PO948

Survey Questionnaire on Improved Quality of Life (QoL) in Chronic Kidney Disease (CKD) Patients with One or More Co-Morbid Conditions Using Renadyl™, a Prebiotic Dietary Supplement

Natarajan Ranganathan,1 Usha N. Vyas,1 Pari Ranganathan,1 Henry I. D’Silva,2 Bohdan Pechenyak,2 Alan D. Weinberg,1 Kibow Biotech Inc, Newtoun Square, PA; Temple Univ School of Medicine, Philadelphia, PA; Mount Sinai School of Medicine, New York, NY.

Background: Probiotics and Prebiotics are widely used for digestive and immune health. Recent scientific advances, in the field of “Gut Microbiome” and its modulation using Probiotics beyond gut health is growing in various diseases including gut-brain connection and gut-kidney connection. Renadyl™; a Pro-Prebiotic dietary supplement has demonstrated its potential to reduce serum uremic toxins in a pharma like validation with in vitro and clinical studies in animals and humans. This case study aimed to collect information on QOL and health status through modulation of gut microbiome in CKD patients using Renadyl™.

Methods: 834 patients using Renadyl™ were sent survey questionnaires. Results were analyzed using SAS V9.2 and MS Excel.

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

Underline represents presenting author.
SA-PO94 Differences in Patient and Renal Provider Assessment of Physical Symptoms, Quality of Life, General Health, and Depressive Symptoms in Chronic Kidney Disease

Fredric Finkelstein,1 Juan Calderon,1 Alan S. Kliger,2 Bridget A. Forbes,2 Monica Cimini,3 *Nephrology, Yale School of Medicine, New Haven, CT; 2Metabolism Associates, New Haven, CT.

Background: Wide discrepancies in symptom burden perception between dialysis patients and their renal providers have been previously well documented. This can result in significant undertreatment of dialysis patients’ symptoms. Providers’ ability to recognize physical symptoms (PS) and perceptions on general health (GH) and quality of life (QoL) in patients with chronic kidney disease (CKD) has not been studied yet. The aim of this study is to examine the degree of patient-provider concordance in terms of their perceptions of PS, GH, and QoL in patients with CKD.

Methods: A standardized questionnaire was administered synchronously to each patient and the treating renal provider at the time of their routine clinic appointment. The survey was comprised of eighteen questions addressing PS, overall GH and QoL. We used a Likert scale to grade severity of symptoms. We compared the net sum of all rated physical symptoms, PHQ2 score, GH and QoL between patients and providers and analyzed discrepancies based on CKD stages.

Results: A total of eighty patients and providers completed the survey. Providers underscored severity of PS in 27% of cases and overscored them in 18% of cases. Net sum of PS severity across the entire sample was 1150 points for providers versus 1301 points for patients. Agreement in severity of physical symptoms occurred in 55% of cases. Underrecognition of PS was highest at stage 5. The percentage of concordance when assessing perception of GH was 34%, with highest percentage of concordance in advanced stages of CKD. For QoL analysis, providers underestimated their patients QoL in 36% of cases. QoL had discordant scores in only 44% of cases.

Conclusions: Underrecognition of the severity of PS and underestimation of perception of quality of life in CKD patients by renal providers, particularly in more advanced CKD, is problematic. In contrast, both providers and patients’ perception of general health have increased concordance, particularly at more advanced CKD stages.

SA-PO950 Is Caregiver Burden Associated with Chronic Kidney Disease (CKD) Patients’ Quality of Life? Tara Linhpat, Khaled Iskandarani, Nasrollah Ghahramani. Penn State College of Medicine, Hershey, PA.

Background: The kidney disease quality of life 36 (KDQOL36) is an instrument developed to measure several components related to the quality of life of patients with CKD. The KDQOL36 survey was used to assess caregiver burden. The aim of this study was to investigate whether caregiver burden indicated by BIS total score is associated with patients’ quality of life components as measured by the KDQOL36.

Methods: Stage 4 and 5 CKD patients were paired/ matched to a caregiver. The patients completed the KDQOL36 instrument, while their respective caregivers completed the BIS. A multivariable linear regression model of caregiver BIS total score predicted by caregiver burden. The aim of this study is to examine the degree of patient-provider concordance in terms of their perceptions of PS, GH, and QoL in patients with CKD.

Results: The sample consisted of 62 patient-caregiver pairs. Lower scores indicating worse performance on the KDQOL36 subscales with the exception of physical components were statistically significantly associated with higher scores on the BIS, indicating increased caregiver burden.

Conclusions: Caregiver burden is associated with CKD patients’ quality of life, whereby improvements in the patients’ quality of life reduce caregiver burden.

Funding Disclosure: Dr. Nasrollah Ghahramani is funded by CDR-1310-07055 from the Patient-Centered Outcomes Research Institute (PCORI).

Funding: Other U.S. Government Support

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

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SA-PO951 Peer Mentoring for Patients with Chronic Kidney Disease and Their Caregivers: A Qualitative Study

Tara Liaiglehat, Eugene Lengerich, Nasrollah Ghahramani, Jennifer Kraschnewski. Penn State College of Medicine.

Background: Peer mentorship may enhance patient engagement for those with advanced chronic kidney disease (CKD) (stages 4 and 5); yet, the approaches and qualities (i.e., online vs in-person) that make a good mentor are unclear. This study sought to describe these qualities by conducting focus groups with mentees from the mentorship program in a randomized peer-education study.

Methods: Seven focus group meetings were conducted with mentees (n=20). Mentees were patients with advanced CKD and their caregivers who were matched with trained peer and caregiver peer mentors for in-person or online mentorships. Meetings were audio-recorded, transcribed, and thematically analyzed by three facilitators who concurred with the significant results.

Results: Three important themes emerged, which were: (1) in-person meetings felt more meaningful than phone or online communication; (2) more than phone or online communication; (3) more than phone or online communication; (4) more than phone or online communication; (5) good mentors were relatable and good listeners: “They have to be a caring person about other people. Be able to relate. I guess they can relate because they are in the same predicament or already was in that predicament... a good listener too.”; and (3) mentorship program provided support: “It changed a whole lot. Him giving me support and also outside my family... so that’s been a big positive change for me. A lot of support for the last year and a half since I started.”

Conclusions: A mentorship program for patients with advanced CKD may provide them with substantial support, particularly when mentorship is conducted in-person and the mentor is relatable, empathetic listener. Funding Disclosure: Dr. Nasrollah Ghahramani is funded by CDR-1310-07055 from the Patient-Centered Outcomes Research Institute (PCORI).

Funding: Other U.S. Government Support

SA-PO952 Assessment of Quality of Life in Children with Chronic Kidney Disease Based on First 5 Years Data of the Pediatric CKD Cohort

Hyun Choo,1 Hee Sun Baek,2 Il-Soo Ha,3 Hee Gyoung Kang,4 Hee Il Cheong,5 Hyun-Jin Choi,2 Young Soon Park,3 Jooh Neo Lee,5 Heeyeon Cho,4 Jae Il Shin,5 Kyoungh Hee Han,6 Seong Heon Kim.1 Pediatrics, Kyungpook National Univ Children’s Hospital; 2Seoul National Univ Children’s Hospital; 3Asan Medical Center Children’s Hospital; 4Samsung Medical Center; 5Severance Children’s Hospital; 6Jeju Univ Hospital; Pusan National Univ Children’s Hospital.

Background: Quality of life (QOL) is an essential subject in children with chronic kidney disease (CKD) and their family. In Korea, a 10-year longitudinal study on the patient and renal survival by specific cause of CKD (KNOW-CKD study) has been pursued from 2011 and pediatric cohort is one of subgroups in the groups of KNOW-CKD study. Methods: We performed a cross-sectional investigation of QOL in children with CKD (Pediatric cohort) using the PedsQL 4.0 Generic Core Scale Module. During 5 years, total 381 pediatric patients with CKD aged 2-18 year old were enrolled from five Korean university hospitals.

Results: The male to female ratio was 295:122 and mean age was 10.1 years old. According to CKD staging, patients were distributed as follows; stage I 72, stage II 75, stage III 124, stage IV 67, stage V 43. Patients with higher CKD stage had significantly lower QOL score in all domains of the parent-proxy reports, but not child-self reports. According to gender, boys had a tendency to present better QOL than girls in the child-self reports, especially in emotional functioning, psychosocial health summary score and total score, but, in the parent-proxy reports, there was no significant difference between these two groups. Age discrepancy was not a significant factor to decide QOL in children with CKD. In addition, there was significant difference between parent-proxy reports and child-self reports and QOL scores in the child-self reports was significantly higher than in the parent-proxy reports.

Conclusions: Residual renal function and gender in children with CKD can be important factors to decide QOL, but there was a significant difference of these results between parent-proxy and child-self reports. Therefore, we need systemic, individualized supporting tools to improve QOL of children with CKD and their families.

Funding: Government Support - Non-U.S.
Exercise and Physical Function in Patients with CKD: The Mediating Role

SA-PO955

Collecting Patient Reported Outcomes in Chronic Kidney Disease: The UK Renal Registry Experience

Fergus J. Caskey,1,2 Retha D. Steenkamp,1 Rachel May Gair,1 Sabine Van der Veer,1 Richard J. Fluck,1 Claire Louise Corps,3 1UK Renal Registry, United Kingdom; 2Univ of Bristol, United Kingdom; 3Univ of Manchester, United Kingdom, 4Royal Derby Hospital, United Kingdom, 5Univ of Leeds, United Kingdom.

Background: Renal registries are starting to collect patient reported outcomes. This study explores the feasibility of collecting such data in people with CKD in secondary care in England and presents initial results.

Methods: Ten of the 52 adult renal units in England participated. The survey consisted of i) 5 questions on overall health (EQ-5D-3L), ii) 17 questions on symptoms (iPOS-S renal) and iii) 13 questions on the patient’s ability to manage their health (PAM). A paper copy of the survey was given to outpatients with pre-dialysis CKD or a transplant patient on maintenance haemodialysis/ prevalent dialysis. Completed surveys were returned to the Registry and scanned into the database. The EQ-5D-3L and iPOS-S renal questions use scales from ’0’ representing no problems/concerns to ’4’ representing the highest level of severity/concern. These were recoded to absent/mild (0,1) and moderate/severe/overwhelming (2, 3, 4). PAM was classified from 1 (least) to 4 (most) activated.

Results: In round 1, 334 patients returned surveys from 6 units. The majority (83%) were on haemodialysis. Most completed the survey on their own (49%); the remainder were helped by friends (24%) or clinical staff (27%). They did so at the renal unit (69%), at home (24%) or in clinic (7%). In all patient groups, at least moderate impairments in mobility, self-care, usual activities, pain/ discomfort, anxiety/ depression were reported in 52%, 30%, 54%, 42%, 31%, respectively. The presence of at least moderate symptoms ranged greatly from 12% for vomiting and 15% for diarrhoea to 45% for difficulty sleeping, 54% for poor mobility and 60% for weakness/lack of energy. Amongst responders, 30% and 10% had activation levels 3 and 4, respectively.

Conclusions: The routine national collection of patient reported outcomes poses practical and logistic challenges. The high burden of symptoms and low activation levels of the majority of patients highlights the importance of capturing these alongside traditional markers of quality of care.

Funding: Government Support - Non-U.S.

SA-PO956

Prognostic Significance of Pre-ESRD Serum Alkaline Phosphatase for Post-ESRD Mortality in Late-Stage CKD Patients Transitioning to Dialysis

Keichi Sumida,1,2 Miklos Zsolt Molnar,1 Praveen Kumar Potulkuri,1 Fridjof Thomas,1 Jun Ling Lu,1 Yoshitsugu Ohi,1 Connie Rhee,2 Elani Streja,3 Kunihiro Yamagata,1 Kanyar Kalantar-Zadeh,1 Csaba P. Kovácsy,1,4 1Univ of Tennessee Health Science Center, Memphis, TN; 2Univ of Tsukuba, Ibaraki, Japan; 3Univ of California, Irvine, CA; 4VA Medical Center, Memphis, TN.

Background: Higher serum alkaline phosphatase (ALP) has been associated with increased mortality in both non-dialysis dependent CKD and ESRD patients. However, little is known about the impact of ALP levels in advanced CKD on outcomes after dialysis initiation.

Methods: We examined the association of the averaged ALP levels over the last 6 months preceding transition to dialysis, with all-cause and cause-specific mortality during the two-year period following dialysis initiation in 17,985 US veterans transitioning to dialysis between 10/2007-9/2011. ALP levels were categorized into quartiles (<66, 66-85, 86-111, ≥112 U/L). Associations were examined using Cox (for all-cause) and competing risk (for cause-specific mortality) regressions and cubic splines with adjustment for demographics, comorbidities, medications, pre-ESRD 6-month averaged serum albumin and eGFR levels, and access type at dialysis initiation.

Results: Higher ALP levels were associated with increased risk of all-cause, CV, and infectious mortality (Figure). The adjusted hazard/subhazard ratios [95% CI] for ALP quartiles 2 through 4 (vs. quartile 1) were 1.10 [1.04-1.17], 1.12 [1.05-1.19], and 1.42 [1.33-1.51] for all-cause; 1.07 [0.95-1.21], 1.12 [0.99-1.26], and 1.30 [1.15-1.47] for CV; and 1.20 [0.93-1.55], 1.24 [0.96-1.59], and 1.39 [1.09-1.78] for infectious mortality, respectively.

Conclusions: Higher pre-ESRD ALP is associated with increased post-ESRD mortality risk. Further studies are needed to determine if interventions that lower pre-ESRD ALP levels reduce mortality in incident dialysis patients.

Funding: NIDDK Support, VA Support

SA-PO954

Exercise and Physical Function in Patients with CKD: The Mediating Role of Self-Efficacy

Amy L. Clarke,1 Joseph Chilcot,2 Alice C. Smith,1 1Leicester Kidney Exercise Team, Univ of Leicester, United Kingdom; 2Inst of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom.

Background: Chronic kidney disease (CKD) is characterized by low physical functioning (PF), associated with increased mortality. Exercise (EX) may help to retain independence but CKD patients are sedentary. Self-efficacy (SE) is both a determinant and construct important for EX behavioural interventions. Interventions should target processes to examine the associations between CKD and the average number of days of poor health and self-reported anxiety.

Results: The prevalence of CKD was 15.5% and of depression was 16.9%. Figure 1 shows unadjusted results. Those with CKD were not more likely to be depressed vs those without CKD after multivariable adjustment. Although they were 1.8 times more likely to have fair/poor health status after adjusting for demographic characteristics, this was non-significant after adjusting for both demographic and clinical confounders. Those with CKD reported 2 more days of poor physical health and being inactive due to poor health in the past month (p-values < 0.01), after multivariable adjustment. No differences were found for self-reported anxiety.

Figure 1: Perceived health status, depression prevalence, and quality of life among U.S. adult population with chronic kidney disease in NHANES 2011-2012.

Conclusion: Those with CKD were not more likely to be depressed vs those without CKD after multivariable adjustment. Although they were 1.8 times more likely to have fair/poor health status after adjusting for demographic characteristics, this was non-significant after adjusting for both demographic and clinical confounders.
In patients undergoing hemodialysis, lower b-ALP/t-ALP ratio in corrected calcium <2.75 mmol/L was associated with a lower risk of death compared to patients in the low TAP group (hazard ratio, 2.6; 95% CI 1.23–5.45, p=0.01). Similarly, patients in the high TAP group had significantly higher risk of death compared to co-factors such age, markers of bone disorder (calcium, iPTH, phosphate) and co-morbidity of 1.4±0.3. During a period of 7 years there were 52 (23.3%) deaths. After adjusting for with a median dialysis vintage of 24 months (IQR, 12–48) and a mean kT/V (single pool) the first day of the laboratory measurement for a maximum of 36 months or until death. A total of 50 patients died. Kaplan–Meier survival analysis showed higher mortality in the first tertile of b-ALP/t-ALP than in the third tertile (P = 0.042). Cox regression hazard analysis identified lower b-ALP/t-ALP as a significant predictor [HR 2.39 (95%CI:1.16–4.90)] for all-cause mortality. After adjustment for various factors, this effect is moderate [HR 1.90(95%CI:0.759–4.751)].

Methods: We used Generalized Estimating Equation models to examine the association between serum AP levels with repeat measures of HtTKV categorized as below and above 800 ml/m. We have previously identified a low bone turnover state in patients with increased levels of serum AP have been associated with progression in chronic kidney disease (CKD), we sought to determine whether serum AP levels are related to the risk of total kidney volume (TKV) progression in ADPKD.

Background: We have previously identified a low bone turnover state in patients with early autosomal dominant polycystic kidney disease (ADPKD) characterized by decreased bone formation, resorption and low serum levels of alkaline phosphatase (AP). While increased levels of serum AP have been associated with progression in chronic kidney disease (CKD), we sought to determine whether serum AP levels are related to the risk of total kidney volume (TKV) progression in ADPKD.

Results: At baseline, participants had a mean age and CKD-EPI eGFR, of 37 ± 8 years and 91.4 ± 17.4 ml/min/1.73m², respectively. The median (IQR) for AP for AP and HitTKV were 56 (45-69) IU/L and 589 (405-869) mU/L, respectively. After adjustment for age, gender, race, randomization group, body mass index, systolic blood pressure, eGFR, urine albumin excretion, serum calcium, phosphate and parathyroid hormone level a lower AP (< 56 IU/L) was independently associated with an increased HitTKV (OR: 1.49; 95% CI: 1.02-2.18; p=0.04).

Conclusions: Low serum AP is independently associated with a higher HitTKV in patients with early ADPKD. These findings suggest that altered bone biology in patients with ADPKD may be related to renal disease progression.

Funding: NIDDK Support

SA-PO958

Association between Serum Alkaline Phosphatase and Mortality in Maintenance Haemodialysis Patients

Bala Waziri,1 Saraladevi Naicker,1

1Internal Medicine, Univ of the Witwatersrand, Johannesburg, Gauteng, South Africa; 2Internal Medicine, Univ of the Witwatersrand, Johannesburg, Gauteng, South Africa.

Background: Studies mainly from the developed countries have revealed higher levels of intact parathyroid hormone (iPTH), calcium, phosphate and alkaline phosphatase as independent predictors of mortality in haemodialysis patients. Data on the existence of this link in African haemodialysis patients are scarce. Therefore, the aim of this study was to assess the impact of serum total alkaline phosphatase (TAP) on mortality in maintenance haemodialysis (MHD) patients.

Methods: This study enrolled a total of 223 patients on MHD from two dialysis centers in Johannesburg between January 2009 and March 2016. Patients were categorized into low TAP group (<112 U/L) versus high TAP group (≥112 U/L) based on median TAP of 112 U/L. In-hospital and 1-year mortality were compared for patients with low and high TAP. Cox regression model was used to access the possible influence of variables on all-cause mortality.

Results: The MHD patients (147 men, 76 women) had a mean age of 54.5±15.6 years with a median dialysis vintage of 24 months (IQR, 12-48) and a mean kT/V (single pool) of 1.4±0.3. During a period of 7 years there were 52 (23.3%) deaths. After adjusting for confounders such age, makers of bone disorder (calcium, iPTH, phosphate) and co-morbidity (DM); patients in the high TAP group had significantly associated with increased odds of a higher HitTKV (OR:149; 95% CI: 1.02–2.18; p=0.04).

Conclusions: Low serum AP, is independently associated with a higher HtTKV in patients with early ADPKD. This relatively inexpensive test may be utilized as a surrogate marker for monitoring treatment in End Stage Renal Disease.
increased SHPT severity, there were higher baseline biomarkers of bone metabolism (BSAP and CTX), a greater percentage reduction in cCa, and a higher proportion of subjects with low calcium.

Table 1. Baseline Laboratory Values by baseline PTH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Entire Cohort (N=3025)</th>
<th>Stratum A (n=1120)</th>
<th>Stratum B (n=1170)</th>
<th>Stratum C (n=735)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/mL)</td>
<td>686 (95.8)</td>
<td>609 (73.0)</td>
<td>674 (76.0)</td>
<td>647 (81.7)</td>
</tr>
<tr>
<td>cCa (mg/dL)</td>
<td>9.4 (0.6)</td>
<td>9.2 (0.6)</td>
<td>9.5 (0.6)</td>
<td>9.2 (0.6)</td>
</tr>
<tr>
<td>BSAP µg/L</td>
<td>41.4 (10.9)</td>
<td>37.8 (11.4)</td>
<td>44.9 (11.4)</td>
<td>39.3 (10.6)</td>
</tr>
<tr>
<td>PTH 300–1000 µg/L</td>
<td>1004 (12.9)</td>
<td>1015 (22)</td>
<td>1019 (20)</td>
<td>1006 (16)</td>
</tr>
<tr>
<td>PTH ≤300 µg/L</td>
<td>1941 (82.9)</td>
<td>1330 (92.5)</td>
<td>1969 (87.0)</td>
<td>1314 (92.5)</td>
</tr>
</tbody>
</table>

Table 2. Efficacy of Cinacalcet by PTH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Entire Cohort (n=1005)</th>
<th>Stratum A (n=349)</th>
<th>Stratum B (n=360)</th>
<th>Stratum C (n=296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH 300–1000 µg/L</td>
<td>625 (62.0%)</td>
<td>222 (63.6%)</td>
<td>379 (66.4%)</td>
<td>224 (75.7%)</td>
</tr>
<tr>
<td>PTH 300 µg/L</td>
<td>807 (80.7%)</td>
<td>302 (86.1%)</td>
<td>480 (83.3%)</td>
<td>305 (101.7%)</td>
</tr>
<tr>
<td>PTH ≤300 µg/L</td>
<td>1009 (100.0%)</td>
<td>347 (100.0%)</td>
<td>520 (100.0%)</td>
<td>362 (100.0%)</td>
</tr>
</tbody>
</table>

Funding: Pharmaceutical Company Support - Amgen Inc.

SA-PO961

Effects of Etecalcetide by Severity of Secondary Hyperparathyroidism John Cunningham,1 Geoffrey A. Block,2 Kerry Cooper,3 Sharon M. Moe,4 Yan Sun,5 David A. Bushinsky,1 UCL Medical School; 2Denver Nephrology; 3Denver; 4U of Rochester School of Med.

Background: Etecalcetide (ETL), a novel calcimimetic, has been shown to reduce levels of parathyroid hormone (PTH), corrected calcium (cCa), phosphate (P) and fibroblast growth factor (FGF-23) in adults on hemodialysis (HD) with secondary hyperparathyroidism (SHPT).

Methods: Adult subjects on HD with SHPT (PTH≥400pg/mL) were randomized to 26 wks ETL or placebo. ETL was started at 5mg IV per HD session and titrated every 4 wks up to a max 15 mg to achieve PTH≤300pg/mL. The efficacy of ETL was evaluated post 26 wks ETL or placebo. ETL was started at 5mg IV per HD session and titrated every 4 weeks (max 15 mg) to achieve PTH≤300pg/mL. Theefficacy of ETL was post-hoc by baseline disease severity. Results shown are for the ETL arm only for % change in PTH, cCa, P and FGF-23. (Table 1) %PTH reduction did not differ across strata. However, % reductions at wk 27 compared with baseline and % of subjects achieving PTH≤300pg/mL, P<5.5 mg/dL and P binder (PB) use; MIM dose; adverse drug reactions (ADR).

Results: 3025 pts were eligible; 2860 (95%) completed study; 345 discontinued (death 28%; transplantation 26%; adverse events 15%; loss to follow-up 11%; other 20%); 2582 (85%) completed ≥144 days of MIM.

Funding: Pharmaceutical Company Support - Amgen Inc.

SA-PO962

WELCOME - Web-Based Evaluation of the Clinical Benefit of Cinacalcet (MIM) in End-Stage Renal Disease (ESRD) in Central and Eastern Europe (CEE) Jaroslav Rosenberger,1 Piotr Mierziak,2 Alexander Seluyt,3 Frantisek Svara,4 Margit Hemetsberger,5 1FMC Kosice and Inst of Health Psychology, Medical Faculty Univ PJ Safarik, Kosice, Slovakia (Slovak Republic); 2Wienerwald Spital Specialitszcyzczas, Chelm, Poland; 3Regional Clinical Hospital Orenburg, Moscow, Russian Federation; 4Strahov General Univ Hospital, Prague, Czech Republic; 5Hemetsberger Medical Services, Vienna, Austria.

Background: This multicenter, observational study was conducted from 01/07 to 10/15. Aims: describe changes in CKD-MBD parameters after MIM start overall and before (BGR) vs after (AGR) KDIGO guideline release; describe characteristics of patients (pts) initiating MIM.

Methods: Eligibility: ESRD pts, MIM use according to SmPC. Data collected at baseline (BL=first MIM dose) and up to 6 months (M6). Endpoints: achieving PTH≤300 pg/mL [primary]; KDOKI target for calcium (Ca) or phosphorus (P); vitamin D (Vit D) and P binder (PB) use; MIM dose; adverse drug reactions (ADR).

Results: 3025 pts were eligible; 2860 (95%) completed study; 345 discontinued (death 28%; transplantation 26%; adverse events 15%; loss to follow-up 11%; other 20%); 2582 (85%) completed ≥144 days of MIM.

Funding: Pharmaceutical Company Support - Amgen GmbH, Headoffice for CEE, Vienna, Austria

SA-PO963

Parathyroidectomy Achieves KDIGO Targets for Mineral and Bone Metabolism on Hemodialysis Patients? Adriana Belo Lopes Prazeres,1 Teg Marcos Veiga,2 Amadeu de Assis Marinho Neto,1 Ana Paula Gueiros,3 Jose Edevanilson Gueiros.1 Nephrology, UFPE, Recife, Pernambuco, Brazil.

Background: Secondary hyperparathyroidism (SHP) is a common complication of chronic kidney disease. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines provides target ranges for serum calcium, phosphorus and parathyroid hormone levels. Parathyroidectomy (PTX) is indicated for patients with refractory SHP despite clinical treatment. The aim of this study was to evaluate how PTX impacts KDIGO targets for CKD-MBD.

Methods: A retrospective review of patients on dialysis that underwent PTX was performed. Total calcium (Ca), phosphorus (P) and intact parathyroid hormone (PTH) levels were analyzed immediately before PTX and after 6 and 12 months and compared with KDIGO targets. The PTX was indicated if the patient had untreated SHP with medications or major complications of SHP (bone fracture, brown tumor, calciphylaxis).

Results: Between January 2004 and april 2015, 79 patients underwent PTX, 64.6% women with a mean age of 45.8 years and mean time on dialysis of 9.7 years. Total PTX with autotransplantation was the most common surgical technique. Laboratory tests are shown in Table 1.

Funding: Pharmaceutical Company Support - Amgen Inc.

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

Underline represents presenting author.
SA-PO964
Long-Term Mortality and Bone Safety in Patients with End-Stage Renal Disease Receiving Lanthanum Carbonate
Ravi I. Thadhani,1 Alastair J. Hutchison,2 Gillian Hall,3 A. Whelton,3 Heinrich Achenbach,3 Jingyang Wu,4 Massachusetts General Hospital, Boston; 5Manchester Royal Infirmary, Manchester, United Kingdom; 6Gillman Hall Epidemiology Ltd, London, United Kingdom; 7Johns Hopkins Univ, Baltimore; 8Shire, Zug, Switzerland; 9Shire, Lexington.

Methods: The exposed group, comprising patients ≥18 years who had received ≥12 consecutive weeks of LaC treatment, included patients from clinical trials of LaC and patients prescribed LaC as part of normal clinical practice. A matched comparator group, comprising patients treated with any other phosphate binder, was identified from the USRDS (1:4 matching). Both groups were on dialysis and were observed for up to 5 years using the USRDS. Primary endpoints were time to all-cause mortality and bone fracture rates requiring hospitalization. Secondary endpoints were time to gastrointestinal disease; liver disease; malignancy; and major infectious episodes requiring hospitalization.

Results: Of the 2136 exposed patients enrolled, 2027 were included in the analysis. Using 2014 USRDS data, a Kaplan–Meier analysis showed that median 5-year survival (95% CI) was 51.6% (49.1, 54.2) and 48.9% (47.3, 50.5) for patients in the exposed (n=2027) and comparator groups (n=8103), respectively. Bone fracture rates were 5.9% and 6.7%, respectively. A Cox proportional hazards model was fitted to adjust for patient baseline characteristics. LaC was not associated with an increased risk of any of the safety endpoints; however, in one of the secondary endpoints, LaC had a significant 17% reduced baseline risk of time to major infectious episodes (P<0.001).

SA-PO965
Effect of Kidney Donation on Bone and Mineral Metabolism: The KARMA Prospective Controlled Observational Study
Thomas F. Hiemstra, Shreya Kulkarni, Ragada El-Damanawi, Carmel M. McEntire, Laurie A. Tomlinson, Ian Wilkinson,1 Univ of Cambridge; 2London School of Hygiene and Tropical Medicine.

Background: Chronic Kidney Disease (CKD) is an independent risk factor for cardiovascular disease. Unilateral nephrectomy for live transplant donation represents an ideal model to study the effects of an acute decrement in GFR in the absence of renal pathology. Recent evidence suggests detectable differences in cardiac morphology early after kidney donation. We sought to determine the effect of kidney donation on bone and mineral metabolism.

Methods: We enrolled pre-donation living transplant kidney donors and healthy controls in this single-centre prospective cohort study. Biochemical parameters were determined before and after donation and after 12 months, and at baseline and 12 months in the control group.

Results: Between 2012-2015, we enrolled 34 donors (male vs 20.59%, and 34 controls (male=16.47%). The mean donor age was 53.10 years, vs controls 50.14 years (P=0.33). Mean daily dialysate Ca++ was used (97.9% respectively). Baseline eGFR was similar between groups (donor 83.15±15 mL/min, control 88.21±15 mL/min, P=0.21). In the control group, biochemical parameters did not change significantly over time. In contrast, kidney donation reduced eGFR significantly to 56.10±15 mL/min after 6 weeks (P=0.0001), and remained lower than baseline after 12 months 63±13 (p=0.0001). Alkaline phosphatase increased from 99±21 IU/L to 106±22 IU/L after 6 weeks (P=0.01), but after 12 months had reduced to significantly below baseline (83±22 IU/L, P=0.0003). PTH increased from 10.55±1.16 to 8.96±1.78 to 8.76±1.27, respectively (P<0.001).

4.7 pg/mL (3.4-5.8) at baseline to 5.8 pg/mL (4.6-8.6, P<0.0007) after 12 months. Soluble u-keratin decreased markedly from 521.68±164.9 pg/mL at baseline to 521.68±164.9 pg/mL (P=0.227), but lower during follow-up. Maximum difference between MWA and calcitriol groups was 275.11 pg/mL at month 8 (554.66±289.78 vs. 279.55±172.78 pg/mL, P=0.002). Minimum difference was 58.06 pg/mL at month 2 (572.58±378.72 vs. 554.52±453.13 pg/mL, P=0.66), which was considered clinically significant. Only one case (7.14%) developed severe SHPT in the MWA group and six (42.86%) in the calcitriol group (P<0.038). Weekly calcitriol dosing was lower than the calcitriol group (8.54 ± 4.72 pg/mL, P=0.003).

Conclusions: MWA decreases iPTH levels significantly for mild-to-moderate SHPT and prevents development into severe SHPT. It is worthwhile attempting to treat mild-to-moderate SHPT with MWA.

SA-PO966
Efficacy of Microwave Ablation for Severe Secondary Hyperparathyroidism in Subjects Undergoing Hemodialysis
Zongli Diao, Wenhu Liu, Gao Weikang. Dept of Nephrology, Beijing Friendship Hospital, Capital Medical Univ, Beijing, China.

Background: Secondary hyperparathyroidism is a serious problem in patients undergoing hemodialysis. The efficacy of microwave ablation, a minimally invasive treatment, for severe secondary hyperparathyroidism is as yet unclear. In this study, we studied its efficacy for patients with severe secondary hyperparathyroidism.

Methods: This was a prospective, single-arm, clinical trial. We enrolled patients with severe secondary hyperparathyroidism attending our hemodialysis center who met the inclusion and exclusion criteria. We then assessed primary outcome measures: serum concentrations of intact parathyroid hormone (iPTH).

Results: Twenty-six patients were enrolled in this study, 10 of whom (38.46%) were responsive to microwave ablation and 16 (61.54%) of whom were not. In response group patients, serum iPTH concentrations declined to within the target range (124–558 pg/mL) immediately after microwave ablation, the changes compared with baseline values being statistically significant (1272.02±440.34 vs. 176.09±75.84 pg/mL, P<0.001). During follow-up, the iPTH concentrations of seven of these patients remained within the target range; however, the remaining three patients experienced recurrences at the 15, 19, and 21-month follow-up. Sixteen patients with No Response followed-up for 3 months (when they were identified as having No Response). Compared with baseline values (1691.42±354.48 pg/mL), iPTH concentrations declined significantly immediately after microwave ablation (1022.02±427.65 pg/mL), and at the 1-week (1161.82±437.21 pg/mL) and 1-month (1210.61±505.34 pg/mL) follow-ups, P-values being <0.001, 0.005 and 0.013, respectively. However, iPTH concentrations did not decline to the target range. Furthermore, they started to increase from immediately after microwave ablation, increasing by the 3-month follow-up to concentrations that did not significantly differ from those at baseline. The main complication was recoverable hypocalcemia (10 cases, 38.46%).

Conclusions: Microwave ablation is relatively ineffective in patients with severe secondary hyperparathyroidism and should not be the initial therapy in such cases.
Calciaphaxis New Aspects of an Old Entity  

Enrique Morales, Maria Fernandez Vidal, Eduardo Hernandez-Martinez, Eduardo Gutierrez-Martinez, Manuel Praga.  
Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain.

Background: Calcific uraemic arteriopathay (CUA), also called calciaphaxis, is a rare but disastrous and life-threatening disease most often affecting patients with chronic kidney disease treated with dialysis. There is little information about the incidence of this entity in patients with a functioning kidney transplant (KT) and patients with normal kidney function (NKF).

The aim of this study was to analyze risk factors (RF) and treatment of CUA in different types of patients.

Methods: Retrospective study that includes patients diagnosed with CUA from December 1999 to December 2015. Clinical features, laboratory evaluation, treatment and outcome were investigated.

Results: Twenty-eight patients (53.6% women) were included. The mean age was 67.2 ± 11.8 (38-88) years. The prevalence of diabetes mellitus and obesity (BMI>30 kg/m²) was 46.4 and 42% respectively. At the time of diagnosis, 53.6% were on hemodialysis (HD), 25% were KT patients and 21.4% had NKF. Skin biopsy confirmation was reported for 78.6% and the remaining were diagnosed clinically. 82.1% of cases showed peripheral CUA. The vitamin K antagonists (VKA) (68.7%) and steroids (100%) were considered a significant RF in patients with KT. The multimodal treatment (66.7% bisphosphonates, 58.3% intravenous sodium thiosulfate and 42.9% cinacalcet) was used in patients. The resolution of CUA was present in 62.5% patients. The mean follow-up time was 26.3 ± 45.2 (1-192) months. The 1-year patient survival in patients with CUA was 23, 56, 100% in the KT, HD and NKF patients respectively (log rank 6.8, p = 0.032). Eleven patients died (39.3%) during the CUA, 6 cases (40%) of HD and 5 cases (71.4%) in patients with KT. The presence of renal insufficiency (p = 0.03), Charlson’s index (CI)> 7 (p = 0.06) and hypalbuminemia (p = 0.02) were the significant RF of mortality in patients with CUA.

Conclusions: Although the incidence of CUA remains low in our population, the mortality is extremely high, especially in the KT. The VKA should be considered as new and significant RF in the majority of groups. The identification of RF before CUA development and standard therapy should be the main objectives to conduct randomized clinical trials.

The Role of Calcioprotein Particles in the Mineralisation Paradox in Chronic Kidney Disease  

Michael Ming Xin Cai,1,2 Edward R. Smith,1,2 Sven-Jean Tan,1,2 Nigel David Toussaint,1,2 Timothy D. Hewitson,1,2 Stephen G. Holt,1,2 Royal Melbourne Hospital, Australia; 2Univ of Melbourne, Australia.

Background: Vascular calcification in chronic kidney disease (CKD) is often accompanied by a paradoxical reduction in bone mineralisation. In CKD, a fraction of serum calcium (Ca) and phosphate (P) circulates as colloidal nanocrystals stabilised by a protein shell, termed calcium-phosphate (CPP) particles (CPPs). CPPs are associated with arterial stiffness, coronary calcification and mortality. This study tested the differential effect of CPP on vascular smooth muscle cell (VSMC) and osteoblast mineralisation.

Methods: Saos-2 (an osteosarcoma cell line) and MOVAS-1 (murine VSMC) were treated for 7 days with either control media (CM), osteogenic media (OM, +3mM Pi), CM supplemented with secondary CPP (CPP) or OM supplemented with CPP (OM+CPP). Mineralisation was detected with alizarin red and von Kossa staining, and quantified by measuring the absorbance at 570 nm.

Results: OM treatment increased Saos-2 mineralization, but not MOVAS-1. OM+CPP treatment yielded a dose-dependent decrease in Saos-2 mineralisation. In contrast, treatment of MOVAS-1 with OM+CPP resulted in a synergistic increase in mineralisation compared to OM and CPP respectively. OM+CPP but not OM reduced MOVAS-1 viability (P<0.01). ALP activity was similar between treatment groups in both cell lines. Compared to freshly prepared OM+CPP, media pre-incubation for 24 h at 37°C reduced monolayer mineralisation in both cell lines despite an increase in CPP-bound calcium.

Conclusions: In high Pi, CPP reduce mineralisation of an osteoblast-like cell but increase mineralisation of a VSMC cell line. Our findings suggest circulating CPP in CKD serum may be a novel mediator of the calcification paradox in CKD.

Funding: Government Support - Non-U.S.
Methods: We conducted a retrospective review of 410 consecutive patients who underwent a renal biopsy and entered into a chronic kidney disease (CKD) program. BMD data, T score and Z scores were collected at four sites: the lumbar spine, total hip, mean of left and right femoral neck, and the proximal radial region (radius 0.5%). We collected data on demographic, lab markers of mineral metabolism and fractures. Result: The mean age of stage III CKD of 28.4% stage IV CKD of 2.7%, and stage V CKD of 1.2% of patients experienced a clinical fracture during the study period. On multivariate analysis, a decline of 1.0 SD in total Hip BMD T-score was associated with a statistically significant increase in the risk of fracture (OR = 1.35, 95% CI: 1.01, 1.82, p = 0.04) while controlling for parathyroid hormone, alkaline phosphatase, calcium and phosphorus and GFR of <30. Compared to a GFR of ≥30 mls/min, the OR of identifying a fracture was 1.54 in comparison to OR of 1.14 in patients with GFR <29 mls/min.

Conclusions: This is the largest Canadian cohort of CKD patients with DXA scans to our knowledge. We were able to show that T-scores predict fractures across stage III, but had a modest ability in stage IV. As fractures lead to significant morbidity and mortality, we believe there is a role for DXA scans which, are inexpensive, non-invasive, safe, and readily available to have a clinical principle in identifying patients for risk fractures in different stages of CKD.

SA-PO973
Association of Dialysate Calcium Concentration, Vitamin D Use, and Hip Fracture in Hemodialysis Patients. Miho Tagawa,1 Takayuki Hamano,2 Shinichi Suetsu,1 Seiji Hashimoto,1 Satoshi Ogata.2 1 Nara Medical Univ; 2 Patient Registration Committee of Japan Renal Data Registry; 3 Kyoto Univ.

Background: The effects of dialysate calcium concentration ([Ca]D) on bone and mineral disorders have not been studied, however, the association between [Ca]D and fractures has not been studied. In Japan, most dialysis facilities use central supply system for dialysate.

Methods: This was a longitudinal study based on the Japan Renal Data Registry from 2008 to 2010. Hemodialysis patients without prior hip fracture were enrolled. Predictor variable was [Ca]D (≤3.0 vs. ≥3.5 mEq/L). Use of active vitamin D (ViD) in each [Ca]D category was also considered. Outcome variable was incidence of hip fracture and has not been studied. Statistical analyses were performed using multivariate logistic regression model, adjusted for potential confounders.

Results: Among 301,649 patients on the database, data for 47,352 patients were available after excluding missing data. There were 979 events of hip fracture during 2 years. Adjusted OR for [Ca]D ≤3.0 mL/L was 0.89 (0.78-1.02), 0.93 (0.77-1.12), 0.89 (0.69-1.14), and 0.75 (0.52-1.08) for total cohort, patients with intact parathyroid hormone (PTH) >150-300 pg/ml, respectively. Among patients with PTH >300 pg/ml, ViD use was associated with significant reduction in hip fracture for both [Ca]D categories and of ≥3.5 mL/L with ViD use was associated with lower incidence of hip fracture compared to ≥3.0 mL/L without ViD use. Among patients with PTH >300 pg/ml, the use of [Ca]D = 2.5 mL/L without ViD use was associated with significant increase in hip fracture.

Conclusions: The effects of [Ca]D of ≥3.5 mL/L on incident hip fracture is dependent on PTH levels and concomitant ViD use. The results suggest that vitamin D should be prescribed not to increase the risk of fracture when using [Ca]D ≥2.5 mL/L.

SA-PO974
The Prevalence and Risk Factors of Low Bone Mineral Density in Chinese Chronic Kidney Disease Patients. Ying Qian, An Jinh Chang, Xiaonong Chen. Nephrology, Ruijin Hospital Affiliated to Shanghai Jiaotong Univ School of Medicine, Shanghai, China.

Background: Bone and mineral disorder is one of the most common clinical complications in CKD patients. Since Chinese research in this field is only at the beginning, we need more data to analysis the prevalence and risk factors of low bone mineral density in Chinese CKD patients.

Methods: We selected CKD inpatients from 2009 to 2015. Patients were excluded if they used glucocorticoid and calcitriol. GFR was estimated using MDRD formula for Chinese. All patients were classified into 5 CKD stages according to K/DOQI guideline and were measured BMD at lumbar spine, femoral neck and total hip by dual energy X-ray absorptiometry (DXA). Osteoporosis was defined by BMD according to the reference values suitable for Chinese population. Clinical characteristics of all patients were also collected. The correlation between BMD and detection indices was analysed and the independent risk factors for low BMD in CKD patients were also explored.

Results: A total of 429 patients were enrolled in the study. Mean age of the patients (221 males and 208 females) was 53.89±16.14 years. Totally 43.59% of all patients were suitable for Chinese population. Clinical characteristics of all patients were also collected. The correlation between BMD and detection indices was analysed and the independent risk factors for low BMD in CKD patients were also explored.

Conclusions: We found that BMD values decreased significantly from L1 to L4 in the lumbar spine and the prevalence of osteoporosis seemed to be much higher in lumbar spine but lower in the hip, which indicating that the bone loss seemed predominant in the load-bearing trabecular bone. Correlation analysis revealed that parathyroid hormone (PTH) was significantly correlated with the BMD Z-scores of the lumbar spine and hip. To further investigate the impact of PTH on BMD changes, we stratified the patients according to their PTH levels (500-1000, 1000-2000, and >2000pg/ml, respectively). We found that along with the increase of parathyroid hormone, the bone loss of mineral content was prior to the bone area reduction. Osteoporosis (PTH > 2000) and higher parathyroid gland weight (P < 0.008).

Funding: Government Support - Non-U.S.
SA-PO977
Free Testosterone Is Positively Associated with Bone Mineral Density in Kidney Transplant Candidates

Hanne Skou Joergensen,1 Simon Winther,2 Lars Rejmark,3 My Svensson,4 Per R. Iversen,5 1Nephrology, Aarhus Univ Hospital, Aarhus, Denmark; 2Cardiology, Aarhus Univ Hospital, Aarhus, Denmark; 3Endocrinology, Aarhus Univ Hospital, Aarhus, Denmark; 4Nephrology, Aarhus Univ Hospital, Oslo, Norway.

Background: Hypogonadism is common in CKD. Both testosterone (T) and estradiol (E) decrease bone resorption and are positively associated with bone mineral density (BMD) in healthy elderly, but little is known of the effects of sex hormones on bone health in CKD. We investigated associations between free T, free E and BMD in male kidney transplant candidates.

Methods: Volumetric BMD (vBMD) of lumbar spine and total hip were measured by quantitative computed tomography. Total T, total E, sexual hormone binding protein (SHBG), intact parathyroid hormone (iPTH) and albumin were analyzed from fasting morning blood samples. Free T and free E were calculated based on constants for protein binding of T to SHBG and albumin.

Results: Analyses included 107 patients. Free T correlated to age (r=-0.20, p=0.04), weight (r=-0.25, p=0.01), Ln Free E (r=0.42, p=0.001) and dialysis treatment (r=0.47, p=0.001). Ln Free E correlated to Free T, type 1 diabetes (r=0.22, p=0.03) and Ln-iPTH (r=0.20, p=0.04). Figure 1 shows the association between sex hormones and vBMD. In the multiple linear regression model, both hormones were significant predictors at lumbar spine and Free T was significant at total hip (Table 1).

Conclusions: Sex hormones may play an important part in bone health in men with late stage CKD.
Funding: Private Foundation Support

SA-PO978
Large Variations between Four Methods for Sclerostin Determination in Patients Undergoing GFR Measurement and in Hemodialyzed Patients before and after a Single Dialysis Session

Étienne Cavaler1, Pierre Delanaye1 1Clinical Chemistry, Univ of Liège; 2Nephrology, Univ of Liège.

Background: Sclerostin (SCL) is a promising biomarker for bone research. It has also been associated, in some studies, with mortality in hemodialyzed (HD) patients. However, literature is conflicting on that point and some authors have pointed out that assays used for SCL might explain these discrepancies. Also, the impact of renal function on SCL levels remains poorly studied.

Methods: We have measured SCL concentration in 150 healthy and CKD patients who had undergone GFR determination with the iohexol method. We have also measured SCL before and after a single dialysis session in 44 patients. Each sample has been measured with 4 different ELISA: Biomedica (B), MSD (M), R&D (R) and Teco (T).

Results: Median (IQR) SCL concentration in the non-HD patients were very different according to the method: B: 1017[546], M: 36[21], R: 629[325] pmol/L. We did not observe any systematic differences between the methods. In univariate analysis, we observed a significant and inverse relation between GFR and SCL when measured by B, R and T but not with M. The different assays also showed a wide variation in HD patients. With B and R methods, HD patients presented median values higher than those whose GFR was >45 mL/min, but were similar with those present GFR <45 mL/min.

With T method, the median observed in HD patients was higher than in non-HD patients. On the contrary, median SCL was lower in HD than in non-HD patients with the M method. After a dialysis session, a significant decrease was observed in HDF, but not in HD mode and was always more important if SCL was measured with T, B and R methods, compared to the M one.

Conclusions: Sclerostin determination in CKD patients is challenging and any conclusion is method-depending. Previously described relations between GFR and SCL levels may be an analytical artifact with inactive SCL fragments that would accumulate when GFR decreases and would be recognized by T, B and R, but not M method. In conclusion, method for SCL determination clearly impacts findings previously observed in CKD and HD patients.

SA-PO979
Sclerostin – A Debutant on the Autosomal Dominant Polycystic Kidney Disease Scene?

Magdalena Jankowska,1 Abdul Rashid Tony Qureshi,1 Bengt Lindholm,1 Peter Stenvinkel,2 Pieter Evenepoel,1 1Div of Renal Medicine and Baxter Novum, Karolinska University Hospital at Huddinge M99, Karolinska Inst, Stockholm, Sweden; 2Dept of Nephrology, Transplantology and Internal Medicine, Medical Univ of Gdansk, Gdansk, Poland; 3Dept of Immunology and Microbiology, Laboratory of Nephrology, Katholieke Univ Leuven, Leuven, Belgium.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease originating from a mutation in genes encoding polycystin 1 and 2. Recent evidence suggests that these polycystins mediate mechanosensation not only in the primary cilium of kidney cells but also in bone cells. The Wnt/catenin signaling pathway plays a central role in mechanotransduction in osteocytes. Mechanical unloading causes the upregulation of the Wnt inhibitor sclerostin. We tested the hypothesis that ADPKD associates with higher circulating sclerostin levels.

Methods: Circulating levels of sclerostin and other laboratory parameters of mineral and bone disease, including intact parathyroid hormone (PTH), calcium, phosphate, magnesium, 25(OH)-vitamin D, 1,25(OH)₂-vitamin and bone specific alkaline phosphatase (bALP) were assessed in 503 patients with end stage renal disease recruited from ongoing longitudinal cohort studies in Stockholm, Sweden (cohort 1: n=180, 19% ADPKD) and Leuven, Belgium (cohort 2: n=403, 19%, ADPKD).

Results: Patients with ADPKD had higher sclerostin levels and lower bALP levels as compared to patients with other primary renal disease. In multivariate analysis, ADPKD associated with circulating sclerostin levels, independent of the established determinants including age, gender, body mass index, diabetes, phosphate, PTH, and 1,25(OH)₂-vitamin.

Conclusions: Circulating sclerostin levels are increased in ADPKD, possibly reflecting impaired mechanosensation. The clinical relevance of this finding, e.g. with regard to vascular and bone health, remains to be investigated. Our finding draws attention to etiology of kidney disease as an important, yet neglected, confounder or the association between renal failure and mineral and bone disease.

SA-PO980
Bone Marrow Adipocyte after GH Supplementation in Pediatric ESKD Patients

Ornatcha Sirimongkolchayvikul, Renata C. Pereira, Katherine Wesseling-Perry, Isbido B. Salusky. Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA.

Background: Mesenchymal stem cells are precursors for both osteoblasts and adipocytes. Marrow adipogenesis is associated with osteoporosis in adults with normal kidney function. GH increases osteoblast proliferation and differentiation and is commonly used to promote growth in children with CKD. The effects of GH on bone marrow adipogenesis; however are unknown.

Methods: 24 pediatric peritoneal dialysis patients age 10.3 ± 4.6 (SD) years with high (n=14) or low/normal (n=10) bone turnover were randomly assigned to treatment with GH or not. Patients with high bone turnover group also received intraperitoneal Calcitriol. Bone biopsy was performed at baseline and after 8 months of therapy.

Results: Marrow adipocytes/tissue area did not change with therapy in patients with either high turnover or low/normal bone turnover, irrespective of treatment with GH versus control therapy.

Table 1: Dietary and lifestyle intervention

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>GH</th>
<th>GH+Calcitriol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>11.0 ± 3.9</td>
<td>11.0 ± 3.9</td>
<td>11.0 ± 3.9</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>33.0 ± 9.3</td>
<td>33.0 ± 9.3</td>
<td>33.0 ± 9.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>136.5 ± 13.7</td>
<td>136.5 ± 13.7</td>
<td>136.5 ± 13.7</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>21.5 ± 4.0</td>
<td>21.5 ± 4.0</td>
<td>21.5 ± 4.0</td>
</tr>
<tr>
<td>GFR (mL/min/1.73m²)</td>
<td>45.0 ± 15.0</td>
<td>45.0 ± 15.0</td>
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</tr>
<tr>
<td>Calcium (mg/d)</td>
<td>1050 ± 300</td>
<td>1050 ± 300</td>
<td>1050 ± 300</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>40 ± 40</td>
<td>40 ± 40</td>
<td>40 ± 40</td>
</tr>
<tr>
<td>25(OH)D (ng/mL)</td>
<td>20 ± 10</td>
<td>20 ± 10</td>
<td>20 ± 10</td>
</tr>
<tr>
<td>Bone Mineral Density (g/cm²)</td>
<td>0.75 ± 0.15</td>
<td>0.75 ± 0.15</td>
<td>0.75 ± 0.15</td>
</tr>
<tr>
<td>Bone mineral content (g)</td>
<td>40 ± 10</td>
<td>40 ± 10</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Total hip BMD (g/cm²)</td>
<td>0.75 ± 0.15</td>
<td>0.75 ± 0.15</td>
<td>0.75 ± 0.15</td>
</tr>
<tr>
<td>Lumbar spine BMD (g/cm²)</td>
<td>0.75 ± 0.15</td>
<td>0.75 ± 0.15</td>
<td>0.75 ± 0.15</td>
</tr>
<tr>
<td>Sclerostin (ng/mL)</td>
<td>0.5 ± 0.5</td>
<td>0.5 ± 0.5</td>
<td>0.5 ± 0.5</td>
</tr>
</tbody>
</table>

Table 2: Changes of marrow adipocytes in patients received GH or noting

<table>
<thead>
<tr>
<th>Measure</th>
<th>GH</th>
<th>GH+Calcitriol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of adipocytes</td>
<td>7.5 ± 5.0</td>
<td>7.5 ± 5.0</td>
</tr>
<tr>
<td>Total adipocytes</td>
<td>100 ± 50</td>
<td>100 ± 50</td>
</tr>
</tbody>
</table>

Conclusion: Marrow adipocytes did not change in response to GH therapy in this sample of pediatric ESKD patients.

Funding: NIDDK Support
SA-PO981

Canonical Wnt Signaling May Contribute to Altered Pre-Osteoblast Maturation Characteristics in CKD

Renata C. Pereira,1 Richard Bowden,2 Isidro B. Salusky,1 Katherine Wesseling-Perry,1 Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; Orthopedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA; Dentistry, UCLA, Los Angeles, CA.

Background: Bone disease in chronic kidney disease (CKD) has been traditionally defined by changes in bone turnover stemming from altered circulating parathyroid hormone (PTH) concentrations. However, we have shown that primary pre-osteoblasts from CKD patients have increased proliferation and decreased mineralization rates ex vivo, suggesting that CKD induces intrinsic changes to osteoblast biology that are independent of circulating PTH concentrations.

Methods: To understand potential mechanisms mediating these changes, primary pre-osteoblasts from 6 adolescent dialysis patients (3 with high and 3 with low bone turnover) and 3 healthy adolescent controls were plated at 10,000 cell/cm² and cultured in the presence of growth media (10% fetal bovine serum and 100 μg/ml ascorbic acid) until achieving confluence. Maturation/mineralization was promoted by the addition of 10nM β-glycerophosphate and cells were grown for 7 days after which time RNA was harvested from cultures for RNA Seq analysis (Genewiz). Parallel cultures were grown for 14 days after which time total protein was isolated.

Results: RNA Seq analysis revealed marked differences in expression of genes of the Wnt signaling pathway; thus, β-catenin expression was evaluated in protein extracts. β-catenin protein was increased in CKD as compared to healthy control cells.

Conclusions: Increased proliferation and decreased mineralization rates in pre-osteoblasts from CKD patients suggests that increased canonical Wnt signaling may contribute to this phenotype.

Funding: NIDDK Support, Pharmaceutical Company Support - Genzyme, Private Foundation Support

SA-PO982

Pre-Osteoblast Maturation Failure Is a Feature of Early Chronic Kidney Disease

Renata C. Pereira,1 Kathleen Noche,1 Richard Bowden,2 Isidro B. Salusky,1 Katherine Wesseling-Perry,1 Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; Orthopedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA.

Background: Primary pre-osteoblasts from ESKD patients have decreased mineralization rates ex vivo (Pereira KC, KI 2015) suggesting that CKD induces intrinsic changes to osteoblast biology resulting in maturation failure.

Methods: To evaluate whether this phenotype is a feature of early CKD, pre-osteoblasts from 7 adolescent patients with CKD stages 2-4 with normal serum calcium, phosphorus, and PTH levels and from 3 healthy adolescent controls were plated at 10,000 cell/cm² and cultured in 10% fetal bovine serum and 100 μg/ml ascorbic acid until achieving confluence. Cells were then treated to mineralize with 10 μM β-glycerophosphate for 21 days then stained with PBS, fixed with 10% formalin, and stained with 2% Alizarin Red S. Mineral content was measured by acetic acid-extracted Alizarin Red S dye OD at 405 nm. Subsequently, the potential of CKD and healthy control pre-osteoblasts to transition to an adipocyte-like phenotype was examined by culturing confluent cells in the presence of insulin (1μM), dexamethasone (10-5 M), and isobutylmethylxanthine (0.5mM) for two weeks. Cells were then stained with Oil Red O; fat was extracted using 100% isopropanol for 30 minutes and absorbance measured at 490 nm.

Results: Cells from pre-dialysis CKD patients with all stages of pre-dialysis CKD mineralized more slowly (figure 1) and transitioned to an adipocyte-like phenotype more readily than healthy controls (Oil red O OD: 0.28±0.06 v. 0.18±0.03, respectively; p<0.05 between CKD and healthy controls).

Conclusions: Decreased mineralization rates and an increased propensity for pre-osteoblasts to transition to an adipocyte-like phenotype may represent bone cell maturation failure in early CKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Genzyme, Private Foundation Support

SA-PO983

Bone Biopsy Results in Chronic Kidney Disease

Orfeas Liangos,1 Silvia Kirschhoff,2 Joachim Buchholz,1 Markus Ketteler,1 Nephrology, Klinikum Coburg, Coburg, Germany; Faculty of Medicine, Univ of Wuerzburg, Wuerzburg, Germany.

Background: Although bone histology remains the gold standard in the differential diagnosis of renal osteodystrophy, biomarkers are commonly used for diagnosis and to guide therapy. However, their predictive value may be questionable. Notwithstanding these facts, data comparing bone biopsy results and biomarkers of bone metabolism remain sparse.

Methods: Here we present a retrospective analysis of bone biopsy results from a single center comprising N=109 patients, categorized according to renal function and compared with intact parathyroid hormone (iPTH), alkaline phosphatase and other biomarkers. We tested associations of these markers with renal osteodystrophy (ROD) class IIIb according to Delling’s classification. Results are shown in mean (SD) or percent, as appropriate.

Results: Mean (SD) age was 69 (13) years, 55% were women, 25% diabetic, 76% hypertensive, 34% had vertebral fracture. Mean alkaline phosphatase (AP) and bone-specific AP were 112 (83) and 21 (14) U/l, respectively, and iPTH 16 (19) pmol/l. 12% of patients had normal renal function, 37% were in CKD stage 3-5 not on dialysis and 50% were in CKD stage 5D (ESRD). iPTH values were significantly higher in ESRD with high-turnover mixed uremic osteodystrophy (ROD IIIb), 29 (18) pmol/l, if compared to patients without, 9 (9) pmol/l (p<0.001). No significant associations were found for AP or bone-specific AP levels. In CKD patients not on dialysis, the finding of ROD IIIb was associated with elevated iPTH, 37 (50) versus 9 (10) pmol/l (p=0.008), bone-specific AP, 55 (44) versus 17 (7) U/l (p=0.04), and decreased blood pH, 7.36 (0.05) versus 7.44 (0.06) (p=0.04).

As expected, no phenotypes of RA were found in patients with normal renal function.

Conclusions: While in ESRD patients, presence of high-turnover renal osteodystrophy on iliac crest biopsy was associated with elevated iPTH and serum urea level but not with bone-specific or total AP; the same diagnosis in patients with CKD not on dialysis was also associated with iPTH but, in addition, with elevated bone specific AP and decreased blood pH.

SA-PO984

Osteitis Fibrosa versus Mixed Disease: What Are the Differences?

Teg Marcos Vega,1 Adriana Belo Lopes Frazeres,1 Amadeu de Assis Marinho Neto,1 Jose Edevanilson Gueiros,2 Ana Paula Gueiros,1 Vanda Jorgetti,2 Nephrology, UFPE, Recife, Pernambuco, Brazil; 2Nephrology, USP, Sao Paulo, Brazil.

Background: Bone mineralization is fundamental for the formation of healthy bone and various factors contribute to this process. In high bone turnover, it is the mineralization deficiency present in mixed disease (MD) that distinguishes it from osteitis fibrosa (OF). The aim of this study was to identify clinical and laboratory parameters capable of clinically distinguishing between these two conditions.

Methods: Retrospective analysis of 166 patients on dialysis with a histological diagnosis of high bone turnover. The clinical data examined were age, sex, underlying disease, time on dialysis, fractures, vascular calcification on radiography and the presence of osteoporosis in the bone biopsy. Laboratory tests consisted of total calcium (Ca), phosphorus (P), intact parathyroid hormone (iPTH) and alkaline phosphatase (AP).

Results: The mean age and time on dialysis were equivalent between OF and MD of 47.5 vs 50.1 years and 9.4 vs 9.9 years, respectively. Female were more prevalent in both groups (61% vs 62.3%). No difference in the occurrence of fractures and the presence of vascular calcification. Laboratory tests are shown in table 1.

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

Underline represents presenting author.

860A
Osteoporosis was present in 29.5% of the patients with OF and 47.5% with MD (P= 0.02). Aluminum toxicity (AT) was more prevalent in OF group (51.4% vs 34.4%; P= 0.03). Calcium levels in OF and the presence of hyperparathyroidism, higher levels of AP in combination with lower levels of P suggest diagnosis of MD and may be of assistance in clinical management of CKD-MBD. Even in patients with high bone turnover, AT is still very prevalent. The deficiency in bone mineralization contributes to the occurrence of osteoporosis.

### SA-PO985

The Profile of Renal Osteodystrophy at a Single Brazilian Center: 12-Year Register

Amadeu Alves,1,2 Jia Jing Quan Feng,1,2 Wen-Chi Su,1,2,4 Xiaowei Zheng,1,2 Lihui Lin,1,2,4 Masafumi Fukagawa,1 Ichiei Narita,1 1Dept of Clinical Nephrology and Hypertension, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan; 2Dept of Health Sciences, Oita Univ of Nursing and Health Sciences, Oita, Japan; 3Ito Bone Histomorphometry Inst, Niigata, Japan; 4Div of Nephrology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan.

**Background:** We studied the calcimimetic R568 and calcitriol in Hpy mice, an animal model of X-Linked hypophosphatemia, which is characterized by elevated levels of FGF23, renal phosphate wasting, 1,25-dihydroxyvitamin D (1,25D) deficiency, and rickets. Current medical treatment with oral phosphate and 1,25D is inefficient, associated with side effects, and secondary hyperparathyroidism (sHPT). We hypothesized that mineral homeostasis is differentially affected by R568 and 1,25D in Hpy mice with respect to the PTH-vitamin D-FGF23-Klotho axis and skeletal function.

**Methods:** Male Hpy mice aged 28 days received R568 (3 and 10 ng/kg BW/d), 1,25D (150 ng/kg BW/d) or vehicle for 4 weeks. Vehicle-treated wildtype mice served as controls. Kidneys were analyzed for Cyp24, Cyp27, and Klotho by qPCR and immunoblotting. Bones were investigated by mcCT, histomorphometry, and qPCR.

**Results:** R568 and 1,25D prevent sHPT, yet only 1,25D raises serum phosphate levels in Hpy mice. Diminished tubular phosphate reabsorption was unaffected by either treatment. 1,25D increases calcitriuria and further enhances FGF23 synthesis in bone and circulating FGF23 levels. By contrast, R568 lowers bone FGF23 expression and serum C-term FGF23 concentration. Renal 1,25D production is further suppressed by 1,25D treatment and improved by R568 treatment. 1,25D but not R568 improved femur length and weight gain, and restored mineralized growth plate and mineralized bone area. R568 significantly improved trabecular but not cortical bone parameters. By contrast, 1,25D improved cortical but not trabecular bone parameters.

**Conclusions:** R568 reduces PTH and skeletal circulating FGF23, improves renal vitamin D synthesis, but only partially corrects skeletal abnormalities in Hpy mice. 1,25D improves body growth, and defective mineralization despite further enhancement of skeletal FGF23 synthesis.

### SA-PO986

Renin-Angiotensin System Inhibition Ameliorates Bone Fragility Through Blocking Both Osteocytic and Osteoblastic Actions in Uremic Rats

Takuya Nakamura,1 Yoshiko Iwasaki,1 Sakaguri Yamamoto,2 Akemi Ito,1 Takashi Hayashi,1 Akira Endo,1 Takahashi,1 Yuuki Koyama,1 Takeshi Isehara,1,2 Masafumi Fukagawa,1 Ichiei Narita,1 1Div of Clinical Nephrology and Hypertension, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan; 2Dept of Health Sciences, Oita Univ of Nursing and Health Sciences, Oita, Japan; 3Ito Bone Histomorphometry Inst, Niigata, Japan; 4Dept of Nephrology and Hypertension, Fukushima Medical University, Fukushima, Japan; 5Div of Nephrology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan.

**Background:** Chronic kidney disease (CKD) patients are at an extremely high risk of bone loss regardless of parathyroid function. Osteocyte apoptosis is elevated in uremic conditions, leading to the deterioration of elastic mechanical properties in weight-bearing bones. The pharmacological use of renin-angiotensin system (RAS) inhibitors is associated with approximately 30% reduction of fracture risk in hemodialysis patients. However, the mechanisms remains unknown.

**Methods:** Sprague-Dawley rats undergone subtotal nephrectomy were administered olmesartan (Nx-O, n=7) or hydralazine (Nx-H, n=6) for 6 weeks. The direct effects of RAS on osteoblasts were observed using MC3T3-E1 cells and primary osteocytes obtained from Nx-O and Nx-H femur.

**Results:** Comparable levels of kidney damage and blood pressure were observed in the Nx-O and Nx-H rats. Compared to Nx-H,Nx-O showed less osteoclast activity (erosion depth: 8.47±1.01 μm vs Nx-H 12.39±2.37 μm, p<0.001). Further, the bone turnover was increased in Nx-H (Tm 3.01×10⁹±1.00×10⁹ Pa vs Nx-H 1.19×10⁹±0.79×10⁹ Pa, p=0.046), and reduced osteocyte apoptosis (empty lacunae; 36.61±12.2MM vs Nx-H 67.9±13.6MM, p<0.01). Angiotensin II (ATII) significantly increased the expression of FRANKL in MC3T3-E1 cells. ATII increased ROS production and osteocyte apoptosis, and blunt the FRANKL anti-apoptotic effect. These changes were inhibited by olmesartan.

**Conclusions:** All modulates bone metabolism through both direct action on osteoblasts and pathways via the promotion of osteocytic apoptosis leading to deteriorated bone mechanical properties, which were improved by ATII receptor-1 blockade.
SA-PO989

The Rapid Down-Regulation of Klotho in an Obstructed Kidney Is Not Accompanied by a Compensatory Up-Regulation in the Contralateral Kidney

Anders Nordholm,1 Maria Lerche Mace,1,2 Eva Gravesen,2 Jacob Hofman-Bang,2 Klaus Olgaard,2 Eva Lewin.1 1Dept of Nephrology, Herlev Hospital, Univ of Copenhagen, Denmark; 2Dept of Nephrology, Rigshospitalet, Univ of Copenhagen, Denmark.

Background: The anti-ageing hormone, Klotho, is a renoprotective protein alleviating acute kidney injury and promoting kidney regeneration. The kidney is a major source of Klotho. In the present study the time course of Klotho changes in experimental unilateral ureter obstruction (UUO) and in the contralateral kidney (CK) was followed.

Methods: UUO rats (n = 57) were studied at 0, 1, 2, 3, 4, and 10 days (D) and the results of the obstructed kidney were compared to those of CK and to kidneys from unilateral nephrectomized (UNX) control rats (n = 35) as well as normal kidneys. Kidney Klotho, the renoprotective BMP7 and LGR5 together with markers of fibrosis, TGF-β and Periostin, gene expressions were examined.

Results: Unilateral ureter obstruction resulted in significantly decreased Klotho expression already at day 1, which decreased further progressively to day 10. Baseline: 191 ± 0.30; D1: 0.91 ± 0.18 (p < 0.01), D10: 0.02 ± 0.02 (p < 0.01). LGR5 was reduced from 8.07 ± 0.30 at baseline to 0.19 ± 0.01 at D1 (p < 0.01) in the obstructed kidney, suggesting stem cell depletion. The decrease in Klotho expression in UUO kidney was associated with a decreased expression of BMP7 (Baseline: 0.87 ± 0.11, D1: 0.57 ± 0.07, D10: 0.63 ± 0.08, p < 0.01) and an increased expression of TGF-β (Baseline: 0.51 ± 0.07, D1: 0.69 ± 0.11, D10: 1.51 ± 0.17, p < 0.01) and induction of Periostin (0.09 ± 0.10 to D1: 0.67 ± 0.40, p < 0.05). The expressions of BMP7, TGF-β, Periostin and LGR5 were similar in contralateral, UNX and normal kidneys. The contralateral kidney had similar expression of Klotho (D1: 2.20 ± 0.27 and D10: 1.80 ± 0.15) compared to normal and UNX kidneys (D1: 1.91 ± 0.28 and D10: 2.05 ± 0.83).

Conclusions: In an unilateral ureter obstruction model a very rapid and significant decrease in the expression of Klotho took place already at day 1 in the obstructed kidney. The unilateral ureter obstruction was associated with upregulation of pro-fibrotic genes and down-regulation of anti-fibrotic BMP7. The contralateral kidney did not respond with a compensatory increase in Klotho.

SA-PO990

Comparison of the Two Types of Iron-Based Phosphate Binders, Sucroferric Oxxyhydroxide and Ferric Citrate, on Lowering Serum Phosphate Effects in Patients on Hemodialysis

Kazuyo Teshima,1 Satoshi Funakoshi,1 Jyunichiro Harada,1 Kenji Sawase,1 Hiroshi Ichinose,1 Osamu Sasaki,1 Kenta Tsukuda,1 Rei Moriyan1a,1 Chiuga Fukagawa,1 Yoko Obata,2 Tomoya Nishino.3 1Nagasaki Univ Hospital, Nagasaki, Japan; 2Nagasaki Kidney Center, Nagasaki, Japan; 3Nagasaki Univ Hospital, Nagasaki, Japan.

Background: Sucroferric oxyhydroxide(SO), a new type of iron-containing phosphate binder, is reported to exerts stronger phosphate lowering effect compared with ferric citrate hydrate (FCH) in equivalent dose resulting in lower pill burden.

Methods: To compare the effects of SO and FCH on medication adherence as well as serum phosphate-lowering effects in patients on hemodialysis (HD) in a crossover study. Thirty-two subjects were already treated with 1500 mg to 2250 mg of FCH daily. Subjects were switched to 750 mg to 1000 mg of SO daily for 4-6 weeks, then previous treatment with FCH. Measurement of plasma bone mineral parameters including phosphate and calcium concentrations in SO or FCH (FCH: 5.6 ± 1.3 – SO: 5.6 ± 1.4 – FCH: 5.5 ± 1.1 mg/dL). A significant increase was observed in medication adherence in SO compared to FCH (79 ± 10 %; SO: 95 ± 15 – FCH: 84 ± 14 %). No significant difference was observed in other bone mineral parameters.

Conclusions: Thus, SO can potentially exert similar phosphate-lowering effects to FCH with better medication adherence and lower pill burden in patients on maintenance HD.

Funding: Private Foundation Support

SA-PO991

Bone Biopsy Findings and Biochemical Markers before and after Two Years of Renal Transplantation

Santu Keromen,1 Leena Martola,1 Patrik Finne,1 Inari S. Burton,2 Tobias E. Larsson,3 Heikki Kroger,3 Eero Honkanen,1 1Abdominal Centre, Nephrology, Helsinki Univ Central Hospital and Helsinki Univ, Helsinki, Finland; 2Univ of Eastern Finland, Terveystalo Jyväskylä, Jyväskylä, Finland; 3Astellas Pharma, Sweden; 4Kuopio Univ Hospital, Kuopio, Finland.

Background: There are only few studies on bone biopsies before and after renal transplantation (RTX). The aim of this study was to investigate the changes in histomorphometric pattern of bone disease after RTX.

Methods: Bone biopsy was taken from the iliac crest and analyzed using the turnover -mineralization -volume classification on 25 consecutive dialysis patients (80 men, 48% on PD) at baseline and 25 (24-26) months after RTX. The median time on dialysis prior to RTX was 24 (15-42) months. Median GFR was 64 (41-70) ml/min per 1.73 m² (MDRD). Immunosuppressive therapy comprised CNI, MMF, and prednisone. Serum markers of bone turnover were obtained.

Results: The changes in bone histomorphometry before and after RTX are shown in Figure 1. Bone biopsy findings were divided into three subgroups based on bone turnover. Biochemical findings after RTX are shown in Table 1. At baseline, 44% of dialysis patients had OF or MUO, 28% mild OF or normal turnover and 28% of patients had OM or ABD. After two years of RTX 24%, 56% and 20% of patients had OF/MUO, mild OF/normal or OM/ABD, respectively. Following RTX osteocalcin and bone alkaline phosphatase (BAP) were significantly higher in OF+ MUO group.

Figure 1. The changes in bone histomorphometry before and after renal transplantation

<table>
<thead>
<tr>
<th>BONE HISTOMORPHOMETRY</th>
<th>DURING DIALYSIS</th>
<th>AFTER TRANSPLANTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OM (1)</td>
<td>ABD (6)</td>
</tr>
<tr>
<td></td>
<td>ABD (5)</td>
<td>anabolic bone disease</td>
</tr>
<tr>
<td></td>
<td>MILD (5)</td>
<td>mild osteosclerosis</td>
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<tr>
<td></td>
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<td></td>
<td>OF (2)</td>
<td>osteoid fibrosis</td>
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<tr>
<td></td>
<td>MUO (4)</td>
<td>non-osteoabodrophy</td>
</tr>
<tr>
<td></td>
<td>NORMAL (6)</td>
<td>normal bone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>All n = 25 (median + IQR)</th>
<th>OM + ABD n=5</th>
<th>MILD OF + normal n=14</th>
<th>OF + MUO n=6</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR ml/min per 1.73m²</td>
<td>64 (41-70)</td>
<td>48</td>
<td>68</td>
<td>35</td>
<td>0.19</td>
</tr>
<tr>
<td>osteocalcin ug/l</td>
<td>41 (35-74)</td>
<td>37</td>
<td>37</td>
<td>86</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BAP ug/l</td>
<td>15 (11-27)</td>
<td>14</td>
<td>14</td>
<td>36</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Conclusions: After two years of renal transplantation bone turnover normalized in almost 80% of the patients. Lower GFR might explain higher osteocalcin and BAP seen in OF+ MUO group.

Funding: Pharmaceutical Company Support - Shire Pharmaceuticals

SA-PO992

Kidney Transplantation Alters the Association between Serum Sclerostin and Bone Sclerostin Expression

Mathias Haarhans,1 Henrik Boltenstiel,1 Abdul Rashid Tony Qureshi,1 Gerit J. Behets,2 Bengt Lindholm,1 Peter Stenvinkel,1 Patrick C. D’Haese.1 1Div of Renal Medicine and Baxter Novum, Karolinska Univ Hospital at Huddinge, Karolinska Inst, Stockholm, Sweden; 2Laboratory of Pathophysiology, Dept of Biomedical Sciences, Univ of Antwerp, Antwerp, Belgium.

Background: The osteocyte derived protein sclerostin inhibits bone turnover. Serum sclerostin rises early in chronic kidney disease (CKD) but to what extent this reflects osteocyte sclerostin production is not clear. We investigated associations between serum sclerostin, bone sclerostin expression and different types of renal osteodystrophy.

Methods: Immuno histochemical staining of sclerostin was performed in bone biopsies from 43 CKD patients (pts), including 15 pts undergoing dialysis and 20 pts who had received a kidney transplant. Bone sclerostin expression was correlated to bone histomorphometric parameters and serum sclerostin levels.

Results: Pts with low bone formation rate (BFR <97μm²/mm²/day) had higher serum and bone sclerostin expression than pts with normal or high BFR.

<table>
<thead>
<tr>
<th>Low BFR (N=13)</th>
<th>Normal/ high BFR (N=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>serum sclerostin (pg/ml)</td>
<td>224.7 (126.5-393.0)</td>
<td>141.7 (55.3-302.9)</td>
</tr>
<tr>
<td>sclr / BAP (number/mm²)</td>
<td>12.1 (1.3-68.1)</td>
<td>3.0 (18.3-6.0)</td>
</tr>
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</table>

Whereas a strong association between serum and bone sclerostin expression was observed in non-transplanted pts (figure 1) no such association was observed in transplanted

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Underline represents presenting author. 862A
pts, independent of kidney graft function. Females had higher bone sclerostin expressions than males (P = 0.046), despite similar serum sclerostin levels and bone histomorphometric parameters.

Conclusions: Serum sclerostin and bone expression of sclerostin are inversely associated with bone turnover in CKD. In non-transplanted CKD pts, serum sclerostin reflects bone sclerostin expression. Bone sclerostin expression is affected by gender in CKD. Funding: Government Support - Non-U.S.

SA-PO993
Kidney Transplantation Increases Bone Esclerostin Expression

Background: Most of the metabolic disorders improve after kidney transplantation (Tx), although bone metabolism can remain compromised, which is evidenced by high rates of bone loss, fractures and vascular calcification. Osteocytic bone protein expression is dysregulated in CKD, and this seems to contribute negatively to bone health in these patients. It has been described that FGF-23 and sclerostin (Scl) expression is increased in children after solid organ transplantation. Nonetheless, little is known about bone-related proteins expression in adult recipients, which were analyzed prospectively in this study.

Methods: Transplacian bone biopsies were obtained from 30 adult patients one week before and one year after Tx. Bone fragments were used for histomorphometric analysis, as well as for bone proteins, measured by immunohistochemistry and MILLIPLEX® MAP.

Results: Patients were relatively young (41 ± 11 yrs), with a pre Tx dialysis vintage of 30 (15-55) months. After a successful Tx, there was an increase in serum calcium and a decrease in PTH and alkaline phosphatase. No changes were seen in bone DKK1, whereas a decrease was observed in osteoprotegerin (OPG) and FGF-23. Although serum Scl decreased after KTx [1.2 (0.6-1.9) vs. 0.5 (0.4-0.6) ng/ml; P = 0.001], an increase of this protein in bone was observed with both methods.

Conclusions: Kidney function recovery after Tx is accompanied by significant changes in most bone proteins expression. Contradictory to the decrease in levels of serum Scl, its bone expression, actually, has increased. This finding may explain the persistence of bone metabolism in CKD patients.

SA-PO995
Cinacalcet Hydrochloride Increases Sharpey Fiber Area in Patients with Secondary Hyperparathyroidism
Aiji Yajima,1 Ken Tsuchiya,1 Kosaku Nitta,2 Biomedical Engineering, Indiana Univ, Indianapolis, IN; 2Medicine, Kidney Center, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Some papers regarding the relationship between sclerostin (Scl) and bone turnover and osteocytic pericellular/canalicular remodeling was published (Poole KE. FASEB 2005, Kagawa M. Bone Miner Res 2013, Nakashima T. Nat Med 2011, and etc.). However, only one basic paper regarding the relationship between Scl and marrow adipocyte has been published (Ukita M. Sclerostin enhances adipocyte differentiation in 3T3-L1 cells. J Cell Biochem 2016). And parathyroidectomy increased marrow adipocyte differentiation in dialysis patients (Yajima A. presented). We analyzed the relationship between serum Scl or i-PTH and marrow adipocyte parameters in hemodialysis patients.

Methods: We measured serum Scl (ELISA, BIOMESA Medizinprodukte, Vienna, Austria) and intact parathyroid hormone (iPTH) (Electrochemiluminescence immunoassay, Elecsis PTH, Roche Diagnostics GmbH, Mannheim, Germany) levels in 23 hemodialysis patients (Age: 60.5±6.0 yrs, dialysis duration: 10.7±3.3 yrs). At the same time, iliac bone biopsy specimens were obtained from the patients to measure (1) adipocyte volume/marrow volume (Ad.V/Ma.V (%)), (2) Number of adipocyte/Ma.V (N/Ad/Ma.V (N/mm²) and (3) mean adipocyte area (Ad.V/Ad (μm²)). The relationship between serum parameters and adipocyte parameters were analyzed by linear regression analysis.

Results: In 1, Serum Scl was 70.6±44.3 ng/mL, ranging from 25.0 to 172.2 and i-PTH was 589.3±479.2 pg/mL, ranging from 5 to 1430. Ad.V/Ma.V was 37.8±18.5 %, N/Ad/Ma.V was 212.6±57.8 N/mm², and Ad.V/Ad was 1815.6±644.3 μm². IL 1, Serum Scl was positively associated with Ad.V/Ma.V (r=0.752, p=0.001) and Ad.V/Ad (r=0.582 (p=0.005)). But Scl was not associated with N/Ad/Ma.V. 2, Serum i-PTH was negatively associated with Ad.V/Ma.V (r=0.526, p=0.01) and Ad.V/Ad (r=0.511 (p=0.01)). But i-PTH was not associated with N/Ad/Ma.V.

Conclusions: In dialysis patients, marrow adipocyte parameters were strongly associated with serum Scl as compared with i-PTH levels. It is highly possible that sclerostin regulates the metabolism of marrow adipocyte. Sclerostin is important because adipocyte suppresses osteoblast function. Funding: Private Foundation Support

SA-PO996
Increase of Bone Marrow Adiposity Is Associated with Decrease of Bone Formation and Volume in Pre-Dialysis Chronic Kidney Disease Patients
Joao Victor Salgado, Maria Dalboni, Aluzio B. Carvalho, Maria Eugenia F. Canziani. Discipline of Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Sao Paulo, Brazil.

Background: Metabolic disorders and accumulation of uremic toxins might contribute to bone fat deposition and skeletal fragility in CKD patients. We aimed to investigate the relationship between bone marrow adiposity and bone Turnover, Mineralization and Volume (TMV system) in CKD patients not yet in dialysis.

Methods: Twenty-two transilic bone biopsy specimens obtained in a cross-sectional study previously performed in 2-5 stages CKD patients (52±11 yrs; 59% male; 32% diabetes, 33±17 ml/min/1.73m²) were evaluated by quantitative histomorphometry to assess bone and marrow adipocyte parameters. For TMV system, bone formation rate (BFR/BS) was considered as Turnover, mineralization lag time (MLT) as Mineralization and trabecular bone volume (BV/TV) as Volume. Adipocyte parameters were calculated as marrow adipocyte volume / total volume (Ad.V.TMV) was used as adipocyte parameters. Serum bone and biochemical markers were measured.

Results: Ad.N and Ad.V.TMV did not differ significantly with regards to age, gender, diabetes mellitus and CKD stages. Ad.N correlated negatively with LDL-cholesterol (r = 0.48, p=0.02) and BV/TV (r = 0.58, p=0.005). Ad.V.TMV correlated negatively with BV/TV (r = -0.46, p=0.002) and BFR/BS (r = -0.46, p=0.03). Adipocyte parameters, Ad.N and Ad.V.TMV, did not correlate with MLT.

Conclusions: Increase of bone marrow adiposity seems to be associated with decrease of bone formation and volume but not with mineralization in pre-dialysis CKD patients.

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

863A
SA-PO997

Association of Pre-ESRD Red Cell Distribution Width and Early Dialysis Mortality: A Transition of Care in CKD Study  Melissa Soo Boo, 1  Miklos Zsolt Molnar, 1  Elani Streja, 3  Connie Rhee, 1  Daniel L. Gillen, 1  Csaba P. Kovesdy, 1  Kamyar Kalantar-Zadeh. 1  "UC Irvine; "Univ of Tenn.

Background: Recent studies have shown that red blood cell distribution width (RDW), a marker of red blood cell size and variability and likely an iron store marker, is a predictor of mortality in the hemodialysis population. However, the association of RDW in the prelude period prior to transitioning to end-stage renal disease (ESRD) and post-ESRD mortality is unknown.

Methods: We examined a cohort of 18,924 US Veterans transitioning to ESRD between 2007-2011 with RDW measured in the 6 months prior to dialysis initiation (prelude period). We analyzed the association of RDW with all-cause and cardiovascular mortality in a cohort using Cox proportional hazards and Fine & Gray competing risk regression models, respectively. Each analysis was adjusted for case-mix (demographics and comorbidities) and laboratory measurements. RDW was divided into 5 categories (<13.5, 13.5-<14.5, 14.5-<15.5, 15.5-<16.5, and ≥16.5 %).

Results: The mean age (mean±SD) of the cohort was 68±11years old and included 2% females, 71% diabetics and 25% African Americans. Across all levels of adjustment, higher 6-month prelude RDW was linearly and incrementally associated with higher all-cause mortality compared to the reference group (14.5-<15.5 %). This association was consistent for 3-, 6-, 12 and 24-month all-cause mortality. In addition, 6-month prelude RDW was also linearly associated with post-ESRD cardiovascular mortality, although the magnitude was somewhat attenuated.

6-month Averaged Prelude Red Cell Distribution Width (%)

Conclusions: In very advanced CKD patients, higher RDW is associated with higher all-cause and cardiovascular mortality in patients transitioning to ESRD independent of comorbidities and laboratory measures. Future studies are needed to confirm these findings as well as to further understand the mechanism underlying these RDW associations.

Funding: NIDDK Support

SA-PO998

Correlates of Red Blood Cell Life Span in Chronic Hemodialysis Patients  Jie Mu, 1,3  Yanna Dou, 1  Hanjie Zhang, 1  Stephan Thijsse, 1  Schantel Williams, 1  Viktoryia Kuntsevich, 1  Nathan W. Levin, 1  Peter Kotanko, 1,2  Research Dept, Renal Research Inst, New York, NY; 1Mount Sinai Beth Israel, New York, NY; 1Nephrology, Peking Union Medical College Hospital.

Background: The pathogenesis of anemia in hemodialysis (HD) patients is multifactorial, with decreased red blood cell life span (RBC-LS) being a significant contributor. The impact of reduced RBC-LS is recognized but not well researched. The objective of this study was to investigate the relationship between RBC-LS and ESA dose and inflammatory markers in HD patients.

Methods: The RBC-LS (calculated from measured alveolar carbon monoxide concentrations), inflammatory markers IL-6, IL-18, IL-10 (measured by LuminexÒ) and hsCRP were assessed at baseline and during follow up. Monthly hemoglobin (Hgb) levels, weekly ESA dose and clinical parameters were obtained from electronic health records. The association between RBC-LS, weekly ESA dose and inflammatory biomarkers was evaluated by using linear mixed effects models.

Results: Forty-five HD patients were enrolled with an average age of 58.5±13.9 years, 71% male, 46.7% diabetics, and a mean HD vintage 47 ± 46 months. In 22 patients up to 5 repeated RBC-LS measurements were available. RBC-LS was 74± 23 days (range 30 to 125). RBC-LS was inversely correlated with the ESA requirement.

By Month 16 (Cohort 1), ESA doses increased to 82% of their baseline levels. Hgb levels were 11.3±0.5 g/dL. Iron dose returned to 120% of pre-treatment levels. Patients of a shorter dialysis vintage (<4 years, n=31, -16%) compared to patients of a longer vintage (4-17 years, n=109 patients) reverted to the control bloodlines (Nikkiso/Gambro) in the crossover phase for a further 8 months. Cohort 2 (33 patients) remained on the Oxyless bloodlines for 14 months without crossover.

Results: Mean ESA dose fell by 34% (p<0.01) by Month 8, further reducing to 53% (p<0.05) by Month 14. Hemoglobin (Hb) levels were stable throughout at 11.5 g/dL. IV iron dose fell by 12% (Month 8) and 25% (p<0.05) by Month 14 each compared to baseline.

Funding: Pharmaceutical Company Support - Oxyless Ltd
SA-PO1000
Modeling Outcomes by Dopps-Identified Modifiable Dialysis Practices in the Monitor-CKD5 Study
Christian Combe,1 Johannes F. Mann,2 Gerard M. London,3 David Goldsmith,4 Philippe Zouari,5 Frank Dellanna,6 Michael Gorry,7 Nadja Hoebel,5 Karen Macdonald,4 Ivo Abraham.6
1Centre Hospitalier de Bordeaux, Univ of Bordeaux, Bordeaux, France; 2Friedrich Alexander Univ Erlangen-Nürnberg, Erlangen, Germany; 3Centre Hospitalier FH Manns, Fleuré-Mérogis, France; 4Guy’s and St. Thomas’ NHS Foundation Hospital, London, United Kingdom; 5Univ de Grenoble-Aples, Grenoble, France; 6Dialysezentrum, Düsseldorf, Germany; 7Sanwo/Hexal AG, Holzkirchen, Germany; 8Univ of Arizona, Tucson, AZ.

Background: Six modifiable hemodialysis (HD) practices were found to be predictive of mortality in the Dopps (Port et al. Blood Purif. 2004). We assess associations between the 6 modifiable practices and 4 outcomes in Monitor-CKD5, a prospective 2-year real-world study of 2033 HD patients with renal anemia in 10 European countries.

Methods: Exploratory analysis between 6 modifiable HD practices (adequate dialysis dose, partial correction of serum albumin, phosphate control, reduced interdialytic weight gain, use of fistula, anemia correction) at baseline and 4 outcomes: chronic hypo-response to erythropoiesis stimulating agents (ESAs), thrombo-embolic event (TEE), hospitalization, and mortality. Each outcome was modeled with each HD practice using multi-level logistic regression corrected for center effect.

Results: Table 1 presents modeling results. Rates of modifiable HD practices and outcomes are also listed.

SA-PO1002
Transfusion Practice for Incident Dialysis Patients in Canada: A Prospective Observational Study
Aminu K. Bello,1 Christine M. Ribic,2 Serge Cournoyer,1 Mercedeh Kiatii,3 Martine Leblanc,4 Melanie Poulin-Costello,5 David N. Churchill,1 Norman Muirhead,6 1Univ of Alberta, Edmonton, AB; 2McMaster Univ, Hamilton, ON; 3Univ de Sherbrooke, Sherbrooke, QC; 4Univ of British Columbia, Vancouver, BC; 5Univ de Montréal, Montréal, QC; 6Ampen Canada Inc.; 7Univ of Western Ontario, London, ON.

Background: KDIGO guidelines in 2012 recommended conservave ESA use. Study objectives were to identify blood transfusion (BT) rates in incident dialysis patients in Canada after 2012 factors associated with BT and the clinical context.

Methods: Data were obtained by monthly chart review. Transfusion data were recorded as units transfused and as transfusion episodes (≥ 2 units within 24 hrs.)

Results: 314 patients were enrolled; 80% completed 12 months follow-up. 65% were male and 75% were Caucasian with mean age of 64 yrs. 75% received pre-dialysis care for > 12 months. Overall, 30% received at least 1 unit during follow-up. During the first 90 days, 168 units were transfused over 76 patient-years (PY) (221 units/100 PY). From day 91-365, there were 215 units transfused over 208 PY (104 units/100 PY). Expressed as transfusion episodes, the rates per 100 PY were 148 for the first 90 days and 63 for days 91-365. Univariate Cox regression for time to first transfusion showed an association with older age, no pre-dialysis care, BT prior to starting HD, use of temporary dialysis catheter and starting dialysis as an inpatient (p < 0.05). The most common reason for transfusion was a low hemoglobin value (92%) with concurrent clinical reasons being gastrointestinal bleeding (10%) and peri-surgical blood loss (9%).

Conclusions: The transfusion rate was higher in the first 90 days. The time to first transfusion was associated with age and factors associated with pre-dialysis care. The most common indication was a low haemoglobin value rather than clinical factors. Funded: Pharmaceutical Company Support - Amgen

SA-PO1003
Effect of Altitude on Dosage Requirement of C.E.R.A. (Continuous Erythropoietin Receptor Activator) to Correct Hemoglobin (Hb) Levels in Chronic Kidney Disease (CKD) Patients (pts) Maria Guadalupe Suarez,4 Alfredo Chew-Wong,5 Raymundo Alfredo Alives,6 Luis E. Morales-Buenrostro,7 Francisco Eduardo Quintana,1 Sandro Avila Pardo,8 Manuel Avendano Garcia,9 Octavio Cabrera-Anaya,1 1Hospital Angeles Lindavista, Mexico City, Mexico; 2Clinica San Cosme, Aguascalientes, Mexico; 3Hospital San Juan Marin, Pto Vallarta, Mexico; 4Nefros Investigacion S.C., Mexico City, Mexico; 5Hospital Star Médica, Morelia, Mexico; 6Hospital Reg Alta Esp, Veracruz, Mexico; 7Centro de Hemodiálisis del Norte, Mexicali, Mexico; 8Rocche Servicios de México SA de CV, Mexico City, Mexico.

Background: Severe anemia in CKD pts is associated with increased risk of adverse clinical events and mortality. Iron and erythropoiesis-stimulating agents (ESAs) are the standard of care for dialysis pts. Hemodialysis (HD) pts living at higher altitudes have higher Hb levels and lower ESA requirements. The long-life, low binding affinity and low systemic clearance of C.E.R.A. allow once-monthly dosing. The primary objective of the multicenter Phase IV ALTITUDE trial (NCT01519947) was to determine the C.E.R.A. dose needed to achieve an Hb of 11–12 g/dL in ESA-naive CKD pts living either <5000 ft above sea level (masl) or ≥1800masl.

Methods: C.E.R.A. was administered according to label to 86 pts (29 <5000ft; 57 ≥1800masl) for 4 weeks. The primary endpoint was the percentage of pts who achieved the target Hb range of 11-12g/dL

Conclusions: Lower C.E.R.A. doses are required to correct Hb in CKD pts living at altitude than at sea level.

C.E.R.A. dose required (µg)

<table>
<thead>
<tr>
<th>Dose (µg)</th>
<th>Percentage of pts achieving target Hb (11-12 g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>100%</td>
</tr>
<tr>
<td>70</td>
<td>97.4%</td>
</tr>
<tr>
<td>100</td>
<td>71.4%</td>
</tr>
<tr>
<td>180</td>
<td>57.1%</td>
</tr>
</tbody>
</table>

*p<0.05

Conclusions: Lower C.E.R.A. doses are required to correct Hb in CKD pts living at altitude than at sea level.
Dialysis: Anemia, Iron Metabolism
Poster/Saturday

SA-PO1004

Efficacy of Continuous Erythropoietin Receptor Activator (CERA) on End-Stage Renal Disease Patients with Renal Anemia before and after Peritoneal Dialysis (PD) Initiation

Bolzano; 2Verbania; 3Colleferro; 4Massa; 5Montevarchi; 6Vercelli; 7Rovigo; 8Messina; 9A U.S. Phase III Trial to Compare HX575 (Proposed Biosimilar Epoetin Alfa) with Epogen®/Procrit® in Renal Anemia Patients

Matthew R. Weis,1 Rajiv Agarwal,2 Jeffrey C. Fink,3 Nelson P. Kopyt,1 Susanne Schmitz,4 Gregor Schaffar,5 Jim Mckay,6 Radmila Kanceva,7 Pablo E. Pergola,4 'Univ of Maryland School of Medicine, Baltimore, MD; 3Indiana Univ School of Medicine, Indianapolis, IN; 4Lehigh Valley Hospital, Allentown, PA; 5Sandoz/Hexal AG, Holzkirchen, Germany; 6Sandoz Inc, Princeton, NJ; 7Univ of Texas Health Science Center at San Antonio, San Antonio, TX.

A U.S. Phase III Trial to Compare HX575 (Proposed Biosimilar Epoetin Alfa) with Epogen®/Procrit® in Renal Anemia Patients

Matthew R. Weis,1 Rajiv Agarwal,2 Jeffrey C. Fink,3 Nelson P. Kopyt,1 Susanne Schmitz,4 Gregor Schaffar,5 Jim Mckay,6 Radmila Kanceva,7 Pablo E. Pergola,4 'Univ of Maryland School of Medicine, Baltimore, MD; 3Indiana Univ School of Medicine, Indianapolis, IN; 4Lehigh Valley Hospital, Allentown, PA; 5Sandoz/Hexal AG, Holzkirchen, Germany; 6Sandoz Inc, Princeton, NJ; 7Univ of Texas Health Science Center at San Antonio, San Antonio, TX.

Background: There have been few reports on the management of renal anemia using CERA throughout the period from pre- to post-PD initiation. We investigated the usefulness of CERA in PD patients to examine its efficacy and dosage before and after PD initiation.

Methods: 16 patients (6 males; mean age, 59.9 years) who started PD between 2011 and 2015 were investigated. Hemoglobin (Hb) levels, iron parameters (transferrin saturation and ferritin), CERA dosage, and erythropoietin resistance index (ERI) (CERA amount / body weight kg / Hb (g/dL) / 4) for 24 weeks were examined retrospectively before and after PD initiation.

Results: The mean Hb levels were 10.4 ± 0.9 g/dL at 24 weeks prior to PD initiation, 10.2 ± 0.9 g/dL at PD initiation and 11.7 ± 0.9 g/dL at 4 weeks after that, showing a significant increase after PD initiation. The proportion of patients whose Hb levels were 11g/dL or higher increased from 40.0% to 81.2% after PD initiation. The mean CERA dosage was 73.3 μg/month(M) at 24 weeks prior to PD initiation, 87.5 μg/M at initiation, and 71.9 μg/M at 4 weeks after that. Thus, CERA dosage tended to increase just before PD initiation and then decreased after that. In non-diabetic patients, CERA dosage to maintain Hb levels decreased after PD initiation by approximately 25% compared to that prior to PD initiation. In contrast, it did not change after PD initiation in diabetic patients. ERI was 0.027 at 8 weeks prior to PD initiation, 0.036 after PD initiation and then decreased after that. With regard to iron metabolism, no significant changes in TSAT or ferritin levels were observed, suggesting relatively stable iron metabolism with CERA treatment during PD initiation.

Conclusions: Treatment with CERA prior to PD initiation resulted in fair anemia management for both diabetic and non-diabetic patients. Our data also suggest that CERA dosage might be reduced in non-diabetic patients after initiation of PD.

SA-PO1005

Dosing Penalty after Switching from ESA Originator to Biosimilar: Matched Cohort Study in Stable Hemodialysis Patients

Roberto Minutolo,1 Piergiorgio Bolaso,2 Domenico Santoro,3 Maurizio Mb Borzumati,4 Alberto Santobono,1 Stefano Sposini,4 Carlo Mura,4 Oliviero Filiberti,5 Fulvio Fiorini,6 Gianni Carraro,6 Luca De Nicola,1 Domenico Russo,1 'Nephrology Div, Hospitals of Il Univ of Naples; 3ASL Cagliari,1 Univ of Messina; 2Verbania; 4Colleferro; 5Massa; 6Montevarchi; 7Vercelli; 8Rovigo; 9Padova; 10Univ Federico II, Italy.

Background: In hemodialysis (HD), switch from ESA originator to biosimilar associators with dosing penalty (DP) of about 10% according to industry-driven studies. However, DP in daily clinical practice is ill-defined.

Methods: From 12 non-profit centers, we selected consecutive ESA treated HD patients (2011-14) receiving stable i.v. ESA dose and not transfused in the previous 3 months. Patients switched from originators to biosimilars (BIO, n=153) were matched with those (2011-14) receiving stable i.v. ESA dose and not transfused in the previous 3 months.

Results: Mean ESA dosage to maintain Hb levels decreased after PD initiation. The same held true for iron therapy, and ferritin (398±244 and 382±282 ng/mL, respectively) were similar at each visit and unchanged versus baseline. The same held true for iron therapy, and ferritin (398±244 and 382±282 ng/mL, respectively) were similar at each visit and unchanged versus baseline. The same held true for iron therapy, and ferritin (398±244 and 382±282 ng/mL, respectively) were similar at each visit and unchanged versus baseline. The same held true for iron therapy, and ferritin (398±244 and 382±282 ng/mL, respectively) were similar at each visit and unchanged versus baseline. The same held true for iron therapy, and ferritin (398±244 and 382±282 ng/mL, respectively) were similar at each visit and unchanged versus baseline. The same held true for iron therapy, and ferritin (398±244 and 382±282 ng/mL, respectively) were similar at each visit and unchanged versus baseline. The same held true for iron therapy, and ferritin (398±244 and 382±282 ng/mL, respectively) were similar at each visit and unchanged versus baseline. The same held true for iron therapy, and ferritin (398±244 and 382±282 ng/mL, respectively) were similar at each visit and unchanged versus baseline. The same held true for iron therapy, and ferritin (398±244 and 382±282 ng/mL, respectively) were similar at each visit and unchanged versus baseline.
Conclusions: Combinations of C.E.R.A., DA, EB, and EA are used in European faces to maintain an Ht at recommended levels. As C.E.R.A. and EA biosimilars become available in the US, this real-world practice data can provide useful insight for US clinicians interested in the use of these medications.

Funding: Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Protein, Relynx, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain. All grants are made to Arbor Research Collaborative for Health and not to Mr. Fuller directly

SA-PO1008

Serum Concentration of Non-Transferrin Bound Iron in HD Patients Is Higher Than Normal Control and Is Increased after Intravenous Iron Administration

Noriroko Saito,1 Shigeru Miyazaki,2 Kazuhide Saito,2 Tetsuo Morioka,1 Tetsuo Morioka,1 Hikaru Shimaguchi,1 Yutaka Tsubata,1 Yutaka Tsubata,1 Kazuhiro Yoshita,1 Yutaka Kohgo.3 1Shinraku-en Hospital, Niigata, Japan; 2Niigata Univ, Niigata; 3International Univ of Health and Welfare Hospital, Nasushibara, Japan.

Background: Non-transferrin bound iron (NTBI), which appears in the serum under iron overload, is associated with organ damage through free radical production. Intravenous iron administration (IVIA) is a common treatment for severe anemia in hemodialysis (HD) patients.

Methods: NTBI, Hepcidin25, soluble Transferrin Receptors (sTfR), 8-oxo-2'-deoxyguanosine, high sensitive CRP, serum iron, TSAT and ferritin were evaluated in 44 HD patients who were not received iron administration nor erythropoietin stimulating agents (ESA) for at least 2 months and as a control 30 healthy volunteers. NTBI was measured by recently described assay system (Clin Chim Acta 437(2014) 129). 23 HD patients without any iron load within 2 weeks were administered saccharated ferric oxide (Fe 40 mg) intravenously after HD session. 19(83%) patients had received ESA. We evaluated the NTBI and above markers before and at 0.5, 1, 2, 4, 6, 24, 44 hours after IVIA.

Results: The NTBI levels in HD patients was higher than that in control in 3(3.0~3.9) vs 2(2.5~3.0) mg/ml p<0.001. In HD patients NTBI correlated with Tf and the predictor of NTBI was Tf by stepwise analysis (r=0.38, p=0.030, R2=0.107). TSAT before IVIA was 20(14~27%), and increased to 81(65~100%) at 0.5 hours after IVIA and then decreased to the level before IVIA at 44hours. NTBI before IVIA was 1.5(1.1~2.25) μg/dL, increased to 2.2(1.8~2.7) μg/dL at 4 hours (p=0.021) and decreased to 1.8(1.2~2.25) μg/dL at 44 hours. Maximum increase rate of NTBI (NTBI at peak - NTBI before IVIA)/ NTBI before IVIA was 80(50~146%). By stepwise analysis, sTfR before IVIA was a negative predictor for NTBI increase rate (β=-0.494, p=0.016, R2=0.244). (Medians (interquartile range) or numbers(%)).

Conclusions: NTBI in HD patient was higher than healthy control, correlates to Tf and significantly increase at 4 hours after IVIA. The predictor of NTBI maximum increase rate was sTfR of before IVIA. NTBI could be a novel marker to assess iron metabolism in HD patients.

Funding: Private Foundation Support

SA-PO1009

The FACT-Study: A Randomized Controlled Trial of Repeated Doses of Ferumoxytol or Iron Sucrose in Patients on Hemodialysis

William Strauss, Naomi V. Dahl, Kristine Bernard, Zhu Li. AMAG Pharmaceuticals, Inc., Waltham, MA.

Background: Data from prospective randomized controlled trials comparing different IV iron formulations over a period of >1 year are lacking. The purpose of this study was to gain a better understanding of the long-term safety, efficacy, and frequency of use of IV iron in the episodic treatment of iron deficiency anemia (IDA) in CKD-HD patients.

Methods: This open-label multicenter, prospective study (NCT01227616) conducted at 35 sites in 3 countries, randomized patients with Hgb<11.5 and TSAT<30% 2:1 to Ferumoxytol (FER) or Iron sucrose (IS) (10 X 100 mg at consecutive HD sessions), administered by infusion or injection. Patients with persistent or recurrent IDA (Hgb<11.5 g/dL and TSAT<30%) at any monthly observation visit over the following 12 months were treated again with an additional course of their randomized treatment. Safety was continuously monitored.

Results: Demographics were balanced between the two treatment groups (196 FER; 97 IS). Mean age was 58.8 (SD 13.96), 58.4% were male, 50.5% were White, and 30% were Black or African American. Over the 13-month study period, adverse events (AEs) were reported in 158 (80.6%) of FER and 81 (83.5%) of IS patients. These were considered treatment related by the investigators in 9 (4.6%) of FER and 4 (4.1%) of IS patients. Serious AEs were reported in 93 (47.7%) of FER patients and 49 (50.5%) of IS patients, none of which were considered treatment related by the investigators. For both treatment arms, the median month-by-month change in ESA dose remained zero throughout the study.

Iron isomaltoside maintains Hb levels and adequate iron status in patients converted from iron sucrose. Higher Hb values with iron isomaltoside are the result of higher (16%) elemental iron doses; with a consequential reduction in ESA requirement of 6%. Iron isomaltoside is well tolerated. One patient experienced headache and one patient metallic taste (1%). In comparison, 28% experienced metallic taste with iron sucrose. Logistical benefits were enabled by fast push injection requiring less than 3 minutes for preparation and intradialytic administration of iron isomaltoside.

Conclusions: Iron isomaltoside 5% safely and effectively maintains Hb levels for CKD patients on HD. By optimising the iron dose, ESA use can be reduced. This novel formulation that reduces labile iron may have potential benefit to patient outcomes but this requires determination.

Funding: Pharmaceutical Company Support - Pharmacosomos A/S

SA-PO1010

An Observational Study of Iron Isomaltoside 5% in Haemodialysis: A Novel Intravenous Iron for Dialysis

Ashraf I. Mikhail,1 Staffan Schön,2 Jorgen B.A. Hegbraut,3 Christopher Brown,1 Inger Nilsson,2 Gert Jensen,3 Jason Moore,1 Lennart D. Lundberg,1 1ABMU HB, United Kingdom; 2Diaverum Sweden AB; 3Sahlgrenska Univ Hospital, Sweden; 4Royal Devon & Exeter Hospitals, United Kingdom; 5Norrland Univ Hospital, Sweden.

Background: Iron isomaltoside 5% (Diafer®) is a recently approved IV iron for dialysis patients. The controlled-release matrix minimises labile (free) iron. Minimising labile iron may be important to reduce iron toxicity which may carry long term risks. The tight iron binding also allows for fast push injection. This study aims to determine the effectiveness and safety of iron isomaltoside in clinical practice in a haemodialysis (HD) cohort.

Methods: This interim analysis includes data from 95 patients for the first 3 months of an ongoing 12 month study of 209 HD patients in Sweden and the UK. Patients entering the study had to have 3 month data for iron sucrose within month -9 to 0 from the start of the prospective phase. Data for iron sucrose are compared to cross-over data for iron isomaltoside. The primary endpoint is comparison of Hb levels.

Results:

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

867A
SA-PO1011 Comparison of Hb Levels and Dose of Iron Associated with Adverse Events between Younger and Elderly Hemodialysis Patients Takahiro Kuragano, Takeshi Nakanishi. Dept of Internal Medicine Div of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Japan. 

Background: We recently demonstrated that high dose of ESA and iron were associated with higher risk of death and/or adverse events in maintenance hemodialysis patients (MHD) in TRAP study (Kidney Int. 2014). Elderly MHD are increased and the optimal renal anemia treatment for them should be examined. We performed a secondary analysis of the patients enrolled in the TRAP study. 

Methods: In 1095 MHD, we compared the relation of anemia, nutritional and inflammatory markers to adverse events between younger (<65 yo) and elderly (≥65 yo) during 3 years. The composite events (CEs) were defined as cerebrovascular and cardiovascular disease, infection, hospitalization, and death. A time dependent Cox hazard model was applied to the evaluation of the association between these clinical factors and CEs. 

Results: Compared with younger MHD, serum albumin level and body mass index were significantly lower (P<0.05) and high sensitive CRP was higher (p=0.05) in elderly MHD. In elderly MHD, Hb levels was significantly lower (p<0.02), and ferritin (p<0.01) and the index of ESA hypo-responsiveness (ESA/Hb) (p=0.01) were higher than those of younger MHD. In the elderly MHD, the risk of CEs was significantly smaller in only the patients Hb levels with 10-11g/dL (HR:0.67, P=0.035), but not in those <11g/dL. In younger MHD, compared to the patients with Hb<10g/dL, the risk of CEs was significantly decreased in higher Hb levels (10-11g/dL (HR:0.47, p=0.02), 11-12g/dL (HR:0.31, p=0.01), and >12g/dL (HR:0.12, p=0.04)). Both of younger and elderly MHD, higher ESA/Hb levels (>400) was significantly associated with higher risk for CEs (HR:2.24, p=0.01, HR:1.90, p=0.01). Dose of intravenous iron was significantly associated with higher risk of CEs in both younger (HR:1.2, p=0.02) and elderly (HR:1.2, p=0.02) MHD. 

Conclusions: The elderly MHD might have the higher ESA hypo-responsiveness and iron storage which could be related to chronic inflammation and malnutrition. In elderly MHD, targeting higher Hb level similar to younger might not be necessary for the prevention of adverse events. Further studies for examining the adequate anemia management for elderly MHD are needed.

SA-PO1012 The Relationship between Iron Dysutilization for Erythropoiesis and Adverse Events or Survivals in Patients Undergoing Hemodialysis Takahiro Kuragano, Takeshi Nakashita, Dept of Internal Medicine Div of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Japan. 

Background: Patient with high serum ferritin and low transferrin saturation(TSAT) levels could be considered as dysutilization of iron for erythropoiesis in which iron administration might increase TSAT and Hb levels. Long-term safety of iron administration to these patients has not been well studied. 

Methods: Study design was the observational multicenter study for period of 3 years. We defined dysutilization of iron for erythropoiesis as the patients with lower TSAT(<20%) and higher ferritin(>100ng/mL) levels. In 805 patients with maintenance hemodialysis (MHD), the association between dysutilization of iron for erythropoiesis and adverse event was investigated with the time dependent cox hazard model. 

Results: Compared with low TSAT(<20%) level, patient with normal TSAT(20-30%) was significantly lower risk for cerebrovascular and cardiovascular disease(CCVD) (HR:0.25, P=0.04), and patients with higher TSAT(≥30%) were lower risk for death(HR:0.12, P=0.01). Male, younger patients, without diabetes, low high sensitive CRP, and low β2microglobulin were selected as significant predictors of high TSAT. Compared with low ferritin(<100ng/mL) and high TSAT(20%), patients with high ferritin(≥100ng/mL) and low TSAT, and with high ferritin and high TSAT had a significantly higher risk of CCVD. Patients with high ferritin and low TSAT had a significantly higher risk of death than low ferritin and high TSAT.

Fig. 1 Relationship between TSAT and ferritin levels and adverse events 

Conclusions: Although patients with low TSAT levels had a significantly higher risk of CCVD or death, higher TSAT level was not associated with iron administration or iron storage. Patients who were suspected as dysutilization of iron for erythropoiesis had a higher risk of CCVD and death. The administration of iron should be cautious to the patients with dysutilization of iron for erythropoiesis.

SA-PO1013 Dysregulated Iron Metabolism in Bone Marrow of a Mouse Model of Chronic Kidney Disease Tomoko Kimura, Kiyoko Yamamoto, Yuki Morikami, Takanori Nagai, Masayoshi Nanami, Yasuyuki Nagasawa, Yukiko Hasuikem, Takahiro Kuragano, Takeshi Nakashita. Div of Kidney and Dialysis, Dept of Internal Medicine, Hyogo College of Medicine, Japan. 

Background: Causes of anemia in CKD are thought to be primarily caused by inadequate EPO synthesis, shortened erythrocyte life span, and failure in bone marrow(BM) due to chronic inflammation. But the major mechanism has not been well clarified. In the present study,we examined the differentiation pattern of erythroid in the BM using flow cytometry(FACS),renal EPO production and hepatic hepcidin expression using mouse model of adenine-induced renal failure(RF). 

Methods: RF was induced by the administration of 0.1% to 0.3% adenine-containing chow for 8weeks to male C57BL/6j mice. Liver,kidney,BM, and blood were obtained from control(C) and RF mice. Then,Bm,serum iron and ferritin levels were measured. Serum hepcidin levels were quantified using LC-MS/MS methods. Hepatic hepcidin(Hamp),renal EPO and BM Fam132b(erythoferrone) mRNA from C and RF were semi-quantified using RT-PCR. To evaluate the maturation of erythron,BM erythroid precursors were analyzed using CD71(Transferrin receptor) and Ter119 markers by FACS. 

Results: We confirmed that Hb levels were significantly lower(8.8±0.3vs13.1±4.1g/ dL) and serum ferritin levels were higher(2.6±0.6vs1.0±1.1ng/mL) in RF than C. Renal EPO mRNA expression in RF was increased compared to C(2.5±1. FACs analysis showed the percentages of Pro Epo(ECD71+Ter119+) and Baso Epo(ECD71+Ter119+) in the BM were decreased in RF compared to C. Hepatic Hamp mRNA expression was increased(2.4±1) and serum hepcidin levels were also higher(397.6±79.4vs6.6±9.9ng/dL) in RF compared to C. Serum iron(105.4±5.1vs121.3±4.8ng/dL) and TSAT(37.2±1.1vs43±0.1%) was lower in RF than C. Further,BM Fam132b mRNA expression was significantly decreased(0.6±1) in RF compared to C. 

Conclusions: Erythroblast maturation was affected in the steps of late differentiation,those are the decrease in CD71+cells. In RF,erythoferrone might be decreased,which could cause the increase in hepcidin although renal EPO expression was increased.Finally we presumed that the increase in hepcidin expression could be associated with the dysregulated erythropoiesis differentiation in RF model.

SA-PO1014 Disturbance of Iron Utilization in Erythropoiesis of Presensitized High-Risk Kidney Transplant Recipients Treated by Non-Antigen-Specific Immunoabsorption Sebastian Markus Schaefer, Martin G. Zeier, Matthias Schairer. Div of Nephrology, Heidelberg Univ Hospital, Heidelberg, Germany. 

Background: Non-antigen-specific immunoadsorption (IA) is a established method for desensitization of presensitized high-risk kidney transplant recipients. Despite of concomitant intravenous iron and erythropoietin substitution, patients under IA treatment regularly show significant decrease in haemoglobin levels. We hypothesised that IA influences systemic iron homeostasis and subsequently affects the erythropoiesis. Hepcidin is the key regulator of systemic iron homeostasis that coordinates iron uptake, storage and release to the blood streams. In contrast, iron overload inhibits hepcidin secretion from hepatocytes, thus increasing the intestinal iron uptake and iron levels in blood. 

Methods: In a pilot study in eight presensitized high-risk transplant recipients, different parameters of iron homeostasis were measured. 

Results: Haemoglobin levels decreased over the course of IA treatment (Δhaemoglobin ±SD: after 6 treatments 0.55 ±0.90, after 10 treatments 1.16 ±1.29). In pre-post-treatment comparison, hepcidin levels in blood were reduced following an IA treatment cycle, suggesting direct elimination through adsorption. Hepcidin levels increased until next treatment cycle, however did not reach baseline levels. Despite hepcidin depletion as concomitant intravenous iron and erythropoietin substitution, the percentage of hypochromic erythrocytes constantly increased during the entire IA treatment. Conversely, transferrin and ferritin levels as indicators of iron deposits remained unchanged during the course of IA. Furthermore, continuously declining levels of soluble transferrin receptor indicated sufficient erythroid iron deposition. 

Conclusions: Collectively, our data indicate clinically relevant disturbed iron utilization in erythropoiesis of IA treated patients leading to hypochromic anaemia despite of sufficient iron and erythropoietin substitution. 

Funding: Pharmaceutical Company Support - Fresenius AG

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Discriminative Effect of Oral and Intravenous Iron Administration on the Fibroblast Growth Factor-23 and Inflammatory Cytokines in Patients on Maintenance Hemodialysis with Iron Deficiency Anemia

Yukiko Hasukic, Wataru Fukao, Soshi Yorifujid, Yuki Morikamia, Kazuhiro Toyoda, Takeshi Nakashinisi, Wataru Kato, Tetsuo Kubota, and Tetsuhide Murakami

Background: FGF-23, a bone-derived hormone, plays an important role in the pathogenesis of several complications in patients with chronic kidney disease. The effect of iron supplementation, oral vs intravenous (IV), on fibroblast growth-factor-23 (FGF-23) and inflammatory cytokines were examined in maintenance hemodialysis (MHD) patients with iron deficiency anemia (IDA).

Methods: MHD patients with absolutely iron deficiency (n=61, serum ferritin <50 ng/ml) treated with erythropoietin stimulating agents (ESA) were enrolled. Oral iron (ferric citrate hydrate 50 mg daily, Oral group, n=29) or IV iron (saccharated ferric oxide 40 mg weekly, IV group, n=32) were administered for 10 weeks. Iron supplementation was halted when serum ferritin level was >100 ng/ml. Factors related to anemia, iron metabolism, inflammation, oxidative stress (pentosidinene), and FGF-23 (ELISA, Kinos) were measured at the start and after 3 months of iron supplementation.

Results: Mean age of 68.6±11.1 years, mean dialysis vintage 7.3±6.7 years, and serum ferritin levels of 11.3±7.2 ng/ml in both the 2 groups, HB, MCV, serum ferritin, TST, hepcidin, IL-6 (Oral: 5.71 to 8.20 pg/ml, IV: 5.17 to 5.45 pg/ml, median), and TNF-α (Oral: 34.8 to 42.0 pg/ml, IV: 36.4 to 47.9 pg/ml, median) were significantly increased and ESA resistance index was decreased by the iron supplementation. Soluble transferrin receptor of only the Oral group was decreased (p=0.0058), and FGF-23 of only the IV group was increased compared with the at the start (1800 [614-4300] pg/ml to 2859 [659-6850] pg/ml, p=0.0004). There was no change of high-sensitivity CRP and pentosidinene levels of the 2 groups.

Conclusions: Iron supplementation might stimulate the production of inflammatory cytokines. Iron administered intravenously could increase the elevation of serum FGF-23 level.

Association between Fibroblast Growth Factor 23 and Iron Metabolism in Hemodialysis Patients

Hirokazu Honds, Tetsuo Michihana, Kanji Shishido, Tanakori Shibitab, Div of Nephrology, Dept of Medicine, Showa Univ Kato Toyosu Hospital, Tokyo, Japan; Ebara Clinic, Tokyo, Japan; Dept of Dialysis, Kawasaki Clinic, Kawasaki, Japan; Div of Nephrology, Dept of Medicine, Showa Univ School of Medicine, Tokyo, Japan.

Background: Recent study demonstrated the association among inflammation, iron metabolism and fibroblast growth factor (FGF) 23 (Klj2016;69:135). The present clinical study aimed to assess associations between anemia, iron metabolism and FGF23 in hemodialysis (HD) patients.

Methods: This prospective observational study examined a cohort of prevalent HD patients (n=282). Blood samples were obtained before dialysis session at baseline to measure the association of 25-OH Vitamin D, 1,25-(OH) Vitamin D and Paricalcitol on the Erythropoietic Response of Anemic Hemodialysis Patients

Soshi Morikami,1 Sheila Cabello Pelegrin,1 Angel Garcia-Alvarez,2 Manuel Luque-Ramírez,2 Nephrology, San Esuses Univ Hospital, Palma de Mallorca, Islas Baleares, Spain;2 Pharmacy, Inca Hospital, Palma de Mallorca, Islas Baleares, Spain; Endocrinology, Ramón y Cajal Univ Hospital, Madrid, Spain.

Background: Vitamin D(VD) deficiency is associated to renal anemia. However, it is not well-known if there are differences between 25(OH)-VD or 1,25-(OH)-VD, and the potential interaction of paricalcitol(PCR) use, on the erythropoietic response. We evaluate the association of 25VD, 1,25VD levels and paricalcitol use on the iron metabolism and hematologic parameters in hemodialysis patients.

Methods: This is a post-hoc analysis from the Mir-Epo study(EudraCT: 2009-015511-40). Erythropoietic stimulating agents(ESA) and iron supplements were administered to maintain hemoglobin(Hb) levels between 12.0 and 12.5 g/dl. Changes in iron saturation(TSAT), 220% s-klotho were measured after 3 months of ESA titration at 2 time points (month 3 and 6). We assessed s-klotho changes throughout the study and the differences among its mean changes as a function of IPTH subgroups.

Results: In the Group A, s-klotho did not change throughout the study [y=0.10+0.12*p<0.001, P=0.021 and Δferritin decreased (C=-0.12; p<0.01), and -0.06pg/ml(Δferritin (P<0.01), respectively]. Percentage mean change of s-klotho between groups A and B was significantly (28%, P<0.01). No significant differences among other groups were found. As a whole, a positive correlation between changes in s-klotho and serum iron, TSAT, and transferrin saturation were observed. A log-linear regression model determined that increased s-klotho levels in group A were associated with a decrease in iron supplementation and ESA needs (X2=5.0, P=0.02, and X2=3.9, P=0.04, respectively).

Conclusions: Iron supplementation may be associated with s-klotho levels.
SA-PO1020
Cholecalciferol Supplementation and Serum Hepcidin-25 Concentrations in Hemodialysis Patients - A Randomized Controlled Trial
Yoshitsugu Ohb, Takayuki Hamano, Yusuke Sakaguchi, Akihiko Shimomura, Yoshitaka Isaka, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; Univ of California Irvine, Orange, CA.

Background: A previous study demonstrated that nutritional vitamin D supplementation decreased serum hepcidin levels in healthy subjects. However, it still remains unknown whether it is also true with maintenance hemodialysis (MHD) patients.

Methods: This is a double-blind RCT of cholecalciferol (VD3) supplementation in MHD patients. Patients were randomly assigned to either thrice-weekly (TW) 3,000 IU VD3, once-monthly (OM) VD3 (equivalent to 9,000 IU/week), TW placebo, or OM placebo. The primary outcomes were log-transformed serum hepcidin levels at Day 3 and Month 3. Based on the intention-to-treat principle, we compared VD3 vs. placebo by using a priori defined generalized linear model ignoring the administration intervals. We also examined the differences between TW vs. OM VD3.

Results: Out of 96 participants, 3 dropped out between Day 3 and Month 3. Median (IQR) serum 25(OH)D levels at baseline and Month 3 were 13 (10–15) and 13 (11–17) ng/mL in the placebo group and 10 (8–13) and 24 (20–29) ng/mL in the VD3 group, respectively. Likewise, median (IQR) hepcidin levels at baseline, Day 3, and Month 3 were 18 (8–54), 13 (2–25), and 18 (9–42) ng/mL in the placebo group, and 23 (5–43), 15 (6–31), and 22 (9–50) ng/mL in the VD3 group, respectively.

Vitamin D supplementation increased serum hepcidin-25 levels in the short term among MHD patients. Patients were randomly assigned to either TW 3,000 IU VD3, TW placebo, or OM placebo. After baseline adjustment, VD3 was associated with 1.7 (95%CI, 1.2–2.4) times higher hepcidin levels at Day 3, which lost significance at Month 3 [1.1 (95%CI, 0.7–1.9)]. There were no significant differences in serum levels of TNF-α, IL-6, hemoglobin, or ferrodynamics. Any indices did not show any interaction effects of TW vs. OM VD3.

Conclusions: The individualized erythropoiesis model predicts individual VD3 levels for up to 21 weeks with clinically satisfactory accuracy and precision. These findings indicate that the mathematical model is able to capture patient-level hemoglobin dynamics, a necessary requirement for its intended use as an individualized anemia management tool.

SA-PO1022
Optimal Hemoglobin Level in Patients with Chronic Kidney Disease on Hemodialysis in High Altitude Cities
Cesar O. Toral, Nephrology, Univ of Azuay / Unidad Renal del Austro, Cuenca, Ecuador.

Background: In patients with anemia due to chronic renal disease, it is recommended in order to avoid complications, to maintain hemoglobin levels between 10-12 g/dL according to studies conducted at sea level; however, the optimal value allowed in patients residing in high altitude cities is still unknown.

Methods: A descriptive study was conducted in the Renal Unit of the Austro (UNIREAS) Cuenca, Ecuador, (altitud: 2,560mts) during the period January 2010 to December 2011, obtaining data from physical medical records of each patient.

Results: A total of 3,423 measurements of hemoglobin in patients with chronic renal disease stage 5D was obtained, of which 57% were women and 43% men. The complications were divided into different ranges of hemoglobin, from 10 to 12 g/dl (31.2%), from 12.1 to 13 g/dl (45.5%), from 13.1 to 14 g/dl (30.3%), from 14.1 to 15 g/dl (21.2%) and over 15 g/dl (3%). Additionally, the distribution of complications according to the chronic pathologies assessed was evaluated. Arterial Hypertension (43.7%), Arterial Hypertension plus Diabetes Mellitus type 2 (34.3%), Diabetes Mellitus type 2 (6.2%), Diabetes Mellitus type 1 and others (14%).

Conclusions: The complications increase as the value of hemoglobin increases. However, from the total of measurements greater than 12 g/dl only 1.84% showed complications. In addition, the complications rate found in the groups with a range of 10 to 12 g/dl hemoglobin was 1.49% compared with a rate of 1.62% found in the group with a wider range of 10 to 13 g/dl.

SA-PO1023
Achievement of Renal Anemia KDIGO Targets by Two Different Strategies - A European Hemodialysis Multicenter Analysis
Maciej B. Drozd, Stefan H. Jacobsson, Werner Kleophas, Mahesh Krishnan, Abdulkareem Alsuwaida, Fatima Ferreira Silva, Andre L. Weiert, DaVita, Poland; Karolinska Inst, Stockholm, Sweden; DaVita, Europe; DaVita, Germany; DaVita Inc; DaVita, Saudi Arabia; DaVita, Portugal.

Background: Hemoglobin target levels can be achieved through more frequent i.v. iron use with less ESA or vice versa. ESA therapy to correct anemia may result in adverse clinical outcomes and i.v. iron may exacerbate oxidative stress, potentiate atherogenesis and increase the propensity to infections.

Methods: We included 1,247 patients on hemodialysis from Portugal (n=730) and Poland (n=517) in an analysis of the achievement of KDIGO renal anemia targets and focused on treatment strategies.

Results: In Poland, in the use and doses of i.v. iron were 35% higher than in Portugal (p<0.001) while the use and doses of ESA were 17% higher in Portugal (5034 vs 3133 IU [adjusted]×week, p<0.001). Hb 10-12 g/dL was achieved in 70% of pts in Poland and in 66% of pts in Portugal (NS, Chi-2). In Poland vs Portugal, 74% and 78% of pts had ESA (p=0.056), 87% vs 83% had ferritin<200 μg/L (p=0.08), 36% vs 16% had ferritin>800 μg/L (p<0.001), 89% vs 76% had TSAT ≥20% (p<0.001), and 15% vs 8% had TSAT>50% (p<0.001). Comorbidity index ≤7 (Poland 52%, Portuguese 39%) vs 7-12 (45% and 58%) vs >12 (3% and 4%) were significantly different between countries (p<0.001).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**Conclusions:** The KDIGO hemodialysis anemia target was achieved in the two countries through different treatment strategies in terms of ESA use and doses of i.v. iron. These differences may have clinical implications: future evaluations will show how these differences in treatment strategies correlate with the future risks of complications, hospitalization and mortality.

**Funding:** Pharmaceutical Company Support - DaVita

**SA-PO1024**

Nurse Based Anemia Management in Hemodialysis: An Observational Prospective Study

**Background:** The concept of anemia nurse manager (ANM) was explored because of her availability in the dialysis unit which provides a chance to address management swiftly and timely. We did a prospective observational study to compare our new ANM model to our standard of care (SOC) in regard to achieving hemoglobin (Hg) in target (10-12 g/dL) and avoid extreme Hg (below 9 or above 13).

**Methods:** ANM team consisted of two part-time nurses under supervision of an expert nephrologist who provided extensive training for them for 2 months. We randomly selected and gradually included all patients located in 1st floor (our center is the largest in Qatar and has 380 patients in 2 floors). They were followed for 8 months (September 2015 to May 2016). We followed Hg, iron sat and ferritin per our protocol. Nurses reviewed the results one day after blood draw with the nephrologist and prescriptions for erythropoietin (EPO) were made. We started with 66 patients and gradually reached 211 patients by May 2016. Percentage of patients with Hg within target range steadily improved.

**Results:** With 66 patients and gradually reached 211 patients by May 2016. Percentage of patients with Hg within target range steadily improved.

**Conclusions:** Our ANM model designed to fit local requirements in Qatar significantly improved percentage of Hg in target and decreased extreme Hg levels compared to SOC.

**SA-PO1025**

Trajectories of Hemoglobin Levels Before and after Initiation of Dialysis

**Background:** Anemia affects about 82% of stage 5 chronic kidney disease (CKD) patients (Ps) (Shaheen FA, et al. Saudi J Kidney Dis Transpl 2011). As reported by the USRDS these Ps exhibit a drop in mean hemoglobin levels (Hgb) from about 13g/dL to <11g/dL in the 5 years prior to end stage renal disease (ESRD). We studied Hgb trajectories in Ps who transitioned from CKD to ESRD by survival status in the first year of dialysis.

**Methods:** We analyzed data from the Fresenius Medical Care CKD Data Registry on 14,095 Ps with Hgb results in the 12 months pre-dialysis who transitioned to ESRD between 2008 and 2016. Changes in mean monthly Hgb were analyzed by survival status in the 12 months after starting dialysis.

**Results:** Two main observations are notable: i) Hgb gradually declined in the year prior to dialysis initiation, more precipitously in the final 2 months (Figure 1A); ii) Those who survived the first year of dialysis, the Hgb decline is more pronounced in those who die (Figure 1B). In Ps who died in the first year of dialysis, the Hgb increase was lower than, and never reached Hgb levels of survivors.

**Conclusions:** We found Hgb declines during the 12 months before transition from CKD to ESRD. Hgb rebounds during the incident dialysis period exceeding levels 6-12 months before dialysis initiation. The drop in Hgb is most pronounced in Ps who die within the first year of dialysis. Our study is limited since ESA doses prior to dialysis are not available in this dataset.

**Funding:** Financial support from Fresenius Medical Care North America
erthropoietin and/or iron was administered. 516 patients were used for the analysis with a minimum of 90 schedule treatments during the calendar year. The following information was calculated: percentage of treatments completed, total ESA and iron administered, and the yearly mean run time, ultrafiltration, hemoglobin, T sat, and ferritin achieved. ESA and iron doses were adjusted by dry weight and reported as weekly dose. Statistical analysis was by decision tree classification technique.

Results: Results of the decision tree analysis are shown in the following table.

<table>
<thead>
<tr>
<th>Nodes</th>
<th>Population Mean Hemoglobin 11.4 ± 1.3</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>13.6, 12.5</td>
</tr>
<tr>
<td>2</td>
<td>11.2, 11.6</td>
</tr>
<tr>
<td>3</td>
<td>10.6, 11.2</td>
</tr>
<tr>
<td>4</td>
<td>10.3, 10.9</td>
</tr>
<tr>
<td>5</td>
<td>11.3, 11.8</td>
</tr>
</tbody>
</table>

The analysis resulted in 26 decision points (nodes), with 7 nodes related to ESA dose shown as the dose range included and mean Hb for that node. In nodes 1, 4, 5, and 6, ferritin significantly added 11 further nodes and is shown as a single break point or range with the corresponding mean Hb for that node. In nodes 4 and 6 adherence significantly added 8 additional nodes. All p values were < 0.012.

Conclusions: Adherence less than 92 to 95% resulted in significantly decreased Hb levels in females compared to males. Cu* and Se** were positively and Mo** was negatively correlated to CRP. V** was negatively correlated with hepcidin. Zn was negatively correlated with EPO and ERI. Sn was positively correlated with EPO.

Figure 1. Plotted of calculated differences between sample 2 and sample 1 for each parameter. Differences are normalized as percentage of sample 2 (S2/S1)%.

SA-PO1029

Hemodialysis Patient Plasma Trace Metals Associate with Dialysis Incidence versus Prevalence, Gender, and Response to Erythropoiesis Stimulating Agents

Methods: EDTA-Plasma from 110 HD patients (77 prevalent, 33 incident) participating in the NIDDK funded study (R01-01DK091584) were analyzed by ICP-MS for the plasma concentration of As, Cd, Co, Cu, Cr, Mn, Mo, Ni, Pb, Sh, Se, Sn, V, and Zn. Associations were determined between trace metals and gender, race, HD status, monthly hemoglobin (Hgb) values, total ESA dose for the month the sample was collected, erythropoietin response index (ERI), transferrin percent saturation, ferritin, iron, hepcidin and c-reactive protein (CRP).

Results: Cd and Cu concentrations were inversely correlated with Hgb levels, and positively correlated with EPO and ERI. Sn was positively correlated with EPO. Zn was negatively correlated with Cu and Cd concentrations were significantly higher in females compared to males. Cu and Se were positively and Mo was negatively correlated to CRP by multivariable regression. V was negatively correlated with hepcidin.

Conclusions: Plasma trace metal concentrations associate with dialysis vintage, gender, correlate with ESA response, and may be useful in guiding HD patient specific approaches to anemia management. We hypothesize specific trace metals may play a causal role in ESA resistance.

Funding: NIDDK Support

SA-PO1030

Levocarnitine Injections Decrease the Need for Erythropoiesis Stimulating Agents in Hemodialysis Patients with Renal Anemia

Methods: Eight patients with CVCs undergoing HD gave informed consent to have two samples of blood taken from CVCs for monthly tests. The first sample (S1), experimental, was drawn after less blood is discarded with those using the current protocol. Methods: Eight patients with CVCs undergoing HD gave informed consent to have two samples of blood taken from CVCs for monthly tests. The first sample (S1), experimental, was drawn after less blood is discarded with those using the current protocol.

Results: For each of the values measured, there was no significant difference between the experimental and control values. P-values ranged from 0.12 to 0.50. Predetermined power to detect a 1-4% difference was 95%. There was no systematic bias suggesting lower values in S1 compared with S2 that would indicate dilution in the first sample.

Conclusions: Discarding 6 versus 10mL blood from CVCs did not change values of measured variables or blood values in any way that would affect clinical care. The proposed protocol of discarding less blood when accessing CVC lines could save at least 600mL blood/HD patient/year and may be generalizable to non-dialysis patients with CVCs.

Funding: NIDDK Support, Other NIH Support - R01-01DK091584 (MMMB). RTI RCMRC NIH Common Fund Program grant U24 DK079715 (SS). NIH Common Fund Program grant K01 GM09320 (JG). This research was supported by an unrestricted gift from the Northwest Kidney Centers to the Kidney Research Institute, VA Support

Figure 1. Plotted of calculated differences between sample 2 and sample 1 for each parameter. Differences are normalized as percentage of sample 2 (S2/S1)%.
SA-PO1031

Glucocorticoids Inhibit HAMP mRNA in HEPG2 Cells and in CKD Patients with Vasculitis

Adam Rumjon, Iain C. Macdougall. Dept of Renal Medicine, King’s College Hospital, London, United Kingdom.

Background: Heparin is the master regulator of iron homeostasis encoded for by the HAMP gene, and CKD patients have increased circulating levels of the hormone. Knowledge on factors controlling its production is expanding, and previous studies showed that heparin is suppressed by oestrogen and testosterone. There are no data on the effect of glucocorticoids on heparin, and the aim of this study was to investigate the effect of steroids on HAMP gene expression, as well as on heparin levels in CKD patients with acute vasculitis.

Methods: HepG2 cells were exposed to increasing doses of dexamethasone from 1.25 to 80 ng/mL, for a period of 18 hours. HepG2 cells were pre-treated with dexamethasone (10ng/mL) or vehicle for 4 hours before the addition of 12.5 ng/mL of interleukin-6 or vehicle, for 2 hours. Total cellular RNA was extracted and reverse-transcribed; quantitative rt-PCR was then performed and amplification was performed using Taqman HAMP and GAPDH (housekeeping) primers. Serum heparin-25 levels were measured using mass spectrometry in 6 patients admitted with suspected ANCA-positive vasculitis before and after the administration of 500mg IV methylprednisolone.

Results: The dexamethasone-HAMP dose-response curve showed suppression of HAMP at concentrations ≥20 ng/mL. IL-6 stimulated HepG2 cells not pre-treated with dexamethasone showed an 11-fold rise in HAMP compared to only a 7.5-fold increase in cells pre-treated with dexamethasone. Heparin-25 levels in all 6 patients were lower 24 hours post-administration of methylprednisolone.

Conclusions: These data suggest that the glucocorticoid dexamethasone suppresses HAMP expression in vitro, and this may be IL-6-mediated. Administration of methylprednisolone reduced levels of circulating serum heparin within 24 hours. The consistency of both the in vitro and human in vivo data increases confidence in the validity of this effect.

SA-PO1032

A Single Center Retrospective Review of Incident Catheter Rates in an Academic Outpatient Dialysis Unit

Eric Loman, Thurin Kyaw, Brendan T. Bowman. Nephrolog, Univ of Virginia, Charlottesville, VA.

Background: K/DOQI guidelines recommend an Arteriovenous Fistula (AVF) rate of 68% in prevalent End Stage Renal Disease (ESRD) patients and at least 50% in incident ESRD patients. We reviewed data of all incident ESRD patients initiating hemodialysis (HD) in a University based outpatient unit to identify factors associated with catheter starts.

Methods: We conducted a chart review of all 78 incident HD patients (Nov 2012–Aug 2015). Data included demographics, ESRD cause, pre-dialysis nephrology care, documented episodes of AKI, eGFR drop preceding ESRD, and time to access placement referral.

Results: 65 patients (83.3%) initiated HD with a catheter versus 13 patients (16.7%) with AVF or AVG. There were no major differences in demographics or cause of ESRD between the two groups. The main factor associated with a catheter start was AKI occurring in 62% of patients. The catheter group had a profound loss of GFR in the 12 months preceding ESRD: nearly 80% of the group experienced a GFR loss of 50% or more compared to the gradual decline in the AVF/AVG group. 73.3% of the catheter group had a CRD diagnosis at HD start, with only 61.5% seen by a Nephrologist previously. In the AVF/AVG group, all patients were followed for at least 3 years by a Nephrologist prior to HD. 83% of patients starting with an AVF/AVG were seen by a surgeon 6 months or longer before initiating HD vs 40% in the catheter group. Less than half of catheter patients changed to an AVF or AVG.

Conclusions: Previous studies have shown high incident catheter rates associated with late diagnosis of CKD, lack of pre-dialysis nephrology care, and AKI. Our study confirms this. In addition, our study demonstrates the importance of rapid loss of GFR from prior stable moderate CKD on incident catheter rates. This suggests focusing access placement in outpatients with gradual GFR loss will not prevent high incident catheter rates. Further emphasis should be also placed on inpatients with rapid GFR loss/AKI leading to ESRD; ideally during the index hospitalization.

SA-PO1033

The Associations between Vascular Access Care and Mortality Rates in Hemodialysis Patients

Hao Han, Marta Reviriego-Mendoza, Sheetal Chaudhuri, Karen G. Butler, Sophia Rosen, Irene Brozowski, John W. Larkin, Walead Latif, Elise Koh, Len A. Usyvat, Gregg Miller, Melvin Rosenblatt, Murat Sor, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA; Fresenius Vascular Care, Berwyn, PA.

Background: Fresenius Vascular Care (FVC) offers outpatient vascular access (VA) care for Fresenius Medical Care North America (FMCNA) hemodialysis (HD) patients. We studied the associations in mortality rates for FVC outpatient VA care versus other VA providers that are mostly in a hospital setting or no VA care received at all.

Methods: We analyzed data from 4,691 HD patients who visited FVC at any time during calendar year 2014. Control patients were selected by 1:1 matching exactly for concurrent year of FVC care, state of residence, gender, race, and access type, as well as, nearest neighbor matching on the log of the propensity score for age, dialysis vintage, albumin, body mass index, and Kt/V. Further analysis was performed for 4,376 FVC patients with a pre-existing arteriovenous graft (AVG). Six month mortality rates per 100 patient years were compared between study groups after 1/1/2015.

Results: Data from a total of 9,382 HD patients was analyzed for this study. Compared to matched control patients, mortality rates in FVC patients were decreased by 33% (p<0.001; Figure 1A). Similarly, in patients enrolled in FVC with a pre-existing AVF/AVG showed a 20% reduction in mortality when compared to controls (p=0.001; Figure 1B).

Conclusions: The results of this analysis suggest that outpatient VA care may have the potential to reduce mortality rates in HD patients. Further analysis of survival outcomes for patients receiving VA care in other settings or no care at all. Ongoing studies are warranted to determine the long term mortality outcomes associated with FVC VA care.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO1034

Analysis of 5,000 Cases of Vascular Access Interventional Therapy for Vascular Access Failure at a Single Facility – How Well Were the AVG Maintained?

Teruhiko Maeba, Shigeru Owada. Internal Medicine, Asao Kidney Clinic, Kawasaki, Kanagawa, Japan.

Background: Sustaining a functional vascular access (VA) is one of the most important factors in the maintenance of an HD modality. The application of vascular access interventional therapy (VAIVT) for VA trouble is increasing recently but the effectiveness of VAIVT has not been entirely satisfactory because of the relatively high rate of re-stenosis.

Methods: We have experienced 5,028 cases (in 947 patients) of VA trouble treated with VAIVT over the last twelve years in which primary assisted and secondary assisted rates were analyzed.

Results: 1. We have used a noncompliant type of balloon catheter for 98.6% of cases and primary assisted patency rates were 99.2%. 2. Secondary assisted patency rates were 72.3% at two years, 66.4% at 4 years, 78.2% at 6 years, 50.0% at 8 years and 47.7% at 11 years in all patients. 3. In diabetic patients, assisted patency rate was 47.4% at 11 years and it was 47.6% in non-diabetic patients (p=0.82, Log rank). There were no significant differences found between the arteriovenous fistulas (AVF) and the arteriovenous grafts (AVG); 49.8% and 37.0% at 11 years, respectively. 4. Failure of secondary assisted patency was observed in 517 patients. In these, a new AVF was made on the same side in 38.0% of the patients, a contralateral side AVF was made in 6.0% and an AVG in 34.0%, superficialized reposition of brachial artery in 4.0% and death occurred in 18.0%.

Conclusions: The results for the initial clinical success rate and secondary assisted patency rates were excellent. It was possible to reduce the economic burden for patients by using a noncompliant type of balloon catheter. Long-term maintenance of AVG was possible by the use of VAIVT.
SA-PO1035
Outcomes of Multi-Disciplinary Interventional Nephrology Service in Singapore General Hospital
Chee Yong Ng, Swee Ping Teh, Ru Yu Tan, Chieh-Sui Tan. Renal Medicine, Singapore General Hospital, Singapore.

Background: Singapore General Hospital (SGH) has established an interventional nephrology suite (INS) for management of vascular access issues. This is a multidisciplinary set-up comprising of interventional nephrologists (IN), interventional radiologists (IR) and vascular surgeons (VS).

Methods: This study reports the outcome of thrombolyis / thrombectomy of haemodialysis access performed in INS from 1st March 2015 to 29th February 2016.

Results: A total of 198 patients with thrombosed access had interventions done in INS during this period. Of these, 104(52.5%) were arteriovenous fistula (AVF). Mean age of study subject was 63.5±11.9, predominantly Chinese (62.6%), and of male gender (51%). Majority of patient in this study develop End Stage Renal Disease (ESRD) from diabetes mellitus (38.6%). Procedures performed by IN, IR and VS were 38.9%, 51.6% and 9.5% respectively. 96.5% of patient had reestablishment of flow in the vascular access radiologically, while 94.9% had successful haemodialysis via procedure. There was no significant difference in baseline characteristics among patients who underwent procedure done by the 3 groups of proceduralist. Radiological success rate of procedures done by IN, IR and VS were 98.7%, 94.1% and 100% (p=0.176) and clinical success rate was 98.7%, 92.2%, 94.7% (p=0.141) respectively. Complications occurred in 4.5% of patients but there’s no significant difference in complications rate among the 3 groups of proceduralist.

Conclusions: There was no statistically significant difference in the radiological and clinical success rate of interventional nephrologists, interventional radiologists and vascular surgeons. The centre’s 3 month primary failure after percutaneous thrombectomy and clinical success rate of intervention for AVGs are in keeping with NKF KDOQI guideline standards of 40% and 85% respectively.

SA-PO1036
Vascular Access (VA) Triage and Clinical Events in Haemodialysis (HD)
Sandro Silverio,1 Sandro Mazzaferro,2 Maria Luisa Muci,1 Lida Tartaglione,2 Luciano Carbone,2 Silverio Rotondi.1 1Sciencia Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, Sapienza Univ, Rome, Italy; 2Nephrology and Dialysis Unit, ICoT Hospital, Latina, Italy.

Background: VA type (AVF vs CVC) affects morbidity and mortality in HD, but its performance is not routinely evaluated. We developed a system of VA triage representative of its monthly performance. We report here on the relationship between this VA triage and clinical events.

Methods: Nurses report each session data (weights, BP, HR, Blood flows, VA pressures, symptoms, clots and KT/V) on a data sheet. Pathologic values generate a score that, with empiric thresholds, flags the VA green, yellow or red. We retrieved clinical events (admissions and deaths) of those patients whose VA had been triaged for >3 months between 1/1/2014 and 12/31/2015. For each patient we considered the average triage of the available follow-up, separately for different VA types.

Results: 111 patients (62 AVF and 49 CVC), followed for 18±7 months, experienced 12 deaths and 170 hospital admissions which lasted 16±26 days. Prevalence of events was greater in CVC as compared to AVF patients (75% vs 51%; p<.02). Based on average 12 deaths and 170 hospital admissions which lasted 16±26 days. Prevalence of events was greater in CVC as compared to AVF patients (75% vs 51%, p<.02). Based on average 12 deaths and 170 hospital admissions which lasted 16±26 days. Prevalence of events was greater in CVC as compared to AVF patients (75% vs 51%, p<.01) but not for triage, patients were separated into groups that resulted different for prevalence of events. 1/1/2014 and 12/31/2015. For each patient we considered the average triage of the available follow-up, separately for different VA types.

Conclusions: We confirm the role of VA type as a risk factor for events and suggest that a triage system evaluating the performance of each type of VA could represent, in particular for AVF, a useful sensor of increased clinical risk.

Funding: Private Foundation Support

SA-PO1037
Twelve-Month Patency Rate after a First PTA for Failed Arteriovenous Fistula: Comparison between Low- and High-Pressure Balloon Dilation (YOROI Study)
Koki Wakamoto, Kensuke Sasaki, Toshinori Ueno, Ayumu Nakashima, Shigehiro Doi, Takao Masaki. Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.

Background: Low-pressure balloon dilation for failed haemodialysis fistulas has recently exhibited a better rate of revascularity in comparison with conventional strategy in achieving complete balloon expansion, even in patients with residual stenosis. In this study, we investigate the 12-month patency rates for low- and high-pressure dilation in patients who underwent their first percutaneous transluminal angioplasty (PTA) for failed arteriovenous fistula.

Methods: This study was a multicenter, prospective, randomized, two-comparison, non-inferiority trial. The YOROI balloon (Kaneka Medics, Osaka, Japan), with a diameter of 4 mm, was used for dilation of stenotic lesions. Balloons were inflated to a pressure of 8 atm (low-pressure group), or to a pressure of up to 30 atm to achieve complete expansion (high-pressure group). The 12-month patency rate after balloon angioplasty was analyzed by Kaplan–Meier analysis and a log-rank test. We also investigated the incidence of complications.

Results: A total of 71 patients who received their first PTA were enrolled. One patient in the low-pressure group dropped out due to peripheral ischemia after PTA, and one patient in the high-pressure group died during the observation period. 12-month patency rates did not show a significant difference between the low- and high-pressure groups. In addition, the patency rate of the group with incomplete expansion was not significantly lower than that of the group with full balloon expansion.

Conclusions: Full expansion of the balloon using high pressure was highly probable. However, with no significant difference noted in the 12-month patency rate, our results suggest that complete balloon expansion does not affect patency rates.

SA-PO1038
Hemodialysis Center of Frequent Percutaneous Transluminal Angioplasty Use Is Not Associated with Fewer Vascular Access Recreation-A Nationwide Population Study at Taiwan
Yiwen Chiu, Feng-Xuan Jian, Ming-Yen Lin, Shang-Jyh Hwang. Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung Medical Univ, Kaohsiung, NA, Taiwan.

Background: The percutaneous transluminal angioplasty (PTA) frequency increased dramatically but its effect on vascular access (VA) recreation was not so clear.

Methods: Prevalent patients under maintenance hemodialysis (HD) at Taiwan from 2004 to 2012 were included. The demographics, baseline clinical characteristics, number of PTA and VA recreation for each patient were collected. The mean/median/portion/frequency which appropriate for all the variables above was assigned annually to each center as its characteristics. Generalized estimating equation was used to test the association between center’s PTA frequency and VA recreation rate.

Results: Total 81,225 patients were included (mean age 61±13.9 y/o, male 50 %, DM 49 %, mean HD vintage 5.2±(3.9) y) as well as 820 HD centers. PTA frequency increased by 3 times from 1.10 at 2004 to 3.57 at 2012 (per 1000 HD sessions) and VA recreation rate were kept around 0.80 (per 1000 HD sessions). Compared with the HD centers of infrequent use of PTA (annual lowest quartile, range: 0.2-1.9 per 1000 HD sessions), the ones of frequent use (annual highest quartile, range: 2.12-29.4 per 1000 HD sessions) didn’t have lower VA recreation.

The independent predictors for HD center of lower VA recreation rate were those with more female, at earlier time cohort, fewer myocardial infarction history history, shorter HD vintage, and lower mortality (all p<0.05), but not frequent PTA use (p=0.37).

Conclusions: Frequent use of PTA seems not improve VA patency at center level for no significant association identified with lower VA recreation. The indication of PTA in daily practice should be re-evaluated with regard to its efficiency in term of lowering VA recreation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO1039

Diagnostic Accuracy of Computed Tomography Angiography and Magnetic Resonance Angiography in the Detection of Hemodialysis Arteriovenous Fistula Dysfunction: A Meta Analysis

Weiying Li, Yuliang Zhao, Ping Fu.

Div of Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China.

Background: We sought to evaluate the diagnostic accuracy of computed tomography angiography (CTA) and magnetic resonance angiography (MRA) compared with invasive digital subtraction angiography (DSA) or surgery for the detection of arteriovenous fistula dysfunction in hemodialysis patients.

Methods: PUBMED, MEDLINE, Cochrane library, and EMBASE searches were performed until May 31th, 2016 for potential related articles. Inclusion criteria were 1) at least one of the following diagnostic methods: CTA or MRA were included as a diagnostic test for hemodialysis AVF; (2) >50% diameter stenosis or occlusion selected as the cut-off criteria; (3) DSA or surgery as the standard of reference; (4) absolute numbers of true positive, false positive, true negative, and false negative results could be derived. Standard meta-analyses were applied.

Results: Seven studies reported the diagnostic accuracy for detection of AVF malfunction by CTA. They indicated a pooled sensitivity of 95% (90% to 97%), specificity of 96% (93% to 97%), positive likelihood ratio of 17.01 (11.40 to 25.36) and negative likelihood ratio of 0.09 (0.04 to 0.19) with a sDOR of 207.32 (97.85 to 473.12) and AUC of 0.98. Seven studies reported the diagnostic accuracy for detection of AVF dysfunction by MRA. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, sDOR and AUC were 97% (93% to 99%), 98% (96% to 99%), 27.21 (14.68 to 50.43), 0.05 (0.03 to 0.09), 788.21 (350.38 to 1773.15) and 0.9865 respectively.

Conclusions: CTA and MRA have a good diagnostic accuracy for detection of AVF dysfunction in hemodialysis patients.

SA-PO1040

Dynamic Access Pressure Surveillance Predicts Venous Needle Dislodgment

Stanley Frinak, Jerry Yee, Anatole Besarab, Gerard Zasuwa.

1Nephrology, Henry Ford Hospital, Detroit, MI; 2Nephrology, Stanford Univ, Palo Alto, CA.

Background: Venous needle dislodgment (VND) incidents may be as high as 200/day with 2 serious adverse outcomes/day. Venous pressure (VP) measured during dialysis is variable > 130 mmHg. Recent data showed 56% of fistulas (AVF) and 6% of grafts had intraccess pressures (AP) ≤ 30 mmHg; 39% of AVF had AP ≤ 20 mmHg. Therefore, the current alarm threshold (T) for VND must be lower T<VP – (20 to 30 mmHg) yet not produce excessive false alarms. Low AP could place patients at greater risk for VND. We evaluated a Dynamic access pressure surveillance (DAPS) algorithm which continuously monitors AP for a more sensitive detection device for VND.

Methods: A Fresenius 2008 K dialysis machine (DM) was tested. A DAPS alarm for VND was implemented using LabVIEW software from National Instruments. VP data was obtained using an A to D converter connected to the analog output of the VP module, TX data was read every 2 sec from the DM serial port. A sham dialysis circuit with an artificial access site, Q=800 ml/min and AP variable 40 to 0 mmHg was used for testing. DAPS alarm threshold was AP<5 mmHg and the DM asymmetric VP limit was 25 mmHg. Circuit was filled with blood, Q=400 and the height of a 1L blood reservoir was adjusted to set the AP to 40mmHg. Reservoir height was decreased to set AP = 0 mmHg and alarms recorded. Procedure was repeated for Q=400 and 300. AP values of 30, 20, 15 and 10 were also tested for all Q values.

Results: Figure shows the results of the study. The DM alarm was only activated when the AP was decreased from 40 to 0 mmHg. In contrast, DAPS alarm was consistently positive even down to AP of 10 mm Hg. Tests repeated at Q=500 showed variable results for the DM alarm. In total 75% of studies produced no DM alarm.

Conclusions: The DAPS alarm implemented in a DM could be used for a more sensitive alarm system to detect VND.
**Access Pressure Reduced to Zero to Determine Alarm Status**

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**SA-PO1041**

An Increase in Mean Platelet Volume / Platelet Count Ratio Is Associated with Vascular Access Failure in Hemodialysis Patients Dong Ho Shin, Eunju Kim, Jung-Woo Noh, Ja-Ryong Koo. Hallym Univ College of Medicine.

**Background:** After stenosis of arteriovenous vascular access in hemodialysis patients, platelets play a crucial role in subsequent thrombus formation, leading to access failure. In a previous study, the mean platelet volume (MPV)/platelet count ratio, but not MPV alone, was shown to be an independent predictor of 4-year mortality after myocardial infarction. However, little is known about the potential influence of MPV/platelet count ratio on vascular access patency in hemodialysis patients.

**Methods:** A total of 143 patients undergoing routine hemodialysis were recruited between January 2013 and February 2016. Vascular access failure (VAF) was defined as thrombosis caused by stenosis after having undergone thrombectomy, or as greater than 50% stenosis on angiography requiring either surgical revision or percutaneous transluminal angioplasty. Platelet indices, including MPV/platelet count ratio and their changes were compared in patients with and without VAF by using linear mixed model analysis. Additionally, Cox proportional hazards model analysis ascertained that the change of MPV/platelet count ratio between baseline and 3 months ([MPV/platelet count ratio]baseline vs. [MPV/platelet count ratio]3mo) had prognostic value for VAF.

**Results:** Of the 143 patients, 38 (26.6%) were diagnosed with VAF. During a median follow-up of 26.9 months, MPV/platelet count ratiobaseline significantly increased in patients with VAF compared to that in patients without VAF [6.7 (3.1–18.9) vs. 3.9 (0.9–9.9), P < 0.02]. Moreover, a linear mixed model revealed that there was a significant difference in the increased MPV/platelet count ratio over the first 3 months in patients with VAF compared to those without VAF (P = 0.003). In multivariate analysis, MPV/platelet count ratiobaseline was an independent predictor of VAF (hazard ratio, 1.04; 95% confidence interval, 1.00–1.08; P = 0.03).

**Conclusions:** An increase in MPV/platelet count ratio was an independent risk factor for VAF. Therefore, continuous monitoring of the MPV/platelet count ratio may be useful to stratify the risk of VAF in patients undergoing routine hemodialysis.

**SA-PO1042**


**Background:** The current surveillance protocol for vascular access (VA) recommends intraaccess flow volume (Qac) should be measured within the first one and a half hours during hemodialysis (HD) to avoid errors. Several previous studies access resistance, which may cause Qac variation, was different among VA types. Therefore, we investigated Qac variation according to VA types.

**Methods:** Qac was measured at 30, 120, and 240 minutes in each HD session in 144 VA for comparison. 58 VA were lower arm arteriovenous fistula (AVF), 14 were lower arm arteriovenous graft (AVG), 27 were upper arm AVF and 45 were upper arm AVG. The other Qac (%) were expressed as the percentages of Qac at 30mins (100%). The variation of Qac over time was analyzed using repeated measures ANOVA.

**Results:** Qac was measured at 30, 120, and 240 minutes in each HD session in 144 VA for comparison. 58 VA were lower arm arteriovenous fistula (AVF), 14 were lower arm arteriovenous graft (AVG), 27 were upper arm AVF and 45 were upper arm AVG. The other Qac (%) were expressed as the percentages of Qac at 30mins (100%). The variation of Qac over time was analyzed using repeated measures ANOVA.

**Results:** Repeated measures ANOVA revealed that the time factor significantly affected access flow (P < 0.001), which decreased over time. With regard to group effect, there was significant difference among Qac (%) by VA types (P < 0.001). Qac (%) of lower arm AVG at 240 minutes was 72.8 ± 11.3 whereas Qac (%) of upper arm AVF at 240 minutes was 99.5 ± 7.8. There also existed a significant interaction between the effects of time and VA type (P < 0.001) suggesting that VA type affected Qac variation during HD. Post hoc analysis revealed Qac variation during HD was significantly different in lower arm AVG.

**Conclusions:** Our study suggested that Qac of lower arm AVG should be measured according to the current surveillance protocol, but Qac of the other VA types, especially upper arm AVF one, can be measured at anytime during HD.

**Funding:** Clinical Revenue Support

**SA-PO1043**

Intimal Hyperplasia Does Not Explain Focal Stenosis in Two-Stage Arteriovenous Fistulas Marwan Tabbbara, Laisel Martinez, Juan Camilo Duque Ballesteros, Angela Paez, Guillermo Selman, Loay H. Salaman, Roberto I. Vazquez-Padron, DeWitt Daughtry Family Dept of Surgery, Leonard M Miller School of Medicine, Univ of Miami, Miami, FL; Dept of Medicine, Miller School of Medicine, Univ of Miami, Miami, FL; Section of Interventional Nephrology, Miller School of Medicine, Univ of Miami, Miami, FL.

**Background:** Intimal hyperplasia has been historically recognized as the cause of venous stenosis. Recently, we have revealed that IH is not associated with two-stage arteriovenous fistula (AVF) maturation failure. The purpose of this study is to compare the degree of IH in stenotic and nearby non-stenotic segments collected from the same AVF.

**Methods:** Focal areas of stenosis were detected in the operating room in seven patients (n = 7) during the second stage basal vein transposition procedure. The entire vein was inspected prior to the transposition and the areas of stenosis were visually located with the aid of manual palpation and hemodynamic changes in the vein peripheral and central to the narrowings. In parallel, up photography was used for documentation before tissue collection (7 tissue pairs). Intimal area, thickness and intimal to media ratio were assessed in hematoxylin and eosin stained cross-sections, followed by pairwise statistical comparisons.

**Results:** The intimal area in stenotic and non-stenotic segments ranged from 1.25 to 5.57 mm² and 0.16 to 5.30 mm², respectively. There was no significant difference between these two groups (p = 0.8). The intimal thickness (p = 0.6) and intima/media area ratio were also similar between both segments (p = 0.8).

**Conclusions:** Although a higher number of patients are needed to confirm these findings, our results concur with our previous study and suggest that IH does not explain focal venous stenosis in two-stage brachiobasilic fistulas.

**Funding:** NIDDK Support

**SA-PO1044**

Overexpression of Cathepsins in Arteriovenous Fistula Stenosis in Maintenance Hemodialysis Patients Shang Guo Piao, Jian Jin, Can Li. 1Nephrology, YanBian Univ Hospital, Yanji, Jilin, China; 2Nephrology, The Catholic Univ of Korea, Seoul, Korea.

**Background:** Increasing evidence has demonstrated that cathepsins (Cats), a family of lysosomal cysteine proteases, play a critical role in various cardiovascular diseases. However, their role and expression in arteriovenous fistula (AVF) dysfunction are undetermined. The present study was undertaken to examine the expression of Cats and extracellular matrix (ECM) components in maintenance hemodialysis patients with AVF stenosis.

**Methods:** A total of 38 maintenance hemodialysis patients in YanBian University Hospital were enrolled. Of these, 18 subjects with AVF occlusion or severe stenosis served as AVF stenosis group, and 20 subjects with end-stage renal disease served as control group. Tissue samples were obtained from vein segments undergoing surgical AVF repair or creation. Basic parameters, histopathology, oxidative stress (MnSOD), and expression of cytokines (K and S) and ECM components (PIA-1, TIMP-1, and βig-h3) were examined by immunohistochemistry and immunoblotting. In addition, the Pearson single-correlation coefficient analysis were used to compare Cats expressions with Ig-h3 and MnSOD expression.

**Results:** Compared with the control group, serum CatK and CatS levels were increased in the AVF stenosis group. These increases in serum Cats levels were accompanied by upregulation of CatK and CatS protein expressions in the intima and medial layers of vein segments by approximately of 3-folds and 2.5-folds. In parallel, expression of TIMP, PAI-1 and βig-h3 were examined by immunohistochemistry and immunoblotting. In addition, the Pearson single-correlation coefficient analysis were used to compare Cats expressions with Ig-h3 and MnSOD expression.

**Conclusions:** Our observations indicate that an increase in Cats expression, along with ECM components upregulation, is closely associated with AVF stenosis in maintenance hemodialysis patients with AVF stenosis.

**Funding:** Other NIH Support - National Natural Science Foundation of China, Other U.S. Government Support, Government Support - Non-U.S.
SA-PO1045
Stenosis at Arteriovenous Anastomosis of Fistula: A Challenge for Dialysis Pressure Surveillance
William D. Paulson, Kim Hirschman, Sulav Bastola, John Jason White, Steven A. Jones, Medicine, Augusta Univ, Augusta, GA; Vasc-Alert LLC, Lafayette, IN; Charu Polyclinic and Diagnostic Center, Kathmandu, Nepal; Biomedical Engineering, Louisiana Tech Univ, Ruston, LA.

Background: Dialysis pressure surveillance is widely recommended for detection of stenosis in vascular accesses. However, the native fistula (AVF) is problematic in that dialysis needles are downstream to the arteriovenous (AV) anastomosis, where stenosis often develops. We used a mathematical model of the brachiocephalic AVF and clinical dialysis arterial pressures to determine the limitations in detecting AV anastomosis stenosis.

Methods: The model used engineering equations to determine influence of stenosis at the AV anastomosis on dialysis arterial pressure. The model included cephalic V anastomosed end to side to brachial A, radial & ulnar A, palmar arch, and vein that drains the hand and connects to cephalic V. Mean arterial pressure = 93 mmHg, central venous pressure = 5 mmHg. Luminal diameter of inflow artery was less than outflow vein (0.6 vs. 0.8 cm). We used data from 49 patients with trouble-free AVFs in the Vasc-Alert on-line surveillance program to determine variability of arterial needle pressures with blood pump running.

Results: Model predicts AVF pressures at stenosis = 0%, 50%, 100% are 15.7, 10.0, 5.0 mmHg, respectively. Thus, stenosis causes only small pressure changes. The SD for differences in pressure between 2 measurements with similar blood pump speed = 14.1 mmHg, so that change in pressure must be >28.3 mmHg to be significant at P < 0.05.

Conclusions: Stenosis at the AV anastomosis causes a decrease in pressure that may be too small to detect when the dialysis pump is running. Static pressure measurements or on-line surveillance programs that apply trend analysis and adjust for the effect of blood pump speed on pressure may compensate for this problem.

Funding: Clinical Revenue Support

SA-PO1046
Treatment of Arteriovenous Fistula Complications Using Far Infrared Therapy: Cambridge Experience
Regin Lagraa, Nicholas Pritchard, Renal Medicine, Cambridge Univ Hospitals NHS FT, Cambridge, United Kingdom; Renal Medicine, Cambridge Univ Hospitals NHS FT, Cambridge, United Kingdom.

Background: It is vital that Arterio Venous Fistulas (AVF) will continue to function efficiently. Complications of AVF includes pain of the AVF site, bruises and infiltration, haematoma formation and those experiencing AVF pain during HD. It is a safe and effective treatment modality that has been shown to reduce complications and improve the efficiency of AVFs through its direct anti-inflammatory properties.

Methods: A protocol has been developed by the Cambridge renal team to decide which patient will undergo the FIR treatment. It should be used for patients with the following characteristics: just undergone AVF surgery, with a maturing AVF, with steal syndrome, with low access blood flow, showing early signs of stenosis, and AVF bruises due to infiltration from previous cannulation. FIR therapy is a 40 minutes applications during each haemodialysis session for 4 to 6 weeks. Discontinuation of the treatment based on on-line surveillance programs that apply trend analysis and adjust for the effect of blood pump running.

Results: 22 patients received FIR therapy. In summary, 6 patients had an improvement of pain score on needling of AVF, 14 patients AVF needle-site haematomas resolved quicker and 2 AVFs matured with demonstrably better blood flow rates on doppler.

Conclusions: We have found FIR therapy to be of use in the maturation of AVFs, particularly in patients with challenging access, as well as in the treatment of problems such as haematoma formation and those experiencing AVF pain during HD. It is a safe and effective treatment modality that has been shown to reduce complications and improve the efficiency of AVFs through its direct anti-inflammatory properties.

SA-PO1047
Statin Treatment Improves Vascular Access Outcome among Diabetic Hemodialysis Patients
Manabu Kanda, Satoru Sanada, Yasunori Miyasaka, Atsuhiko Kanno, Kozi Sato, Mitsuhiro Sato, Yoshiho Tabuma, Toshinobu Sato, Dept of Nephrology, Japan Community Health Care Organization Sendai Hospital, Sendai, Miyagi, Japan.

Background: An effective therapeutic approach to reduce the risk of hemodialysis vascular access dysfunction is still unclear despite previous studies. Prior research has shown conflicting results of statin treatment probably because the pathogenesis of vascular access dysfunction is multifactorial and some confounding factors such as underlying causes of end-stage kidney diseases or type of vascular access could influence the results. In this study, we focused on diabetic hemodialysis patients and evaluated the impact of statin treatment on vascular access patency.

Methods: A retrospective cohort study of 243 consecutive patients who newly started hemodialysis due to diabetic nephropathy between January 2011 and December 2013 at Japan Community Health Care Organization Sendai Hospital was performed and the patients were followed for two years. The primary outcome was vascular access dysfunction. Effect of statin treatment was examined using Kaplan Meier analysis and Cox proportional hazard, after adjusting for covariates.

Results: The mean follow-up period was 426.7 days, and 131 (53.9%) patients developed vascular access dysfunction. Vascular access survival was significantly longer among statin users (547.9±29.9 versus 430.6±21.2 days, log-rank: P =0.008). The two-year patency rate was 58.7% among statin users and 38.6% in non-users. In multivariable analysis, statin treatment is significantly associated with better vascular access outcomes, in which the hazard ratio was 0.73 (95%CI, 0.54 to 0.97; P=0.03) in the unadjusted model and 0.63 (95%CI, 0.46 to 0.87; P=0.004) after adjustment for covariates.

Conclusions: The present study provided better vascular access outcomes among statin users in diabetic hemodialysis patients, which was only performed with diabetic hemodialysis patients. Native radiocephalic arteriovenous fistula was mainly used as a vascular access. This could account for the difference between our results and those of previous studies.

SA-PO1048
Creation of a Pig Model of Chronic Renal Insufficiency
Diego Celdran-Bonafonte, Begolia Campos, Aous Jarrouj, Sanjay Misra, Matthew Kurian, Sukit Rakasah, Prabir Roy-Chaudhury, Univ of Arizona; Univ of Cincinnati; Mayo Clinic.

Background: Uremia is an important contributor to the huge increase in the incidence of cardiovascular morbidity and mortality in CKD and ESRD patients; as a result of inflammation, oxidative stress and endothelial dysfunction. Despite this, we do not at the present time, have a reliable large animal model that replicates the uremic milieu. The objective of the current study was to develop a pig model of uremia with a GFR between 15-30 ml/min.

Methods: 4 Yorkshire pigs were used in this study. Renal insufficiency was induced through a total nephrectomy of the right kidney followed by selective ligation of the vascular supply of the contralateral kidney under direct vision. 2 animals were left with 15% renal remnant mass (caudal pole of the left kidney was left perfused), while the other two animals were left with 7% remnant renal mass (ventral aspect of the mid hilum was left perfused). Blood samples were collected sequentially over a 42 day period for BUN and creatinine. Samples were stored for future measurement of inflammatory markers and also for genomic, proteomic and metabolic analyses.

Results: Animals with 15% of remnant renal mass (left panel in Figure 1) had an initial increase in the creatinine to 4-5mg/dL followed by a stabilization at 1-2mg/dL by 2 weeks. In contrast, animals with only 7% of remnant renal mass had an initial increase in creatinine to greater than 8mg/dL followed by a stabilization between 3-4 mg/dL by 2 weeks. A macroscopic post mortem evaluation of the animal with the caudal pole left unligated demonstrated significant hypertrophy of this region with ischemic necrosis of the upper pole (right panel in Figure 1).

Conclusions: Our data describe the development of a reproducible large animal model of uremia (7% remnant renal mass) that could be used for mechanistic and therapeutic investigation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO1049
Cellular Integration and Early Cannulation Potential in a Bioengineered Arteriovenous Vascular Access (Phoenix)  
Diego Celdran-Bonafonte,1 Chelsea Elizabeth Stowell,1 Begona Campos,2 Aous Jarrouj,1 Sukit Rakasuk,1 Peter L. Jernigan,2 Yadong Wang,2 Prabir Roy-Chaudhury.  
1Univ of Arizona; 2Univ of Cincinnati; 3Mayo Clinic.

Background: Hemodialysis vascular access dysfunction continues to be the Achilles heel of hemodialysis. The objective of our study was to develop a bioengineered scaffold (the Phoenix), which when placed in-situ would allow for both early cannulation and rapid cellular integration.

Methods: Porous vascular graft cores were electrospun from a blend of polyglycerol sebacate (PGS) prepolymers and polyvinyl alcohol (PVA). Cores were reinforced with polycaprolactone (PCL) and a non-porous synthetic sealant layer. Phoenix grafts of varying sizes were surgically placed between the carotid artery and jugular vein in four Yorkshire Cross pigs.

Results: Reinforcement significantly improved structural tensile strength and suture retention load. Ultrasound examination documented flow and patency until sacrifice at 2 weeks. Movat staining revealed an active cellular repopulation of the scaffold (progressing radially outward from the lumen up to 2/3 of the wall thickness) with muscle cells and ECM deposition. Endothelial (CD31 positive), and possible intimal and medial layers were identified. No such repopulation was evident in a contralateral PTFE graft. Successful cannulation of the Phoenix was performed in-vivo, and ex-vivo attempts at cannulation revealed rapid closure of the needle site.

Conclusions: Our results indicate that the Phoenix appears to combine the autogenous benefits (note active host cell repopulation of the scaffold) of an AVE, with the early cannulation benefits (downstream reduction of catheter complications) of an AVG. Patency studies are currently in progress but these initial data suggest that the Phoenix could significantly reduce the morbidity and mortality currently associated with dialysis vascular access dysfunction.

Funding: Other NIH Support - NIH/NCATS

SA-PO1050
Impact of Social Support Types on Nutritional Status and Catheter Utilization in Hemodialysis Patients  

Background: The associations between outcomes and the type of social support dialysis patients receive from family, friends, or caregivers have not been widely studied. We aimed to investigate whether social support types in hemodialysis (HD) Pts are associated with nutritional status. Also, we studied catheter utilization, since it was hypothesized that stronger family support may help patients have a permanent access placed.

Methods: We analyzed data from Jan 2014 to Dec 2015 on 168,688 Pts at Fresenius Medical Care North America who completed a social work questionnaire. We captured data on social support types, the type of support Pts received from no-one or a friend/neighbor, “a member of my family”, “a friend/neighbor”, or “health staff/community resource/church”. We compared support types to the proportion (%) of Pts achieving mean albumin (Alb)≥4.0g/dL and the % of Pts with a catheter during the 6 month period prior to completing the questionnaire.

Results: We observed that Pts who received social support from no-one or a friend/neighbor were found to have a higher % of Pts with an Alb≥4.0g/dL, as compared to others. Those who received support from no-one had the lowest % of Pts with a catheter (Figure 1).

Conclusions: The findings indicate the social support type that Pts receive may have a small impact on their nutritional status and use of catheters. Although we found that support from no-one was associated with the most Pts meeting Alb≥4.0g/dL and least Pts utilizing catheters, these observations could potentially be representing a healthier or younger sub-population. Further analyses are needed controlling for differences in demographic and clinical parameters.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO1051
Epidemiology of Dialysis Catheter-Associated Bloodstream Infections in an Emergent Dialysis Cohort  
Hal Zhang,1 Maulin Shah,1 Nicolas Cortes-Penfield,2 Jingbo Niu,1 Eric Wu,1 Roya Zamani,1 Daniel Chen,1 Sreedhar A. Mandayam,1 1Nephrology, Baylor College of Medicine, Houston, TX; 2Infectious Disease, Baylor College of Medicine, Houston, TX; 3Internal Medicine, Baylor College of Medicine, Houston, TX.

Background: Dialysis catheter-related bloodstream infections (CRBSIs) cause significant morbidity and mortality in end-stage renal disease (ESRD) patients. Harris Health in Houston provides dialysis to hundreds of undocumented immigrants on an emergent basis and is often unable to support fistulas, leaving these patients chronically dependent on tunneled dialysis catheters. The epidemiology of CRBSI in this population has not been described until now.

Methods: We performed a retrospective chart review of all ESRD patients who receive hemodialysis solely on an emergent basis through Harris Health System in Houston, Texas between 1/1/2012 and 12/31/2015. We recorded patient demographics, comorbidities, and all CRBSIs that occurred during the study period. We defined CRBSI as a positive blood or catheter tip culture and treated as catheter-related infection by the treatment team. We assessed the association between potential risk factors and the number of CRBSIs using negative binomial regression. The magnitude of the association for risk factors significantly related to CRBSIs in the crude model were assessed in a multivariate model adjusting for each other.

Results: Of the total 342 ESRD patients, 78 patients had 120 CRBSIs. The infection rate was about 1/1000 catheter days. 23 patients had multiple CRBSIs and there were 17 recurrent infections (recurrence rate 16.5%). The risk of CRBSIs was 1.7 (95% CI: 0.7, 3.9), 2.8 (95% CI: 1.2, 6.4), 1.8 (95% CI: 0.7, 4.7) and 0.5 (95% CI: 0.2, 1.7) among patients age 40-49, 50-59, 60-69 and 70 years older compared with patients younger than 40 years. Patients with hemodialysis frequency≥6 sessions per month had 2.3 (95% CI: 1.0, 5.6) times higher risk of CRBSI than those with frequency<3.

Conclusions: In our cohort of emergent HD patients, CRBSI was less frequent than the CDC national average and is more frequent in the 50-59 age group and in patients receiving more frequent dialysis.

SA-PO1052
Hemodialysis Infection Prevention Using Polysporin Ointment with Shower Technique in Satellite Centres (HIPPO-SAT): A Pilot Randomized Controlled Trial  
Sarah Daisy Kosa,1,2 Amiram Gafni,2 Gabrielle Ene,1 Andrew A. House,3 Julieann L. Lawrence,1 Louise M. Moisit,1 Paul Y. Tam,1 Lehana Thabane,2 George G. Wu,6 Charmaine E. Lok,1,2 1Toronto General Hospital; 2McMaster Univ; 3London Health Sciences Centre; 4Mackenzie Health Hospital; 5The Scarborough Hospital, Scarborough, ON, Canada; 6Credit Valley Hospital.

Background: We developed the Toronto Hemodialysis Catheter Shower Technique protocol (STP) to permit HD patients with catheters to shower without increase infection risk. The study objective was to determine the feasibility of conducting a definitive parallel randomized controlled trial (RCT) called HIPPO-SAT that will evaluate the impact of STP on catheter-related bacteremia (CRB) in adult satellite HD patients.

Methods: Adult HD patients using catheters were recruited from 3 in-centre and 8 satellite HD units, randomized to receive STP or standard care, and followed for 6 months (Registration:NCT02002169). The primary outcome of study feasibility was based on 5 outcome measures, each with its own statistical threshold for success (threshold), of which 4 must be achieved for HIPPO-SAT to be deemed feasible. Secondary exploratory outcomes included CRB rates and patient-reported satisfaction with their vascular access care.

Results: 68 patients were randomized (33 in STP group) and 4/5 feasibility measures of feasibility were achieved: 1) accurate CRB rate documented (threshold: kappa level...
Prevention of Hemodialysis Catheter-Associated Bloodstream Infection: A Single Center Experience


Background: Central-line-associated bloodstream infection (CLABSI) is a dangerous health care-associated infection that increases hospital costs and length of stay. Several reports have shown that using a multidisciplinary team and "prevention bundles(PB)" approach, which includes staff education, hand hygiene, the use of maximum sterile barrier precautions, the use of chlorhexidine gluconate (CHG), and catheter checklists, has markedly reduced the infection rate. However, there are limited data on CLABSI in dialysis access. This study investigated the efficacy of PB in patients using dialysis access in our dialysis center.

Methods: We retrospectively evaluated the incidence of CLABSI before (October 2012 to March 2013) and after (April 2013 to April 2015) the intervention PB were adopted for patients with dialysis access using the formulae of the Dialysis-related Infections Surveillance Research Consortium (DRISRC) in Japan: [infection cases/dialysis sessions] × 100. The PB included hand hygiene, maximum sterile barrier precautions, the use of 1% CHG, avoiding the femoral vein, and checklists for dialysis access. The checklist for dialysis access included the date and place of insertion, type of catheter (short- or long-term), reason for insertion and withdrawal, and appearance of the insertion site. We then checked the compliance status and obtained feedback from staff members.

Results: Overall, four patients developed CLABSI in the 6 months before adopting the PB versus only two cases per year after the intervention. The incidence of CLABSI in dialysis access before intervention was 6.97 (4575/1000), which was comparable with the value of 6.96 from DRISRC in Japan. After the intervention, the incidence decreased to 3.19 (2626/1000), 2.52 (2793/1000), and 3.3 (2606/1000) in 2013, 2014, and 2015, respectively.

Conclusions: PB effectively reduced CLABSI in dialysis access. Checking the compliance with technique and methods, and feedback from staff are important for maintaining the PB system.

A Novel Device for Reducing Catheter-Related Bloodstream Infections: A Single Center, Uncontrolled, Randomized Clinical Trial of the ClearGuard HD Antimicrobial Barrier Cap

Jeffrey L. Hynes, Ann Mooney, Carly R. Van Zandt, Laurie Lynch, Robert Ziebel, Douglas Killion, Fresenius Medical Care North America, Waltham, MA; Fresenius Renal Research, Waltham, MA; Pursuit Vascular, Inc., Maple Grove, MN.

Background: Bloodstream infections (BSIs) have been a significant problem for hemodialysis catheter patients for decades, leading to poorer outcomes such as death and hospitalization, and increased cost to the healthcare system. This clinical trial studied use of antimicrobial central venous catheter (CVC) caps intended to prevent BSI.

Methods: 12-month, prospective, cluster-randomized, multi-center, pragmatic, open label clinical trial conducted at 40 Fresenius Medical Care North America dialysis facilities. We matched facilities by positive blood culture (PBC) rate and number of CVC patients. Patients were randomized in a 1:1 ratio to use ClearGuard HD Antimicrobial Barrier Caps or standard CVC caps. 2,470 patients participated in the study, accruing approximately 350,000 CVC-days. The primary endpoint was PBC rate as an indicator of BSI rate. PBCs, hospital admissions for BSI, hospitalization-days for BSI, IV antibiotic starts, and CVC-days were measured.

Results: The treatment and control groups were well matched. Use of ClearGuard HD CVC caps was associated with a 55% reduction in PBC rate compared to standard CVC caps during the 12-month study (0.27 vs. 0.60/1000 CVC-days, P<0.001). Sustained use of ClearGuard HD CVC caps (last 6 months of study) demonstrated a 69% reduction in PBC rate (0.22 vs. 0.70/1000 CVC-days, P<0.001) and 43% reduction in hospital admissions for BSI (0.27 vs. 0.48/1000 CVC-days, P<0.03), and a 51% reduction in hospitalization-days for BSI (2.41 vs. 4.93/1000 CVC-days, P<0.001). No device-related adverse events were reported.

Conclusions: Use of ClearGuard HD Antimicrobial Barrier Caps significantly reduced BSI hospital admissions for BSI, and hospitalization-days for BSI.

A New Dialysis Catheter Dressing (Cath Dry) Significantly Reduces Catheter Infections


Background: Dialysis catheter infections are a significant cause of morbidity/mortality and adversely impacts quality of life. We evaluated the use of a novel, water resistant, and breathable dialysis catheter dressing, Cath Dry.[figure1]

Methods: Participants were recruited from a dialysis center in Mission Hills, CA. The dressing was applied to enrolled participants (n=45) via sterile technique by dialysis nurses. Participants were instructed to not remove the dressing and advised to shower without restriction. All participants completed a quality of life survey before and after the study. Data on infections were collected during the study period.

Results: Participants were enrolled for 3 months, for a collective study period of 139 catheter-months. The expected infection rate for our population was approximately 3 episodes (based on National Healthcare Safety Network (NHSN) 2014 data of 2.16 infections per 100 catheter-months). During the study, we observed no catheter related infections. We compared our rate of zero infections to the 2014 NHSN infection rate using a one-sided exact test based on the binomial distribution. Our infection rate was significantly less than the NHSN rate (p = 0.0449). Quality of life survey results showed 78% of patients felt their catheter was not clean/protected prior to the study whereas 100% of patients felt their catheters were clean/protected during the study. Similarly, 68% of participants felt their inability to shower adversely affected their quality of life. At the end of the study 100% of participants felt that Cath Dry improved their dialysis experience.

Conclusions: Cath Dry, a water resistant and breathable dialysis catheter dressing significantly reduced infections in our participants when compared to 2014 NHSN infection rates. Use of Cath Dry contributed positively to the quality of life, dialysis experience and hygiene of our participants.

Randomized Controlled Trial of Tauraolidine Citrate versus Taurulinide Urokinase Lock to Prevent Tunneled Catheter Thrombosis in Hemodialysis Patients: Cost Analysis and Effectiveness Study


Background: Catheter malfunction is a frequent complication and responsible for most of catheter removals. In a recent trial, we found benefit of using Taurulinide citrate with Urokinase (T/U) versus Taurulinide Citrate with Heparin (T/Hep) in decreasing catheter thrombosis and infection. We are presenting a cost effectiveness analysis of the trial.

Methods: In a prospective randomized controlled trial in Qatar. HD patients received T/Hep or T/U catheter locks and followed for 6 months. We analyzed incremental cost. Cost was calculated based on actual purchasing price for our hospital for T/Hep, T/U and rt-PA. Hospitalization and procedure costs estimated from hospital billing department.

Results: There were 93 patients in T/Hep and 84 in the T/U. Total 7 catheters were removed in T/Hep versus 1 only in T/U. rt-PA use was lower in T/U than T/Hep. Cost for T/U lock was significantly higher than T/Hep ($8000 USD versus $61700 USD pValue = 0.05). Cost difference was eliminated when adding additional costs of hospitalizations, catheter removal procedure and rt-PA (total cost was $82000 USD in T/Hep versus $84720 USD in T/U, p Value 0.9 NS). Detailed cost analysis shown in Table 1/Figure 1.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO1057

Use of Taurolidine Citrate with Urokinase Lock for Dialysis Catheter Malfunction: A Prospective Pilot Study


Background: Thrombolytics are used to treat hemodialysis (HD) catheter malfunction. Blood flow rate (BFR) during dialysis is a surrogate outcome and an established marker of catheter malfunction. We are presenting a prospective pilot study to introduce Taurolidine-urokinase-U25.000 (T/U) catheter lock in regard to improving catheter malfunction.

Methods: All HD patients in the 2 largest outpatient facilities in Qatar (460 patients) were evaluated. Patients were included if they have permanent dialysis catheter with poor BFR (mean of less than 250 ml/min for 6 weeks prior to inclusion in study) (phase 0). We have 2 phases. Phase 0 was observation for 6 weeks with our current practice followed by phase 1 where patients were started on T/U catheter lock every session for 6 weeks. BFR in HD sessions and need for recombinant tissue plasminogen activator (rt-PA) treatment for acute nonfunctioning catheters were monitored in both phases.

Results: 25 HD patients included in the study (14 Males and 11 females). Baseline catheter locks (phase 0) were heparin 5000 unit/ml (11 patients), heparin 5000 unit/ml with rt-PA lock on weekend session (10 patients) and 4 patients on Tauroline with Heparine 500 units. Mean BFR was significantly higher in phase (1) with T/U (252 +/-36 ml/min) compared to phase 0 lock solutions (198 +/-23) (p Value 0.0001 95% CI of this difference). From 65 to 40, rt-PA treatment needed for acute catheter malfunction was significantly less in T/U (phase 1) versus other locks (phase 0) (0.7 +/- 1.4 versus 3.2 +/- 3.1 p Value 0.0007, 95% CI 1.12 to 3.92). Sixteen patients (64%) achieved BFR > 250 ml/min after applying T/U while 3 patients only (12%) showed no improvement in BFR. One patient expired due to congestive heart failure complications 3 weeks into the study. No adverse events reported during study period. Cost analysis comparison was 12700 (T/U) versus 8080 (Heparine) (US dollars) (baseline locks).

Conclusions: In a pilot study to introduce T/U catheter lock, we found significant improvement in BFR, decrease in need for rt-PA and most patients achieved BFR above 250 ml/min but with 84% increase in cost.

SA-PO1058

A Novel Technique for Catheter-Related Sheath Removal

Grant Meltzer,1,2 Adam S. Przebinda,1 Zahid Bashir Ahmad,1,2 1Dept of Nephrology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK; 2Dept of Nephrology, Veterans Affairs Hospital, Oklahoma City, OK.

Background: Catheter-related sheaths (CRS) are sore-like structures composed of inflammatory cells and connective tissues which form on the outside of indwelling central venous catheters (CVC), as a thrombogenic response. CRS, also known as fibrin sheaths or sleeves can inhibit tunnelled dialysis catheter function through obstruction of the side ports or catheter tip.

Methods:

Step 1: Angiogram estimates terminal position of CRS. Balloon is deployed beyond this point and partially retracted

Step 2: CRS is folded and trapped against the 10 French catheter

Step 3: Balloon and sheath are withdrawn.

Results: Current techniques to salvage affected catheters include thrombolytic agents and/or stripping procedures. However, standard care at most centers is catheter exchange with balloon disruption of the CRS. Disruption of the CRS, though generally well tolerated, raises concern for potential complications, notably pulmonary embolism of CRS fragments.

Conclusions: We report a new technique which retrieves the CRS, thereby eliminating the risk for pulmonary embolism.

Funding: VA Support

SA-PO1059

Outcomes after Stent Graft Placement for Cephalic Arch Stenosis – Effect of Access Flows and Cephalic Arch Angle

Florian E. Fogiel,1 Patrick McGlynn,1 Praekrit C. Acharya,2 Adina Simona Vosculescu,2 Dirk M. Hentschel,1 1Nephrology, Brigham and Women’s Hospital, Boston, MA; 2Medicine, Mount Auburn Hospital, Cambridge.

Background: Cephalic arch stenosis (CAS) is a common complication of brachio-cephalic autogenous accesses and limits access survival. Treatment with angioplasty (PTA) is complicated by high recurrence rates. Covered stent placement is widely practiced but outcomes data are limited. We report the long-term outcome after CAS stent graft placement in relation to access flows and cephalic arch angle.

Methods: Retrospective chart review of patients undergoing PTA and stent graft placement between 2008-2013.

Results: 50 patients underwent placement of stent grafts for CAS after failure of PTA due to recoil and clinical symptoms < 90 days, or rupture during any PTA. Time from fistula creation to first procedure in the cephalic arch averaged 564 days. Progression from first angioplasty for CAS to stent graft placement averaged 342 days (range 23-1369) and follow up after stent graft placement was on average 2.7 years (1001 days). An average number of 1.5 stents was placed per cephalic arch. The acuteness of the cephalic arch angle was neither associated with time to first intervention nor with recurrence of stenosis after initial angioplasty, but a more acute angle was associated with a higher number of procedures after stent placement. Time between interventions before stent graft progressively declined from 131 days to 85 days and decline was faster with higher access flows. After stent placement time between procedures significantly increased to 379 days, 187 days and 307 days (1st, 2nd and 3rd procedure) and procedure frequency significantly declined to an average of 0.97 procedures per year. Higher flow accesses had a longer intervention-free interval after stent placement (440 days flow >1400 ml/min, 247 days flow 800-1400ml/min, 174 days flow < 800 ml/min).

Conclusions: Stent graft placement extends the procedure free interval, extending access life. Higher flow accesses benefited proportionally more from stent graft placement compared to lower flow accesses. The acuteness of the cephalic arch angle is associated with a higher number of procedures after stent graft placement.

Funding: V A Support

SA-PO1060

Blood Flow Velocity Predicts Cephalic Arch Stenosis in Patients with Brachiocephalic Fistula Access

Mary S. Hamms, Sydeak Watson, Alkesh A. Amin, Brian Funaki. Univ of Chicago.

Background: The lower arm radiocephalic fistula (RCF) is the first access recommended for patients with ESRD on hemodialysis; however, there is a high failure rate compared to other arteriovenous fistula (AVF) configurations. An upper arm brachiocephalic fistula (BCF) is the next recommended access to be placed, but these most commonly fail owing to cephalic arch stenosis (CAS). Patients with BCF are 3 times more likely to develop
Hemodialysis Vascular Access – II
Poster/Saturday

SA-PO1061
Impact of Banding Procedure and Factors Associated with Cephalic Arch Stenosis in Brachiocephalic Fistulae
Yae Mi Kim, Ji Hyun Yu, Byung Ha Chung, Bumsoon Choi, Cheol Whee Park, Chul Woo Yang, Yong-Soo Kim.

Background: Cephalic arch stenosis (CAS) is the most common stenosis in brachiocephalic fistula (BCF). Recurrent stenosis and unacceptable primary patency rate after performing percutaneous transvenous angioplasty (PTA) are major concerns. We aimed to evaluate the patency rate of CAS in dysfunctional BCF and to identify factors that may affect their patency rate and the impact of banding procedure.

Methods: Out of 374 angiography in 178 patients with dysfunctional BCF from 2015 to 2017 in our center, 234 angiography in 86 patients revealed CAS. CAS was the first choice of management. Cutting balloon angioplasty was performed when resistant to high pressure PTA. Endovascular banding (MILLER) was done in cases of recurrent CAS (>3 times) with high access flow (>1.5 L/min). Kaplan–Meier method was employed to evaluate patency rates.

Results: Primary, primary assisted, and secondary patency rates of CAS were 60.9%, 96.3%, and 94.1% at 3 months and were 52.1%, 95%, and 93.1% at 6 months and were 33.4%, 86.9%, and 88% at 1 year, respectively. Number of PTAs less than or equal to 1.65 per access-year showed favorable primary and secondary patencies when compared to those with more than 1.65 PTAs per year. Maximum diameter of distal cephalic vein to cephalic arch (CV/CA) ratios showed a significant difference between dysfunctional BCF with CAS and without CAS. ROC curve drawn to predict the value of CV/CA ratio in the development of CAS showed cut-off of 1.61 had sensitivity and 100% specificity in predicting the development of CAS. Proximal 1/3 lesion in CAS was associated with poorer primary patency rate than those with distal lesion. MILLER procedures were performed in 15 patients. The number of PTA prior to MILLER was 4.26 per access-year, whereas it was 2.78 per access-year when adjusting for BMI, coronary artery disease (CAD), diabetes, and gender (p < 0.001).

Conclusions: Size discrepancy between CV/CA during fistula maturation might be a risk factor for developing CAS. MILLER procedure could improve the outcome of recurrent CAS. We need further studies to determine the indications for the banding in dysfunctional BCF with CAS.

SA-PO1062
Survival and Central Vein Stenosis in Catheter-Only Dialysis Patients
Sarah Hildebrand, Neill D. Duncan, Damien Ashby.

Background: Compared to other forms of access, arteriovenous fistulae are associated with improved survival in haemodialysis patients, and are widely believed to be superior. In a recent review, patients supplied to fistula catheters were found to have significantly increased risk for mortality with hazard ratio 1.5, though the substantial potential for bias was noted. Centre level data avoids some of this bias, so the outcome in centres with unusual practice patterns can be informative.

Methods: This retrospective study examined survival after 90 days, in a cohort of patients who never had non-catheter access. A subgroup were assessed for the presence of central venous stenosis.

Results: Between March 2006 and November 2014, 1514 patients (mean age 61.4, range 18-94) were identified in our cohort. None of the patients who had been catheters prior to dialysis via tunnelled catheter, reached at least 90 days, and remained on this type of access throughout the observation period. Over a follow-up period covering 4758 patient-years, there were 608 deaths (40.2%) and unadjusted median survival was 80.3 months. One year (after 90 days) survival was 89%, with survival rates of 87%, 83% and 80% at 2, 5, and 10 years, respectively. Over the same period, average survival in UK prevalent dialysis patients was 89% (standardized to age 60). Adjusting for national fistula prevalence, this suggests that compared to dialysis by fistula, dialysis

by catheter access carries a modestly increased risk for mortality with hazard ratio 1.2. For catheter-only patients, comparison to fistula survival constant over at least the first three years, at 87.8%. Over the same period, average survival was 60.3 months. One year (after 90 days) survival was 89.0%, with survival rates of 87.5%, 84.0% and 80% at 2, 5, and 10 years, respectively. Over the same period, average survival in UK prevalent dialysis patients was 89% (standardized to age 60). Adjusting for national fistula prevalence, this suggests that compared to dialysis by fistula, dialysis

SA-PO1063
Superior Vena Cava Stenosis in Hemodialysis Patients with a Tunnelled Cuffed Catheter: Prevalence and Risk Factors
Benjamin Serodio, Michel J. Jadoul, Ralph Crott. Laura Labriola.

Background: Central vein stenosis (i.e. subclavian/internal jugular/superior vena cava) is a major cause of vascular access (VA) failure and morbidity in hemodialysis (HD) patients. However the actual prevalence and risk factors of superior vena cava stenosis (SVCS) are unknown.

Methods: In this prospective retrospective observational study, all in-center HD patients with a tunneled cuffed catheter (TCC) between Jan 1st 2008 and Dec 31st 2012 were included (n=117, 65.9 ± 15 y, 43.5% diabetes). SVCS was defined as >50% reduction of vein diameter on phlebography or injected CT (and/or need of angioplasty). Imaging was triggered by clinical SVCS syndrome or VA dysfunction. We recorded demographics, comorbidity (primary or secondary case: heart failure, coronary artery disease, (CAD), diabetes, and gender (p < 0.001)). Imaging was triggered by clinical SVCS syndrome or VA dysfunction. We recorded demographics, comorbidity (primary or secondary case: heart failure, coronary artery disease, (CAD), diabetes, and gender (p < 0.001)). Imaging was triggered by clinical SVCS syndrome or VA dysfunction. We recorded demographics, comorbidity (primary or secondary case: heart failure, coronary artery disease, (CAD), diabetes, and gender (p < 0.001)).

Results: Among the 117 patients [214 TCC carried for 697 (range 44–2,464) days, total 80,911 catheter-days, median HD vintage 1,202 (60–6,126) days], 11 had a SVCS (9.4%, 0.136/1,000 catheter days). Only 2 presented with clinically obvious SVCS, with complete occlusion in one. Of TCC per patient was 1.8 (range 1–7). 2.64 ± 1.8 in SVCS group vs 1.75 ± 0.94 in negative group (p = 0.13). On multivariate analysis (Poisson), diabetes [IRR 4.63 (1.27-18) p = 0.03] and total duration of TCC catheter [IRR 1.47 (1.21–1.7) per y, p = 0.0001] (but not HD vintage, n of previous AVF, n of TCC, site or length of TCC) were associated with SVCS. Limitations: As not all patients underwent imaging, the prevalence of SVCS may be higher than detected.

Conclusions: Superior vena cava stenosis is all except a rare condition, mostly asymptomatic, strongly associated with diabetes, and promoted by long-term TCC catheter. Thus, the prevalence of TCC is growing worldwide, the morbidity associated with SVCS may be expected to grow in the future.

SA-PO1064

Background: The insertion of hemodialysis catheter is an integral part of the management of critically ill patients requiring continuous renal replacement therapy (CRRT). Doppler ultrasound imaging guidance for the insertion compared with anatomic landmarks has benefits regarding clinical outcomes and its use is strongly recommended. Traditionally, a postprocedural chest radiography (CXR) is performed for catheter confirmation; however obtaining one can take up to several hours, delaying catheters use in patients requiring emergent dialysis initiation. The primary goal of this study was to determine if sonography microbubble protocol after central venous access was accurate to identify catheters tip correct position compared to CXR and mean time of each procedure.

Methods: This study included a convenience sample of critically ill patients requiring CRRT with supradiaphragmatic hemodialysis catheters and a CXR for confirmation. Ultrasound was used for confirmation by visualizing microbubble artifact in the right atrium after injection of saline through the distal port. Blinded chart review was performed to assess accuracy, timing and cost of procedure. Sensitivity, specificity, positive predictive value, negative predictive value, positive predictive value and time difference between the procedures relative to the standard value, the CXR, were analyzed.

Results: 97 patients were enrolled. The microbubble test was 87.5% sensitive (95% CI 0.42–1.0) and 97.6% specific (95% C1 0.92–1.00) in confirming catheter placement, with 75% PPV, 98.8% NPV. Concordance between the tests was 97%, with an expected agreement of 59%. The mean time required to perform microbubble protocol was 10.55±3.89 minutes vs 133.51±44.75 minutes for CXR. The interrater reliability was strong: k=0.78 (95% CI 0.54–1.02) for all images (p<0.001).

Conclusions: The rapid appearance of prominent turbulence in the right atrium on chest ultrasound after CVC saline flush serves as a precise bedside screening test of optimal hemodialysis catheter position and was significantly faster than CXR in our population of critically ill patients requiring CRRT.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Effect of Argatroban for the Prevention of Hemodialysis Tunneled-Cuffed Catheters Thrombosis

Hua Jiang, Kehui Jiang, Xun Zhu, Pan Yan, Hua Hua, Zeyu Ding, Seyed Iyengar, G. Iyengar, Kaitlyn Plante, Ron Ratkowiak, Ronald Plattner, Xiaoming Zheng, Shuqin Li, Akihiko Togawa, Seyed Sadjadi, and Akashi Togawa.

Background: Thrombosis-related malfunction of tunneled-cuffed central venous catheters (TCCs) for hemodialysis (HD) currently leads to a high rate of untimely catheter removal. To examine argatroban in the prevention of thrombosis of TCCs, and to investigate further the effectivity and safety of argatroban in preventing thrombosis.

Methods: To compare the effect of preventing thrombosis between using urokinase group (UK group) and argatroban group (AT group), the 42 patients of TCCs were collected since Jan. 2013 to Jan. 2014, including 23 patients using UK, 19 patients using AT, and drugs were taken monthly, a total of 12 months. The adverse events and interventions of pre-dialysis, blood flow, transmembrane pressure and venous pressure of dialysis were observed in two groups in two periods.

Results: The intervention rates of the two groups after treatments were 4.8% vs. 10.3% (AT vs. UK, P < 0.05). In the two groups, the blood flow were all increased after treatments, and transmembrane pressure and venous pressure were all reduced (P < 0.05). Before and after each preventive therapy, there was significant difference in activated partial thromboplastin time (APTT) in the two groups (UK vs. AT, P<0.05). In AT group, the CRP gradually reduced during 12 months of treatment (P < 0.05).

Conclusions: Argatroban or urokinase could prevent the thrombosis of TCCs, by dripping at regular periods, and the blood flow of dialysis was increased. Argatroban group had higher safety, less thrombosis incidence and inflammatory reaction than urokinase group, which may predict that the long-time argatroban application could reduce inflammatory in maintenance hemodialysis patients.

SA-PO1066

Tunneled Hemodialysis Catheter (TDC) Survival with Use of Tissue Plasminogen Activator (tPA) Instillation


Background: In the United States up to 80% of patients start dialysis by way of TDCs despite attempts to reduce this. Besides carrying a higher risk of infection, TDC’s may cause formation of blood clots, impeding blood flow and thus adequate dialysis, causing increased morbidity and mortality. Prior studies have shown that tPA is effective in maintaining patency of PDs, especially short term and in the setting of catheter dysfunction. In our study we attempt to establish evidence for long-term patency with use of thrombolytics.

Methods: This is a retrospective cohort study with 169 study subjects. The Nephrology dialysis unit database was searched to identify all hemodialysis patients with TDC’s placed. The electronic medical records was reviewed to see if subjects had or had not received tPA. The data was analyzed to compare “early” (30 days), “late” (90 days) and “very late” (180 days) TDC survival with and without tPA. Secondly we also determined average number of tPA doses used.

Results: With regards to “early” catheter survival at 30 days, there was no significant difference in survival between catheters that did and did not receive tPA (p value 0.591). There was no significant difference in “late” catheter survival at 90 days either (p value 0.497). With regards to “very late” catheter survival at 180 days, the difference was not significant (p value 0.252). The number of tPA doses averaged 4.9 doses with a wide standard deviation of 8.8. With regard to catheter survival, catheters treated with tPA survived 80 days versus 77 days in those catheters not treated with tPA (p value 0.124). With regards to TDC location, left versus right sided, there was no significant difference in survival (p value 0.392).

Conclusions: If one considers the “gold standard” for a TDC as one that remains functional without the need for tPA until removal. In our study, the overall catheter survival in days was improved with the use of tPA by 3 days, neither statistically or clinically significant. TDCs treated with tPA survived the same length of time as the “gold standard” catheters, thus leading to our conclusion that use of tPA in TDC’s is non inferior to the “gold standard.”

SA-PO1067

Expanded Indications of Occluded Arteriovenous Fistula Puncturing with Ultrasound Guide

Akashi Togawa. Dept of Nephrology, Shizuoka Saiseikai General Hospital, Shizuoka, Japan.

Background: We have tried placing a regular needle catheter through the occluded arteriovenous graft (AVG) to the brachial artery as a temporary vascular access (“occluded AVG puncturing”). We previously reported that the occluded AVG puncturing is useful as a back-up hemodialysis vascular access (Togawa 2012 J Vasc Access). After the first report, we tried to expand the indication of occluded AVG puncturing with ultrasound-guiding puncturing technique.

Methods: Occluded AVG puncturing was performed approximately 15-30 mm from the site of anastomosis between the artery and graft. The body of the catheter passes through the cagulated blood in the graft and the tip of the catheter is placed in the artery. We used 50mm needle for occluded AVG puncturing. The subcutaneous veins or deep veins were used for the return circuit of hemodialysis. In some patients, ultrasound guided puncturing was performed for catheter insertion of veins.

Results: From June 2011 to May 2016, we performed 143 punctures of 12 patients. Puncturing was performed in patients with difficulty of immediate intervention or re-surgery. In the patients undergoing the longest period, we performed 75 occluded AVG puncturing for 6 months. Even if there was a bend in the anastomotic side in some degree, it was possible to place the tip of the catheter in the artery under ultrasound guide. Sufficient blood flow was able to obtain in all patients. None of the patients experienced complications such as hemothoma formation, injury of the artery, arterial occlusion or puncture-related infection. With the occluded AVG puncture, the patients were able to avoid hospitalization with catheter insertion and urgent VA repair. In addition, with the occluded AVG puncturing, some patients were able to continue hemodialysis as an outpatient for long-time.

Conclusions: Occluded AVG puncturing with ultrasound guide might be safe for long-term use. Occluded AVG puncturing might be considered in patients who have difficulty in AVG re-creation because of low cardiac function or vulnerability of the skin.

SA-PO1068

Should We Abandon Frequently Thrombosed Accesses? Janet Yanying Mei,1 Zubin Irani,2 Jie Cui,3 Harvard School of Public Health; 2Interventional Radiology Div, Massachusetts General Hospital; 1Renal Div, Massachusetts General Hospital.

Background: Whether and when a frequent thrombosed access should be abandoned is unclear. In this study, we had a 5 year follow up of those accesses, which defined as having 2 thrombectomies within 30 days.

Methods: This is a retrospective cohort study. Patients received thrombectomy/declotting procedures in 2012 in interventional radiology division at Massachusetts General Hospital were included. Information regarding all arteriovenous accesses those patients have had until April, 2016 were collected. Kaplan-Meier estimator was used to evaluate the rate of access-in-use.

Results:

- Patients (n=43)
  - Age at 1st access: 58±15.0
  - Men: 60.5%
  - No. of access per patient: 2±1
  - Access type: Fistula: 30
  - Graft: 68
  - Hypertension: 81.4%
  - Diabetes: 60.5%
  - CHF: 53.5%
  - CHF: 53.5%

Sixty-eight accesses had at least one clotting event and 48 (70.6%) had subsequent events. Thirty-three accesses had at least three events; three cases showed decreasing intervals between each event. There were 31 accesses with two declots within 30 days; 5 had new accesses within approximately 3 months (range: 21 to 98 days); 65.2% had a following declot within 30 days. Frequently thrombosed group had similar rate of access-in-use across time compared to access group that did not need frequent declot.

Conclusions: In this study, the intervals between clotting events generally do not hold a decreasing pattern. For frequently clotted accesses, they have a moderate risk of a following declot within 30 days. Their longevity is similar to that of their counterparts. We conclude that frequent-thrombosed accesses should not be abandoned quickly.

SA-PO1069

Successful Arteriovenous Graft Placements in Hemodialysis Patients: Results from the USRDS

Kenneth J. Woodside,1 Sai Hurrish Dharmarajan,1 Brett W. Plattner,1 Douglas E. Schaubel,2 Purna Mukhopadhyay,1 Kaitlyn Ratkowiak,2 Ronald L. Pison,2 Rajiv Saran,1 Univ of Michigan; 1Arbor Research Collaborative for Health.

Background: While an arteriovenous fistula (AVF) is the vascular access of choice for hemodialysis (HD), some patients cannot support an AVF, and an arterovenous graft (AVG) is placed. We previously described AVF maturation in prevalent HD patients. Herein, we describe predictors of successful AVG placement.

Methods: We assessed the relationship between patient characteristics and time to first AVG use by Cox regression in HD patients with AVG placements in 2013 or 2014 using ESRD Medicare claims data and CROWNWeb in the USRDS, with follow-up through 12/31/15.

Conclusions: In this study, the intervals between clotting events generally do not hold a decreasing pattern. For frequently clotted accesses, they have a moderate risk of a following declot within 30 days. Their longevity is similar to that of their counterparts. We conclude that frequent-thrombosed accesses should not be abandoned quickly.
Results: There were 24,222 AVGs placed in 22,634 prevalent HD patients. Of these AVGs, 18,229 (73%) were successful by multiple centers. Of successful AVGs, 52.8% were used by 2 months and 85.2% by 4 months (median 57 days [IQR 39-87 days]). Patients 22–44 years were less likely (HR 0.94 [95% CI 0.89, 0.99]), and those ≥75 years were more likely (HR 1.11 [95% CI 1.07, 1.16]), to successfully use the new AVG, compared to the 45–64 year reference group. Successful AVG use was more likely in black vs white HD patients (HR 1.05 [95% CI 1.02, 1.09]). There were no significant differences by sex or comorbidities. HD vintage interval ≥2 years were associated with successful AVG use. Those with AVG at HD initiation were more likely (HR 1.33 [95% CI 1.22, 1.44]), and those with AVG at HD initiation were less likely (HR 0.95 [95% CI 0.89, 1.01]), to have subsequent successful AVG, compared to patients who initiated HD by catheter only. There was wide variation in successful AVG placement by ESRD Network.

Conclusions: We have characterized AVG maturation in a national US sample and identified important predictors of successful AVG use. National time to AVG first use was longer than expected and requires further study.

Funding: NIDDK Support

SA-PO1070

An Innovative Vasculature Access for Chronic Hemodialysis: Subcutaneous Polytetrafluoroethylene (PTFE) from Internal Iliac Artery to Left Renal Vein

Nelia Antunes,1 Marcio Gomes Filippo,2 Alessandra Collares Motta,2 Eduardo Rocha.1 1Nephrology Div, Federal Univ Rio de Janeiro, Rio de Janeiro, RJ, Brazil; 2Vascular Surgery Div, Federal Univ Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

Background: The longer hemodialysis (HD) patients survive, the longer vascular access becomes a problem. This may reach life-threatening proportions and eventually lead to the need for innovative solutions.

Methods: We report a case of a 44-yr old woman with unknown etiology stage 5 CKD on HD for 14 years, during which she had thrombosed fistulas on both upper and lower extremities and also failed peritoneal dialysis (PD) and kidney transplantation (KT). A second KT was discarded by the transplant team. HD became temporarily possible due to extreme vascular accesses: two arterio-arterial PTFE grafts (bilateral axillary-axillary bypass) and a transverse inferior vena cava tunneled catheter, successful for only a short period. Considering the exhaustion of options, we placed a double-lumen catheter (DLC) into right femoral artery as an emergency access, until a whole-body CT angiography revealed occlusion of all main venous trunks – with the exception of the left renal vein and suprarenal vena cava – to successfully use the new AVG, compared to the 45–64 year reference group. Successful AVG use was more likely in black vs white HD patients (HR 1.05 [95% CI 1.02, 1.09]). There were no significant differences by sex or comorbidities. HD vintage interval ≥2 years were associated with successful AVG use. Those with AVG at HD initiation were more likely (HR 1.33 [95% CI 1.22, 1.44]), and those with AVG at HD initiation were less likely (HR 0.95 [95% CI 0.89, 1.01]), to have subsequent successful AVG, compared to patients who initiated HD by catheter only. There was wide variation in successful AVG placement by ESRD Network.

Conclusions: We have characterized AVG maturation in a national US sample and identified important predictors of successful AVG use. National time to AVG first use was longer than expected and requires further study.

Funding: NIDDK Support

SA-PO1071

Role of CTGF in Peritoneal Fibrosis in Mice

Naohiro Toda,1 Masato Kasahara,2 Kiyoshi Mori,3 Masashi Mukoyama,2 Motoko Yanagita,1 Hideki Yokoi.1 1Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 2Inst for Advancement of Clinical and Translational Science, Nara Medical Univ, Nara, Japan; 3School of Pharmaceutical Sciences, Univ of Shizuoka, Shizuoka, Japan; 4Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.

Background: Connective tissue growth factor (CTGF/CCN2) regulates signaling of other growth factors and promotes fibrosis. CTGF is shown to be an aggravating factor in thickening peritoneum and peritoneal function. Inhibition of CTGF using knockout mouse has not been examined in peritoneal fibrosis because of its perinatal death.

Methods: To study the role of CTGF in peritoneal fibrosis of adult mice, we generated CTGF floxed mice, and these mice were crossed with RosaCreER2 mice. We administered tamoxifen (TAM) to 3, 6-week old mice to delete CTGF gene throughout the body in Rosa-CTGF cKO mice. We evoked peritoneal fibrosis by intraperitoneal injection of chloroethylenegluconate (CG) in wild-type and Rosa-CTGF cKO mice and examined peritoneal injury by Masson’s trichrome staining, immunohistochemistry, mRNA expression of peritoneum and peritoneal equilibration test.

Results: After induction of peritoneal fibrosis in wild-type mice, mice showed increased CTGF expression and severe thickening of peritoneum. In contrast, CTGF-treated Rosa-CTGF cKO mice showed reduced thickening of peritoneum by 30% on day 28. Peritoneal CTGF mRNA expression was decreased by 80% in Rosa-CTGF cKO mice in peritoneal fibrosis. Peritoneal equilibration test also revealed that increase of peritoneal pressure in CG-CTGF wild-type mice was normalized in CG-treated Rosa-CTGF cKO mice. Immunohistochemical study revealed that CG-treated Rosa-CTGF cKO mice showed number of αSMA- and CD31-positive cells in peritoneum. Analyses of peritoneal mRNA showed that CTG-treated Rosa-CTGF cKO mice exhibited reduced expression of αSMA, CD31 and VEGF.

Conclusions: These results indicate that the deficiency of CTGF can reduce peritoneal thickening and maintain peritoneal function by reducing angiogenesis and fibrosis in peritoneal fibrosis model, suggesting that CTGF plays an important role in the progression of peritoneal fibrosis.

SA-PO1072

Blocked Heat Shock Factor 1 as Novel Pathomechanism Caused by Relevant Stressors in Peritoneal Dialysis Fluid

Rebecca Herzog,1,2 Klaus Kratochwill,1 Christoph Aufricht.1 1Christian Doppler Laboratory for Molecular Stress Research in Peritoneal Dialysis, Medical Univ of Vienna, Austria; 2Zytoprotec GmbH, Vienna, Austria; 3Pediatric Nephrology, Medical Univ of Vienna, Austria.

Background: PD-fluids (PDF) cause injury of mesothelial cells but also induce cytoprotective mechanisms. Recent studies, however, suggest that PDF blocks the heat shock response, one of the evolutionary most important stress responses. The result increased vulnerability of the mesothelial cells could lead to progressing fibrosis of the peritoneal membrane. The aim was to identify the molecular mechanisms leading to the PDF-induced inadequate stress response.

Methods: The induction of the stress response in mesothelial cells was analyzed using combined in-vitro and in-vivo models of PDF exposure and heat stress as the gold standard. In addition single cytotoxic components of PDF, like glucose degradations products (GDP) and acidosis as well as the impact of cytoprotective additives were investigated. The status of heat shock factor 1 (HSF1) activation, Hsp72 expression, the stress-protoceme and viability of the mesothelial cells were analyzed.

Results: Compared to heat, PDF leads to increased lethality but decreased Hsp72 expression. A concurrent blockade of the nuclear shift, phosphorylation and DNA-binding of HSF1 with reduced activity of the promoter was found. The inadequate HSF1 activation could be unblocked by a neutral pH, filter-sterilized PDF (without GDPs) or addition of alanyl-glutamine. The HSF1 blocking caused by the acidosis was associated with activation of GSK-3β, while the GDPs directly interfered with HSF1 promoter activity.

Conclusions: The PDF-mediated inadequate induction of the cellular stress response represents a new pathomechanism in PD. Our results demonstrate that the cytotoxic factors such as acidosis and GDPs of PDF lead to a HSF1 block via different molecular mechanisms and post-translational modifications resulting in decreased stress response and increased vulnerability of mesothelial cells exposed to PDF which could be restored by addition of alanyl-glutamine.

Funding: Pharmaceutical Company Support - Zytoprotec GmbH

SA-PO1073

The Role of WNT Signalling in Peritoneal Membrane Injury

Manreet K. Padwal, Limin Liu, Peter Margetts. Medicine, McMaster Univ, Hamilton, ON, Canada.

Background: Patients on peritoneal dialysis are at risk of developing peritoneal fibrosis and angiogenesis which can lead to a decline in peritoneal membrane function. Transforming growth factor beta (TGFB) is the primary cytokine involved in inducing epithelial to mesenchymal transition (EMT) and fibrosis. The Wnt/b-catenin (canonical) signalling pathway has been shown to interact with the TGFb pathway to promote fibrogenesis. In contrast, non-canonical WNT signalling may have protective effects. Therefore, we investigated the role of WNT signalling in peritoneal membrane injury.

Methods: Using adenovirus mediated gene transfer of TGFB, we induced fibrosis and EMT in the mouse peritoneum. Using an adenovirus, we concurrently overexpressed the WNT inhibitor DKK1, or the non-canonical WNT5a, and evaluated EMT, fibrosis, and increased vulnerability of mesothelial cells.

Results: The addition of DKK1 to AdTGFB mediated injury resulted in attenuation of angiogenesis in the mouse peritoneum. This also resulted in a decrease in EMT and an increase in the expression of the epithelial marker E-cadherin. This demonstrates that the Wnt/b-catenin pathway is involved in peritoneal membrane angiogenesis. The treatment of mouse peritoneum with AdTGFB and AdWNT5a also resulted in a decrease in angiogenesis and reduction in vascular growth factor expression. Furthermore, addition of WNT5a inhibited glycogen synthase kinase 3 phosphorylation suggesting WNT5a may antagonize the canonical WNT pathway.

Conclusions: The Wnt/b-catenin pathway is involved in epithelial cell transition and angiogenesis. WNT5a may be protective against peritoneal membrane injury by antagonizing β-catenin dependent WNT signalling.

Funding: Private Foundation Support
The Effect of Protein Transduction Domain Recombinant Bone Morphogenetic Protein-7 on Epithelial-Mesenchymal Transition in Peritoneal Mesothelial Cells

**Background:** We investigated the effect of Protein transduction domain (PTD)-mediated bone morphogenetic protein-7 (tissue-formation polypeptide 2, TRP2) on TGF-β1-induced epithelial-mesenchymal transition (EMT) in cultured human peritoneal mesothelial cells (HPMCs). In addition, we investigated how to deliver the drugs to peritoneum in vivo models.

**Methods:** In vitro, HPMCs were cultured in normal glucose + TGF-β1 with or without TRP2. In vivo, saline (control group, n=3), 4.25% PD solution (PD group, n=3), or 4.25% PD solution + TRP2 (PD + TRP2 group, n=5) were infused for 4 weeks in 11 Sprague-Dawley rats, then sacrificed after 4 weeks. E-cadherin, ZO-1, α-SMA, snail, vimentin, type I collagen, and fibrinectin were estimated. PF was assessed by non-trichrome (MT) staining.

**Results:** In vitro, protein expression of E-cadherin and ZO-1 (epithelial marker) were significantly decreased, while α-SMA, snail, vimentin (mesenchymal marker), type I collagen and fibrinectin were significantly increased in TGF-β1-stimulated HPMCs compared to control, and these changes were significantly improved by TRP2 treatment. In vivo, peritoneal EMT and PF were significantly increased in PD rats compared to controls. The thickness of mesothelial layer and the intensity of MT staining in the peritoneum of PD rats were also significantly higher compared to control rats. These changes of the peritoneum in PD rats were significantly ameliorated by the administration of TRP2.

**Conclusions:** This study suggests that TRP2 directly inhibits the process of TGF-β1-induced PD via peritoneal EMT in HPMCs. In addition, TRP2 mitigates PF in PD rats. The effect of PTD-mediated TGF-β1 in mesothelial cell delivery system may be a potential therapeutic strategy for prevention of PF in PD patients.

**SA-PO1075**

MicroRNA-200c Inhibits TGF-β1-Induced Epithelial-to-Mesenchymal Transition and Fibrogenesis in Peritoneal Mesothelial Cells

**Background:** Progressive peritoneal fibrosis is a common complication that limits the effectiveness of long-term peritoneal dialysis (PD). Epithelial-to-mesenchymal transition (EMT) of mesothelial cells is a salient feature in peritoneal fibrosis but how this is triggered remains obscure. This study investigated the role of microRNA-200c (miRNA-200c) in EMT and fibrogenesis in a murine PD model and cultured peritoneal mesothelial cell.

**Methods:** Male C57BL/6N mice were administered PBS or glucose-based PD fluid twice daily by intra-peritoneal injection for up to 30 days. Parietal peritoneum was obtained from mice infused with saline, 4.25% glucose peritoneal dialysis fluid (PDF), or PDF combined with 5 mg/kg ICG-001 for 30 days. Mouse peritoneal epithelial cells (mPEC) were cultured in 4.25% glucose or combined with 10 μM ICG-001 for 48 h.

**Results:** The activation of β-catenin signaling participated in the process of high glucose induced peritoneal fibrosis, and the epithelial-to-mesenchymal transition (EMT) of mPECs is one of underlying mechanisms of this pathological change.

**Conclusions:** The activation of β-catenin signaling participated in the process of high glucose induced peritoneal fibrosis, and the epithelial-to-mesenchymal transition (EMT) of PECs is one of underlying mechanisms of this pathological change.

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

**Periostin-Binding DNA Aptamer Ameliorates Peritoneal Dialysis-Induced Peritoneal Fibrosis**

**SA-PO1080**

**Inhibition of the H3K9 Methyltransferase G9a Ameliorates Methylglyoxal-Induced Peritoneal Fibrosis**

**SA-PO1083**

**Angiotensin Blockade Limits Peritoneal Inflammation Caused by Short-Term Peritoneal Dialysate and Catheter Effects in Rats**

**SA-PO1079**

**The Effect of Periostin on the Progression of Peritoneal Fibrosis**

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

*Underline represents presenting author.*

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**Background:** Periostin expression becomes higher in the peritoneal cavity of PD patients and its level can differentiate the peritoneal permeability after 1 year from the patients for PF in PD patients. The study implicate periostin signaling in the mediation of peritoneal fibrosis and its level can differentiate the peritoneal permeability after 1 year from the patients for PF in PD patients. Our study is the first to demonstrate that periostin expression is related to the peritoneal fibrosis in PD mice. Thus, our study implicate periostin signaling in the mediation of peritoneal fibrosis.

**Results:** Mean periostin protein concentration was 6.54±3mg/ml in first overnight effluents (1 month after start of PD) and 7.46±0.4mg/ml in 1 year effluents of the patients. Peritoneal permeate type and equilibration ratios between dialysate and plasma for creatinine were significantly related with the periostin level of the 1 year effluents of the patients. Periostin expression was strongly induced in peritoneal fibrosis model. Periostin was expressed predominantly in submesothelium and in lesser abundance in upper margin of abdominal muscle layer of mice with peritoneal fibrosis. Periostin messenger RNA was increased in peritoneal fibrosis model compared to the control. Messenger RNA expression of periostin and other chemotactic protein-1, smooth muscle actin, fibronectin and collagen 1 was also increased in periostin fibrosis model.

**Conclusions:** Periostin expression becomes higher in the peritoneal cavity of PD patients and its level can differentiate the peritoneal permeability after 1 year from the patients for PF in PD patients. The study implicate periostin signaling in the mediation of peritoneal fibrosis and its level can differentiate the peritoneal permeability after 1 year from the patients for PF in PD patients. The study implicate periostin signaling in the mediation of peritoneal fibrosis and its level can differentiate the peritoneal permeability after 1 year from the patients for PF in PD patients.

**Periostin-Binding DNA Aptamer Ameliorates Peritoneal Dialysis-Induced Peritoneal Fibrosis**

**SA-PO1080**

**Inhibition of the H3K9 Methyltransferase G9a Ameliorates Methylglyoxal-Induced Peritoneal Fibrosis**

**SA-PO1083**

**Angiotensin Blockade Limits Peritoneal Inflammation Caused by Short-Term Peritoneal Dialysate and Catheter Effects in Rats**

**SA-PO1079**
Tamoxifen Attenuates High Glucose-Induced Peritoneal Fibrosis by Reducing β-Catenin Activation In Vivo and In Vitro

Background: Peritoneal fibrosis is a severe complication of long-term peritoneal dialysis, which has been successfully attenuated by Tamoxifen in clinic treatment; however, the definite mechanism remains obscure.

Methods: C57BL/6 mice received daily intraperitoneal injection of saline, 4.25% high glucose or PD fluid (HGF-20mmol/L or HGF-40mmol/L or HGF-60mmol/L) combined with tamoxifen for 30 days, and mouse peritoneal epithelial cells (mPECs) were cultured in 4.25% glucose or combined with tamoxifen for 48h. Results: Tamoxifen alleviated thickening of peritoneum and reversed the expression of E-cadherin, Vimentin and β-catenin induced by PD in mice model. Furthermore, Tamoxifen diminished epithelial-to-mesenchymal transition, as well as the phosphorylation of GSK3β, nuclear β-catenin and Snail in mPECs after high glucose exposure.

Conclusions: Tamoxifen significantly attenuates EMT progression of peritoneal epithelial in fibrosis pathology via suppressing β-catenin signal activation.

Funding: Government Support - Non-U.S.

SA-PO1085

Biocompatibility of a New Bicarbonate Containing PD Solution, Reguneal - Measured as In Vitro Proliferation of Fibroblasts

Background: Long term exposure to conventional peritoneal dialysis fluids (PDFs) often leads to peritoneal membrane remodeling and failure. Such fluids typically have suboptimal pH and supraphysiologic concentrations of lactate, and high concentrations of glucose degradation products (GDPs) mainly formed during heat sterilization. Many GDPs are highly reactive carbonyl compounds that are cytotoxic and promoters of advanced glycation end products. To improve biocompatibility, a new bicarbonate-based PDF for Japan has been developed (Reguneal™, Baxter), manufactured in a two-compartment bag and optimized on pH and GDPs. This study investigates biocompatibility of Reguneal™ using a well-established in-vitro fibroblast proliferation assay with neutral red uptake.

Methods: PDFs were diluted 1+1 with tissue cultures media plus 10% serum before 72 h exposure for cytotoxicity testing. Reguneal™ and other enhanced-biocompatibility two-compartment PDFs available in Japan were compared to a lab-made sterile filtered control. Results: Data are presented as % inhibition of proliferation (means±SD), from 2 assays, in 2 bag of each PDF. The results demonstrate that the Reguneal™ is comparable and optimized on pH and GDPs. This study investigates biocompatibility of Reguneal™ glucose degradation products (GDPs) mainly formed during heat sterilization. Many GDPs

Conclusions: These findings suggest that neutral peritoneal dialysis solutions prevent morphological changes after long term PD treatment, particularly in terms of vasculopathy.

Funding: Pharmaceutical Company Support - Baxter International Inc

SA-PO1086

Effects of a Bicarbonate/Lactate-Buffered Neutral Peritoneal Dialysis Fluid on Angiogenesis-Related Proteins in Patients Undergoing Peritoneal Dialysis

Background: Angiogenesis plays a significant role in the progression of peritoneal membrane fibrosis and is associated with the formation of ECM and peritoneal membrane failure. Angiogenesis-related molecules, such as VEGF, basic fibroblast growth factor (bFGF), angiotensin II, are upregulated in the peritoneal fluid of PD patients, and these molecules have been implicated in the pathogenesis of peritoneal membrane failure in patients undergoing PD.

Methods: This was an 8-week crossover trial of 10 PD patients. Five patients each completed 4 weeks on each of the following two neutral PDFs: bicarbonate-lactate buffered neutral PDF (Reguneal™ Lc4®) or lactate-buffered neutralPDF (Dianzel ND P-4®) and crossed over to the other treatment arm with no change of glucose concentration in the PDF. The concentrations of 19 angiogenesis-related proteins in the dialysate after each treatment were semi-quantitatively determined using the RayBiotech C-Series Human Angiogenesis Antibody Array, and were compared between the two treatments.

Results: In the 19 angiogenesis-related proteins investigated, the expression of CXCL1/2,3, which belongs to the CXC chemokine family, significantly decreased after use of the bicarbonate/lactate-buffered PDF compared to the lactate-buffered PDF (P<0.04).

Conclusions: The bicarbonate/lactate-buffered neutral PDF may modulate the profile of angiogenesis-related proteins, including CXC chemokines, in the effluent of PD patients, suggesting that bicarbonate/lactate-buffered PDF is more biocompatible than lactate-buffered PDF.

SA-PO1087

Neutral Peritoneal Dialysis Solutions Prevent Morphological Changes in the Peritoneal Membrane

Background: The morphological changes induced by biocompatible peritoneal dialysis solutions are well known. However, the morphological damage induced by long-term neutral peritoneal dialysis solutions has not been reported in detail. The aim of this study was to investigate the effects of pH neutral solutions on the peritoneal membrane.

Methods: In this study, we collected peritoneal fluid and immunohistochemical analysis of normal peritoneal membrane biopsy samples from peritoneal dialysis patients treated with acidic solutions or neutral solutions.

Results: The morphological changes were compared between the acidic solution group (n=33) and the neutral solution group (n=45). According to the analyses, the ratio of lumen diameter to vessel diameter (L/V ratio) was significantly smaller (p<0.01), peritoneal membrane was thicker (p<0.01) and accumulation of advanced glycation end-products (AGES) was higher (p<0.01) in the acidic solution group than in the neutral solution group. In addition, the L/V ratio in the acidic solution group significantly decreased over time (p<0.01), although no such change was seen in the neutral solution group. There was no significant difference in the number of CD31 positive vessels between the two groups. Furthermore, we compared biopsy samples from subjects in the acidic solution group (n=33) with samples from subjects in the neutral solution group (n=22) who were treated for 4 to 10 years. In this cohort, PD duration was matched between the two groups. Further, while the L/V ratio (p<0.01) and AGES (p<0.01) were significantly different, there was no significant difference in peritoneal thickness and number of CD31 positive vessels between the two groups.

Conclusions: These findings suggest that neutral peritoneal dialysis solutions prevent morphological changes after long term PD treatment, particularly in terms of vasculopathy.

Funding: Non-U.S. - Pharmaceutical Company Support - Maiko Furuya, Yudo Tanno, Yu Honda, Nanako Matsuo, Yukio Maruyama, Ichiro Ohkido, Masato Iida, Keitaro Yokoyama, Takashi Yokoo. Dept of Nephrology and Hypertension, Jikei Univ School of Medicine, Tokyo, Japan.
Ferric Pyrophosphate Citrate (Triferic) Delivery via Peritoneal Dialysate for Iron Supplementation in Rats

**Background:** Iron deficiency is commonly present in peritoneal dialysis (PD) patients. Intrapерitoneal (IP) route is convenient and merits investigation for iron delivery. In previous animal studies IP iron dextran was found ineffective in delivering iron in CKD-PD patients (Montes et al, 2007), while causing iron deposition, inflammation, and fibrosis in peritoneal membrane. Soluble FeCl₃ by IP administration also failed to increase serum iron levels in an animal study (Suzuki et al, 1994). Administration of ferric pyrophosphate citrate (FPC, Triferic®) via hemodialysate is safe and effective in maintaining iron balance and hemoglobin in CKD patients (Fishbane et al, 2015). We have examined toxicity (T) and toxicokinetics (TK) of intraperitoneal FPC in iron-replete rats.

**Methods:** Rats with chronic implanted catheters were administered intraperitoneally 10 mL/kg of either Dianee (1.5%) or FPC (50, 150, or 450 µg iron/kg with 1.5% Dianee) 4 times/week for 4 weeks. Controls were 4 rats each week for control (C) animals, n=5 for each group. Using similar procedure, another group of animals were administered vehicle (n=6) or FPC (n=18/dose group) according to the same schedule for determination of serum iron parameters (T animals). Animals were euthanized at the end of the dosing period or after a 3-week recovery period.

**Results:** FPC did not cause any significant histologic changes in peritoneal membrane and abdominal organs including liver. There was a dose dependent increase in total serum iron and transferrin saturation (TSAT) with each dose of Triferic.

**Conclusions:** The administered dose of FPC was well tolerated in rats without signs of toxicity. FPC induced increase in serum iron levels and peak TSAT achieved in TK animals

<table>
<thead>
<tr>
<th>Dose (µg FPC/kg body weight)</th>
<th>Increase in serum iron above baseline (µg/dL)</th>
<th>Peak TSAT</th>
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<tbody>
<tr>
<td>50</td>
<td>91</td>
<td>55%</td>
</tr>
<tr>
<td>150</td>
<td>124</td>
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</tr>
<tr>
<td>450</td>
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<td>88%</td>
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</tbody>
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There was no histologic evidence of systemic iron accumulation.

**SA-PO1098**

**Matrine Prevents Escherichia Coli Biofilm Formation Through Blockade of Outer Membrane Protein A Expression**

**Background:** Escherichia coli (E. coli) is the common pathogenic bacteria causing peritoneal dialysis (PD)-associated peritonitis. In our previous studies we found that sophorosides had the interventional effect of E. coli biofilm (BF) formation. However, the precise mechanism is largely unknown. The present study is to investigate the relationship between matrine and OmpA expression.

**Methods:** We established a model of matrine interfere with E. coli biofilms in vitro. We observe the effect of effective of E. coli BF formation using the crystal violet staining. Detecting the expression of OmpA mRNA in different stages of BF formation by real-time fluorescence quantitative PCR.

**Results:** The minimum inhibition concentration (MIC) for E. coli of Matrine and levofloxacin were 4096 µg/mL and 0.038 µg/mL, respectively. In presence of 1/2MIC of matrine at 1.3 and 7days, the E. coli viable counts was significantly increased from 111.3±12.9 to 1040±0.335 (r=0.634, p<0.0001) and SGA (r=0.758, p=0.007). The 24-hour loss of VDBP correlated with HDL (r=-0.600, p=0.039) and LDL cholesterol (r=-0.737, p=0.004). The dialed VDBP concentration correlated with LDL (r=0.634, p=0.049) and SGA (r=0.758, p=0.009). The 24-hour loss of VDBP correlated with the 24-hour loss of albumin (r=0.806, p=0.005), muscle mass (r=0.857, p=0.007) and bone mass (r=0.738, p=0.037). The serum Bio-DBP was higher among WN/MNR patients than those with mild/moderate malnourished (5.6±2.9 vs 2.0±0.0 mg, p=0.030). VDBP did not differ between H/HA and L/LA patients (94.2±38.7 to 221±145 pg/mL, p=0.020). Nineteen patients had hypercalcemia (Serum Ca >9.5 mg/dL) at the start of PD, and except one, all of them normalized their calcium levels in peritoneal dialysis solution in Transperitoneal Calcium Balance in Peritoneal Dialysis Patients

**Background:** Calcium balance in peritoneal dialysis (PD) patients is critical to maintain bone health. PD patients typically have low serum calcium levels and high parathyroid hormone (PTH) levels, which leads to an increase in bone resorption and a decrease in bone density. However, the calcium balance in PD patients is often not well understood, and the factors that influence the calcium balance are not well characterized. The aim of this study was to investigate the calcium balance in PD patients and to identify factors that influence the calcium balance.

**Methods:** We performed a retrospective analysis of 24 PD patients. The calcium balance was calculated as follows: calcium balance = calcium intake - calcium output. Calcium intake was calculated based on the volume of dialysate and the calcium concentration of the dialysate. Calcium output was calculated as the sum of the calcium lost through the dialysate and the calcium lost through the peritoneum. The calcium output through the peritoneum was calculated based on the calcium concentration in the dialysate and the volume of dialysate used. The calcium balance was then calculated by subtracting the calcium output from the calcium intake. We then performed a correlation analysis to identify factors that influence the calcium balance. We also performed a subgroup analysis to identify factors that influence the calcium balance in different subgroups of PD patients.

**Results:** The calcium balance was significantly different between the two subgroups (H/HA and L/LA). The calcium balance was higher in the H/HA subgroup (r=0.634, p=0.049) and SGA (r=0.758, p=0.009). The 24-hour loss of VDBP correlated with the 24-hour loss of albumin (r=0.806, p=0.005), muscle mass (r=0.857, p=0.007) and bone mass (r=0.738, p=0.037). The serum Bio-DBP was higher among WN/MNR patients than those with mild/moderate malnourished (5.6±2.9 vs 2.0±0.0 mg, p=0.030). VDBP did not differ between H/HA and L/LA patients (94.2±38.7 to 221±145 pg/mL, p=0.020). Nineteen patients had hypercalcemia (Serum Ca >9.5 mg/dL) at the start of PD, and except one, all of them normalized their calcium levels in peritoneal dialysis solution in Transperitoneal Calcium Balance in Peritoneal Dialysis Patients

**Conclusions:** The administered dose of FPC was well tolerated in rats without signs of toxicity. FPC induced increase in serum iron levels and peak TSAT achieved in TK animals

**Funding:** NIDDK Support

**SA-PO1091**

**Pig Trial of Automated Wearable Artificial Kidneys Based on Peritoneal Dialysis**

**Background:** We have developed an automated wearable artificial kidney (AKA PD) using Tidal PD. To test the safety and efficacy of the AWA PD we needed a pig model. There are no reports in the literature of pigs maintained on PD other than our recent published article on CAPD and APD. Our objective was to maintain pigs on the AWA PD for 1 week.

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

**Underline represents presenting author.**

**887A**
after treatment. (9.8±0.26 to 9.5±0.23 mg/dL, P<0.001). The transthoracic echocardiographic mean aortic valve gradient was significantly decreased after treatment (32.8±9.5 to 29.8±7.0 mmHg, P<0.05). The mean aortic valve area increased significantly after treatment (1.3±0.2 cm² to 1.6±0.3 cm², P<0.05). The left ventricular mass index did not show significant difference after treatment (137.2±25.6 g/m² to 136.9±25.8 g/m², P=0.17).

Conclusions: The changes in echocardiographic parameters were in line with other evidence, thus supporting the role of catheter-based aortic valve replacement in severe AS. The improvement in aortic valve area after treatment was associated with reduced left ventricular mass and increased left ventricular ejection fraction, leading to better clinical outcomes in these patients.

SA-PO1096
The Effects of Peritoneal Effluent Medium on Intrapерitoneal Inflammation and Peritoneal Solute Transport Rate in Peritoneal Dialysis
Xishao Xie, Jianghua Chen. The Kidney Disease Center; The First Affiliated Hospital, College of Medicine, Zhejiang Univ; Hangzhou, Zhejiang, China.

Background: Local chronic intraperitoneal inflammatory status commonly affects peritoneal dialysis (PD) patients. Mitochondrial DNA (mtDNA) released into extracellular subsequence to cell injury and death can promote inflammation in patients and animal models. Therefore, the effects of peritoneal effluent medium on intraperitoneal inflammation and peritoneal solute transport rate (PSTR) in PD patients remain unclear. We aimed to examine the peritoneal effluent mtDNA and elucidate their relationship with intraperitoneal inflammation and PSTR.

Methods: We select the incident patients who began PD therapy at the First Affiliated Hospital of Zhejiang University between January 1, 2009, and December 30, 2010. Peritoneal dialysis effluent was collected at the time of peritoneal equilibration test. The peritoneal effluent mtDNA was detected by quantitative real-time PCR assay, the concentrations of dialysate IL-6, IL-17A, TNF-α and IFN-γ were quantitated by ELISA in the supernatant.

Results: One hundred and eighty-nine patients were included in the study. The average age was 47.1 ± 13.5 years, 55.6% of the patients were males. The median follow-up period was 41.8 months. The average PSTR was 0.66 ± 0.12, the median mtDNA level was 4325 copies/ml. The median concentrations of IL-6, IL-17A, TNF-α and IFN-γ were 25.9, 10.8, 25.8 and 17.9 pg/ml, respectively. We found that peritoneal effluent mtDNA was significantly correlated with PSTR (r=0.461, P<0.001), IL-6 (r=0.368, P<0.001), TNF-α (r=0.454, P<0.001) and IFN-γ (r=0.203, P=0.005). After adjustment for multiple covariates, peritoneal effluent mtDNA was independently correlated with IL-6 and PSTR. Peritoneal effluent mtDNA was not associated with patient and technique survival.

Conclusions: We found that peritoneal effluent mtDNA level correlated with the degree of intraperitoneal inflammation status in PD patients. Peritoneal effluent mtDNA was an independent determinant of PSTR but did not affect patient and technique survival.

SA-PO1097
Irisin Levels and Adequate Dialysis in Nondiabetic Peritoneal Dialysis Patients
Hai Peng, Zhijun Tan, Zengchun Wang, Xun Liu, Tan-Qi Lou. Div of Nephrology, Dept of Medicine, 3rd Affiliated Hospital of Sun Yat-Sen Univ, Guangzhou, Guangdong, China.

Background: Irisin is a recently discovered hormone thought to be involved in energy regulation. However, only a single study has focused on irisin levels in peritoneal dialysis patients, but that study did not control for multiple factors. Therefore, it remains unclear whether irisin is affected by dialysis adequacy or whether irisin is associated with protein-energy wasting and insulin resistance in chronic kidney disease.

Methods: A total of 59 nondiabetic peritoneal dialysis (PD) patients and 52 healthy controls were enrolled in this cross-sectional study. Case histories and blood, urine, and dialysate samples were analyzed. Serum irisin levels were measured by ELISA and compared between the two groups.

Results: Serum irisin levels were lower in nondiabetic PD patients (median interquartile range: 17.02 (11.27-20.09) ng/ml) compared with age- and sex-matched healthy controls (22.17 (17.60-26.57) ng/ml). Multivariate regression analysis revealed that fasting glucose levels were independently correlated with serum irisin levels in PD patients. No association of serum irisin levels with homeostatic model assessment of insulin resistance was observed, nor was there an association between the Geriatric nutritional risk index and serum irisin levels. Conversely, peritoneal Kt/Vurea (r=0.493, 95% CI, 0.356-0.391; P<0.029) and peritoneal Ccr (r=0.259, 95% CI, 0.053-0.465; P<0.015) were positively associated with serum irisin levels among PD patients.

Conclusions: Serum irisin levels in non-diabetic PD patients were lower than those in healthy controls, and peritoneal Kt/V and creatinine clearance were positively correlated with serum irisin levels. Thus, adequate dialysis may improve irisin secretion.

Funding: Government Support - Non-U.S.

SA-PO1098
Peritoneal Dialysis Removes More Serum Sclerostin Than Hemodialysis in Uremic Patients
Lin Yang; Lihua Luo; Yaohui Chen; Chunjian Yang; Zunhua Liu; Yun Li. Nanchang Univ, School of Medicine, Nanchang, Jiangxi, China; Dept of Nephrology, Jiangxi Provincial People's Hospital, Nanchang, Jiangxi, China.

Background: It's not known whether PD could remove serum sclerostin in uremic patients or not. This study observed the removal of sclerostin by PD and compared the difference of the removal of it between PD and HD.

Methods: Subjects in four groups were from Jiangxi Provincial People's Hospital. Control group included 16 healthy volunteers of CKD5: 24 cases. In addition, multiple cases in stage 5 CKD but not on dialysis: HD- 42 cases on HD; PD: 100 cases on PD (only 81 serum samples). Sclerostin was determined with ELISA kit.

Results: (1) Compared with control, serum sclerostin in CKD5 and HD groups was increased, with it was higher in CKD5 than in HD, the differences among all groups were statistically significant (P < 0.05); on the other hand, sclerostin in serum and PD fluid in PD group was close to that in control.

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(2) Patients in PD group were stratified according to age (45yrs or older) or PD time (on PD for 12 months or longer). For resulting groups, the differences in serum or PD fluid sclerostin were all not statistically significant (P>0.05) (Table-1, 1-3).

Conclusions: Serum sclerostin was increased in CKD5 patients than in normal individuals. HD and PD both could remove serum sclerostin while PD removed more. Patient’s age and time in PD had no effects on the removal of it in PD group. The findings could provide insights for CKD-MBD pathogenesis in CKD patients and the basis for choosing dialysis modes.

Funding: Government Support - Non-U.S.

SA-PO1099

Relationship between Glucose Spike and Cardiovascular Risk Factors in Diabetic Patients with Peritoneal Dialysis: A Cross-Sectional Study

Keni Harada, Shigeki Tamaka, 1Hidetoshi Kanai. 1Div of Nephrology, Kokura Memorial Hospital, Kitakyusyu, Fukuoka, Japan; 2Div of internal medicine, Fukuoka Dental College, Fukuoka, Japan.

Background: Several reports have reported that glucose spike (GS), postprandial increase in blood glucose, may be a risk factor for mortality and CVD incidence in patients with diabetes. We investigated relationship between glucose spike and cardiovascular risk factors in diabetic PD patients.

Methods: We measured diurnal variation in blood glucose for 7 days using continuous glucose monitoring (CGM, ipm2: Medtronic, Northridge, CA, USA). GS was defined as mean amplitude of glycemic excursion (MAGE), which calculated as an average value of times exceed over 1SD of average blood glucose. We evaluated relationships between MAGE and cardiovascular risk factors, including HbA1c, GA, blood pressure (BP), peritoneal function, echocardiographic findings, pulse wave velocity (PWV).

Results: Overall, 22 diabetic PD patients were included (mean age; 65.7 year old, male female; 16/6, average PD vintage; 31 months). Median value of MAGE was 60.2±22.85. We deviated participants into two groups; Low MAGE (<60) group and high MAGE (≥60) group. Low MAGE group was older, longer PD vintage and lower PWV levels. There was no difference in HbA1c, ejection fraction, BP, peritoneal function, past history of CVD, and smoking between two groups. In the multiple regression analysis, higher level of MAGE was an independent predictor for worsening PWV (P=0.0045).

Conclusions: Higher MAGE was more correlated with high level of PWV. Even after adjusting by cardiovascular risk factors, higher level of MAGE was an independent predictor for PWV. These results suggest that GS might be involved in atherosclerosis progression in diabetic PD patients.

SA-PO1100

Adequacy of a Single Daily Icodextrin Exchange as Initial Therapy for Incident End-Stage Renal Disease Patients with Residual Kidney Function: Predictions from the Three-Pore Model


Background: Incremental dialysis is the treatment of ESRD patients with gradually increasing dialysis doses in response to declines in their residual kidney function. Incremental PD may impose fewer restrictions on patients’ lifestyle, help attenuate lifetime peritoneal and systemic exposure to glucose and its degradation products, and minimize connections that could compromise the sterile fluid path. In this study, we utilized a three-pore kinetic model to assess fluid and solute removal for single daily icodextrin regimens for patients with varying glomerular filtration rates (GFR).

Methods: Single icodextrin exchanges of 8 to 16 hours using 2 and 2.5 L bag volumes were simulated for different patient transport types (i.e. high to low) to predict daily peritoneal ultrafiltration (UF), daily peritoneal sodium removal, and weekly total (peritoneal + residual kidney) Kt/V (GFR ranges from 0 to 15 mL/min/1.73m²). Adequacy of treatment was assessed based on weekly Kt/Vtrag ≥ 1.7.

Results: Daily peritoneal UF varied from 359 to 607 mL and daily peritoneal Na removal varied from 52 to 367 mEq depending on length of icodextrin exchange and bag volume. Both were effectively independent of patient transport type. GFR needed to achieve adequate dialysis varied between 5 and 10 mL/min/1.73m² depending on patients’ total body water (TBW) and bag volume.

Conclusions: Single daily icodextrin exchange can be tailored to provide adequate UF and Na removal in incident ESRD patients with sufficient Kt/V. UF and Na removal are relatively independent of patient transport, but achieving an adequate Kt/Vtrag is highly dependent upon TBW/BSA. Small patients (i.e. 55 kg) may achieve adequate dialysis (weekly Kt/Vtrag ≥ 1.7) with GFR as low as 6 mL/min/1.73m². A solitary icodextrin exchange may therefore be reasonable initial therapy for some incident ESRD patients. Potential lifestyle and clinical benefits need to be evaluated.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

SA-PO1101

The Role of Inflammation in the Effect of BMI on Patient Survival in Peritoneal Dialysis Patients: Results from the GLOBAL Cohort Study

Mark Lambie, Emma H. Elphick, Simon J. Davies. Inst for Applied Clinical Research, Keele Univ, Stoke on Trent, United Kingdom.

Background: A higher body mass index (BMI) is known to predict better survival in haemodialysis, with a recent report demonstrating that this is primarily in patients with high levels of systemic inflammatory markers. Studies of patients on peritoneal dialysis (PD) have not shown a consistent relationship between BMI and survival but the reasons for this are unclear. We hypothesised that the reason for the lack of association in previous studies was due to lower levels of systemic inflammation in PD patients.

Methods: We used incident (measures within 3 months of starting) and prevalent PD patients from the Global Fluid Study, a cohort study of 10 centres from Korea, Canada and the UK. Plasma samples were assayed for IL-6 and a contemporaneous BMI was measured. The primary analysis was Cox regression stratified by centre testing the effect of BMI in a univariable model on patients with plasma IL-6 above median, with sensitivity analyses including using plasma IL-6 levels above the 75th centile, testing plasma IL-6 and BMI for an interaction, using patients with albumin levels <35g/l and <30g/l and testing for an effect of dialysate glucose load and restricting the analysis to 1 year follow up.

Results: Of the 559 incident and 376 prevalent patients, 241 and 186 respectively died during follow up. The median and 75th centile for plasma IL-6 levels were 1.49 and 2.83 in incident patients and 1.26 and 2.46 in prevalent patients respectively. There was no benefit of BMI in the inflamed group in either incident (HR 1.03, 95% CI 0.99-1.07) or prevalent (HR 0.98, 95% CI 0.95-1.02) patients. This pattern was replicated in patients with plasma IL-6 levels >75th centile and there was no interaction between IL-6 and BMI in either incident or prevalent patients. There was no benefit in patients with albumin levels <35g/l or <30g/l, nor any interaction or effect of dialysate glucose load.

Conclusions: The protective effect of BMI for inflamed haemodialysis patients is absent in inflamed peritoneal dialysis patients. This might be due to the extra caloric loading in PD but it is not affected by the amount of dialysate glucose prescribed.

SA-PO1102

Association between Diuretic Use and Residual Kidney Function in Peritoneal Dialysis Patients: International Comparison from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)

Simon J. Davies,1 Juhui Zhao,2 Brian Biecher,3 Bruce M. Robinson,2 Angela Yee Moon Wang,4 Jeffrey Perl,5 Keele Univ, Stoke-on-Trent, United Kingdom; 1Arbor Research Collaborative for Health, Ann Arbor, MI; 2Univ of Hong Kong, Hong Kong, China; 3Univ of Toronto, Toronto, ON, Canada; 4On Behalf of the PDOPPS Dialysis Prescription and Fluid Management Workgroup, Ann Arbor, MI.

Background: Preservation of residual kidney function (RKF), as determined by urine volume, mean area and creatinine clearances (GFR), is strongly associated with better survival on dialysis. Most sized trials have demonstrated that diuretics can maintain urine volume and that renin angiotensin system inhibitors (RASI) might preserve RKF in PD patients.

Methods: The PDOPPS is a prospective cohort study of PD treatment and outcomes in Australia, Canada, Japan, New Zealand, Thailand, the United Kingdom and the United States (US). Based on an initial cross-section of 1,655 patients in Australia, Canada, Japan and US, linear models were used to estimate the associations of diuretic, ACEi or ARB use with plasma IL-6 levels, mean urea and creatinine clearances (GFR) in PD but it is not affected by the amount of dialysate glucose prescribed.

Conclusions: Among patients with RKF, diuretic use was highest in Japan (74%) and lowest (39%) in Australia. ACEi and/or ARB use was highest in Japan. In adjusted models, greater urine volume and higher GFR, were associated with shorter PD vintage and diuretic use, but not with ACEi or ARB use.
Dialysis Patients with Diabetes Mellitus after Discontinuation of Tolvaptan: Impact on Residual Renal Function and Quality of Life

Dialysis Patients Using Contrast Medium Administration

Results: After discontinuation of tolvaptan, renal function and QOL were substantially decreased after tolvaptan discontinuation.

Conclusion: Diuretic use is strongly associated with urine volume in this early cross-sectional analysis. As the study accrues follow-up time, PDOMPS will provide important longitudinal data on practice variation and outcomes to evaluate the role that diuretics may play in preserving residual kidney function among PD patients.

SA-PO1103

Substantial Decrease in Renal Function and Quality of Life in Peritoneal Dialysis Patients with Diabetes Mellitus after Discontinuation of Vasopressin-2 Receptor Antagonist, Tolvaptan

Background: Last year we reported that tolvaptan preserved residual renal function in peritoneal dialysis (PD) patients. Here, we investigated the patients after tolvaptan discontinuation.

Methods: Twenty-four incident PD patients with congestive heart failure were followed for 24 months. Patients were divided into two groups, Group A (n = 15) and Group B (n = 9). In Group A, patients received 15 mg/day of tolvaptan from the initiation of PD, and in Group B, tolvaptan was administered when urine volume lowered below 500 mL/day. We evaluated the medical costs, urine volumes, urine Kt/V, quality of life (QOL) assessed with Short-Form Health Survey (SF-36), and comorbidities which occurred during 12 months after tolvaptan discontinuation.

Results: In Group A, urine volume, urine Kt/V, and QOL scores were substantially decreased after tolvaptan discontinuation (*p < 0.05 vs at baseline).

Conclusion: Residual renal function and QOL were essentially reduced after tolvaptan discontinuation. Diuretic use may be associated with urine volume in this early cross-sectional analysis. As the study accrues follow-up time, PDOMPS will provide important longitudinal data on practice variation and outcomes to evaluate the role that diuretics may play in preserving residual kidney function among PD patients.

SA-PO1104

Association of Plasma Brain Natriuretic Peptide Concentration with Loss of Residual Renal Function in Peritoneal Dialysis Patients

Background: Plasma brain natriuretic peptide (BNP) concentration is widely accepted as a marker of fluid status in patients with chronic kidney disease (CKD) including dialysis. We have reported that BNP is independently associated with kidney function decline in predialysis CKD patients (Yoshitomi R, et al. J Hypertens, 2016). However, the relationship between plasma BNP concentration and residual renal function (RRF) in peritoneal dialysis (PD) patients remains unclear. The aim of this study was to elucidate the relationship between BNP and loss of RRF in PD patients.

Methods: We followed retrospectively 104 PD patients who started PD in our hospital between June 2006 and May 2016. Five patients were excluded because of missing data. We divided the remaining 99 subjects into two groups with high and low BNP by a median of plasma BNP concentration (95.7 pg/mL). We estimated the association between BNP and loss of RRF (daily urine volume <100 mL) using a Kaplan-Meier method and Cox proportional hazards model.

Results: During a median range follow-up period of 24 (12-36) months, 31 patients had lost RRF. The event-free RRF survival in the high BNP group was significantly lower than in the low BNP group by the Kaplan-Meier method (p = 0.004). After adjusting for potential confounders such as age, sex, diabetic nephropathy, systolic blood pressure, urinary protein/creatinine ratio, and renal Kt/V, high plasma BNP concentration was independently associated with loss of RRF (hazard ratio for high BNP group vs. low BNP group, 3.34; 95% confidence interval, 1.29 to 9.17; p = 0.012).

Conclusion: Plasma BNP concentration at PD initiation could be an independent predictor of loss of RRF in PD patients.

SA-PO1105

Association of Serum Total Bilirubin with Loss of Residual Renal Function in Peritoneal Dialysis Patients

Background: Bilirubin has been recognized as a novel endogenous antioxidant. Low serum bilirubin has been reported to be associated with the progression of kidney disease in patients with chronic kidney disease. However, it is unclear whether a relationship exists between low serum bilirubin and loss of residual renal function (RRF) in peritoneal dialysis (PD) patients. The aim of this study was to investigate the relationship between serum total bilirubin concentration and loss of RRF within 3 years after starting PD.

Methods: We followed retrospectively 104 PD patients who started peritoneal dialysis in our hospital between June 2006 and May 2016. Ten patients who had chronic liver disease or cirrhosis were excluded and the remaining 94 patients were included in the present study. Patients were divided into three groups based on tertile of serum total bilirubin concentration: tertile 1 (TB) <0.3 mg/dL, tertile 2 (TB) 0.3-1.0 mg/dL, tertile 3 (TB) >1.0 mg/dL. We estimated the relationship between serum bilirubin and loss of RRF (defined as daily urine volume <100 mL) within 3 years after starting PD using a Cox proportional hazards model.

Results: During the 3-year observation period, 22 patients had lost RRF. The incidence rate of loss of RRF increased linearly with the decrease in serum total bilirubin levels (P for trend <0.05). After adjusting for confounding factors, low serum total bilirubin level was an independent predictor of loss of RRF (hazard ratio [HR] for every 0.1 mg/dL decrease, 1.50; 95% confidence interval [CI] 1.01 to 2.51; HR [95% CI] for T2 and T3 vs. T1) 2.03 (0.67-7.88) and 3.70 (1.00-12.59), respectively.

Conclusion: This result suggests that lower serum total bilirubin level is associated with loss of RRF in PD patients.

SA-PO1106

Statin Treatment Strongly Prevents Residual Renal Function in Peritoneal Dialysis Patients Using Contrast Medium Administration

Background: Recently, prospective studies have demonstrated that statins have a protective effect in preventing contrast-induced nephropathy (CIN), but there has been no study that statins have prevent residual renal function (RRF) in peritoneal dialysis (PD) patients. Here, we investigated whether or not statins prevent RRF and decrease the rate of transfered to hemodialysis (HD) in PD patients undergoing iodinated contrast medium administration (ICMA).

Methods: This study was based on a single-center retrospective registry that consisted of 116 patients initiated PD between January 2010 and December 2012. We allocated 85 patients who underwent ICMA. The patients were divided into two groups according to...
use of statin at the time of ICMA, as follows: statin-treated group (Group A, n=41), and statin-naive group (Group B, n=44). RRF was determined based on the mean 24-hour urine volume and estimated glomerular filtration rate (eGFR). These measures of RRF were determined on the day before ICMA (baseline), and 48 hours, 2 weeks, and 4 weeks after ICMA. The primary endpoint was defined as the rate of decline in RRF. Secondary endpoints were defined as the rate of transfer to HD. The 3-year event rates were estimated by Kaplan Meier analysis with P values from log-rank tests.

Results: Group A had higher BMIs, and higher baseline eGFR than Group B. There were significant differences between Group A and Group B with respect to the decline in urine volume 2 weeks after ICMA (192±205 vs. 335±329 mL, P=0.018). Between the two groups, there were no significant differences in the rate of decline of eGFR. After 3 years, the rate of transferred to HD of Group A was significantly lower than that of Group B (P<0.001, log-rank test). In multivariate Cox proportional hazard model, we demonstrated that statin treated group was a significant lower risk for the transferred to HD (HR 0.280, P=0.05). There was no statistically significant difference in the overall catheter survival at 365 days between the two groups.

Conclusions: The fluoroscopic and ultrasound guided placement of PDC offers a clinically effective alternative to laparoscopic placement with similar survival rates. The rate of catheter malfunction was higher in the LAP group, while the rate of catheter leak was higher in the IR group.

**SA-PO1107**

Comparison of Advanced Image-Guided Percutaneous (AIP) versus Advanced Laparoscopic Surgical (ALS) Technique for the Placement of Peritoneal Dialysis (PD) Catheters

Neeleman M. Bhalla, Todd Drasin, Sijie Zheng, Jeanne A. Darbiniac, Paul Dybyro.

Kaiser Permanente, Northern CA.

Background: PD offers more advantages to patients with ESRD. Timely placement of a functional PD catheter with minimal complications is crucial to ensure patient acceptance and long-term PD success. AIP and ALS techniques both represent best practice catheter placement options as taught by the PD University. We conducted a retrospective cohort study to compare access time to procedure, complications, and overall catheter survival between placement techniques.

Methods: Patient charts for a subpopulation of KPNC members who had either an ALS or AIP PD catheter placed between 1/1/2011 and 12/31/2013 were reviewed by two nephrologists and two Interventional Radiologists. Wilcoxon two-sample tests were employed to compare access times. Occurrence of complications was compared using chi-square tests. Modified least squares regression was used to compare adjusted one-year catheter survival.

Results: We identified 191 PD catheters placed via AIP and 238 via ALS technique. Adjusted one-year PD catheter survival was 80% by AIP vs. 91% by ALS. Major complications were rare in either group (<1%). Minor complications occurred in 45.6% of AIP and 38.7% of ALS cases. Median access time to procedure was 12 and 33 days for AIP and ALS patients, respectively.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AIP (n=191)</th>
<th>ALS (n=238)</th>
<th>p-value</th>
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<tr>
<td>Age (median, IQR)</td>
<td>54.7 (41.3–64.3)</td>
<td>56.4 (47.2–66.4)</td>
<td>0.0232</td>
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<tr>
<td>Gender</td>
<td>Male 106 (55.6%)</td>
<td>58 (24.4%)</td>
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<tr>
<td>Diabetes</td>
<td>115 (59.8%)</td>
<td>50 (21.1%)</td>
<td>0.0123</td>
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<tr>
<td>Hypertension</td>
<td>222 (116.5%)</td>
<td>88 (36.8%)</td>
<td>0.1917</td>
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<tr>
<td>BMI (median, IQR)</td>
<td>28.3 (24.1–32.7)</td>
<td>28.9 (26.6–34.6)</td>
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<tr>
<td>Urgent Start</td>
<td>29 (12.9%)</td>
<td>179 (75.2%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Elective</td>
<td>182 (90.2%)</td>
<td>68 (28.6%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions: Both AIP and ALS techniques have excellent one year survival with very low major complication rates. Though a slightly lower one year catheter survival rate was demonstrated among AIP cases, these patients had a much shorter access time. The techniques complement each other; therefore either may be used based upon local resources and expertise to increase the adoption of PD.

Funding: Private Foundation Support

**SA-PO1108**

Fluoroscopic and Ultrasound Guided Placement versus Laparoscopic Placement of Peritoneal Dialysis Catheters: A Single Center Experience

Ammar Almejmi,1 Bradford Jackson,2 Ahmed Kamel Abdel Aal.1 1Nephrology and Radiology, UAB; 2Preventive Medicine, UAB; 3Radiology, UAB.

Background: A variety of peritoneal dialysis catheter (PDC) placement techniques are available including laparoscopic placement by surgeons, and percutaneous placement by interventional radiologists. The aim of this study was to compare the one-year outcomes of both techniques.

Methods: We retrospectively reviewed the medical records of 240 patients who had their first PDC placed between January 2005 and December 2015. We compared the outcomes of the catheters placed using fluoroscopic and ultrasound guidance (IR group, n=50), with the catheters placed using laparoscopic technique (LAP group, n=190). The primary endpoints were defined as the complication-free catheter survival at 365 days. Secondary endpoints were complication-free catheter survival at 90 days, overall catheter survival at 365 days, median days-to-first complication and median days-to-catheter removal. Between-group differences were assessed using Chi square, Mann-Whitney U tests and Kaplan Meier methods.

Results: The study included 240 patients, 134 females (56%), median age was 54.7 years (IQR=41.3–64.3), and median BMI was 28.3 (IQR=24.1–34.5). There was no significant difference in the baseline characteristics of both groups. In the IR group, the complication-free catheter survival at 90 and 365 days were 64% and 48%, compared to 70.5% (p=0.37) and 53.4% (p=0.49) respectively, in the LAP group. Catheter malfunction was significantly higher in the LAP group (30%) compared to the IR group (16%, p=0.05). Catheter leak was significantly higher in the IR group (10%) compared to the LAP group (3.2%, p=0.05). There was no statistically significant difference in the overall catheter survival at 365 days between the two groups.

Conclusions: Both AIP and ALS techniques have excellent one year survival with similar survival rates. The rate of catheter malfunction was higher in the LAP group, while the rate of catheter leak was higher in the IR group.

**SA-PO1109**

Laparoscopic versus Radiologic Peritoneal Catheter Outcomes in Urgent and Elective Dialysis Starts

Ammar Almejmi,1 Bradford Jackson,2 Ahmed Kamel Abdel Aal.1 1Nephrology and Radiology, UAB; 2Preventive Medicine, UAB; 3Radiology, UAB.

Background: Urgent unplanned dialysis starts are commonly seen in clinical practice, responsible for about one third of the incident dialysis cases. Both radiologic (IR) and laparoscopic (LAP) placement of peritoneal catheters (PDC) have been utilized in both urgent and elective dialysis starts. The aim of our study is to compare PDC outcomes between urgent dialysis start and elective dialysis start in both LAP and IR groups.

Methods: We retrospectively reviewed the medical records of 240 patients who underwent no novo PDC placement. The study cohort was divided based on dialysis start and placement technique as shown in Table 1. Medians and interquartile ranges (IQR) were calculated for continuous variables, and frequencies and percentages for categorical variables. Between group differences were compared using Fisher’s Exact test and Kruskal- one way analysis of variance. Complication free survival and overall catheter survival curves were estimated using the Kaplan Meier approach, and Log-Rank tests were used to assess homogeneity across strata.

Results: In the urgent start cohort, the complication-free catheter survival at 90 and 365 days were 61% and 39%, respectively, in the IR group, as compared to 73% (p=0.69) and 73% (p=0.07), respectively, in the LAP group. Further, in the elective start cohort, the
SA-PO1110
Modified Simple Peritoneal Wall Anchor Technique in Peritoneal Dialysis
Hideaki Oka,1 Shunjiro Yamada,2 Taro Kamimura,1 Yutaro Hirashima,1 Tomoya Shukuri,1 Seishi Aihara,1 Atsushi Harada,1 Kazukiko Tsuruya,1,2 1Div of Kidney Center, Matsuyama Red Cross Hospital, Matsuyama, Japan; 2Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 3Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: Outflow obstruction, a common complication in patients with peritoneal dialysis (PD), usually results in unnecessary catheter removal or replacement. This study describes a modified, simple method of anchoring a PD catheter on the anterior peritoneal wall without using a laparoscopic system (peritoneal wall anchor technique, PWAT).

Methods: We performed a retrospective cohort study of consecutive PD catheter insertions, and compared the catheter survival rate between the traditional method and the modified PWAT. The traditional method was used in 54 cases and the modified, simple PWAT was used in 17 cases. The primary endpoint was the occurrence of surgical catheter repair because of outflow obstruction by day 365. The secondary endpoint was the occurrence of catheter migration with obstruction requiring any interventions, including the alpha-replacement method by day 365. Catheter survival was analyzed by Kaplan-Meier survival curves.

Results: Migration-free catheter survival was significantly (P=0.02) higher in the PWAT group (100%, 17/17) than in the traditional group (72.2%, 39/54). Catheter survival without surgical repair or cessation of PD was also significantly (P=0.04) higher in the PWAT group (82.1%, 15/18) than in the traditional group (77.8%, 42/54). Similarly, migration-free and surgery-free catheter survival rates in cases with a straight-type catheter in the PWAT group were significantly higher than those in cases with a straight-type catheter in the traditional group.

Conclusions: Our results suggest that the modified simple PWAT provides a better catheter survival rate than the traditional method by preventing catheter migration with obstruction in PD.

SA-PO1111
A Modified Seldinger’s Percutaneous Peritoneal Dialysis Catheter Implantation Method; Viable Option for Patients requiring Unplanned Urgent-Start Peritoneal Dialysis
Il Young Kim,1 Jong Man Park,2 Harin Park3 1Dept of Internal Medicine, Pusan National Univ School of Medicine, Busan, Korea; 2Univ of Minnesota, Minneapolis, MN; 3Yale Univ, New Haven, CT.

Background: Urgent-start peritoneal dialysis (UPD) is applied to patients who need PD in less than 2 weeks, but are able to wait for more than 48 hours before starting PD. A modified Seldinger’s percutaneous PD catheter implantation method with no break-in time performed by nephrologists has been used for more than 10 years in our institution. To evaluate the usefulness and safety of this method in patients undergoing UPD, we reviewed the clinical outcomes of the two (percutaneous and surgical) PD catheter implantation methods in our university hospital.

Methods: This study included 172 patients who underwent UPD. Based on the PD catheter implantation method, the patients were divided into a percutaneous group (n = 104) and a surgical group (n = 68). PD catheters for percutaneous group were placed using a modified Seldinger’s method with tapered dilators. Results: The percutaneous group showed higher BUN, higher serum creatinine, lower hemoglobin, and lower serum albumin levels compared with the surgical group. The percutaneous group showed significantly shorter break-in time after catheter implantation (0.6±2.5 vs. 6.4±3.9 days, p<0.05). There were no significant differences in 90-day infectious complications (peritonitis, exit site infection, and tunnel infection), and also 90-day mechanical complications (pericatheter leakage, catheter migration, diminished outflow, hemorrhage, bowel perforation, hernia and catheter reinseration) between the two groups. The peritoneal catheter survival was 96.2% in percutaneous group, and 97.1% in surgical group with no significant difference.

Conclusions: The percutaneous group showed more advanced kidney dysfunction, but was able to start PD successfully with shorter break-in time. Moreover, no significant differences of 90-day infectious/mechanical complications and 1-year catheter survival rates were seen between both groups. A modified Seldinger’s percutaneous catheter implantation method by nephrologists can be a safe and effective option for unplanned UPD.

SA-PO1112
Tailoring the Peritoneal Catheter Access: One Size Does Not Fit All
Mozaher-blâtrâ,1 Antonio Vazequez,2 Belen Vizcaíno,2 Pablo Molina,3 Luis M. Pallardo,4 Nephrology, H. Univ Dr. Peset; Nephrology, H. Univ Dr. Peset; General and Digestive Surgery, H. Univ Dr. Peset; Nephrology, H. Univ Dr. Peset; Nephrology, H. Univ Dr. Peset.

Background: Tackoff catheter remains the first choice in the treatment of peritoneal dialysis (PD). The selection of the catheter length is not usually done increasing the risk of catheter dysfunction. The objective of the study was to analyze the correlation between patient’s height and intraperitoneal length (IP-L), measured from the peritoneal entry (at the level of the deep cuff) to the Pouch of Douglas during catheter insertion procedure.

Conclusions: A protected catheter was used in the peritoneal cavity during catheter insertion and when the Pouch of Douglas was reached, the protected guide was removed and length measured with a sterile ruler. If IP-L was less than 19 cm, a 16.3 cm of IP-L self-locating PD-catheter was placed (short-catheter), and if it was higher than 19 cm, a 21.5 cm IP-L self-locating PD-catheter (long-catheter) was used. Test of correlation were made with patient’s height and with navel-pubic symphysis length. Mechanical complications were recorded.

Results: 64 catheters were placed. The mean follow-up was 14.6±6.7 months. The patient’s height was positively correlated with IP-L (R=0.136, p=0.03). Mean patients’ height with long-catheter was 171.63±7.45 cm vs 166.18±8.45 cm for patients with short-catheters (p=0.009). Patients’ height was divided in three groups: > 170 cm, between 171 to 168 cm and < 168 cm. A significantly higher percentage of differences between IP-L and height were observed in the 171 to 168 cm group (53%, 91% and 38%, respectively, p=0.008). There was no significant correlation of IP-L measured with this procedure with navel-pubic symphysis length (R=0.69±p=0.08). During all the follow-up period, only five patients (3%) had an omental wrapping that required surgical repair.

Conclusions: Measuring IP-L during the catheter insertion procedure is an easy way of ensuring the election of the right catheter length. Patients of height from 168 to 171 cm could benefit from this new measurement.

SA-PO1113
Mortality and Hospitalizations in Intensive Dialysis: A Systematic Review and Meta-Analysis
Anna Mathews1, Jody-Ann Meglennon2, Nirav R. Mehta3, Sam Leung1, Valerie Suzanne Barta1, Thomas Meginn1, Gihad E. Nesrallah2 1Hofstra Northwell School of Medicine, Northwell Health, NY; 2Dept of Nephrology, Hamner River Hospital, Canada.

Background: Most ESRD patients are treated with 3 times/week hemodialysis (HD), but some receive intensive HD as short or nocturnal regimens. Existing data on mortality and hospitalization in intensive compared to conventional HD is conflicting. The objective of this study was to review the available evidence on intensive compared to conventional HD to evaluate outcomes of mortality and hospitalization.

Methods: We searched Cochrane Central Register, MEDLINE, EMBASE and Web of Science until March 15, 2016. We included observational studies and RCTs comparing intensive HD (IDH) to conventional HD (CHD). Only RCTs with 4 years follow-up were included.

Results: Twenty-three studies (2 RCTs and 21 observational) with 48,018 reported patients (38,300 on conventional HD and 9,718 on intensive HD) were included in the systematic review. Due to incomplete data reporting, 8 studies were included in the meta-analysis. Compared with conventional HD, home nocturnal [HR 0.45; 95% CI 0.32, 0.63; F=31], home short daily [HR 0.86; 95% CI 0.78, 0.96; F=0%] and in-center nocturnal [HR 0.73; 95% CI 0.60, 0.90; F=57%] HD had significantly lower mortality. Compared to conventional HD, hospitalization rate/year [mean difference -0.25; 95% CI -0.41, -0.08; F=7%] and hospitalization days [mean difference -1.87; 95% CI -2.32, -1.41; F=2%] were significantly lower in nocturnal HD. Selection bias, lack of data, and limited number of RCTs precluded some data pooling and comparisons between important subgroups.

Conclusions: Intensive HD may be associated with reduced mortality and hospitalization compared to conventional HD. Confounding by indication and the lack of multiple randomized controlled trials limits the preferential use of intensive HD. Focus is needed on identifying specific patient groups who benefit from intensive HD.

SA-PO1114
Meta-Analysis of Cardiovascular and Quality of Life Outcomes in Randomized Clinical Trials of Intensive Hemodialysis
Eric D. Weinhandl1,2 Fredric O. Finkelstein,2 Allan J. Collins2 1NxStage Medical, Inc., Lawrence, MA; 2Univ of Minnesota, Minneapolis, MN; 3Yale Univ, New Haven, CT.

Background: There have been 3 parallel-group randomized clinical trials of intensive versus conventional hemodialysis: a trial of frequent nocturnal hemodialysis in Canada (JAMA, 298:1291-1299), the Frequent Hemodialysis Network (FHN) Daily Trial (N Engl J Med, 363:2672-2700), and the FHN Nighttime Trial (Kidney Int, 80:1080-1091). We conducted a meta-analysis of individual treatment effects across the registral and quality of life outcomes that were reported in all of these trials.

Methods: We abstracted end-of-study treatment effects in the aforementioned trials for each of the following outcomes: left ventricular mass, pre-dialysis systolic blood pressure

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Underline represents presenting author.

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(SBP) and diastolic blood pressure (DBP), serum phosphorus, and physical component summary (PCS) and mental component summary (MCS) scores from 36-Item Short Form Survey (SF-36). Each summary treatment effect was estimated by a random effects model.

Results: Sample sizes of the trials were 51, 245, and 87. The duration of the Canadian trial was 6 months, whereas the duration of each FHN trial was 12 months. Summary treatment effects for intensive versus conventional hemodialysis are shown in the table. Summary treatment effects on left ventricular mass, pre-dialysis SBP and DBP, serum phosphorus, and SF-36 PCS and MCS were statistically significant (P < 0.01) and all favored intensive hemodialysis. Individual treatment effects on serum phosphorus were heterogeneous (P = 0.02), due to a smaller effect size in the FHN Daily Trial.

### Cumulative Incidence of Kidney Transplant and Death in Incident ESRD Patients on Intensive Home Hemodialysis

**SA-PO1115**

**Background:** Intensive home hemodialysis (IHD) has been primarily prescribed as a reactive therapy for patients who have accumulated years on dialysis. Clinical outcomes in incident ESRD patients on intensive IHD have not been described. We analyzed incidence of kidney transplant and death in incident ESRD patients on intensive IHD with the NxStage System One cycler (NxStage Medical, Inc., Lawrence, Massachusetts).

**Methods:** IHD patients were ascertained from NxStage records. We identified patients who initiated IHD between January 1, 2006, and December 31, 2012, and within 3 months after the date of IRSRD onset. Comparator cohorts of incident ESRD patients on conventional hemodialysis (CHD) or peritoneal dialysis (PD) were ascertained from United States Renal Data System (USRDS) records. We followed patients from dialytic modality initiation to the earliest of transplant, death, or December 31, 2013, but for a maximum of 5 years. For IHD, we estimated cumulative incidence of transplant and death. For each modality, we estimated transplant and death rates, standardized by age, race, and sex with CHD.

**Results:** The IHD cohort comprised 1898 patients. Mean age was 56.6 years, 70.4% were male, and 81.6% were white. At 5 years, cumulative incidence of transplant and death were 34.5% and 35.6%, respectively.

Conclusions: In a meta-analysis of 5 randomized clinical trials that collectively included 383 patients, intensive versus conventional hemodialysis had significant, beneficial effects on left ventricular hypertrophy, blood pressure, phosphorus balance, and health-related quality of life.

### Cumulative Incidence (%)

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<th>Transplant</th>
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SA-PO1116

**Hemodialysis Adequacy and Biochemical Outcomes in the FREEDOM Study of Daily Home Hemodialysis**

**Eric D. Weinhandl,**1,2 Allan J. Collins,2 Michael A. Copland,3 **NxStage Medical, Inc., Lawrence, MA; 4Univ of Minnesota, Minneapolis, MN; 5Univ of British Columbia, Vancouver, BC.**

**Background:** Questions regarding hemodialysis adequacy and biochemical control with low dialysate volume persist. We analyzed dialysis dose and biochemical parameters in Following Rehabilitation, Economics and Everyday-Dialysis Outcomes Measurements (FREEDOM), a prospective cohort study of daily home hemodialysis on the NxStage System One cycler (NxStage Medical, Inc., Lawrence, Massachusetts).

**Methods:** We identified FREEDOM participants who completed 12 months of follow-up on daily home hemodialysis. Urea clearance and ultrafiltration volume were measured once per month, standardized Kt/V was estimated according to Leypoldt et al (Hemo Int, 8:193-197). Biochemical parameters were ascertained from monthly and quarterly blood tests. Adjusted mean differences between month 12 and baseline were estimated by mixed models.

**Results:** The cohort comprised 247 patients. Mean age was 51.4 years, 65% were male, and 63% were white. Mean standardized Kt/V was 2.28 at baseline and between 2.29 and 2.38 during the follow-up months. Mean biochemical parameters at baseline and month 12 and adjusted mean differences between month 12 and baseline are shown in the table.

**Conclusions:** Daily home hemodialysis with low volume dialysate delivered an adequate dialysis dose in patients that completed FREEDOM. Treatment for 12 months was associated with statistically significant increases in bicarbonate and albumin and significant decreases in potassium, sodium, hemoglobin, and phosphorus.

### Incidence of Therapy Cessation among Home Hemodialysis Patients in the United States

**Eric D. Weinhandl,**1,2 Allan J. Collins,3 **NxStage Medical, Inc., Lawrence, MA; 4Univ of Minnesota, Minneapolis, MN.**

**Background:** Therapy cessation is a headwind to home hemodialysis (HHD) program growth and maintenance. Assumptions about the magnitude of incidence of cessation are diverse. We assessed incidence of cessation in a national population of HHD patients.

**Methods:** We identified patients who initiated HHD training on the NxStage System One cycler (NxStage Medical, Inc., Lawrence, Massachusetts) between January 1, 2010, and December 31, 2014, according to NxStage records. We followed patients from training initiation to the earlier of therapy cessation or March 31, 2016. We estimated incidence (CI) of cessation due to technique failure (TF), death, transplant, and composites thereof. We also estimated interval rates of cause-specific cessation.

**Results:** The cohort comprised 15,108 patients. Mean (standard deviation) duration of successful HHD training was 32 (23) days. CI of therapy cessation is shown in the table. After training, 60-month CI was 38.6% for technique failure 32.4% for death and transplant.

With IHD, 5-year rates of transplant and death were 11.6 and 11.6 events per 100 patient-years (PY), respectively. In incident ESRD patients on CHD, standardized rates of transplant and death were 3.7 and 17.7 events per 100 PY, respectively; on PD, corresponding rates were 8.4 and 13.1 events per 100 PY.

**Conclusions:** Prescription of intensive HHD in incident ESRD patients is associated with equal 5-year probabilities of transplant and death. More studies are needed to assess benefits and risks of intensive hemodialysis as a first prescription, relative to both CHD and PD.
Relative to rates of cause-specific cessation during the first year at home, TF was more likely during training and the first 6 months at home.

Conclusions: Most patients who initiate HHD training transition to home. In the long run, roughly half of therapy cessation at home is due to TF. Studies are needed to assess whether TF during training can be reduced and to identify predictors of TF at home.

SA-POI118
Association between Daily Hemodialysis, Access to Renal Transplantation and Patients’ Survival in France
Adélaïde Pladys,1 Sahar Bayat,1 Cécile Couchoud,2 Cécile M. Vigneau,1 METIS, Ecole des Hautes Etudes en Sante Publique, Rennes, France;2 Registre REIN, Agence de la Biomedecine, La Plaine Saint Denis, France;3 Service de Nephrologie, CHU Pontchaillou, Rennes, France.

Background: Daily Hemodialysis (DHD) has been developed to enhance patients’ quality of life and blood purification. But its association with survival remains controversial and the association between DHD and the access to renal transplantation has never been evaluated.

Methods: All incident patients ≥18 years starting DHD between 2003 and 2012 for a period ≥30 days in France were extracted from REIN (Renal Epidemiology and Information Network). Using a propensity score, we matched each patient on DHD to three patients on hemodialysis (HD) 3x/week. Survival was studied using the Cox model and access to renal transplantation using the Fine and Gray model.

Results: Were included 575 patients on DHD and 1696 on HD 3x/week. Survival: At the endpoint (31/12/2013), 48% patients on DHD and 32.5% patients on HD 3x/week were dead. After adjustment, DHD was associated with an increased risk of death (HR=1.4 (95%CI: 1.1-1.8)). The risk of death 2 years after dialysis initiation was 20% in DHD patients and 10% in HD 3x/week patients. Access to the renal transplantation waiting list: Patients older than 80 years were excluded (n=232). By the end of 2013, 176/516 (34.1%) patients on HD and 598/1523 (39.3%) on HD 3x/week were waitlisted. In the adjusted model, DHD was not significantly associated with the probability of being waitlisted. Access to renal transplantation after waitlisting: Patients on HD had a reduced access to renal transplantation (SHR=0.72 95%CI: 0.56-0.91). The probability of transplantation 2 years after placement on the waiting list was 51.5% in HD patients and 60.3% in HD 3x/week patients.

Conclusions: In France, DHD is associated with a lower chance of renal transplantation after being waitlisted and with a higher risk of death. DHD is addressed to various profiles: young patients who access to renal transplantation and old ones in bad clinical conditions. HD indications in France might be different from other countries. However, the development of new low-flux machines might modify the nephrologists’ indications for DHD.

SA-POI119
Cognitive Impairment in Patients with ESRD and Impact on Dialysis Modality Choice
Anuradha Jayanti,1 Philip Foden,1 Alison J. Wearden,2 Sandip Mitra.1 Nephrology, Central Manchester Foundation Trust, Manchester, United Kingdom;2 School of Psychological Sciences, Univ of Manchester, Manchester, United Kingdom.

Background: Kidney disease is associated with significant cognitive dysfunction. We investigate the association between objective and subjective cognitive function in predialysis patients and investigate if either, can predict dialysis modality choice.

Methods: Two hundred and twenty predialysis patients’ data were used to ascertain the demographics, clinical, laboratory and neuropsychometric variables. The latter includes trail making tests A and B- executive function; 3MS- global cognitive function and metacognition questionnaire for subjective assessment of one’s cognitive ability. The outcome variable was hospital and self-care modality choice.

Results: Within the study cohort, 90 patients chose fully-assisted haemodialysis and 114 patients chose self-care dialysis. The median 3MS, TMT-A and B scores were greater for assisted vs self-care group. Metamemory was not significantly different between groups but metacognition score was significantly worse in the ‘assisted-dialysis’ group. Univariate analysis showed that variables significantly (p<0.05) associated with self-care modality choice include lower TMT A and B scores and higher metamemory scores amongst others. Hierarchical regression showed highly significant association between perceived concentration and self-care modality choice (p<0.01). Adjusted and unadjusted analyses showed a significant association between perceived concentration and TMT-B scores (p<0.01). With every 1.6-minute increase in TMT-B there was a one-unit reduction in metacognition score and this was associated with 20% lower odds of choosing self-care over fully-assisted dialysis modality.

Conclusions: Patient’s own perception of their cognitive ability is a significant predictor of self-care dialysis modality choice. Subjective report of ‘metacognition’ is strongly associated with poorer outcome on trials making test B, a test of executive brain function.

Funding: Pharmaceutical Company Support - Baxter Extramural Grant

SA-POI1120
Home Hemodialysis in a Large U.S. Dialysis Organization

Background: The number of home hemodialysis (home HD) patients is growing in the USA. However, little is known of their disease and dialysis characteristics. This study was undertaken to describe the home HD patient population of a large dialysis organization (LDO) in the USA.

Methods: Stable (same modality for last 60 days of first 90 days on dialysis) incident HD home HD patients were identified from 2012-2015 U.S LDO anonymized records. Patient demographics and disease characteristics were compared to in-center population (ICHD) using Student t-tests or Chi-square tests. Home HD treatment characteristics were summarized with descriptive statistics.

Results: 447/673 (66.4%) stable incident home HD patients were men (ICHD: 56.2% (94,645; p<0.001)). Patients were on average 58±14.2 years at dialysis initiation (ICHD: 62±14.8; p<0.0001) with a body mass index of 31.6±8.6 (ICHD: 29.1±10.3 kg/m²; p<0.0001). 74.3% were Caucasians (ICHD: 44.6%; p<0.0001). 26.2% had a Charlson comorbidity index of ≥3 (ICHD: 16.8%; p<0.001). The primary cause of ESRD was: diabetes (34.3%; ICHD: 43.1%), hypertension (23.3%; ICHD: 29.0%), glomerulonephritis (9.1%; ICHD: 4.6%), cystic disease (8.2%; ICHD: 1.4%) (p<0.0001). Baseline serum albumin was 3.7±0.5 (ICHD: 3.4±0.5 g/dL; p<0.0001). Most patients (n=512/549; 93.3%) performed at least 3 sessions per week and 498 (90.7%) regularly (i.e., ≥ 70% of the time) avoided a 2-day gap. Treatment duration was available for ≥10% of dialysis sessions in 362 patients (65.9%); most patients (n=544; 99.1%) dialyzed for ≥4 hours. Four (4) patients used a nocturnal regimen. Weekly standard Kt/V was ≥2.1 in 412/524 patients (78.6%).

Conclusions: Patients on home HD are generally overweight Caucasian males with less comorbidity compared with ICHD patients. In addition, glomerulonephritis and cystic disease are more frequent primary causes of ESRD in home HD patients. Most patients avoid a 2-day gap without dialysis, but 21.4% do not reach the minimal weekly standard Kt/V of 2.1. Better recording of the dialysis parameters, for example through remote connectivity, could ensure optimal treatment monitoring and clinical outcomes.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

SA-POI1121
Usage of High-Dose Hemodialysis at Home in a Large U.S. Dialysis Organization

Background: To date, technological advances in hemodialysis (HD) have not resulted in significant survival improvement. The 2-day weekly gap in the conventional hemodialysis (HD) 3x/week therapy model has been associated with increased mortality. Several large observational studies have shown an association between a high-dose regimen (i.e., more frequent and longer HD with weekly standard Kt/V ≥3.0) and 30-45% superior survival. Home is the best place to perform high-dose HD. There is a growing population of home HD patients in the USA, but the number of patients using a high-dose HD regimen has never been studied. Usage of high-dose HD in-home HD patients was identified from 2012-2015 anonymized records of a large US dialysis organization (LDO). Patients were categorized as using a CHD regimen or high-dose HD regimen (no 2-day gaps without dialysis; if short daily: ≥5 sessions of ≥2 hours per week, if nocturnal: ≥3 sessions of ≥6 hours per week; standard Kt/V ≥3.0). Patient demographics as well as disease and treatment characteristics were to be compared using Student t-tests and Chi-square tests.

Results: 673 stable incident home HD patients were identified with information on the dialysis regimen available for 549. Most home HD patients (n=498; 90.7%) avoided the 2-day gap ≥70% of the time. Only 34 patients (6.5%) reported a standard weekly Kt/V ≥3.0 in ≥70% of the time and only 2 patients (0.4%) had a regimen corresponding to high dose. Hence, no statistical comparison between the high dose HD and CHD cohort was performed.

Conclusions: Despite the wealth of evidence supporting high-dose HD, only 0.4% of home HD patients of a large US LDO have been using this regimen. While patients regularly avoid the 2-day gap; the session durations and/or dialyzer clearance are likely insufficient to reach a high-dose regimen. This may be due to lack of awareness on the benefits of high dose or unfavorable dialysis provider economics in the US single bundle payment environment.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

SA-POI1122
Rapid Training, High Long-Term Retention, and Good Clinical Outcomes in a European Cohort of Home Hemodialysis Patients Using the NxStage System One
Maria Fernanda Slon,1 Natalie L. Borman,2 Maximence Ficheux,3 Hafedh Fessi,4 Giacomo Corciulo,1 Roberto Corciulo,1 Maria A. Bajo.5 Hospital de Navarra, Spain;4 Queen Alexandra Hospital, United Kingdom;2 CHR Clémenceau, France;3 Hospital Tenon, France;4 Niguarda Hospital, Italy;5 Policlinic Univ, Italy;5 Hospital Univ La Paz, Spain.

Background: Home hemodialysis (HHHD) facilitates more flexible and frequent treatment, which may improve clinical outcome and quality of life. We assessed training intensity, therapy cessation, and clinical outcomes in a European cohort of HHHD patients using the NxStage System One.

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Underline represents presenting author.
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Methods: We collected baseline and follow-up data about 127 home hemodialysis patients on the NxStage System One at 7 centers in France, Italy, Spain, and the United Kingdom. We followed patients from HHD initiation until the earliest of death, return to in-center HD, kidney transplant, or October 31, 2015. We analyzed the subset of patients with complete baseline data and >6 months on HHD.

Results: The study cohort comprised 101 patients. Mean age was 49.7 years, 66% were male, and mean lifetime dialysis duration was 3.2 years. Most patients (95%) were prescribed 5 or 6 sessions per week and mean treatment duration was 15.1 hours per week. Mean training duration was 3.8 weeks and 7% required >6 weeks; mean number of training sessions was 16.7 and 9% required >30 sessions. Cumulative incidence of therapy cessation is shown in the figure. After 2 years, 6% had died, 7% had returned to in-center HD, and 21% had received a transplant. After 4 years, 79% of those still on dialysis remained on HHD. During all 162.6 follow-up years, rates of death and transplant were 3.7 and 10.5 events per 100 patient-years, respectively.

Conclusions: Home hemodialysis with the NxStage System One in 4 European countries was associated with rapid training, high long-term therapy retention, and good clinical outcomes, including high incidence of transplant and low risk of death.

SA-PO1124

More Intensive Dialysis in the FHN Daily Trial Provided Limited Reduction in Uremic Solute Levels

Tammey L. Sirich,1 Kara Fong,1 Natalie Plummer,1 Glenn Matthew Chertow,1 Timothy W. Meyer,1 The FHN Trial Group.1 1Ta Palo Alto HCS and Stanford University, Palo Alto, CA; 2NIDDK, NIH.

Background: The Frequent Hemodialysis Network (FHN) Daily Trial compared conventional 3 times weekly hemodialysis to more frequent treatment with a longer weekly treatment time. Evaluation at 1 year showed modest or no effects on physical or cognitive performance.

Methods: This study compared concentrations of uremic solutes in pre-treatment samples at 1 year from 53 FHN subjects who received hemodialysis 3 times weekly for 10.9 ± 1.3 hours/week and 30 subjects who received hemodialysis 6 times weekly for 14.6 ± 1.7 hours/week. Relative concentrations of solutes identified as uremic in previous studies were assessed by metabolic analysis and concentrations of selected solutes were further quantified by liquid chromatography/tandem mass spectrometry with isotopic dilution.

Results: Metabolomic analysis showed that the FHN’s combined increase in frequency and weekly time reduced the levels of 107 uremic solutes by an average of only 15%. Quantitative analysis confirmed limited reduction in the concentrations of selected protein-bound uremic solutes:

<table>
<thead>
<tr>
<th>Solute</th>
<th>3x weekly</th>
<th>6x weekly</th>
<th>% Difference (mean, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-cresol sulfate (mg/dl)</td>
<td>3.2 ± 1.4</td>
<td>3.3 ± 1.6</td>
<td>4 (-8, 20)</td>
</tr>
<tr>
<td>indoxyl sulfate (mg/dl)</td>
<td>2.9 ± 1.1</td>
<td>2.5 ± 1.0</td>
<td>13 (-30, 4)</td>
</tr>
<tr>
<td>hippuric acid (mg/dl)</td>
<td>5.7 ± 4.0</td>
<td>4.8 ± 3.3</td>
<td>-17 (-45, 12)</td>
</tr>
</tbody>
</table>

Kinetic modeling suggested that our ability to lower solute concentrations by increasing hemodialysis frequency and weekly time may be limited by the presence of non-dialytic solute clearances and/or changes in solute production.

Conclusions: The failure to achieve larger reductions in uremic solute levels may account in part for the limited improvement in physical and cognitive performance observed with increasing frequency and weekly treatment time in FHN Daily Trial subjects. Funding: NIDDK Support, VA Support

SA-PO1125

Does the Extracorporeal Blood Flow Affect Solute Removal on Short Daily Hemodialysis with Low Dialysate Flow Rate? Maxence Ficheux,1 Maxime Leclere,1 Patrick Henri,1 Elie Zagdoun,2 Erick Cardineau,3 Clémence Béchade,1 Thierry Lobbedez,1 1Nephrology Transplantation Dialysis Dept, Univ Hospital, Caen, France; 2Nephrology Dialysis Dept, General Hospital, Saint-Lo, France; 3Nephrology Dialysis Dept, General Hospital, Alençon, France.

Background: Short daily home hemodialysis (SHD) with low dialysate flow rate (Qd) confers advantages, especially improved quality of life. The blood pump flow rate (Qb) is an important part of the dialysis prescription, but its effect on solute clearance during a short treatment with low Qd has not been described. We conducted a prospective study to assess the impact of changes in Qb on dialysis dose and solute removal.

Methods: We studied 17 patents starting SHD. Each patient was observed for 3 consecutive HD sessions, across which only Qb was altered (300, 400 and 450 mL/min). For all sessions, Qd was 180 mL/min and session duration was 2 hours. Urea, Beta-2-microglobulin (β2m), and phosphorus were measured in the blood before and after each dialysis session.

Results: Mean (standard deviation) age and dialysis vintage were 42.9 (13.7) and 5.4 (7.8) years, respectively; 53% were male; 62.5% had residual renal function; and 94.1% had an arterio-venous fistula. Mean (standard deviation) single pool Kt/V (spKt/V), B2m reduction ratio (B2mRR), and phosphorus reduction ratio (PRR) are displayed in the table 1.

<table>
<thead>
<tr>
<th>Qb (mL/min)</th>
<th>spKt/V</th>
<th>β2m RR</th>
<th>PRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>0.54(0.1)</td>
<td>0.40(0.07)</td>
<td>0.46(0.10)</td>
</tr>
<tr>
<td>400</td>
<td>0.58(0.08)</td>
<td>0.43(0.06)</td>
<td>0.48(0.08)</td>
</tr>
<tr>
<td>450</td>
<td>0.61(0.09)</td>
<td>0.49(0.06)</td>
<td>0.49(0.07)</td>
</tr>
</tbody>
</table>

In bivariate analysis with accounting for repeated observations, increasing Qb resulted in a significant increase in spKt/V (p = 0.048 [95% confidence interval, 0.03, 0.06]) increase in spKt/V per 100 mL/min increment in Qb (p < 0.05) and a significant increase in β2mRR (5-point [95% confidence interval, 3-7] increase in β2mRR per 100 mL/min increment in Qb (p < 0.05). Increasing Qb had no significant effect on PRR.

Conclusions: Increasing Qb on SHD improves the removal of urea and beta-2-microglobulin, but with potentially limited clinical impact. Patients with a vascular access that does not permit use of a high blood pump flow rate can still benefit from this dialytic modality.
**SA-PO1126**

**Weekly Standard Kt/V and Clinical Outcomes in Home and In-Center Hemodialysis**


*Background:* Patients undergoing hemodialysis (HD) with a frequency other than thrice-weekly are not included in clinical performance metrics for dialysis adequacy. Weekly standard Kt/V (stdKt/V) is comparable across treatment frequencies and location (in-center or home), but there is a paucity of data on its association with clinical outcomes.

*Methods:* We examined data from incident dialysis patients treated with in-center (N = 109,273) or home HD (N = 2,373). We used multivariable linear regression to examine the association of baseline stdKt/V with blood pressure and metabolic control (serum potassium, calcium, bicarbonate, and phosphorus) stratified by dialysis modality. We used Cox regression to examine the association of stdKt/V with mortality, first hospitalization, and for home HD, transfer to in-center HD.

*Results:* There were no clinically significant associations between baseline stdKt/V and markers of metabolic control, irrespective of dialysis modality. Patients with stdKt/V >2.3 had lower adjusted blood pressures compared to patients with stdKt/V ≤2.1, and this difference was greater for home HD relative to in-center HD. There was no association between stdKt/V and adjusted risk for mortality, hospitalization, or transfer to in-center HD among patients undergoing in-center HD (Table). Among patients undergoing in-center HD, stdKt/V ≥2.3 was associated with a 4% lower risk (95% CI: 2% to 7% lower) for death compared to stdKt/V ≤2.1 to ≥2.3.

*Conclusions:* Differences in achieved stdKt/V are associated with few clinically meaningful differences in blood pressure or metabolic complications. Additionally, current targets for stdKt/V have limited utility in identifying individuals at increased risk for adverse clinical outcomes among those undergoing home HD.

**Funding:** NIDDK Support

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**SA-PO1127**

**Profiles of Quality of Life in Home and In-Center Dialysis Patients in a Large National Population**

Nwamaka Denise Eneanya, Sophia Rosen, Marta Reviriego-Mendoza, Dugan Maddux, Stephanie Johnstone, John W. Larkin, Len A. Usvyat, Franklin W. Maddux, *Div of Nephrology, Massachusetts General Hospital; 2Fresenius Medical Care North America.*

*Background:* Although profiles of quality of life (QOL) are well-characterized for the in-center hemodialysis (HD) population, there is limited data investigating QOL in home dialysis patients (Pts). We aimed to determine the profiles of, and differences in, Kidney Disease QOL (KDQOL) survey scores in dialysis Pts treated at home versus in-center, within a large national population.

*Methods:* We analyzed data from 3,434 home peritoneal and HD dialysis Pts who completed the KDQOL survey during 120 to 365 days after the first date of dialysis (FDD) between Jan 2013 to Dec 2015. The Pt’s modality was determined using the active record of modality 120 days from FDD. Clinically similar in-center Pts during the same time frame were identified using 1:1 nearest neighbor matching on logit of propensity score for: age and comorbidities, antihypertensive medication, and episodes of IDH. We collected the same data from in-center hemodialysis patients matched for age and co-morbidities who had received 21 consecutive hemodialysis sessions at their usual center as a comparison group.

*Results:* Home hemodialysis patients had a lower systolic blood pressure (131mmHg vs 139mmHg; p=0.052) and a lower drop in their systolic blood pressure (0.84% vs 7.2%; p=0.0013) than in-center Pts. Ultrafiltration volume (1.6L vs 1.8L; p=0.001) and rate (4.66ml/kg/hr vs 6.3ml/kg/hr; p=0.001) were also lower. In-center patients were more likely to experience IDH than those dialysing at home (RR=2.48; p<0.019). IDH complicated more in-center sessions than home haemodialysis sessions (RR=6.47; p=0.001). Antihypertensive use was similar in both groups.

*Conclusions:* Home haemodialysis is associated with better blood pressure control and less IDH than in-centre haemodialysis.

**Funding:** NIDDK Support

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**SA-PO1129**

**Improved Long-Term Clinical Parameters in Nocturnal Hemodialysis**

Thomas Janss, Akin Ozyilmaz, Tiny Hoekstra, Brigita C. van Jaarsveld. *Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; 2Diagnosis Centers Groningen, Groningen, Netherlands.*

*Background:* Nocturnal hemodialysis (NHD), characterized by 8hr dialysis sessions at least three weekly, has been shown to improve clinical parameters in HD patients. However, it is not yet known to what extent these improvements last in the long run. We aimed to study long-term clinical parameters in NHD.

*Methods:* A longitudinal historical cohort was created by collecting data from medical records of 159 in-center and home-treated NHD patients from two centers in the Netherlands, from switch from conventional HD to NHD (any time after April 2004) until discontinuation of NHD. We followed patients until February 1, 2016. Data were collected on phosphate and hypertension control, nutritional status and anemia control at 0, 3, 6, 12, 18, 24 months of NHD treatment, and yearly thereafter. We compared data between baseline and 12 months, and also used generalized linear mixed models for a 6 year longitudinal analysis, adjusting for patient demographics and clinical parameters.

*Results:* At baseline, mean age was 52.0 ± 12.2 years, 32.1% of patients were female, and median duration of end-stage renal disease was 41 (IQR 12-101.5) months. Patients underwent NHD 8 hrs 3.5 times weekly. Median follow-up duration was 18.4 (IQR 7.5-35.4, range 0.4-129.6) months. Phosphate levels and number of phosphate binding pills were lower at 12 months (p=0.01), decreasing predominantly in the first 3 months and remaining stable afterwards. Diastolic blood pressure decreased -1.2 ±0.4 mmHg annually (p=0.01), and number of types of antihypertensive agents was lower at 12 months (p=0.01), again with a major decrease in the first 6 months. CRP decreased -0.08 ±0.04 mg/lannually (p=0.03), while albumin increased 0.22 ±0.07 g/l annually (p=0.01). Post-dialysis weight remained stable over the years. Erthropoiesis-stimulating agent (ESA) resistance index decreased significantly over time (p<0.01), with a 43% reduction in median weekly ESA dose (p=0.01) and a stable hemoglobin.

*Conclusions:* After switching to NHD, patients develop a considerably lower need for phosphate binding pills, antihypertensive agents and ESA, while clinical parameters remain stable or improve during a 6-year follow-up period.

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

**Underline represents presenting author.**

896A
SA-PO1130

Pregnancy Outcomes in Women on Intensive Hemodialysis Compared to Renal Transplant Recipients  
Arthi A. Bhasin, Anny V. Gonzalez, Nusrat Zaffar, Sarah Mullin, Dini Hui, Rohan D’Souza, Christopher T. Chan, Michelle H. Bladewenich. Medicine, Obstetrics and Gynecology, Univ of Toronto, Toronto, ON, Canada.

Background: Data from the US and Italy suggest that patients with a functional renal graft typically have more successful pregnancy outcomes than those with end-stage renal disease (ESRD) on dialysis. As a result, pregnancy counselling often encourages women to wait until after transplantation to conceive. However, reported pregnancy outcomes to date have included women on conventional hemodialysis (HD), while comparisons to women on intensive HD regimens (>36 hours of HD per week) have yet to be made. As such, we sought to compare pregnancy outcomes in renal transplant recipients to women with ESRD on intensive HD.

Methods: In this retrospective cohort study that spanned 2000-2016, pregnancy outcomes of 19 women with ESRD on intensive HD were compared to 45 pregnancies among women conceived post renal transplantation. The primary outcome was the live birth rate, with secondary outcomes including gestational age, birth weight and pregnancy-associated complications.

Results: The two cohorts were comparable with respect to age and cause of ESRD with the average age being 32 in both cohorts. There was no significant difference in the live birth rate at 89 vs 86% in the HD patients and the transplant recipients, respectively (p = 0.71). Similarly, there was no significant difference in gestational age (39.9±7 vs 31.5±11 weeks). However, babies born to women on intensive HD were significantly smaller (2257 ± 500 g vs 2920 ± 640 g, p<0.001). With respect to pregnancy complications, significantly more transplant recipients were delivered by caesarean section than dialysis patients (47 vs 17%, p<0.003), and fewer pregnancies were without complications (26 vs 53%, p=0.04) with the most frequent complications in transplant recipients being hypertension, preeclampsia and cholestasis while the intensively dialyzed HD population most frequently developed cervical incompetence.

Conclusions: Pregnancy outcomes in intensively dialyzed HD patients are similar to renal transplant recipients. As such, pregnancy on intensive HD can be considered a viable reproductive option.

SA-PO1131

Association between Bioimpedance, Overhydration and Inflammation Biomarkers in a Spanish Home Dialysis Unit  
Loreto Fernandez,1 Maria Fernando Slon,1 Carmen Sayon-Orea,1 Jesus Arteaga,1 Nephrology, Complejo Hospitalario de Navarra (CHN), Spain; 2Prevéntive Medicine, CHN, Pamplona, Spain.

Background: Peritoneal dialysis (PD) and in-center hemodialysis patients are at increased risk of overhydration thanks to cardiovascular events and mortality. Bioimpedance is a useful tool to assess body composition. However, there is scarce data of this tool in frequent home hemodialysis (HHD). The aim of this work is to compare hydration status in two Home-dialysis groups (PD versus HHDD) measured by means of bioimpedance and BNP (Brain Natriuretic Peptide). Interestingly, we analysed their correlation and also with some inflammation markers (PCR, IL-6).

Methods: This is a cross- sectional study of 53 Spanish home- dialysis patients: 37 on PD and 16 on HHDD. Demographics, dialysis adequacy and cardiovascular risk (prevalence of hypertension, diabetes, smoking, LDL and CRP levels) measured by bioimpedance (OH) were collected from their medical records. Hydration status biomarker (Brain Natriuretic Peptide, BNP), (CRP, IL-6) and nutritional (albumin, cholesterol) parameters were collected from blood tests. Also a bioimpedance was conducted. We took as overhydration (OH) parameter the OH/ECW (extracellular water), and for nutrition: LTI (lean tissue index), FTI (fatty tissue index).

Results: We found no differences among DP and HHDD groups in terms of demographics and cardiovascular characteristics. The OH%ECW was >10% in only 30% of patients with no differences among groups. Moderate and positive association was observed between OH% (ECW) and BNP levels (r = 0.4; p <0.002); however among groups only held significance in PD (r = 0.4 and p 0.01). Cholesterol was positively associated with FTI (r = 0.29 and p <0.03), while albumin did with LTI (r = 0.28, P = 0.03). IL-6 and CRP were positively associated with OH (r = 0.42, p = 0.002) and this association was stronger among the HD group (r = 0.75, p = 0.0019). No relationship between inflammatory markers and hydration status, LHV or time on dialysis was observed.

Conclusions: BNP levels may be a good marker of overhydration in home dialysis patients, especially in those on PD. HHDD patients have better control of dry weight, nevertheless they could be more inflamed than PD patients.

SA-PO1132

The Relationship of Hydration Status to Macro and Microcirculation in Conventional and High Dose Hemodialysis  
Nicolas Mijides,1 Tom Corinellis,1 Nanda Diederen,2 Natascha Broers,1 Jeroen Kooman,1 Sandip Mitra,1 Manchester Academic Health Science Centre, United Kingdom; 2Jessa Hospital, Hasselt, Belgium; 3Univ Hospital Maastricht, Netherlands.

Background: Fluid management presents one of the greatest challenges in hemodialysis(HD). Overhydration(OH) has been linked to adverse cardiovascular outcomes but the link between circulation and fluid compartments remains poorly defined.

Methods: We report the baseline findings of a 2yr multicentre, longitudinal study investigating compartmental fluid balance with macro and microcirculation parameters in conventional (CHD) and high dose HD (HDHD). We assessed Fluid compartments with Multifrequency bioimpedance, macrocirculation with pulse-wave velocity(PWV) and mean arterial pressure (MAP) measurements and microcirculation with sublingual dark-field capillaroscopy.

Results: 72 participants, were equally split between CHD and HDHD (>12hrs/wk). Visit MAP correlated with OH index (p=0.02), Total Body Water (TBW)(p=0.01), Extracellular Water (ECW)(p=0.01) and Intraacellular Water (ICW)(p=0.02) in a linear regression model adjusting for age, cardiovascular disease(CVD), diabetes(DM), BMI and dialysis modality. 24hr MAP was also linked to TBW (p=0.02), ECW (p=0.03) and ICW (p=0.03). Although PWV correlated with MAP (p=0.01), it was not associated with fluid indices. Microvascular luminal diameter (percentage % Cell filling) was correlated with TBW (p=0.02) but the positive relationship of injury to the Perfused Bed was neither caused by endothelial glyocalyx to ECW/ICW ratio (p=0.04) was explained by loss of ICW (p=0.01).

MAP was not associated with microcirculation parameters but high PWV did and correlated well with dynamic Red Cell volume (p=0.02).

Conclusions: MAP shows strong association with all fluid indices but PWV is predominantly linked to microcirculatory parameters across all haemodialysis modalities.

Funding: Clinical Revenue Support

SA-PO1133

Dalteparin for Circuit Anticoagulation in Patients Undergoing Daily Hemodialysis  
Karen Qi,1 Norman Muirhead,1,2 Seadna Lodger,1 Nicole Seymour,1 Jarrin D. Penny,1 Shih-Han S. Huang,1,2 London Health Sciences Centre, London, ON, Canada; 2Dept of Medicine, Nephrology, Western University; London, ON, Canada.

Background: Dalteparin, a low molecular weight heparin, has been shown to be effective and safe for hemodialysis (HD) circuit anticoagulation and has advantages over unfractionated heparin (UFN). However, there is limited evidence for its use in frequent HD (FF-HD). We conducted an observational study in our in-center short-hour daily HD program to assess the effectiveness, the dosing and the bleeding risk of dalteparin in this patient population.

Methods: We recruited 7 patients who were part of the in-centre short-hour daily HD program at the London Health Sciences Centre. All patients were switched from UFN to dalteparin at a starting dose of 2500 units(48 h). The dosage was titrated based on the circuit clotting score and the bleeding risk. All patients were followed from May 2015 to May 2016. We used descriptive analysis to report the mean (± standard deviation) UFN and dalteparin doses, number of bleeding episodes and mean clotting scores.

Results: Of the 7 patients (57% male, age 52 ± 6 y, dialysis vintage 11 ± 6 y, receiving median 12 hours over 6 HD treatments/week), the mean UFN dose during HD treatments was 1142± 351 u/h and the clotting score was <2 over 99% of the treatments. Within the first 4 weeks of switching, the mean dalteparin dose was 1687 ± 602 u/ treatment and 99% of the treatments had clotting score > 2. One patient required dose increase. All anti-Xa levels were <0.4. After 1 year, one patient passed away due to sepsis, one discontinued due to new diagnosis of diabetic retinopathy and another was dialyzing well without anticoagulation.

Conclusions: This small but important pilot study has demonstrated the effectiveness and safety of dalteparin in short-hour HD. This should be further assessed in a larger study and in perhaps the HD population, which is being conducted at this point.

SA-PO1134

Comprehensive Dialysis Transportation: The Way to Sustain a Long-Term In-Center Short Daily Hemodialysis Program  
Felipe Pacsaol,1 Adolfo Simon,1 Kelia Xavier, Vilber Bello, Juliane Laur, Istenio Pascoal.1 Centro Brasileiro de nefrologia, Brasilia, DF, Brazil.

Background: There is a rising demand for dialysis treatment among senior population. Dialysis physical toll prevents many patients arriving at the dialysis clinic via traditional transit from safely returning home the same way. While in-center short daily hemodialysis has consistently been associated with better outcomes, the availability of convenient transportation by its most important treatment factor to microcirculation parameter of a comprehensive transportation program on in-center daily hemodialysis compliance, vintage and survival.

Methods: We assessed the prevalence of absences from hemodialysis sessions (no shows), length of time on dialysis and the actuarial survival rate of 145 privately insured patients (93M/52F; mean age 56.1±19.3 yrs, range 8-95) receiving in-center short daily hemodialysis treatments (6-7 times/week; lasting 118±18.7 min; range 90-180; ultrapure dialysate and single-use highflux dialyzer). Round-trip free of charge shared passenger- transportation has been provided by company (microcirculation parameter of a comprehensive transportation program on in-center daily hemodialysis compliance, vintage and survival).

Results: From June 2006 to May 2016, 74% (108/145) of our short daily hemodialysis patients were <0.4. After 1 year, one patient passed away due to sepsis, one discontinued due to new diagnosis of diabetic retinopathy and another was dialyzing well without anticoagulation. Three patients remained on starting dose. During the 1 year period, no patient experienced significant bleeding events requiring hospitalization or interventions. No fistula/ clamping compression times were increased.

Conclusions: This small but important pilot study has demonstrated the effectiveness and safety of dalteparin in short-hour HD. This should be further assessed in a larger study and in perhaps the HD population, which is being conducted at this point.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO1135

Short Daily Hemodialysis Is Feasible and Safe with Physidia S3 Monitor

Louis De Lafosse,

Roula Galland,

Walid Arkouche,

Maezone Ficheux,

Patrick Henri,

Francois Babine,

Maurice Laville,

Dept of Nephrology, Hopitaux Civils de Lyon, Pierre Bénite, France;

Unit 1060 CarMeX, Univ Lyon 1; Claude Bernard, Oullins, France;

Calydial, Vénissieux, France;

AURAL, Lyon, France;

Nephrology Hemodialysis, CHU Caen, Caen, France;

Nephrology Hemodialysis, CH Cherbourg, Cherbourg, France;

ECHO Association, Le Mans, France.

Background: Short daily hemodialysis (SDH) improves hemodynamic tolerance, life quality and cardiac outcomes. Physidia S3 is a low flow dialysis machine designed for SDH.

Methods: We designed a multicentric, prospective, observational study. Main inclusion criteria were: patients treated with hemodialysis since 3 months or more, clinically stable, who were 18 years old or more, stable vascular access (No catheter). Included patients underwent SDH (5 or 6 times a week) on Physidia S3machine with bicarbonate buffer, during 2 weeks. Primary outcome was the ability to deliver a conform dialysis session (session duration with a ±15% tolerance and weight loss with a tolerance of ±300g in accordance with medical prescriptions).

Results: 11 patients (6 men) were included. Median age was 53 years, median dry weight was 60 kg, median BMI was 24.4 kg/m2. 126 sessions were analysed, dialysis duration was respected in 96% of the sessions, and weight loss in 85%. 82% of the dialysis respect both duration and weight loss criteria. After excluding human errors in weighing or result reporting, 93% of the dialysis sessions were conform.

Conclusions: SDH with Physidia S3 provides a good conformity with medical prescriptions, and a good adequation of dialysis.

SA-PO1136

An Analysis of Patient Interest in In-Center Self-Care Hemodialysis with a Novel Hemodialysis System

Sarah S. Prichard,

Luis Alvarez,

Glenn Matthew Chertow,

Independent Consultant, North Palm Beach, FL;

Div of Nephrology, Dept of Medicine and Nephrology, Palo Alto Medical Foundation, Palo Alto, CA;

Div of Nephrology, Dept of Medicine and Nephrology, Stanford Univ School of Medicine, Stanford, CA.

Background: Patients on hemodialysis (~70%) are interested in performing in-center self-care hemodialysis (ICSDH) because it provides flexibility and control relative to in-center hemodialysis (ICH). Yet, only ~8% of patients are on self-care in the US. Lack of adoption has been attributed to complexity of technology, and fear of self-cannulation. ICSDH combines the clinical benefits of self-care with the security of a clinic setting. We assess the capability of patients performing ICSDH with the Tablo™ Hemodialysis System.

Methods: We evaluated a subset of patients (n=20) who transferred to ICSDH using the Tablo™ System. Using internal log file data that can be transmitted wirelessly after treatment, we measured the time required to set-up, and the number and type of alarms that occurred. After each set-up step is completed or an alarm occurs a flag is logged in the data. The timing between flags was measured to determine set-up and alarm resolution times.

Results: System data files for 356 treatments were analyzed. Patients did not have dexterity or visual deficiencies, age ranged from 28-69 and there were 11 females. In 90% of treatments patients were able to set-up Tablo™ in 5 minutes.

Conclusions: A high percentage of patients across broad demographic lines indicate interest in performing ICSDH with the Tablo™ Hemodialysis System.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

SA-PO1137

Initial Experience of In-Center Self-Care Patients with the Tablo™ Hemodialysis System

Sarah S. Prichard,

Luis Alvarez,

May L. Yau,

Dean Hu,

Paul Chen,

Michael A. Aragon,

Glenn Matthew Chertow,

Independent Consultant, North Palm Beach, FL;

Div of Nephrology, Dept of Medicine and Nephrology, Palo Alto Medical Foundation, Palo Alto, CA;

Outset Medical, Inc, San Jose, CA;

Div of Nephrology, Dept of Medicine and Nephrology, Stanford School of Medicine, Stanford, CA;

North Texas Kidney Consultants, Grapevine, TX.

Background: Patients on hemodialysis (~70%) are interested in performing in-center self-care hemodialysis (ICSDH) because it provides flexibility and control relative to in-center hemodialysis (ICH). Yet, only ~8% of patients are on self-care in the US. Lack of adoption has been attributed to complexity of technology, and fear of self-cannulation. ICSDH combines the clinical benefits of self-care with the security of a clinic setting. We assess the capability of patients performing ICSDH with the Tablo™ Hemodialysis System.

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Results: System data files for 356 treatments were analyzed. Patients did not have dexterity or visual deficiencies, age ranged from 28-69 and there were 11 females. In 90% of treatments patients were able to set-up Tablo™ in 5 minutes.

Conclusions: Patients performing ICSDH can quickly set-up and successfully manage their treatments using the Tablo™ Hemodialysis System.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

There were 472 alarms, or 1.32 alarms per treatment, with a weighted average of 22.4 seconds to resolve an alarm, using the Tablo™ touchscreen. In 183 (51%) treatments there were no alarms.

Conclusions: Patients performing ICSDH can quickly set-up and successfully manage their treatments using the Tablo™ Hemodialysis System.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

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

Underline represents presenting author.

898A
SA-PO1138

Institutionalization before and after the Transition from CKD to ESRD on Dialysis

Maria E. Montgomery-Rath,1 Yuanchao Zheng,1 Manjula Kurella Tamura,1 Vanessa Grubbs,2 Wolfgang C. Winkelmayer,3 Tara I. Chang.1,3 Stanford,1 UCSF,1 Baylor,2 UCSF; 3Baylor.

Background: The transition from CKD to ESRD can be particularly unstable. We sought to examine the frequency of days spent institutionalized (hospital or nursing home) during the 1-year prior to and after dialysis initiation in older patients.

Methods: We used the USRDS to identify patients aged ≥67 at the time of incident ESRD with Medicare A+B. We created “heat maps” by color-coding each day in the 365 days pre- and post-ESRD; each patient is represented by a single horizontal row with dark/light blue indicating institutionalized days. We used zero-inflated negative binomial models that accounted for number of days alive to quantify the mean number of institutionalized days in the 1st year post-ESRD, adjusting for baseline characteristics.

Results: The top heat map (Figure) depicts 67-70 year-olds without cardiovascular disease (CVD). The larger amount of black vs. blue reflects the larger proportion of time spent at home vs. in an institution. The bottom heat map depicts 80+ year-olds with dementia/frailty, and shows a relatively large proportion of institutionalization and death.

The adjusted average number of institutionalized days differs widely depending on the subgroup (Table).

Table: Adjusted average number of institutionalized days in the first 365 days post-ESRD

<table>
<thead>
<tr>
<th>Age Category (y)</th>
<th>67-70</th>
<th>71-74</th>
<th>75-79</th>
<th>80+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>49</td>
<td>55</td>
<td>63</td>
<td>75</td>
</tr>
<tr>
<td>CVD+</td>
<td>53</td>
<td>59</td>
<td>67</td>
<td>79</td>
</tr>
<tr>
<td>CVD-</td>
<td>33</td>
<td>37</td>
<td>42</td>
<td>54</td>
</tr>
<tr>
<td>Dementia+</td>
<td>75</td>
<td>85</td>
<td>88</td>
<td>103</td>
</tr>
<tr>
<td>Dementia-</td>
<td>47</td>
<td>53</td>
<td>61</td>
<td>72</td>
</tr>
<tr>
<td>Frail+</td>
<td>86</td>
<td>93</td>
<td>96</td>
<td>105</td>
</tr>
<tr>
<td>Frail-</td>
<td>41</td>
<td>47</td>
<td>54</td>
<td>66</td>
</tr>
<tr>
<td>Dementia+Frail+</td>
<td>108</td>
<td>113</td>
<td>113</td>
<td>120</td>
</tr>
<tr>
<td>Dementia-Frail-</td>
<td>42</td>
<td>46</td>
<td>52</td>
<td>59</td>
</tr>
</tbody>
</table>

Conclusions: Older patients who initiate dialysis spend a substantial proportion of time institutionalized, particularly octogenarians and patients with dementia, frailty and CVD. Continued efforts to improve shared decision-making about dialysis initiation in high-risk subgroups are needed.

Funding: NIDDK Support

SA-PO1139

Generalisability of SPRINT to Community Dwelling Individuals over the Age of 75: Informing Estimation of Baseline Adverse Event Risk

Donal J. Sexton,1,2,3 Mark Canney,1,2,4 Mark Alan Little,2 Conall M. O’Seaghdha,3 Rose Anne Kenny.1,2 The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin, Dublin, Ireland;3 Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland;4 Dept of Renal Medicine, Beaumont Hospital, Dublin, Ireland.

Background: With the publication of the ≥ 75 yrs subgroup analysis of the SPRINT trial, the generalisability of this study merits evaluation. SPRINT found reduced cardiovascular events and all-cause mortality in those randomized to a systolic BP target of < 120 mmHg.

Methods: Data from the 1st (2009-2011) and 3rd wave (2015) of The Irish Longitudinal Study on Ageing, a prospective cohort study of community dwelling older adults in Ireland (N=5390). We applied the inclusion/exclusion criteria for SPRINT.

Results: Mean follow up was 3.42 yrs. For those ≥ 75 yrs meeting final inclusion criteria we compared characteristics and outcomes of those with CKD: 37.8% (45,586 in the population) to those without CKD: 62.2% (74,933). Frailty (by Fried Index) was more common at baseline in CKD: 12.6% Robust (15,121), 19.4% Pre-frail (23,200) and 5.9% Frail (7,100) compared to 23.8% (28,703) Robust, 35.2% Pre-frail (42,450) and 3.2% Frail without CKD (3,805) P = 0.02. Those reporting difficulties climbing one flight of stairs was more common in CKD (28.8% No, 9% yes) than without CKD (53.4% no and 8.8% yes), P=0.04. A history of having previously fractured a hip, was more common in CKD (33.1% No, 4.8% Yes) than without CKD (59% No and 3.2% Yes) P=0.03. Reporting a fear of falling was also more common at baseline in CKD (29.8% No, 8% Yes) than without CKD (56.7% No and 5.5% Yes), P=0.003. Outcome rates over follow up in this study per 100 person years (95%CI) were: Systolic 1.4(0.5-3.6) in CKD and 1.2(0.5-2.7) without CKD, Injuries falls 14.8(6,6,25,5) in CKD vs 11(6.3, 19.4) without CKD, fractures (hip/wrist/spine) due to falls 0.7(0.2,2.7) in CKD vs 0.6 (0.2, 1.8) without CKD.

Conclusions: Community dwelling individuals ≥ 75 yrs meeting eligibility for SPRINT are a heterogeneous group. Given the observation of higher baseline frailty in those with CKD than without in this study, the balance of risk-benefit when implementing the results of SPRINT may be influenced by the presence of CKD.

SA-PO1140

A Delphi Study on Frailty in Adults with End Stage Renal Disease

Sarah Rasmussen, Dorry L. Segev, Mara McdAdams-DeMarco. JHU.

Background: End stage renal disease (ESRD) patients are at higher risk of frailty, a loss of physiologic reserve that is associated with poorer outcomes. However, some components of the frailty phenotype may not accurately characterize frailty in ESRD patients.

Methods: In a two-round Delphi study we distributed 2 anonymous surveys to nephrologists, geriatricians and transplant surgeons at JHU (round 1 n=41; round 2 n=36). Consensus and moderate consensus were defined as >80% and 60-80% agreement, respectively. Fisher’s exact test was used to examine differences by specialty.

Results: The response rate for both rounds was 87%. 98% of clinicians said ESRD patients are more likely to be frail than healthy adults. There was consensus that 4 of the 5 Fried frailty components should not be removed from the definition of frailty in ESRD patients, but only moderate consensus that weight loss should not be removed (71%). Nephrologists were less likely to want to remove weight loss (p=.03). 10 new ESRD-specific components were identified (9 included in round 2). There was moderate consensus that history of falls and physical decline should be added. Nephrologists were more likely to want to add history of falls (p=.01); gerontologists were less likely to want to add cognition (p=.03).

Table: 1st round: components identified

<table>
<thead>
<tr>
<th>1st round: components identified</th>
<th>2nd round: % wanting to add component</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of falls</td>
<td>64</td>
</tr>
<tr>
<td>Physical decline</td>
<td>64</td>
</tr>
<tr>
<td>Cognition</td>
<td>39</td>
</tr>
<tr>
<td>Nutrition, diet</td>
<td>36</td>
</tr>
<tr>
<td>Albumin</td>
<td>17</td>
</tr>
<tr>
<td>Nutrition, diet</td>
<td>36</td>
</tr>
<tr>
<td>Physical decline</td>
<td>64</td>
</tr>
<tr>
<td>Cognition</td>
<td>39</td>
</tr>
<tr>
<td>Nutrition, diet</td>
<td>36</td>
</tr>
<tr>
<td>Albumin</td>
<td>17</td>
</tr>
<tr>
<td>Health care utilization</td>
<td>11</td>
</tr>
<tr>
<td>Metabolic bone disease</td>
<td>6</td>
</tr>
<tr>
<td>Excess fluid</td>
<td>3</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>3</td>
</tr>
</tbody>
</table>

Conclusions: There was consensus that prehabilitation could make transplant patients less frail (97%) and that patients will be interested in prehabilitation (97%). There was moderate consensus that using foot paddles during dialysis would make patients less frail (80%) and that patients would be interested in foot paddles (69%).

Conclusions: There is consensus that frailty is common in ESRD patients and that interventions could improve frailty in this population. However, some clinicians suggest a need for an ESRD-specific definition of frailty.

Funding: Other NIH Support - NIA, Private Foundation Support

SA-PO1141

Kidney Function and Objective Markers of Frailty in Community-Dwelling Older Adults

Mark Canney,1,2 Donal J. Sexton,1,2 Matthew D.I. O’Connell,1 Neil O’Leary,1 Rose Anne Kenny,1 Mark Alan Little,2 Conall M. O’Seaghdha,3 1The Irish Longitudinal Study on Ageing; Trinity College Dublin; 2Trinity Health Kidney Centre, Trinity College Dublin; 3Nephrology Dept, Beaumont Hospital, Dublin.

Background: Frailty is a means of risk-stratification in advanced chronic kidney disease (CKD). We sought to determine the association between objective physical performance tests and kidney function across the spectrum of estimated glomerular filtration rate (eGFR) in older adults.

Methods: Cross-sectional analysis of 4562 participants from The Irish Longitudinal Study on Ageing, a representative national cohort of community-dwelling adults aged

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: We observed a relationship between eGFR and physical performance of older adults. eGFR modified the relationship between age and physical performance.

SA-PO1142

Distribution of Cystatin C and Creatinine with Advancing Age

Mark Canney,1,2 Donal J. Sexton,1,2 Neil O’Leary,1 Rose Anne M. Kenny,1 Mark Alan Little,2 Conall M. O’Searghda.1 The Irish Longitudinal Study on Ageing, Trinity College Dublin;1 Trinity Health Kidney Centre, Trinity College Dublin;1 Nephrology Dept, Beaumont Hospital, Dublin.

Background: Little is known about filtration marker distribution as we age. We modelled creatinine and cystatin C distributions across the age spectrum in a large population of older adults.

Methods: Cross-sectional analysis of 5387 participants from The Irish Longitudinal Study on Ageing, a representative national cohort of community-dwelling adults aged ≥50 years. Creatinine and cystatin C were measured simultaneously using standardised assays. Using generalised additive models we flexibly modelled the distribution of each biomarker from four parameters of the Box-Cox Power Exponential distribution: location, dispersion, skewness and kurtosis. The best fitting model for each parameter was sought using cross-validation.

Results: Mean(s) age was 63.9(8.2) years and 53% were female. We observed a strong non-linear relationship between creatinine C and age, with an uptake at age 65 beyond which creatinine C levels rose sharply. The shape of the cystatin C distribution differed by age in both genders. As well as having higher median values, older individuals demonstrated greater variability in creatinine C compared to younger participants. The trajectory of creatinine with age was comparatively flat. Creatinine distribution also varied with age but to a lesser extent.

Conclusions: The relationship between cystatin C and age is complex and non-linear. Older adults demonstrate progressively greater variability in filtration marker distribution with advancing age, particularly for cystatin C. Such variability may contribute to the uncertainty of estimation of kidney function in the ageing population.

SA-PO1143

Low Body Mass Index as Risk Factor for Mortality in Older Adults

Natalie Ebert,1 Olga Jakob,2 Peter Martus,3 Elke Schaeffner.1 1Inst of Public Health, Charité, Berlin, Germany; 2Inst for Clinical Epidemiology and Biostatistics, Charité, Germany; 3Inst for Med. Biometry, Eberhard Karls Univ Tübingen, Germany.

Background: High body mass index (BMI) is a known risk factor for cardiovascular events and mortality in middle aged adults. Its relationship in older age is less clear.

Methods: We used baseline and follow-up data from the Berlin Initiative Study (BIS), a population-based cohort that examines kidney function over time in subjects who are 70 years and older. Kaplan Meier analysis and Cox proportional hazard models were applied to assess the predictive value of BMI (3 categories: ≥30, 25-29, <25) with regard to overall mortality. Analyses were done for BMI only and adjusted for age, gender and additional known risk factors. Median follow-up were 54 months.

Results: 2068 BIS participants with a mean age of 80 years were followed. 52.6 % were female, 26.1 % had diabetes, 14 % had suffered from myocardial infarction (MI), 8.7 % from stroke, 78.8 % had antihypertensive medication, 53 % had a GFRcr <60 ml/min/1.73m². Mean albumin was 39.9 g/l. Mean albumin was 39.9 g/l. Mean albumin was 39.9 g/l. Mortality was lowest for subjects with a BMI <25 compared to subjects with a BMI >30 (log rank <0.001).

Conclusions: BMI ≤25 is associated with lower mortality in older adults.

Funding: Private Foundation Support

SA-PO1144

Prevalence of Frailty in Chronic Dialysis Patients in Japan

Hidemi Takeuchi,1 Haruhito A. Uchida,1 Yuki Kakio,1 Yuka Okuyama,1 Ryoko Umebayashi,2 Michihito Okuyama,2 Taro Sugimoto,1 Hitoshi Sugiyama,1 Jun Wada.1 1Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ, Okayama, Japan; 2Cardiovascular Surgery, Okayama Univ, Okayama, Japan.

Background: Recently, frailty has raised as the problematic expression of the elderly population, especially dialysis patients. Since potential causative factors of frailty present in the patients with CKD and ESRD, they are prone to develop frailty. The prevalence of frailty has reported 14 % of CKD patients and 42 % of dialysis patients in Western studies. However, that in dialysis patients in Japan remains unknown. The aim of this study was to examine the prevalence and the predictors of frailty in Japanese hemodialysis patients.

Methods: This study was a multicenter, cross-sectional and observational investigation, which was conducted at 6 institutions including 5 general hospitals and 1 clinic. The subjects were all chronic hemodialysis patients who regularly visited the institutions and were included in this study. Participants were 67 ± 12 years old, with more male gender (62.4 %). In total, 21.4 % of participants were categorized as frailty, 52.6 % as pre-frailty and 26.0 % as normal.

Conclusions: After multivariable adjustment for age, gender, albumin, diabetes, smoking, MI, stroke, hypertension, and decreased kidney function (GFR <60 ml/min/1.73m²) the relationship was less strong but still statistically significant.

<table>
<thead>
<tr>
<th>BMI (reference)</th>
<th>p-value</th>
<th>HR (95% CI)</th>
<th>p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥30</td>
<td>&lt;0.001</td>
<td>0.57 (0.49-0.67)</td>
<td>0.003</td>
<td>0.67 (0.57-0.80)</td>
</tr>
<tr>
<td>BMI 25-29</td>
<td>0.14</td>
<td>1.01 (0.84-1.23)</td>
<td>0.79</td>
<td>0.96 (0.73-1.28)</td>
</tr>
<tr>
<td>BMI &lt;25</td>
<td>&lt;0.001</td>
<td>0.12 (0.06-0.25)</td>
<td>0.02</td>
<td>1.43 (1.06-1.92)</td>
</tr>
</tbody>
</table>

Hazard ratios were attenuated by albumin, stroke, smoking and hypertension (not shown). Decreased GFR did not influence the results.

Conclusions: Lower BMI was associated with higher mortality in older adults.

Funding: Private Foundation Support

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

Underline represents presenting author.
The prevalence of frailty increased steadily with age, was more prevalent in female and polypharmacy. Next, we performed multivariate logistic regression analysis for the predictors of frailty. The factors independently associated with frailty were determined as follows: female (OR = 3.864, 95% CI: 1.595-9.361), 75 years and over (OR = 5.375, 95% CI: 1.932-14.933), the number of medications (OR = 1.335, 95% CI: 1.156-1.541), DM (OR = 2.885, 95% CI: 1.818-7.048) and MNA-SF score ≤ 11 (OR = 8.550, 95% CI: 3.300-22.149).

Conclusions: The prevalence of frailty in Japanese dialysis patients was relatively lower than that of previous studies in Western countries. The patients of 75 years old and over, female, DM, polypharmacy and MNA-SF were closely related with frailty.

SA-PO1145

Dementia and Alzheimer’s Disease among Older Kidney Transplant Recipients

Mara McAdams-DeMarco, Sunjace Ba, Dorry L. Segev, Johns Hopkins.

Background: End stage renal disease and cognitive impairment share a common pathogenesis and dialysis increases the risk of cognitive impairment. KT is a growing treatment option for older adults yet, older recipients may develop dementia and Alzheimer’s disease (AD) as the result of both their long standing kidney disease and the lifelong dependence on immunosuppressants, which are known to be neurotoxic.

Methods: We studied 43,606 older (aged ≥55) KT recipients who were Medicare Primary (between 1/1/99-12/31/11) using SRTR data linked to Medicare claims. We estimated the cumulative incidence of dementia and AD (based on claims) using the Kaplan-Meier method. We developed a prediction model based on recipient, transplant, and donor factors known prior to KT for the post-KT incidence of dementia and AD (separately) using an AIC-based selection method for the Cox proportional hazards model.

Results: We estimated the post-KT cumulative incidence of dementia and AD to be 5.0% and 2.0% at 5 years and 12.7% and 5.6% at 10 years, respectively.

SA-PO1147

Symptom Burden in Geriatric Hospitalized End Stage Renal Disease Patients: Quantifying Symptoms to Improve Nephrologist Awareness and Use of Palliative Care Consultation

Areeba Jawed, Sharon M. Moe, Ranjani N. Misir, Alexia Torke, Michael T. Egan, Div of Nephrology, Dept of Medicine, Indiana Univ School of Medicine, Indianapolis, IN; *Internal Medicine, Indiana Univ School of Medicine, Indianapolis, IN.

Background: End Stage Renal Disease (ESRD) patients have significant symptom burden. Reduced provider awareness of symptoms contributes to undertreatment of symptom management resources. We hypothesized that improved nephrologist awareness of symptoms leads to symptom improvement.

Methods: In this prospective, multicenter intervention study, 51 geriatric ESRD inpatients underwent symptom assessment using the modified Edmonton Symptom Assessment System (ESAS) at admission and 1 week post-discharge. Enrollees were sequentially randomized into 2 groups. The nephrologist of each individual was provided baseline symptom assessment in group 1, but was unaware of group 2. Severity ratings were compared between in-hospital and post-discharge scores and between groups.

Results: 50 patients completed the study; 1 died. Baseline characteristics were compared. For 70% of the total cohort physicians reported not being surprised if their patient died within a year. There was no difference in baseline scores between groups. Total ESAS scores improved more in group 1 (13.3) than group 2 (9.5) (p=0.04). Among individual symptoms, there was greater improvement in pain control (p=0.01), and itching (p=0.05) in Group 1 as compared to Group 2. There were three palliative care consults.

Conclusions: Our findings reinforce the high symptom burden prevalent in geriatric ESRD patients. The improvement in total scores, and individual symptoms of pain and itching in group 1 indicates better symptom control when physician awareness is increased and simple pharmacological interventions are available. Residual symptoms post hospitalization and low utilization of palliative care resources is suggestive of a missed opportunity by nephrologists to address the high symptom burden at the inpatient encounter which is selective for sicker patients and/or inadequacy of dialysis to control these symptoms.

Funding: Private Foundation Support

SA-PO1148

Use of Arteriovenous Fistulae within 1 Year of Hemodialysis Initiation Was Associated with Better Survival in Comparison with Catheter Use among Patients Older Than 80

Tae Woo Ravel, Csaba Zadeh, Ik Yoshitsugu Oh, Tae Soohoo, Zhao Yuan, Vanessa McAdams-DeMarco, Hoon Yi, Ik Yoshitsugu, Jawed Zadeh, Quynh Tran, Hamid Moradi,1 Vanessa A. Ravel,1 Csaba P. Kovesda,2 Elani Streja,1 Kamyar Kalantar-Zadeh,3,4 UC Irvine; 2Univ of Tenn.

Background: While arteriovenous fistulas (AVFs) are recommended as the preferred vascular access type in most hemodialysis (HD) patients, this remains widely debated in very old HD patients given their lower rates of AVF maturation and limited life expectancy.

Methods: We examined the conversion of access types within 1 year after HD initiation, and evaluated the association of dialysis access with mortality using Cox regression with adjustment for case-mix (demographics, comorbidities) and markers of malnutrition and inflammation (MICS) in 8,326 incident HD patients age 80 years, who survived the first year of HD from a large dialysis organization during 2007-2011.

Results: During the first year of HD, 27% of elderly patients exclusively used a central venous catheter (CVC). Ever use of AVF (CVC-to-AVF or initial AVF) within the first year of HD was associated with better survival compared to the CVC-only use. In fully adjusted models, no significant differences were noted between ever-use of AV graft in the first year compared to CVC-only. Longer use (>90 days) of number of days in the first year of HD) of CVC following HD initiation was associated with incrementally worse survival (right panel).

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: It is suggested to consider converting access type to AVF from CVC and decreasing the periods time using CVC even in very old HD patients. Initiation of dialysis with a CVC catheter could be an acceptable option in elderly patients, as long as it is converted to an AVF as soon as possible.

Funding: NIDDK Support

SA-POI1149

Death due to Dialysis Withdrawal among Elderly Incident Hemodialysis Patients Gang Jeo,1 Tae Ik Chang,1 Connie Rhee,1 Tae Woo Kim,1 Yoshitsugu Obi,1 Rieko Erguchi,1 Melissa Sooho,1 Daniel L. Gillen,2 Vanessa A. Ravel,1 Csaba P. Kovesdy,1 Elani Streja,1,1 Kamyar Kalantar-Zadeh,1,1 UC Irvine; 2Univ of Tenn.

Background: The population of elderly patients is rapidly growing among ESRD patients initiating dialysis. However, it is not clear whether death due to withdrawal from dialysis differs across age and which pattern it has, in particular among octogenarian and nonagenarian patients.

Methods: We compared causes of death, including withdrawal from dialysis, within the first year of dialysis among incident hemodialysis (HD) patients aged ≥80 years (N=17,296) vs. those <80 years of age (N=115,866) from a large national dialysis organization over a 5 year period (2007-2011). Comparisons were modeled using reported frequencies and logistic regression.

Results: Compared to patients <80 years of age, octogenarian and nonagenarian were more likely to be female (45.8 vs. 43.0%) and non-Hispanic White (67.7 vs. 43.7%), and were less likely to have diabetes (45.6 vs. 57.0%). Loss to follow-up during the 1st year of HD was more frequent in octogenarian and nonagenarian, and a greater proportion of these events was due to dialysis withdrawal as compared with younger patients (7.2 vs. 2.9%) besides death. Among octogenarian and nonagenarian, death due to dialysis was the second most common cause of death (left panel), and we observed higher rates of dialysis withdrawal among death with increasingly older age (right panel). Octogenarian and nonagenarian showed a higher likelihood of death due to dialysis withdrawal compared to younger patients even after adjustment for demographics and comorbidities: adjusted OR 1.61 (95% CI: 1.47-1.77).

Funding: Private Foundation Support

SA-POI1150

Survival and Outcomes in Advanced Age with Renal Insufficiency (SOAAR) Hui Xue,1 Shayna L. Henry,1 Quaeling Chen,1 Mi Chang,1 Nichole Mihara,1 Mark P. Rutkowski,1 Nephrology, Kaiser Permanente Southern California, CA; 2Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA.

Background: While the elderly are the fastest growing segment of individuals with End Stage Renal Disease (ESRD), there is limited evidence for an overall survival or quality adjusted life advantages of Renal Replacement Therapy (RRT) compared to conservative approaches in this group. This study aims to illuminate the outcomes and survival of elderly patients with advanced renal failure with respect to RRT choice, and to identify factors associated low survival and worse outcomes.

Methods: From 2003 to 2008, 2,062 adults, mean age 81.14±4.7yrs (range 75-99), 49.5% female, who initiated RRT or maintained GFR ≤ 20 for at least 3 consecutive months were followed for 5 years with censoring at December 31, 2013. Subjects who did not initiate RRT were censored until death or censor date. Risk of transition to ESRD vs death was stratified into 5 year age groups. Healthcare utilization was also assessed based on RRT use.

Results: The risk of progression to ESRD is higher than death up to age 90, p<0.001. Median survival was 33 (95% CI 30, 36) and 20 (17, 22) months for RRT and non- RRT groups, respectively (p<0.001). Quality-adjusted survival was 21 (19, 23) and 14 (12, 15) months for RRT and no RRT groups, respectively (p<0.001). Peritoneal dialysis offered greatest survival benefit compared to hemodialysis or no RRT (p<0.001). Initial results suggest that age is a better predictor of death than baseline eGFR, with age and survival strongly related, and those patients initiating RRT at the oldest ages (90+ years) experiencing the most limited survival ([logrank p<0.001). However, RRT was associated with greater healthcare utilization, including more hospitalizations and ER visits, greater SNA use, and lower hospice referral (p<0.001).

Conclusions: RRT approach to elderly adults with ESRD a survival advantage overall conservative, non-RRT approaches, but decrements in quality of life may still limit its utility among the elderly. The potential for these findings to provide decision support for initiating or forgiving RRT in elderly patients will be discussed.


SA-POI1151

Impact of Race and Socioeconomic Factors on Mortality among Nursing Home Patients on Maintenance Dialysis Robert Neg,1 Lawrence Agodou,2 Kevin C. Abbott,3 Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; 1NIDDK, National Insts of Health, Bethesda, MD.

Background: The impact of race and socioeconomic factors on survival rates of nursing home (NH) patients with treated end-stage renal disease is unknown. We evaluated race/ethnicity, health insurance and ZIP code-level median household income (MHI) as predictors of mortality of NH patients on dialysis.

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 56,194 nursing home patients initiated on maintenance dialysis from January 1, 2007 to December 31, 2013, followed until 31 May 2014. Covariates include demographic and clinical characteristics and other co-morbid conditions from the Medical Evidence Form 2728. ZIP code-level MHI data was obtained from the 2010 United States Census. We conducted adjusted Cox regression analyses with all-cause mortality as the outcome variable.

Results: Within this NH cohort, 50.5% were female, 26.7% were African-Americans (AA), 8.9% were Hispanic, and the mean age was 71 ± 12.1 years. Adjusted Cox analysis showed significantly lower risk of death among AA vs non-AA NH patients (adjusted hazard ratio [AHR] 0.89; 95% confidence interval [CI] 0.87-0.91) and Hispanic vs non-Hispanic NH patients (AHR 0.87; 95% CI 0.84-0.91). Employer group health insurance (AHR 0.94; 95% CI 0.91-0.97) and dual-eligibility for both Medicare and Medicaid (AHR 0.75; 95% CI 0.73-0.77) were significantly associated with lower risk of death. However, Medicare (AHR 1.12; 95% CI 0.99-1.15) and Medicaid (AHR 1.13; 95% CI 1.10-1.16) alone were significantly associated with higher risk of death. Compared to those in higher area-level MHI quintile levels, NH patients in the lowest quintile were significantly associated with higher risk of death (AHR 1.10; 95% CI 1.07-1.13).

Conclusions: AA and Hispanic NH patients on dialysis had an apparent survival advantage. The type of health insurance coverage and area-level income were also independent predictors for survival.

Funding: NIDDK Support

SA-POI1152

Association of Dietary Sodium Intake with Change in Cognitive Function and Brain Magnetic Resonance Imaging Indices Kristen L. Nowak,1 Linda F. Fried,2,1 Anna Jeanette Jovanovich,3,4 Joachim H. Ix,5 Anne B. Newman,2 Zhiying You,1 Suzanne Satterfield,3 Michel Chonchol,1 1Univ of Colorado Anschutz Medical Campus; 2Univ of Pittsburgh; 3VA Pittsburgh Healthcare System; 4Denver VA Medical Center; 5Univ of California San Diego; 6Univ of Tennessee Health Science Center.

Background: Dietary sodium may influence cognitive function via its influence on cerebrovascular function and cerebral blood flow. We hypothesized that high dietary sodium intake is associated with a decline in cognitive function over time. We further hypothesized that sodium intake is associated with micro- and macro-structural brain magnetic resonance imaging (MRI) indices.

Methods: 1,216 participants in the Health ABC study with measurement of dietary sodium intake were analyzed. Linear regression models were used to assess the association of sodium intake with micro- and macro-structural brain MRI indices.

Results: Participants were 74±3 years with a mean dietary sodium intake of 2,645±1098 mg/day. During follow-up, 340 (28%) had a clinically significant decline in 3MS score after 7 years (≥5 points or <80 points). In a sub-group who participated in the Healthy Brain substudy (n=257), multiple linear regression models were used to assess the association of sodium intake with micro- and macro-structural brain MRI indices.

Conclusions: AA and Hispanic NH patients on dialysis had an apparent survival advantage. The type of health insurance coverage and area-level income were also independent predictors for survival.
Conclusions: In the Health ABC study, higher sodium intake was not associated with a decline in cognitive function over time or with micro- and macro-structural brain MRI indices.

Funding: Other NIH Support - NIA

SA-PO1153
Chronic Hyponatremia and Association with Bone Frailty Associated Falls and Fractures Simran K. Bhandari,1 Annette Adams,1 Bonnie H. Li,1 Shirin Sundar,2 Holly Kraksa,2 Siddhesh Kamat,2 John J. Sim.1 1Dept of Nephrology and Hypertension, Kaiser Permanente Southern California; 2Otsuka Pharmaceuticals.

Background: Chronic hyponatremia is known to cause cognitive impairment and contribute to osteoporosis, both of which may lead to greater risk of serious falls/fractures (FX) among the elderly. We sought to evaluate whether chronic hyponatremia was associated with increased risk for FX based on serial sodium (Na) measurements among a large diverse population.

Methods: A cohort study was performed within Kaiser Permanente Southern California between 1/1/98 – 12/31/14 among individuals ≥ 55 years with ≥ 2 Na measurements and with dual x-ray absorptiometry (DXA) result. Time weighted (TW) and arithmetic mean Na values were used to define chronic hyponatremia as Na < 135 mEq/L. FX were determined from combinations of ICD-9 diagnosis codes, procedure codes, and E codes. Multivariable logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for FX.

Results: 385,778 subjects were identified for the study (68% women and mean age 63). Osteoporosis (DXA T-score < -2.5) was found in 43.7%. Chronic hyponatremia was identified in 12% (n=46,444) and 2.8% were found to have TW Na mean of Na < 135 mEq/L. A total of 49,840 (13%) subjects had a FX. Hyponatremia was present in 24.1% with FX compared to 10.3% without a FX. Individuals who had FX were more likely female and had higher rates of osteoporosis and cardiovascular disease. Compared to Na ≥ 135, chronic hyponatremia was associated with an increased risk of FX (OR 1.41 (1.38, 1.45)). A 5mEq/L increase in TW mean Na was associated with a decreased risk of FX (OR 0.89 (0.84, 0.93)).

Figure 1. Unadjusted and adjusted estimates of the association between hyponatremia and falls/fractures.

Conclusions: Among a large population with DXA measurements, we found chronic hyponatremia was associated with higher risk for having FX. There was a dose dependent protective association with higher TW mean Na values and FX.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceuticals

SA-PO1154
Medicare Advantage Plan Star Rating and Voluntary Disenrollment of Incident Dialysis Patients Qianm Li,1 Amal Trivedi,1 Omar Galarraga,1 Daniel E. Weiner,1 Vincent Mot.1 1Health Services, Policy and Practice, Brown Univ; 2Tufts Medical Center.

Background: There has been limited focus on Medicare Advantage (MA) plan quality ratings and beneficiaries’ decisions to disenroll, particularly among high-cost populations with intensive health care needs. Accordingly, we assessed the association between publicly reported MA plan quality ratings and voluntary disenrollment by incident dialysis patients.

Methods: Data on 50,391 incident dialysis patients were assembled from four national administrative databases spanning 2007 and 2013. We used conditional logistic regression, controlling for patient and plan characteristics, to examine the association between MA plan star ratings at the time of initiating dialysis and disenrollment rates from MA plans to Traditional Medicare.

Results: Disenrollment rates for incident dialysis patients ranged from 8.8% among plans with 5 stars to 22.7% among plans rated with 4 or more stars. Compared to MA plans with star ratings of 4 or above, adjusted disenrollment rates were 3.9% (95% CI 2.4 to 5.5), 5.0% (95% CI 3.5 to 6.5), and 12.1 percentage points (95% CI 10.0 to 14.3) higher among MA plans with star ratings of 3, 2.5 or less, respectively. The disenrollment rate from MA plans to Traditional Medicare among incident dialysis patients was significantly higher than among all MA beneficiaries (14.9% vs 12.0%; p = 0.01). Among MA plans with 2.5 or fewer stars, the adjusted disenrollment rate of incident dialysis patients was about 5.8 percentage points (95% CI 1.4 to 10.1) higher than that of all MA beneficiaries.

Funding: Other NIH Support - R36 AHRQ Dissertation Grant

SA-PO1155
Serum 25-Hydroxyvitamin D Status, Body Composition, and Muscle Strength in Ambulatory Patients on Hemodialysis Dong Ho Yang,1 So-Young Lee.1 1Internal Medicine, CHA Bundang Medical Center, Seongnam, Gyeonggi-do, Republic of Korea; 2Internal Medicine, Seoul Bukbu Geriatric Hospital, Seoul, Republic of Korea.

Background: Sarcopenia and muscle weakness are prevalent in patients with end stage renal disease, and vitamin D has various actions in skeletal muscle. We investigated the relationship between serum 25-hydroxyvitamin D [25(OH)D] status and skeletal muscle mass and muscle strength in ambulatory hemodialysis patients.

Methods: The current study involved 122 ambulatory hemodialysis patients. We evaluated serum 25(OH)D, body composition including skeletal muscle mass as measured by bioimpedance, muscle strength as measured by dynamometer (handgrip strength), and 4-meter walking speed in these participants. Allow muscle mass was defined by the SMM index (SMM: SMM [kg] / height [m2] ≥ 7.0 kg for men, > 5.7 kg for women). Sarcopenia was defined if the patients having a hand grip or walking speed (thresholds defined on the basis of the lowest sex-specific quintiles among general population) were identified as having a low muscle mass.

Results: The participants’ average age was 60.6±1.2 years old, 51.4% were male, 57.4% had diabetes mellitus, and their mean duration of dialysis was 44.7±46.9 months. The mean 25(OH)D serum level was 16.2±0.9 ng/ml. Sarcopenia was identified in 16.4% of the participants. An analysis using the Pearson’s correlation coefficient revealed a positive correlation between serum 25(OH)D levels and skeletal muscle mass (Pearson = 0.455, p < 0.001). Patients having a higher serum 25(OH)D level had a better hand grip strength (Pearson = -0.351, p < 0.001). Binary logistic regression analysis showed that ambulatory hemodialysis patients with above-median serum 25(OH)D levels had significantly more skeletal muscle mass (odd ratio [OR] 1.34, 95% Confidence interval [CI]: 1.20-1.51, p <0.001) and better hand grip strength (OR 1.06, 95% CI: 1.02-1.10, p=0.03).

Conclusions: In this study, serum 25(OH)D level was significantly associated with handgrip strength as well as skeletal muscle mass among ambulatory hemodialysis patients.

SA-PO1156
The Utility and Reliability of a Provider-Based Subjective Health Measure in Older Adults with CKD Stage 4-5 Andrea Javier,1 Rocio Figueroa,1 Huzafiah Salat,1 Cesar Y. Cardona,2 Jennifer Morse,1 Thomas G. Stewart,1 Manisha Jham,1 Edward D. Siew,1 Talat Alp Ikizler,1 Khaled Abdel-Kader,1-2
1Vanderbilt Univ; 2Univ of New Mexico; ‘Meharry Medical College; ‘Univ of Pittsburgh.

Background: Nephrologists report prognostic uncertainty as a key barrier to advance care planning. We hypothesized the surprise question (SQ) would demonstrate acceptable test-retest and inter-rater reliability (until now uncharacterized) and be an effective predictor of mortality in older adults with CKD 4-5.

Methods: We enrolled 388 patients at a nephrology clinic from June 2014 to January 2015. Eligibility criteria were age > 60 years and CKD stage 4-5. Exclusion criteria were ESRD or kidney transplant prior to enrollment or eGFR > 60 within 12 months. Baseline characteristics were obtained from the health record. We collected SQ responses from attendings and fellows in a blinded fashion immediately after each visit.

Results:

<table>
<thead>
<tr>
<th>Total</th>
<th>N=388 (%)</th>
<th>SQ “Y” N=251 (65%)</th>
<th>SQ “N” N=137 (35%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>71 (65-77)</td>
<td>69 (65-74)</td>
<td>74 (68-80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>195 (50)</td>
<td>127 (51)</td>
<td>68 (50)</td>
<td>0.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>321 (83)</td>
<td>209 (84)</td>
<td>112 (82)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>58 (15)</td>
<td>56 (14)</td>
<td>22 (16)</td>
<td></td>
</tr>
<tr>
<td>DM with microvascular daz</td>
<td>196 (51)</td>
<td>117 (47)</td>
<td>79 (58)</td>
<td>0.04</td>
</tr>
<tr>
<td>HTN</td>
<td>381 (98)</td>
<td>247 (98)</td>
<td>134 (98)</td>
<td>0.9</td>
</tr>
<tr>
<td>CAD</td>
<td>151 (39)</td>
<td>86 (34)</td>
<td>65 (47)</td>
<td>0.01</td>
</tr>
<tr>
<td>CHF (reduced EF)</td>
<td>54 (9)</td>
<td>10 (4)</td>
<td>24 (18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>97 (25)</td>
<td>49 (20)</td>
<td>48 (35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebrovascular daz</td>
<td>88 (23)</td>
<td>49 (20)</td>
<td>39 (28)</td>
<td>0.04</td>
</tr>
<tr>
<td>PVD</td>
<td>78 (20)</td>
<td>48 (19)</td>
<td>30 (22)</td>
<td>0.5</td>
</tr>
<tr>
<td>eGFR</td>
<td>23 (16-28)</td>
<td>24 (18-29)</td>
<td>20 (15-25)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author. 903A
in surviving patients were as follows: sCr (mg/dl): 1.02±0.20/1.14±0.91 (not significant [ns]); urea (mg/dl): 43.0±8.12/66.16±57.08 (ns); MDRD (ml/min/1.73m2): 60.21±12.0/63.33±20.0 (ns). No significant differences in changes in RF by groups. Deterioration of sCr (mg/dl) was higher in those with/without proteinuria baseline: 1.25±0.35/2.80±2.68 vs 0.99±0.18/0.93±0.32, P=0.002. Three patients (Group 2) progressed to end-stage renal disease (ESRD), only one is alive at 10 years.

Conclusions: Elderly patients with worse baseline RF, the risk ESRD is attenuated when an excess of mortality is taken into account. Only proteinuria determined worse follow-up of RF. Therefore allow us an optimist message for elderly with low eGFR without proteinuria.

SA-PO1159

One Year Mortality after Dialysis Initiation in a Portuguese Elderly Cohort: Development of a Predictive Mortality Risk Score

Andrea Campos, Josefina Lascasas, Jorge Malheiro, Sofia Correia, Sofia Santos, António Cabrita. CHP, Nephrology Dept.

Background: In the last years, Portuguese elderly (≤65 years old) population has grown significantly. Because early mortality after dialysis (D) initiation is common, we aimed to analyze 1y mortality in elderly starting D and to establish a predictive risk scoring model (SM).

Methods: We selected a cohort of 208 patients (P) who initiated D between 2012-2015. A scoring system was constructed in which points (Ps) were assigned to each risk factor by using the b-coefficient (B) from the final Cox regression. A risk score was made by adding points for each risk factor (RF). We compared SM with others previously described.

Results: The overall 1y mortality was 20.2%. In a univariate analysis of demographics, clinical and social variables, the significant predictors of mortality were: nephrology follow-up (1y) (P=0.001), age (P=0.001), ischemic nephropathy, congestive heart failure (CHF), hemiplegia, past malignancy history (M), chronic lung disease, lower albumin level (A), need of urgent D and beginning by catheter. These variables were included in a multivariate analysis: independent predictors of mortality were identified and points were assigned to each RF for the SM.

Conclusions: This simple prediction tool based on readily available clinical and laboratory data can assist in predicting short-term prognosis among elderly patients starting D. It may be useful in counseling patients and guiding clinical decision making.

SA-PO1157

The Pattern of Renal Histopathology in Elderly Korean with Renal Diseases: A 12-Year Review of a Single-Centre Renal Biopsy Database

Yong Un Kang, Ha Yeon Kim, Chang Seong Bae, Seong Kwon Ma, Soo Wan Kim. Chonnam National Univ Medical School.

Background: Studies on biopsy-proven renal disease in the elderly are extremely limited in Korea. This study aimed to investigate the spectrum of renal histopathology and their clinical manifestations in elderly patients undergoing renal biopsy.

Methods: All native renal biopsies (n=99) performed in patients aged ≥65 years from January 2004 to December 2015 were retrospectively analyzed. The results were compared with a control group of 1,045 patients aged <65 years receiving renal biopsy during the same period.

Results: The number of the elderly was 99 patients with an age of 69.78±4.11 (range 65-81) years at the time of biopsy (men, 55 patients; women, 44 patients). The most common indication for renal biopsy was nephrotic syndrome (NS) (44.5%), followed by acute kidney injury (AKI) and NS (16.2%) and AKI (14.1%). Idiopathic membranous nephropathy (IMN, 16.2%) was the most frequent diagnosis, followed by minimal change disease (14.1%), diabetic nephropathy (DN, 12.1%), focal sclerosing glomerulonephritis (6.1%), IgA nephropathy (IgAN, 6.1%), lupus nephritis (LN, 6.1%) and vasculitis (5.1%) and amyloidosis (4%). In patients with NS and AKI, IMN (25.0%) and vasculitis (20.0%) was the leading cause. Comparison with the control group showed IMN (P=0.004), DN (P=0.005), vasculitis (P=0.001) and amyloidosis (P=0.001) to be more frequent and IgAN was the leading cause. Comparison with the control group showed iMN (P=0.004), DN (P=0.001), focal sclerosing glomerulonephritis (6.1%), IgA nephropathy (IgAN, 6.1%), lupus nephritis (LN, 6.1%) and vasculitis (5.1%) and amyloidosis (4%). In patients with NS and AKI, IMN (25.0%) and vasculitis (20.0%) was the leading cause. Comparison with the control group showed IMN (P=0.004), DN (P=0.005), vasculitis (P=0.001) and amyloidosis (P=0.001) to be more frequent and IgAN was the leading cause.

Conclusions: These data indicate that their clinical manifestations and histopathology differ between elderly and non-elderly Korean with renal diseases. Our data are an important contribution to the epidemiology of renal disease in elderly Korean.

Funding: NIDDK Support, Private Foundation Support

SA-PO1158

10 Years Follow-Up of Renal Function in Elderly with Chronic Kidney Disease

Manuel M. Heras,1 María Teresa Guerrero,2 María Jose Fernandez Reyes,1 Angelica Muñoz,2 Álvaro Molina,1 María Astrid Rodriguez Gomez,1 Ramiro Callejas,1 Leonardo Calle,1 Carmen Rita Martin Varas.1 Nephrology, General Hospital Segovia, Segovia, Spain; 2Geriatrics, General Hospital Segovia, Segovia, Spain.

Background: Chronic Kidney Disease (CKD) is a global public health problem. Prevalence of low estimated glomerular filtration (eGFR) increases with age. We followed-up for 10 years the renal function (RF) of elderly with CKD.

Methods: 80 clinically stable patients, with an median age of 83 years; women: 68.8%; diabetics: 35%; dialytic recruited in the Departments of Geriatric and Nephrology, within January-April 2006, were followed-up for 10 years. We separated them in two groups based in their serum creatinine (sCr) baseline: Group 1: 38 patients with sCr<1.1 mg/dl (range 0.7-1.1); and Group 2: 42 patients with sCr>1.1 mg/dl (range 1.2-3.0). We measured creatinine, urea in serum; and estimated GFR baseline and 10 years, using abbreviated MDRD. Statistical comparisons using repeated measures, SPSS 15.0 program.

Results: After 10 years of follow-up, 61 patients died (Group 1=23, Group 2=38, P=0.003) and 19 patients (including 2 males) with a mean age of 86.47±16 years (range: 79-97) remained in the study. Overall data regarding changes in RF (baseline/10 years)
Detected the Minimum Recommendation of Physical Activity Level in Hemodialysis Patients: A 7-Year Retrospective Cohort Study

Ryota Matsuzawa, Takahiro Shimoda, Noritaka Mamorita, Kei Yoneki, Manae Harada, Takaaki Watanabe, Mika Matsumoto, Atsushi Yoshida, Yasuo Takeuchi, Atsuhiro Matsunaga, Kitasato Univ Hospital, Sagamihara, Japan; Kitasato Univ, Sagamihara, Japan; Sagami Circulatory Organ Clinic, Sagamihara, Japan.

Background: Sedentary lifestyle is a well-known indicator of poor prognosis in hemodialysis patients. However, because the minimum recommendations for physical activity level are unknown in these patients, we retrospectively investigated the association between physical activity level and mortality risk.

Methods: A total of 282 outpatients (age, 64.8 ± 10.6 years; hemodialysis duration, 7.0 ± 7.8 years) who required hemodialysis 3 times a week were followed up for up to 7 years. Physical activity levels and patient characteristics, including age, sex, body mass index, hemodialysis duration, comorbid conditions, and nutritional status, were obtained at baseline. Physical activity was objectively evaluated using an accelerometer as the number of steps taken on a non-dialysis day based on the data of 4 consecutive non-dialysis days. A Cox proportional hazard regression model with smoothed plot for hazard ratios of all-cause mortality according to physical activity levels was used to detect the minimum recommendation.

Results: Fifty-six patients died during follow-up. In a Cox proportional hazard regression model adjusted for patient characteristics, the hazard ratio in the group with lower physical activity level was 2.18 (95% confidence interval = 1.16 - 4.09) compared with that in the group with higher level. Based on the smoothed plot for hazard ratios, we detected 2500 steps per non-dialysis day as a cut-off point of physical activity for poor prognosis (Fig. 1).

Conclusions: Lower physical activity level is associated with higher mortality risk. We recommend that hemodialysis patients take at least 2500 steps per non-dialysis day to avoid the worst possible outcome.

Effects of Resveratrol on Renin-Angiotensin System in the Aging Kidney

In-Ae Jang, Eun Nim Kim, Tae Hyun Ban, Hye Eun Yoon, Cheol Whee Park, Bumsoon Choi. Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Korea.

Background: The renin-angiotensin system, especially angiotensin II (ANGII) / angiotensin II type 1 receptors (AT1R) axis plays an important role in aging process of kidney through progressively increased oxidative stress. In the present study, we aimed to evaluate the effect of resveratrol, a naturally found polyphenol with antioxidant activities, in modulation of renin-angiotensin system in aging kidney of mice and to identify the putative underlying signaling pathways.

Methods: 18-month-old male C57BL/6 mice were divided into two groups and received either normal mice chow or underwent resveratrol treatment for 6 months. Intrarenal expression of renin-angiotensin system molecules, as well as pro- and antioxidant enzymes were measured, and mice kidney was isolated for histological analysis.

Results: Resveratrol-treated group showed significant improvement in renal function; serum creatinine decreased (0.25 ± 0.05 mg/dL vs. 0.67 ± 0.34 mg/dL; p < 0.03 vs. control group), creatinine clearance increased (0.28 ± 0.07 ml/min vs. 0.10 ± 0.04 ml/min; p < 0.001) and albuminuria decreased (29.47 ± 14.32 mg/24hr vs. 67.69 ± 22.79 mg/24hr; p < 0.03) compared with control group. There were decreases in mesangial volume and tubulointerstitial fibrosis in resveratrol-treated mice. The expressions of ANGII, ACE and AT1R significantly decreased in resveratrol group, whereas those of ACE2, AT2R and MasR increased. Resveratrol increased the expression of phosphorylated eNOS and SOD2 significantly while the expressions of Nox4, fibronectin and collagen IV decreased. Immunohistochemistry revealed that 8-OHdG-positive area and 3-nitrotyrosin-positive area decreased in resveratrol group.

Conclusions: Resveratrol exerts renoprotective effects on aging kidney, associated with reduction of oxidative stress and inflammation through AT2R and MasR activation.

Funding: Government Support - Non-U.S.
EFFECTS OF HIGH DIETARY SODIUM ON RENAL TISSUE CONTENT, RENAL HEPARAN SULFATE PROTEOGLYCANS AND TUBULO-INTERSTITIAL REMODELING

Byung Chul Young, Jianyong Jia

Nephrology, Univ Medical Center Groningen, Groningen, Netherlands.

Background: High sodium intake is associated with hypertension and renal damage. Studies suggest that sodium-induced blood pressure-independent pathways can also cause renal damage. Heparan sulfate proteoglycans act as co-receptors for growth factors and chemokines and orchestrate tubulo-interstitial (TI) remodeling. Our aim is to investigate blood pressure-independent effects of high sodium intake on TI remodeling associated with structure and function of renal proteoglycans.

Methods: Wistar rats (N=5/group) received a normal chow diet for 4 weeks (C) or 8% NaCl diet (High Salt: HS) for 2 or 4 weeks. Blood pressure (BP) was monitored, and plasma, urine and tissue collected. Cortex homogenates were dissolved in nitric acid and sodium was measured by flame spectrophotometry (expressed by dry weight or content). Staining were done for podoplanin (D2-40), lymphocytes, α-SMA, myofibroblasts, collagen III, CD3, T-cells, ED1, macrophages (Mφ), heparan sulfate domains JM403, 10E4 and functional domains for MCP-1 and L-selectin binding. Statistical differences and correlations were tested by Kruskall Wallis and Spearman Rank correlation.

Results: HS rats showed a BP increase of ~10-15mmHg at week 1 (p<0.05), which returned to C values later on. At week 4 cortical sodium increased ~0.1 mmol/mg in HS rats vs. week 2 (p<0.05), accompanied by partial loss of JM403 and 10E4, and increased MCP-1 and L-selectin binding to heparan sulfate. HS rats showed renal lymphangiogenesis, inflammation and proliferative changes (all p<0.05 vs C). Cortical sodium correlated with L-selectin binding (r=0.606, p=0.007) and T-cells infiltration (r=0.554, p=0.03). Reduced (period-)glomerular 10E4 and JM403 correlated with increase of myofibroblasts (r=-0.579, p<0.02) and Mφ (r=-0.644, p<0.01). Reduced JM403 correlated with increased lymphangiogenesis (r=-0.549, p=0.03) and L-selectin binding (r=-0.595, p<0.02).

Conclusions: The high sodium diet changes heparan sulfate structure and contributes to pro-fibrotic and pro-inflammatory tissue responses. Whether this is BP-independent is not clear yet.
oxidative stress and apoptosis levels. Plasma Antithrombin (ATIII) activities were also measured. For in vitro studies, HK2 cells were exposed to lovastatin or H2O2, respectively, and the cyto-protective effects of sulodexide were also determined.

Results: Compared to untreated CIN group, improved renal function, reduced tubular injury, decreased levels of oxidative stress and apoptosis were observed in CIN rats receiving sulodexide injection. In addition, our results also showed that ATIII activity was significantly higher in sulodexide-administered group than that in vehicle-injection CIN rats. Our in vitro experiments demonstrated that sulodexide pretreatment protected HK2 cells against the cytotoxicity of H2O2 via inducing caspase-3 activity, and preincubation with sulodexide could also attenuate H2O2-induced increases in ROS, apoptosis and caspase-3 levels.

Conclusions: Sulodexide could protect against CIN through activating ATIII, and inhibiting stress and apoptosis. Funding: Government Support - Non-U.S.

PUB008
Sulodexide Protect against Renal Ischemia-Reperfusion Injury by Activation of Antithrombin III
Feng Wang, Jiangyong Yin, Zeyuan Lu, Nian-Song Wang. Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People’s Hospital, Shanghai, China.

Background: Sulodexide is a potent atithrombin agent, however, its effect on renal ischemia-reperfusion injury (IRI) is unknown. In present study, we assessed the therapeutic effects of sulodexide for renal IRI and tried to investigate the potential mechanism.

Methods: One dose of sulodexide were injected intravenously in rats immediately after unilateral kidney ischemia for 45 min. The animals were sacrificed at 3h and 24h respectively. Renal function and tubular injury were assessed. TUNEL staining and caspase-3 expression were utilized to assess cell apoptosis. SOD concentration and Antithrombin III (ATIII) activity were also assayed. For in vitro study, hypoxia injury model for HK2 cells were carried out. Apoptosis and ROS level were evaluated after sulodexide pretreatment.

Results: Sulodexide pretreatment improved renal functional and alleviated tubular pathological injury at 24h after reperfusion. Meanwhile, the levels of oxidative stress and cell apoptosis were also remarkably reduced by sulodexide administration. In addition, our results also showed that ATIII activity was activated at 3h after reperfusion, which preceded alleviation of renal injury. It was also observed that sulodexide pretreatment could reduce apoptosis and ROS level in HK2 cells under hypoxia injury.

Conclusions: Injection intravenously of sulodexide could protect against renal IRI. The therapeutic effects might be attributed to its activation of AT-III.

Funding: Government Support - Non-U.S.

PUB009
MicroRNA-375 Is Induced via p53 and NF-κB to Repress Hnf-1β in Cisplatin Nephrotoxicity
Ji Liu, Hui Huang, Liang Liu, Qiming Wei, Shuqin Mei, Lin Lu, Changlin Mei, Zheng Dong. 1Nephrology, Shanghai Changzheng Hospital, Shanghai, China; 2Cellular Biology and Anatomy, Augusta Univ, Augusta, GA; 3Hunan Univ, Kaifeng, Henan, China.

Background: Nephrotoxicity is a major limiting factor for cisplatin-mediated chemotherapy in cancer patients. The pathogenesis of cisplatin-induced nephrotoxicity remains largely unclear and effective kidney protective approaches are currently lacking.

Methods: We tested the PT-Dicer-/- mouse model where Dicer (a key enzyme for microRNA production) was specifically ablated from kidney proximal tubule cells resulting in the depletion of the majority of microRNAs. To identify the specific microRNAs involved in cisplatin nephrotoxicity, we profiled microRNA expression changes by microarray analysis.

Results: We show that cisplatin nephrotoxicity was not affected by overall depletion of microRNAs from kidney proximal tubular cells in different Dicer-knockout mice. mir-375 was identified by microarray and further verified in cisplatin-treated renal tubular cells. Inhibition of mir-375 led to a significant decrease of tubular cell apoptosis during cisplatin treatment, suggesting that mir-375 is injurious or pro-apoptotic. Blockade of p53 or NF-κB decreased the attenuation of mir-375 induction during cisplatin treatment, supporting the involvement of p53 and NF-κB in mir-375. At the downstream of mir-375, hepatocyte nuclear factor 1 homeobox B (Hnf-1β) was identified as a key target of this microRNA.

Conclusions: Together, these results suggest that upon cisplatin exposure, p53 and NF-κB may work collaboratively to induce mir-375, which represses the cytoprotective gene Hnf-1β, resulting in renal tubular cell apoptosis.

PUB010
Correlation between Atherosclerosis and Markers of Kidney Injury in Brazilian Afrodescendentes
Natalino Salgado Filho, Dyego José Araujo Brito, Joyce S. Lages, Gyl Barros-Silva, Bernardete Jorge Leal Salgado, Elton Jonh Freitas Santos, Alcione Santos. Federal Univ of Maranhão.

Background: Atherosclerotic lesions are highly prevalent among afrodescendentes leading to increased morbidity and mortality from cardiovascular events. Thus, the aim of this study was to investigate the association between atherosclerosis and markers of kidney injury in hypertensive afrodescendentes from quilombo remnant communities in northern of Maranhão State/Brazil.

Methods: Cross-sectional study that assessed hypertensive afrodescendentes from PREVITAL different imaging methods for diagnosis of atherosclerosis disease: 1- Carotid doppler ultrasonography (doppler US) to assess the intima-media thickness (cIMT) and/or 2- Coronary computed tomography for determination calcium score (CCS). The markers of kidney injury evaluated were: 1- estimated glomerular filtration rate (eGFR) and 2- urinary albumin excretion (ACE). Informed consent was obtained from PR.118, laboratory and imaging data were collected in PREVITAL study database. To evaluate factors associated with the occurrence of coronary and carotid atherosclerosis was adjusted Poisson model with robust variance.

Results: Two hundred-six patients (mean age 61.32±12.44 years and 61.65% women) underwent carotid doppler US and 155 patients (mean age 61.42±12.42 years and 62.58% women) underwent coronary CT were included in the study. cIMT presented high in 59.22% individuals evaluated and 41.94% of patients had CCS < 0. In the multivariate regression model, age ≥ 60 years (PR 1.23, p-value = 0.001), ACR > 30mg/g (PR 1.18, p-value = 0.045) were independently associated with carotid atherosclerosis. The model for coronary calcification were associated with CCS: male gender (PR 1.53, p-value = 0.010), age ≥ 60 years (PR 1.78, p-value = 0.001), use of ASS (PR 1.67, p-value = 0.018) and smoking (PR 1.51, p-value = 0.011). The occurrence of atherosclerotic lesions was high in this group. Markers of kidney injury were associated only with carotid lesions, whereas traditional factors for atherosclerotic disease were associated with coronary lesions.

PUB011
Ischemic Postconditioning Inhibits Ischemia-Induced AKI-to-CKD Progression via Akt/GSK3β Pathway
Jia Shen, Hao Deng, Yan Jiang, Hongfeng Huang, Jianghua Chen. 1Kidney Disease Center, The First Affiliated Hospital Zhejiang Univ, Hangzhou, Zhejiang, China; 2Kidney Disease Immunology Laboratory, The Third Grade Laboratory, State Administration of Traditional Chinese Medicine of the People’s Republic of China, China; 3Key Laboratory of Zhejiang Province, China.

Background: Ischemia-reperfusion (IR) injury, a relevant factor of acute kidney injury (AKI), will induce renal fibrosis, and thus chronic kidney disease (CKD). Postconditioning can minimize the effect of IRI, while its function and related mechanism in the transition of AKI to CKD remains unknown. It has been reported previously that type II epithelial-to-mesenchymal transition (EMT) in tubular epithelial cells plays a vital role in the pathogenesis of renal fibrosis. This study aims to investigate the underlying molecular mechanism.

Methods: We established a single renal IR model in C57BL/6 mice. All mice with IR injury were divided into 2 groups, which are with IRI group and without (PC group) additional ischemic interruption reperfusion before permanent perfusion. Renal function, fibrosis and EMT-related makers were detected and measured. A protein array was used to evaluate the expression and activation levels of signal node proteins in kidneys.

Results: PC group was associated with reduced BUN of 5.40 ± 5.7 mg/dl and Cr of 0.420 ± 0.035 mg/dl(p>0.05) as well as amelioration in acute tubular necrosis from 2 weeks to 8 weeks compared with I/R group. Immunohistochemistry and western blotting at both 4 weeks and 8 weeks indicated lower expressions of Snail and EMT-related protein markers (α-SMA, fibronectin and S1004A) in PC group. The protein chip showed down regulation of phosphorylation levels of Akt (Ser473), Akt (Thr308), and GSK3β (Ser9), and verified by in vivo Immunohistochemistry and western blotting.

Conclusions: Postconditioning suppressed the EMT of tubular epithelial cells caused by IRI, and it related with a down regulation of Akt/GSK3β signal pathway, and this may be a therapeutic procedure to kidney IR injury and reduce the pathological progression of AKI to CKD.

Funding: Government Support - Non-U.S.

PUB012
A New, Human In Vitro Model for Renal Ischemia Reperfusion Injury

Background: During transplantation long-lasting damage is done to the graft by ischemia reperfusion injury (IRI), which to a large extent are not well characterized until today. Therefore, good models are needed to further investigate diagnostic and therapeutic options for IRI. Mouse models allow complex investigations, but results often cannot be transferred directly to humans. Therefore, we investigated an new evidant of the Krebs cycle and the accumulation of intracellular succinate in the formation of IRI. Therefore, our goal was to establish a new IRI model incorporating new pathological insights in a human cell culture system.

Methods: HK-2 cells were treated with different substances to mimic IRI. Therefore, besides from hydrogen peroxide (H2O2) we used the inhibitors of the respiratory chain Antimycin A and Oligomycin as well as the citric cycle metabolites succinate and malonate. Subsequently, the cell toxicity was assessed by the established LDH release assay and the results were additionally validated using the AO/PI assay. All experiments were repeated at least twice and results were examined for statistical significance using two-sided student’s t-tests.

Results: All substances were able to induce cell death. Because IRI in vivo leads to massive cell death within a short period of time, we concentrated especially on those substances that were able to induce significant cell death in less than two hours. While H2O2 led to massive cell death within a short period of time, we considered especially on those substances that were able to induce significant cell death in less than two hours. While H2O2 doesn’t cause any significant cell death at that point time, the combination of Antimycin A and succinate showed to be very effective (more than 60% cell death) and started to kill cells already after 30 minutes of incubation. Interestingly, Antimycin A and succinate
elicited cell death also in a dose-dependent manner. Cell death in our model involves reversed electron flow in the respiratory chain, since the effect could be completely suppressed by complex II inhibition using malonate.

Conclusions: Significant cell death in human tubular epithelial cells can be induced by IRI typical reversal of electron flow in the respiratory chain. Therefore the combination of Antimycin A and succinate appears to be an appropriate model for renal IRI.

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

PUB013
The Role of Glycophingolipids in Cisplatin-Induced Acute Kidney Injury
Tess Dupre,1 Mark A. Doll,1 Parag P. Shah,2 Cierra Sharp,1 Deanna L. Siow,1 Jadit Megyesi,1 James A. Shayman,4 Levi J. Beverly,4 Leah J. Siskind.1 1Pharmacology/Toxicology, Univ of Louisville; 2Medicine, Univ of Louisville; 3Internal Medicine, Univ of Arkansas for Medical Sciences; 4Medicine, Univ of Michigan.

Background: Acute kidney injury (AKI), resulting from chemotherapeutic agents such as cisplatin, remains an obstacle in the treatment of cancer. Cisplatin-induced AKI involves apoptotic and necrotic cell death, pathways regulated by sphingolipids such as ceramide. Data indicate that C57BL/6J mice treated with cisplatin had elevated ceramide synthase and acid sphingomyelinase activities as well as increased ceramide levels in the renal cortex 72 h following cisplatin treatment. We hypothesized that inhibition of ceramide synthesis would protect mice from cisplatin-induced AKI. Pre-treatment of mice with inhibitors of acid sphingomyelinase and de novo ceramide synthesis (amitriptyline and myriocin, respectively) protected from cisplatin-induced AKI. Data indicate that ceramides are also metabolized into glucosylceramides (GluCers) in the renal cortex following cisplatin treatment. GluCers play a role in kidney aging, diabetic nephropathy, and lupus nephritis. Thus, the development of inhibitors of ceramide and/or its metabolism to GluCers plays a causative role in cisplatin-induced AKI.

Methods: To determine which lipid species is contributing to kidney injury, we treated mice with a potent and highly specific inhibitor of glucosylceramide synthase, the enzyme responsible for catalyzing the glycosylation of ceramide to form GluCers.

Results: Inhibition of glucosylceramide synthase exacerbated cisplatin-induced AKI according to markers of kidney injury, inflammation, cell stress, apoptosis, and mitochondrial homeostasis.

Conclusions: Taken together, data suggest that ceramides play a role in kidney injury in response to cisplatin, whereas the metabolism of ceramides to GluCers is renoprotective.

Funding: NIDDK Support

PUB014
Repeated, Low-Dose Administration of Cisplatin Leads to Long-Term, Irreversible Fibrosis
Cierra Sharp,1 Mark A. Doll,1 Deanna L. Siow,1 Tess Dupre,1 Levi J. Beverly,2,3,4 Leah J. Siskind.1 1Pharmacology/Toxicology, Univ of Louisville, Louisville, KY; 2Dept of Medicine, Univ of Louisville, Louisville, KY; 3James Graham Brown Cancer Center, Louisville, KY.

Background: Cisplatin is a potent chemotherapeutic used in the treatment of many solid tumor cancers. The dose-limiting toxicity of cisplatin is nephrotoxicity, which can lead to acute kidney injury (AKI). Thirty percent of patients treated with a cisplatin will develop AKI. The progressive nature of fibrosis is an increased likelihood of developing chronic kidney disease (CKD). CKD in itself is a progressive, irreversible disease characterized by a permanent loss of kidney function that often culminates in fibrosis. Currently, there are no therapeutic interventions to stop the progression of AKI to CKD. One potential reason for this is that there are no animal models that can be used to study the transition from AKI to CKD. In the standard model of AKI, mice receive a high dose of cisplatin (15-30 mg/kg) that leads to morbidity and death within 5-10 days. Thus, long-term studies are not feasible. We have previously developed a repeated, low-dose cisplatin regimen that allows for long-term studies of kidney function. With this model we found that repeated, low dosing of cisplatin induces fibrosis after 24 days.

Methods: To determine whether the fibrosis induced by this model is irreversible and progressive, we treated 8 week old FVB mice with our repeated dosing regimen and followed treatment with a 6 month age-out.

Results: We found that fibrosis was still present after this 6 month period as evidenced by increased Psa-1 mRNA expression levels, positive staining for α-SMA indicative of myofibroblasts, and elevated levels of overall collagen deposition. Furthermore, BUN remained elevated when compared to baseline levels even though injury as measured by NGAL was no longer detectable.

Conclusions: These data indicate that fibrosis is a permanent pathological outcome following repeated injury from low-dose cisplatin, suggesting that targeting mediators of the fibrotic pathway might be beneficial for the development of therapeutic agents to prevent cisplatin-induced AKI to CKD progression.

Funding: NIDDK Support

PUB015
Sec Inhibition Protects against Ischemic Acute Kidney Injury in Mice
Chongxiang Xiong,1 Xiaozhu Zhou, Monica V. Masucci, Shouang Zhang. Dept of Medicine, Rhode Island Hospital, Brown Univ, Providence, RI.

Background: Activation of Sec has been associated with the development of renal fibrosis and diabetic nephropathy. However, its role in acute kidney injury (AKI) is still poorly understood.

Methods: In this study, we examined the effects of Sec inhibition in a murine model of ischemia-reperfusion (IR)-induced AKI using PPI, a highly selective inhibitor of Sec family kinases.

Results: At 48 h after I/R, mice developed renal dysfunction and renal tubular damage, which was accompanied by elevated expression and phosphorylation of Sec. Administration of Sec was completely protected against renal dysfunction and attenuated kidney damage. The protective actions of PPI were associated with inhibition of renal tubule injury and cell death and suppression of I/R expression of multiple proteins involved in the assembly of cell-cell adhesion and tight junction such as E-cadherin, ZO-1, claudin-1, and Occludin. Similarly, PPI treatment inhibited expression of these proteins in vitro cultured renal tubular cells following oxidant injury. Moreover, UR injury led to an increase in phosphorylation (activation) of STAT3 and NF-kappa B in the kidney; treatment with PPI diminished this response.

Conclusions: Collectively, these results indicate that Sec inhibition is effective against renal tubule injury through maintaining epithelial cellular attachment and integrin/glycoprotein suppressing proinflammatory responses after UR injury. Thus targeting Sec may be a promising therapeutic strategy for treatment of AKI.

Funding: NIDDK Support

PUB016
Contribution of DNases to Kidney Cell Death After Acute Injury In Vitro or In Vivo
Dae Song Jang,1 Todd Fite,1 Dolapo Taiwo Odemuyi,1 Alena Savenka,1 Alexei G. Basnakian.2 1Dept of Pharmacology and Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR; 2Central Arkansas Veterans Healthcare System, Little Rock, AR.

Background: Our previous studies showed that genetic inactivation of two kidney endonucleases, DNase I and EndoG, was protective against renal tubular epithelial cell death by cisplatin. Recent discovery of endonuclease inhibitors provides a unique opportunity to determine the contribution of individual endonuclease to kidney cell death.

Methods: This study was aimed to determine if the two new endonuclease inhibitors recently identified by us, IG-17 for DNase I and PNK-3-82 for EndoG, could ameliorate cinchonotoxin toxicity to kidney tubular epithelial cells in vitro and in vivo.

Results: In vitro experiments using NRK-52E cells showed that the compounds are able to suppress endonuclease activity inside the cells, provide partial protection against cinchonotoxin toxicity measured using LDH release assay and TUNEL. In vivo experiments were done in mice, which received cisplatin (20 mg/kg, IP) after SC injections of the inhibitors (5 mg/kg). Kidney failure was measured by serum creatinine and BUN. Structural kidney damage was assessed by acellular tubular necrosis. The results from both in vitro and in vivo experiments showed that TUNEL was inhibited the most, followed by structural protection, and followed by kidney cell death (in vivo).

Conclusions: These observations suggest that enzymatic DNA fragmentation only partially is responsible for mechanism leading to cell death or spreading of cell death (necrosis). The other part of endonuclease activity, may, in fact, act in an opposite direction by protecting against kidney cell death.

Funding: NIDDK Support, Other U.S. Government Support, VA Support

PUB017
Intra-Arterial Continuous Infusion Is Less Harmful Than Bolus Infusion of Contrast Dye in CI-AKI Rodent Model showing Hyperacute Rise in Serum NGAL and L-FABP
Tsung-Chun Lee,1,2 Chih-Kang Chiang,1,2 Dept. of Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan; 1Dept of Physiology, National Taiwan Univ, College of Medicine, Taipei, Taiwan; 2Graduate Inst of Toxicology, National Taiwan Univ, College of Medicine, Taiwan, Taiwan.

Background: Contrast induced acute kidney injury (CI-AKI) is the second common cause of in-hospital AKI, leads to higher morbidity and mortality. Despite in vitro studies revealed dose proportional toxicity of contrast will, there is yet no data on whether the method of contrast medium administration will alter the risk of CI-AKI. In this preliminary study, we aimed to prove that continuous intra-arterial infusion of contrast media would cause less CI-AKI than bolus infusion, even under the same amount.

Methods: Female SD rats were sedated with urethane and catheterized at left carotid artery. Urografin, high osmolality contrast media, was given intra-arterially via the carotid artery catheter for the same total amount (20ml/kg, LD50 dose). Bolus group received four boluses within 20 minutes, and continuous group received continuous infusion for 20 minutes. Serum and urine samples were taken at baseline and at 5 hours after completion of infusion. After 5 hours, rats were sacrificed, and we further examine survival rates, and measured kidney tissue, serum and urine creatinine and AKI biomarkers (NGAL, KIM-1, L-FABP, Cystatin C) by ELISA.

Results: Bolus group had higher mortality (3/10 rats vs. 1/12 rats), and higher CI-AKI rate (9/10 rats vs. 8/12 rats) than continuous group at 5 hours. There is a trend of higher serum creatinine in bolus group (0.69 +/- 0.32 mg/dL) than in continuous group (0.46 +/- 0.23 mg/dL). Notably, there is an early rise of serum NGAL and L-FABP in bolus group (serum NGAL: baseline ratio: 25.75 vs. 3.62, p=0.017, serum L-FABP: baseline ratio: 55.52 vs. 3.09, p=0.012). Histological examinations demonstrated tubular vacuolization in both bolus and continuous groups, implying cellular stress to contrast toxicity.

Conclusions: Our preliminary data suggested a novel method to ameliorate CI-AKI by continuous infusion to kidneys, in association with a less hyperacute rise in serum AKI biomarkers of NGAL and L-FABP.
Mild Intracellular Acidification by Dexamethasone Attenuates Mitochondrial Dysfunction in a Human Inflammatory Proximal Tubule Epithelial Cell Model

Methods: Mitochondria are assumed to be important targets to improve renal function after acute kidney injury (AKI) and glucocorticoids may exert beneficial effects on these organelles. Here, we investigated the effect of dexamethasone in an experimental inflammatory renal cell model to unravel its mitochondrial target.

Background: Mitochondria are considered to be important targets to improve renal function after acute kidney injury (AKI) and glucocorticoids may exert beneficial effects on these organelles. Here, we investigated the effect of dexamethasone in an experimental inflammatory renal cell model to unravel its mitochondrial target.

Methods: Matured conditionally immortalized proximal tubule epithelial cells (ciPTMC) were treated with the endotoxin lipopolysaccharide (LPS, 10 μg/ml) for 24 hours, with or without dexamethasone (10 μM). ATP, mitochondrial oxygen consumption, and intracellular pH were measured using a Seahorse XF24 analyzer. A panel of mitochondrial parameters and intracellular pH was investigated in the presence or absence of dexamethasone.

Results: LPS treatment of cells led to increased generation of reactive oxygen species (ROS) (20±12% in control vs. 34±7% in LPS, p<0.05), which was attenuated by dexamethasone. In addition, the membrane potential was reduced in LPS challenged cells (85 ± 4 % of control, p< 0.05), which was counteracted by dexamethasone (124 ± 5 %; p< 0.001). The mitochondrial oxygen consumption was decreased in LPS treated cells (17.6 ± 7.5 vs. 55.5 ± 4.7 pmol/s×10^6 cells in control; p<0.001) and again this was improved towards control levels upon dexamethasone co-treatment (43.1 ± 7.5 pmol/s×10^6 cells). Finally, we demonstrated that dexamethasone acidified the intracellular milieu (87 ± 2 % of control; p< 0.05) and reversed the LPS-induced alkalization.

Conclusions: Dexamethasone restored mitochondrial function under inflammatory conditions by decreasing cellular pH. This supports the hypothesis that mitochondria are key modulators in renal inflammation and interesting targets for the treatment of septic-AKI.

Funding: Private Foundation Support

PUB019

Human Peripheral Blood Mononuclear Cells Incubated by Quality and Quantity-Control Culture System Dramatically Improve Ischemia/Reperfusion Acute Kidney Injury in Mice

Methods: IR was induced in male NOD/SCID mice. Human peripheral blood MNCs were incubated for 1 week in QWQ culture media. A hundred μl saline containing 10^9 human post-QQc MNCs was infused via tail vein at 24 hours after IR induction (post-QQc group). 10^9 human pre-QQc MNCs (group of direct MNCs injection without QQ culture pre-QQc group) and vehicle control group (vehicle: 100 μl saline) were used as the controls. A HE and PAS staining assay was used to assess the structural damages of kidneys in different groups.

Results: Our data showed that ischemic injury induced damages to kidney tubules and nephrocytes, and in HI-1 treated group, AKI caused less damage obviously. HI-1 also inhibited AKI induced cell apoptosis, and retained cell proliferation in kidney tissues. We also found the downstream factors ETOR, VEGF, PDH3 was also regulated by HI-1 in response to AKI damage. Finally, it was observed that HI-1 also increased the percentage of adult resident progenitor cells (ARC), which was found very low in AKI rats. The survival of ARC isolated from AKI rat was also increased by HI-1 of.

Conclusions: HI-1 plays a protective role in ischemic AKI model, which was related with the protection of ARPC, indicating a novel potential therapy for AKI.

Funding: National Natural Science Foundation of China, the Key Project of Shanghai Science and Technology Commission.

PUB022

Effect of Adipose-Derived Stem Cells Incubated with Astragaloside IV on the Model of Acute Renal Injury in Mice

Background: The outcome of acute renal failure is poorer in clinical practice compared with experimental models. The mechanisms underlying this discrepancy are not clear. Paracrine effects of bone marrow-derived mesenchymal stem cells (hADSCs) have been studied for the treatment of ischemia/reperfusion injury. The study evaluated the protective effects of hADSCs and Astragaloside IV (Ast) on kidney injury in a mouse model.

Methods: We used P3-P5 cells labeled with PKH26, and observed cell morphology under light microscope and fluorescence microscope. Cellular proliferation was determined by Cell-Counting Kit-8 (CCK8). The experimental model was established 24hrs later, hADSC or Ast-hADSC suspension containing 1105 were injected into tail vein. The AKI mice were injected with 100μl normal saline as the controls. All the mice were sacrificed, the kidneys were dyed by HE and TUNEL. The protein level of Caspase-3, Bax, and Bax in renal tissues was detected by Western blot.

Results: In hADSC and Ast-hADSC group, the level of TNF, IL-6, RANTES in renal tissue homogenates were significantly lower than those in model group. The hADSC and Ast-hADSC deposition in renal tissue homogenate was detected by ELISA. The hADSC and Ast- hADSC desposition in kidney was observed by fluorescence histochemistry.

Conclusions: Absorbance values of cultured cells were significantly increased at different time points but absorbance values was the most obvious change at 72hrs. Renal tubular structure was impaired in AKI group after cisplatin administration, the HE staining tubular necrosis count were lower in hADSC and Ast-hADSC group than those in model group. The levels of TNF, IL-6,RANTES in AKI group's renal tissue homogenate were increased significantly, while hADSC and Ast-hADSC group intervention changed these cytokines levels in opposite direction. Compared with those in the model group, the level of Caspase-3, Bax in hADSC and Ast-hADSC group decreased notably, while the level of Bcl-2 increased significantly. A small quantity of red fluorescent protein from hADSC and Ast-hADSC was presented in renal tissue, but transformation to the renal tubular epithelial cells was not observed.

Conclusions: HIF-1α plays a protective role in ischemic AKI model, which was related with the protection of ARPC, indicating a novel potential therapy for AKI.

Funding: National Natural Science Foundation of China, the Key Project of Shanghai Science and Technology Commission.

PUB023

The Role of Toll-Like Receptors in Myeloma Light Chain Toxicity on Renal Proximal Tubule Cells

Background: The role of innate immunity mediated by Toll-like receptors (TLRs) in myeloma (MM) nephropathy and their potential use as therapeutic target have not been investigated previously. We evaluated the effect of (S,R)-3-phenyl-4,3-dihydro-
Susann [1,2], Hui [1,2], Zheng [1], Huihui [36x302]
term. (II) cystatin C is more sensitive for detecting alterations in renal excretory function
GIT27 may be a potential therapeutic to ameliorate Κ-LC-induced kidney injury in MM.
LC toxicity on kidney and could prove to be promising drug targets. The TLRs suppressor
MM. Innate immunity mediated by TLR2, TLR4 and TLR6 play a major pathogenic role in
upregulated by Κ-LC in RPTECs.
fold). The pro-apoptotic genes (P53, 0.17 fold and Bcl2, 1.3 fold) were also significantly
resulted in increased expression of pro-inflammatory cytokines (IL-6, 35.7 fold; TNF- α,
mRNA expression of both adaptor proteins was significantly upregulated. TLRs activation
upregulated in RPTECs. TLR6 showed the highest increase (5.7 fold) followed by TLR2
(3.5 fold). In this study, TLRs followed both MyD88- and TRIF-dependent pathways as
mRNA expression of both adaptor proteins was significantly upregulated. TLKs activation resulted
in increased expression of pro-inflammatory cytokines (IL-6, 35.7 fold; TNF- α, 21.5 fold and IL-1β, 0.21 fold), chemokines (MCP-1, 23.3 fold), pro-fibrotic (TGF-β1, 1.5 fold).
The pro-apoptotic genes (P53, 0.17 fold and Bcl2, 1.3 fold) were also significantly
upregulated by K-LC in RPTECs.
Conclusions: K-LC is higher nephrotoxic and NGAL could be a diagnostic KIB for
MM. Innate immunity mediated by TLR2, TLR4 and TLR6 play a major pathogenic role in
LC toxicity on kidney and could prove to be promising drug targets. The TLRs suppressor
GIT27 may be a potential therapeutic to ameliorate K-LC-induced kidney injury in MM.
Funding: Private Foundation Support.

PUB024

Improving Long-Term Outcome of AKI by eEPC Pharmacological Preconditioning
Daniel Patschan, Susann Patschan, Gerhard A. Mueller.
Clinic of Nephrology and Rheumatology, Univ Hospital of Göttingen, Göttingen, Niedersachsen, Germany.

Background: Exogenously administered early Endothelial Progenitor Cells (eEPCs)
significantly protect mice from acute kidney injury (AKI). AKI may increase long-term mobility since it has been identified as risk factor for chronic kidney disease. Aim of this study was to analyze long-term alterations of kidney function in mice after systemic eEPC treatment with versus without pharmacological cell preconditioning. Our additional interest focused on the analysis of different markers of renal excretory dysfunction / damage.

Methods: 8-12 weeks old C57Bl/6N mice were subjected to bilateral renal pedicle clamping for 45 minutes. Donor-derived syngeneic eEPCs (0.5-1.000.000) were i.v. injected at the end of ischemia. Cells were either administered natively or after preincubation with established eEPC agonists (Angiopoietin-1 - Ang-2 and Bone Morphogenetic Protein-5 - BMP-5). Analyses were performed 6 weeks later.

Results: Ischemia induced a significant and persistent increase in serum creatinine at week 6. Administration of native eEPCs did not protect from renal excretory dysfunction if evaluated by creatinine levels. Ang-2 failed to further stimulate renoprotective competence of the cells while BMP-5 preconditioning significantly improved serum creatinine. Cystatin C was more sensitive than creatinine since serum levels were lower even after the injection of native cells. There were no differences in serum or urinary KIM-1 concentrations between any of the respective groups.

Conclusions: (I) BMP-5 potentiates AKI-protective competence of eEPCs in the long-term. (II) Cystatin C is more sensitive for detecting alterations in renal excretory function than serum creatinine, even after several weeks. (III) In mice, KIM-1 is not useful for diagnosing kidney damage late after ischemia.

PUB025

Character of Exosomes Secretion under Three In Vivo Models of AKI

Background: Exosomes are cell-produced vesicles of 50-100nm in diameter that contribute to intercellular communication. The production, regulation and function of exosomes in kidneys and kidney cells remain largely unclear. In this study, we characterized exosome production during stress or injury of renal tubular cells.

Methods: Mouse proximal tubular BUMPT cells and were treated with or without Hypoxia (in chamber with 1% oxygen for 8h, 16h, 24h) or Cisplatin (40 nM for 8h, 16h, 24h) or ATP-depletion (10 mM Azide for 1h or 3h ATP-depletion, then recovery in fresh media without FBS for 6h,12h, 24h). The media were collected for exosome isolation by established protocol. Transmission electron microscopy was used to verify the morphology of the isolated exosome. Nanoparticle Tracking Analyzer (NTA, Zeta View) was used to measure the concentration and size of the samples. Immuno blot analysis of exosome markers CD63 and TSG101 was conducted to confirm the quality and quantity of exosome.

Results: Both Invitrogen kit and ultracentrifugation were able to isolate exosomes from cell culture media. The average size of exosome secreted by BUMPT cells in all 3 injury models was 113.18±14.3 nm by the NTZ measurement which was comparable to that from normal control cells[11.2±12.6 nm, P <0.05]. Hypoxia significantly increased both the concentration and production in a time dependent manner (P <0.05). 1.5h ATP-depletion with azide followed by recovery could slightly inhibit exosome release (P<0.05), while 3h ATP-depletion with azide significantly increased exosome production during 12h recovery (P<0.05). Cisplatin might also induce exosome production, but their increase was not statistically significant (P<0.05).

Conclusions: Renal tubular cells may produce more exosomes in response to hypoxia and ATP-depletion with azide recovery, but cell injury or stress does not have significant effect on the size of exosome released by the cells.

PUB026

Acutely Injured Kidneys Release Proteins into the Serum That Cause Oxidative Stress and Are Partially Inhibited by Catalase, N-Acetyl Cysteine, or Rotenone
Jon D. Ahlstrom, Huihui Shi, Christof Westenfelder.
Dept of Medicine, Div of Nephrology, Univ of Utah and Salt Lake City VA Medical Center, Salt Lake City, UT; Dept of Physiology, Univ of Utah, Salt Lake City, UT.

Background: The uremic state that is induced by Acute Kidney Injury (AKI) adversely affects multiple organ systems by mechanisms that are still poorly characterized. To study the consequences of the AKI environment on therapeutically employed Mesenchymal Stem Cells (MSC) and renal tubular cells, we developed a novel in vitro assay of exposing MSCs or cultured rat proximal tubular cells (NRK) to serum from animals that had AKI. Nephrectomy (NPHX), or SHAM surgeries.

Methods: Serum was obtained from rats 24 hrs post ischeemia/reperfusion-AKI (50 min bilateral pedicle clamp, AKI serum, SCr ~4.9 mg/dL), and control serum was obtained following SHAM surgery (SHAM serum), or bilateral nephrectomy (NPHX serum, SCr ~4.8 mg/dL). Serum samples were evaluated for ROS activity with the Amplex Red H2O2 assay.

Results: Culturing normal rat kidney cells (NRK, proximal tubular) or rat MSCs in 10% AKI serum (compared to SHAM or NPHX serum) for 48 hrs resulted in increased oxidative stress, including increased anti-oxidant gene expression, increased GSH levels, decreased cytokine release. Cisplatin Modulated ROS Activity. Compared to SHAM or NPHX serum, serum from rats with AKI had increased Amplex Red activity, which identifies the injured kidney as the source of potentially multiple pro-oxidant factors. The ROS generating proteins of AKI serum were completely eliminated with heat inactivation (65°C for 35 min), which is suggestive of a protein mediator. Catalase, N-Acetyl Cysteine (NAC), or rotenone partially reduced—but did not eliminate-- the ROS activity of AKI serum in a dose-dependent manner.

Conclusions: These results suggest that the injured kidney releases heat-sensitive factors into the bloodstream (likely proteins that generate ROS and may adversely affect both renal tissue and distant organs. The AKI serum ROS activity is only partially reduced by catalase, NAC, or rotenone treatment. The exact nature of the pro-oxidant property that is released by the injured kidney remains to be determined.

Funding: VA Support.

PUB027

Nefirine Modulates Cisplatin-Induced Acute Kidney Injury via Activating Autophagy
Wenbin Tang, Hai Li, Linlin Qiu, Yuchen He, Qiaoling Zhou, Ping Xiao. Dept of Nephrology, Kidney Inst, Changsha, Hunan, China.

Background: Extensive studies have shown that apoptosis and autophagy are crucial in the pathogenesis of cisplatin-induced AKI. Nefirine is not only a strong inducer of autophagy, but also has anti-apoptosis properties. The objective of this study is to determine the effect of Nefirine in cisplatin-induced AKI.

Methods: In vivo, Nefirine with different concentration was used to pretreat the cisplatin induced acute kidney injury (AKI) in BALB/c mice. The pathologic changes were observed by HE staining. The apoptosis was detected by TUNEL assay and cleaved-caspase3 expression level. The autophagge was determined by LC3 expression detection and transmission electron microscope observation. In vitro, changes of apoptosis and autophagge were further clarified in NRK-52E cells treated with cisplatin and different concentrations of Nefirine. Autophagge inhibitor Chloroquine and AMPK inhibitor Compound C were used to indentify the possible mechanism modulating the protective role of Nefirine in cisplatin-induced AKI.

Results: Both in vivo and in vitro, Cisplatin induced extensive renal tubular damage, increased cleaved-caspase3 expression obviously but increased the expression of LC3 slightly. Nefirine pretreatment ameliorated the cisplatin-induced pathological changes and apoptosis, increased the expression of LC3 significantly and decreased cleaved-caspase3 expression obviously. The transmission electron microscope confirmed the observations. Nefirine pretreatment ameliorated the cisplatin-induced pathological changes and apoptosis, increased the expression of LC3 significantly and decreased cleaved-caspase3 expression obviously. The transmission electron microscope confirmed the observations. Nefirine, with different concentration of the AKI environment on therapeutically employed Mesenchymal Stem Cells (MSC) and renal tubular cells, we developed a novel in vitro assay of exposing MSCs or cultured rat proximal tubular cells (NRK) to serum from animals that had AKI. Nephrectomy (NPHX), or SHAM surgeries.

Conclusions: Nefirine plays a protective effect on cisplatin induced AKI possibly through promoting autophagy by AMPK/TOR signaling pathway. Nefirine may serve as a potential treatment strategy to suppress cisplatin-induced AKI.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Inhibition of Histone H3 K27 Demethylase Aggravates Rhabdomyolysis Induced Acute Kidney Injury

Na Lin, Shougang Zhuang. Dept of Nephrology, Shanghai East Hospital, Shanghai, China.

Background: Accumulating data reveal epigenetic change regulates chronic kidney diseases and acute kidney damage. However, role and exact mechanisms of protein methylation mediated acute kidney injury (AKI) are still obscure.

Methods: In this study, we establish a glycerol-induced murine rhabdomyolysis model. Following glycerol (GL) injection intramuscularly, the mice developed severe acute tubular injury as indicated by worsening renal dysfunction, increased NGAL and KIM1 expression and enhanced tubular cell apoptosis. GSK J4, a special JMJD3 inhibitor, treatment significantly enhanced serum creatinine and BUN as well as severe renal pathologic damage in GL injured kidneys. GSK J4 also increased expression of NGAL and KIM1 compared with GL treated alone group. To detect cell apoptosis change with or without GSK J4 in GL injured kidney, we further proceed TUNEL staining and cleaved caspase-3 immunofluorescence. JMJD3 inhibition predominantly upregulated TUNEL and cleaved caspase-3 positive cells in GL treated kidney.

Results: To discuss the underlying mechanisms of GSK J4 on AKI process, we investigate GSK J4 role on histone methylation as well as tubular epithelial cell dedifferentiation and proliferation which play pivotal role in AKI regeneration. After Rhabdomyolysis-induced AKI, the kidney displayed a remarkable regenerative capacity by evidence of increased expression of Pax-2 and vimentin, and upregulation of PCNA. GSK J4 administration predominantly downregulated expression of Pax-2 and vimentin as well as PCNA. Further mechanism studies revealed that the injured kidney after AKI underwent hypermethylation indicated by increased level of di-methyl-histone H3 K27 and tri-methyl-histone H3 K27. JMJD3 inhibition further upregulated methyl-histone H3 K27 after acute kidney injury.

Conclusions: In summary, we have demonstrated that inhibition of Histone H3 K27 demethylation aggravates Rhabdomyolysis induced acute kidney injury. This effect was associated with upregulation of methyl-histone H3 K27 as well as downregulation of tubular epithelial cell dedifferentiation and proliferation. As such, methylation inhibition may hold a therapeutic potential for treatment of Rhabdomyolysis induced acute kidney injury.

Renal Tubular Progenitor Cells Protect Tubular Epithelial Cells by Shutting Extracellular Vesicles


Background: In situ tubule-committed progenitor cells (TPC) contribute to the turnover and repair of the kidney tubule, but their mode of communication is unknown. Extracellular vesicles (EVs) are important mediators of intercellular communication, but the role of TPC-derived EVs in kidney tubular protection is unclear. We hypothesized that TPC may ameliorate kidney tubular cell injury through their EV progeny.

Methods: TPCs (CD133+/CD24+) were isolated from normal pig kidneys, and EVs from the culture medium. Antimycin A (AMA, 1μmol/L) was used to induce mitochondrial injury. PK1 energy production was measured by ATP levels, cellular oxidative stress by hydrogen peroxide assay and Dihydroethidium (DHE), and mitochondrial oxidative stress by PK1 energy production. MTT and LDH activity assays were used to evaluate PK1 proliferation and cellular injury in porcine tubular epithelial cells (PK1), which were then co-cultured from the culture medium. Antimycin A (AMA, 1μmol/L) was used to induce mitochondrial injury.

TPCs alleviated AMA-induced tubular cell injury by releasing EVs that restored energy production and decreased oxidative stress. These findings underscore the endogenous repair capacity of renal tubular cells, and the role of EVs as vectors of the protective effects and intercellular communications of TPCs.

Funding: NIDDK Support

Marta Gozalvez,1 Marta Forina,2 Natacha Rodrigues,3 Joana Gameiro,3 Marta R. A. Neves,1 Joao Gouveia,4 Zelia Costa-e-Silva,4 António Gomes da Costa,1 José António Lopes.1 1Div of Nephropathy and Renal Transplantation, Dept of Medicine, Hospital de Santa Maria, Lisbon, Portugal; 2Div of Intensive Medicine, Dept of Medicine, Hospital de Santa Maria, Lisbon, Portugal.

Background: Using the RIFLE, AKIN and KDIGO systems, the incidence of acute kidney injury (AKI) and their ability in predicting in-hospital mortality in severe sepsis or septic shock was compared.

Methods: Retrospective analysis of 457 critically ill patients with severe sepsis or septic shock hospitalized between January 2008 and December 2014. Multivariate logistic regression was employed to evaluate the association between RIFLE, AKIN and KDIGO with in-hospital mortality. Model fit was assessed by the goodness of-fit test, and discrimination by the area under the receiver operator characteristic (AuROC) curve. Statistical significance was defined as p < 0.05.

Results: RIFLE (84.2%) and KDIGO (87.5%) identified more patients with AKI than AKIN (72.8%) (P < 0.001, respectively). AKI defined by AKIN and KDIGO was associated with in-hospital mortality. Model fit was assessed by the goodness-of-fit test, and discrimination by the area under the receiver operator characteristic (AuROC) curve. Statistical significance was defined as p < 0.05.

Conclusions: RIFLE and KDIGO diagnosed more patients with AKI than AKIN however the prediction ability for in-hospital mortality was similar between the three systems.

Non-Critical Care Hospital-Acquired Acute Kidney Injury: Risk Factors and Clinical Outcomes

Camilo González, Paola García, Kateir Acuna, Melissa Accini, Maite Hurtado. Nephrology, Hospital Univ San Ignacio, Bogotá, Colombia.

Background: Non-critical care hospital-acquired acute kidney injury (Non ICU HA-AKI) is a common complication associated with worse clinical outcomes. We analysed the risk factors and outcomes in this condition.

Methods: Paired case-control 1:2 study was carried out from April-December 2014 at a University Hospital in Bogotá, Colombia. Non ICU HA-AKI was defined by creatinine KDIGO criteria after 24 hours of hospitalization. Controls was paired by date and type of admission. We analysed outcomes and performed univariate and multivariate analysis of risk factors.

Results: Of 16368 admissions, 101 patients fulfill criteria. Mean length of hospitalization to AKI was 7.9±8.8 days, 44.2% fulfilled KDIGO1 criteria and 32.7% KDIGO2. 4.9% required dialysis. Hospital length of stay was longer in patients with AKI (P < 0.01) 13 vs 6 days, ICU admission was higher in cases OR 2.43 [95% CI 2.47, p = 0.004] as well as mortality OR 26.2% [95% CI 18.8-104; p < 0.01]. In multivariate analysis, sepsis OR 3.6 [95% CI 1.3-10.1; p = 0.01], dehydration OR 14.4 [95% CI 4.5-46.2; p < 0.001], baseline eGFR OR 0.96 [95% CI 0.94-0.98; p < 0.001], contrast OR 4.33 [95% CI, 1.60-11.66; p = 0.004], recently NSAsids use OR 3.23 [95% CI 1.22-8.52; p = 0.017] and Charlson comorbidity index OR 1.23 [95% CI 1.05-1.43; p = 0.007] were independent risk factors.

Incidence and Characteristics of Acute Kidney Injury in Children and Adolescents with Diabetic Ketoacidosis

Arushi Verma, Poonam Thakore, Tetyana L. Vasylyeva. Pediatric, Texas Tech Univ Health Sciences Center, Amarillo, TX.

Background: Diabetic ketoacidosis (DKA) is a potentially life-threatening acute complication of type 1 diabetes mellitus (T1DM). DKA is also associated with numerous acid-base, hydration and electrolytes derangements. Acute kidney injury (AKI) is a known complication of DKA, mainly resulting from hypovolemia due to glucosescinduced osmotic polyuria. However, there is paucity of knowledge about acute kidney injury in children with DKA.

Methods: Retrospective chart review of 21 children (with median age of 12 years) hospitalized consecutively with DKA over a one-year period at Northwest Texas pediatric hospital was done after IRB approval. Patients were classified as per the pRIFLE classification into Risk of AKI, AKI and acute kidney failure. Pearson correlation was used to correlate clinical and laboratory parameters in these populations.

Results: Among the 21 children hospitalized with DKA, 4 children (19%) were at risk of AKI, 7 (33.33%) had AKI, 7 (33.33%) had acute renal failure (ARF). No patients required renal replacement therapy or dialysis. Only 2 of 21 patients had an admission diagnosis of AKI. Twentv percent of patients with either AKI or acute kidney failure had severe DKA. Median time of resolution for AKI was 11 days. Admission eGFR was negatively correlated with age (r = 0.35; p = 0.12). No correlation was found between admission eGFR and blood glucose on admission or severity of DKA.

Conclusions: For the first time we showed that there is a high incidence of AKI in pediatric DKA population. AKI is a frequently associated, but underdiagnosed condition in children with DKA. Older age may be a risk factor for AKI. However, it is usually transient and resolves by fluid replacement as per DKA management.

Surgical Prophylaxis with Gentamicin and Acute Kidney Injury

Weeraporn Sirisung.1 Jirapat Tecranakorn,1 Pakpoom Tantrachoti,1 Amputch Karukote,2 Kenneth Nugent.1 Internal Medicine, TTUHSC; 2Mahidol Univ.

Background: Gentamicin has been increasingly used instead of cefalosporins for surgical prophylaxis in an attempt to reduce the rate of “Clostridium difficile” infection. There are limited data regarding nephrotoxicity related to gentamicin in these patients.

Methods: We have conducted a meta-analysis to evaluate the risk of acute kidney injury (AKI) in gentamicin-containing surgical prophylactic regimens, compared to regimens without gentamicin, in several types of surgery. Electronic searches were performed using PubMed and Embase. Statistical analysis was then performed using a random-effect model; heterogeneity (F) was calculated.

Results: Eleven studies with fifteen cohorts with 18,354 patients are included in this analysis. Subgroup analysis was performed according to surgery type. We have found that antibiotic prophylaxis with gentamicin containing regimen has significant risk for developing postoperative AKI in orthopedic surgery (OR [95%CI] = 3.48 [1.98-6.13]). The results were inconclusive in other types of surgery.
Comparison of Tziakas Risk Score versus Mehran Risk Stratification in Predicting Contrast-Induced Acute Kidney Injury among Patients Undergoing Coronary Angiography and/or Percutaneous Coronary Intervention


Background: Contrast-induced acute kidney injury (CI-AKI) is a form of acute kidney injury (AKI) that occurs after the administration of contrast media. In patients who undergo percutaneous coronary intervention (PCI), there was a 3.3% to 19% incidence of CI-AKI. Among these patients, dialysis was needed in 0.3% to 3%. Furthermore, they have a higher mortality rate of 7.1% to 81.2%. It is therefore necessary to measure the patient’s risk to develop CI-AKI in order to prepare them for the procedure.

Methods: This was a cross-sectional analytic study conducted at St. Luke’s Medical Center - Quezon City. Patients aged >18 yrs old who underwent coronary angiography or PCI were included in the study. The following patients were excluded: incomplete data, already on renal replacement therapy, and underwent multiple procedures. Included patients were stratified using both tools. The study outcomes were the occurrence of CI-AKI or need to do dialysis. CI-AKI was defined as an increase in serum creatinine >0.5mg/dL or >25% from baseline.

Results: A total of 414 patients were included. 55 patients (13.28%) developed CI-AKI. Comparing the accuracy indices, Tziakas Risk Score (84.5 [81.1-88.0]) has a higher over-all accuracy than Mehran Risk Stratification (81.6 [77.9-85.4]). Sub-group analysis of patients who underwent coronary angiography showed no statistical difference (p-value=0.51) between the Area Under the Curve (AUC) of the 2 stratification tools. But the sub-group analysis of patients who underwent PCI showed a statistically higher (p-value=0.03) AUC for Tziakas Risk Score (AUC=0.79;SE=0.5) than Mehran Risk Stratification (AUC=0.71;SE=0.06).

Conclusions: In conclusion, Tziakas Risk Score or Mehran Risk Stratification can be used to stratify patients who will undergo coronary angiography. For patients who will undergo PCI, Tziakas Risk Score has a better predictive value compared to Mehran Risk Stratification. In clinical practice, we recommend Tziakas Risk Score as the risk stratification tool.

PUB039

PUB040

Cytokine Clearance in Continuous Venovenous Hemofiltration and Continuous Venovenous Hemodialysis

Ling- Xin Chen, Sevag Demirjian, Suneel M. Udana, Sharon A. Trevino, Jay L. Koyner. Nephrology, Univ of Chicago Hospitals, Chicago, IL; Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH.

Background: Contrast-induced acute kidney injury (CI-AKI) is a form of acute kidney injury (AKI) that occurs after the administration of contrast media. In patients who undergo percutaneous coronary intervention (PCI), there was a 3.3% to 19% incidence of CI-AKI. Among these patients, dialysis was needed in 0.3% to 3%. Furthermore, they have a higher mortality rate of 7.1% to 81.2%. It is therefore necessary to measure the patient’s risk to develop CI-AKI in order to prepare them for the procedure.

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PUB038

Improvements in Recognizing and Managing Medications in Patients with AKI, Better Long-Term Management and Follow-Up Needed

Gang Xu, Dipesh Patel, Richard J. Baines. Dept of Nephrology, Univ Hospitals of Leicester, Leicester, United Kingdom.

Background: Care bundles, education programs, and electronic alert systems have all been cited as possible ways to improve care. However, it is still unclear just how much impact these interventions have in a real life clinical setting, or in which areas valuable resources should be focused on in order to improve outcomes.

Methods: Our hospital has implemented an electronic alerting system for patients with AKI along with a structured education program for clinicians. To assess the effectiveness of these interventions we audited medication and IV fluid prescriptions in patients with AKI over a period of 3 months.

Results: We identified 397 patients with AKI stage 2/3 from August to October 2015. 40% of AKI was identified on admission units, 38% on medical wards. The number of patients prescribed a diuretic, Angiotensin converting enzyme inhibitor(ACE)/ Angiotensin receptor blocker(ARB), Non-steroid anti-inflammatory drugs (NSADS), or given Intravenous fluids pre-admission, 24 hrs post admission, and at point of discharge were shown in Figure 1.

Conclusions: Among individuals with AKI requiring RRT, male gender, pre-existing CKD, mechanical ventilation, and oliguria were negatively associated with RRT withdrawal.

PUB039

Comparison of Tziakas Risk Score versus Mehran Risk Stratification in Predicting Contrast-Induced Acute Kidney Injury among Patients Undergoing Coronary Angiography and/or Percutaneous Coronary Intervention


Background: Contrast-induced acute kidney injury (CI-AKI) is a form of acute kidney injury (AKI) that occurs after the administration of contrast media. In patients who undergo percutaneous coronary intervention (PCI), there was a 3.3% to 19% incidence of CI-AKI. Among these patients, dialysis was needed in 0.3% to 3%. Furthermore, they have a higher mortality rate of 7.1% to 81.2%. It is therefore necessary to measure the patient’s risk to develop CI-AKI in order to prepare them for the procedure.

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Conclusions: In conclusion, Tziakas Risk Score or Mehran Risk Stratification can be used to stratify patients who will undergo coronary angiography. For patients who will undergo PCI, Tziakas Risk Score has a better predictive value compared to Mehran Risk Stratification. In clinical practice, we recommend Tziakas Risk Score as the risk stratification tool.

PUB040

Cytokine Clearance in Continuous Venovenous Hemofiltration and Continuous Venovenous Hemodialysis

Ling- Xin Chen, Sevag Demirjian, Suneel M. Udana, Sharon A. Trevino, Jay L. Koyner. Nephrology, Univ of Chicago Hospitals, Chicago, IL; Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH.

Background: Contrast-induced acute kidney injury (CI-AKI) is a form of acute kidney injury (AKI) that occurs after the administration of contrast media. In patients who undergo percutaneous coronary intervention (PCI), there was a 3.3% to 19% incidence of CI-AKI. Among these patients, dialysis was needed in 0.3% to 3%. Furthermore, they have a higher mortality rate of 7.1% to 81.2%. It is therefore necessary to measure the patient’s risk to develop CI-AKI in order to prepare them for the procedure.

Methods: We conducted a multicenter prospective unblinded randomized trial of patients with severe acute kidney injury. Patients were randomized to CVVH or CVVHD. Blood, urine and effluent were collected at 0, 4, 24 and 48 hours after initiation of CVVH or CVVHD with collections stopping at the time of the first circuit change. Levels of electrolytes and cytokines were tested in both groups of patients and compared. Clearances of each cytokine was calculated and compared between groups and across time-points.

Results: We enrolled 21 patients with 11 patients receiving CVVH and 9 receiving CVVHD. There was no difference in baseline demographics, baseline renal function or ICU type across the 2 groups. The mean(SE) time to first filter change for the cohort was 30(6.7) hours. No significant differences were found between the two modalities in terms of cytokine concentrations at enrollment, 4 and 24 hours. We had sufficient samples to calculate 4 hour cytokine clearances in 19 patients and found no difference in 4 hour cytokine clearances.

Conclusions: In our randomized multicenter study, there was no significant difference in cytokine clearance between CVVH and CVVHD. Funding: Pharmaceutical Company Support - NxStage.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Poor Nutritional Status Is Associated with the Incidence of Acute Kidney Injury in the Treatment of Head and Neck Cancers with Concurrent Chemoradiotherapy Using High-Dose Cisplatin Akihiko Kato,1 Takayuki Tsuji,2 Naro Ohashi,2 Hideo Yasuda.2 1Blood Purification Unit, Hamamatsu Univ Hospital, Hamamatsu, Shizuoka, Japan; 2Internal Medicine 1, Div of Nephrology, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan.

Background: Identifying potential risk factors is critically important for reducing the burden of acute kidney injury (AKI) in cancer patients receiving cisplatin (CDDP) treatment. We aimed this study to explore the risk factors for CDDP-induced AKI in head and neck cancer patients with concurrent chemoradiotherapy.

Methods: We retrospectively reviewed medical records for 40 head and neck cancer patients who underwent chemoradiotherapy including 66-70 Gy with CDDP 80 mg/m2 on Days 1, 22, and 43 (age: 60±10 years old, male/female=38/2). We also evaluated the association of nutritional parameters with CDDP-induced nephropathy in the first-line setting of CDDP.

Results: CDDP-induced AKI developed in 11 out of 40 (27.5%) patients in the first course, 6 out of 35 (17.1%) patients in the second, and 2 out of 34 (5.9%) patients in the third. Serum creatinine levels were increased from 0.76±0.16 in the first to 0.92±0.23 mg/dL in the last administration. No difference was found in baseline creatinine clearance (79.5±21.0 vs. 87.3±26.7 ml/min) and CDDP dosage (120.19 vs. 132.32 mg) between patients with AKI development and those without. Dietary food intake and anthropometric parameters were also identical between the two groups. However, there was a significantly lower level of serum albumin (3.5±0.0 vs. 3.9±0.3 g/dL, p=0.01), cholesterylster (237±49 vs. 299±85 IU/L, p<0.03) and hemoglobin (11.8±1.3 vs. 12.9±1.5 g/dL, p<0.05) in patients with AKI than those without. The Geriatric Nutritional Risk Index (GNRI) was also significantly lower in AKI patients (86±9 vs. 96±10, p<0.01). In patients having high nutritional risk (GNRI<92), the incidence of CDDP-induced AKI was significantly higher than those not having (47.1 vs. 13.0%, p<0.02).

Conclusions: These findings suggest that poor nutritional status just before chemoradiotherapy was associated with CDDP-induced AKI in advanced head and neck cancer patients. GNRI less than 92 may be useful in predicting the risk of AKI in these patients.

Acute Kidney Injury after Laparoscopic Abdominal Surgery Nattachai Suwachitthanan, Thaksin-On Wiratrong, Passiind Laovarevart, Nattachai Sirisawat. Excellence Center for Critical Care Nephrology, Faculty of Medicine, Chulalongkorn Univ and King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Background: Laparoscopic abdominal surgery can induce many physiologic changes including renal function. Many studies demonstrating the relationships of pneumoperitoneum and renal function disturbance were conducted in animal models and showed controversial conclusions. Therefore our objectives were (1) to describe incidence of acute kidney injury (AKI) in patients underwent laparoscopic abdominal surgery and (2) to identify risk factors associated with development of AKI in these circumstances.

Methods: In this prospective cohort study, the medical records of patients who underwent laparoscopic abdominal surgery at King Chulalongkorn Memorial Hospital, Thailand from June 2012 to December 2013 were reviewed. Demographic data (gender and age), preoperative clinical characteristics (body weight, height, heart rate, blood pressure, serum creatinine, estimated glomerular filtration rate and co-morbidities including hypertension, diabetes mellitus and hyperlipidemia) and intraoperative data (operative time, inflation time, mean intra-abdominal pressure and duration of intraoperative hypotension) were collected. We used AKIN criteria to diagnose AKI. Therefore, we collected blood samples, urine samples and we also monitored daily urine output of all patients.

Results: A total of 62 patients were included in this study. Twelve patients (19%) developed AKI. Patients with postoperative AKI had more body weight (p=0.04), more height (p=0.002), more inflation time during surgery (p=0.035) and more exposure index defined as the product of operation time and intra-abdominal pressure (p=0.03). In addition, we found that duration of intraoperative hypotension (mean arterial pressure < 65 mmHg) was independently associated with AKI (adjusted OR=1.19, 95%CI=1.02-1.37, p=0.022).

Conclusions: Our incidence of AKI was 19% which higher than reported in previous studies. Intraoperative hypotension was the independent factor of AKI associated laparoscopic surgery. Therefore, awareness of physician about intraoperative hypotension should be considered in order to reduce the risk of AKI.

Prompt Reversal of Acute Renal Failure (ARF) by Large-Volume Diuresis in 36 Consecutive Patients with Anasarca: Evidence for Congestive Kidney Failure as Suggested by Animal Data Showing Impaired Function by Renal Vein Hypertension/Congestion Grant Meltzer,1,2 Kai Lau,1,2 1Dept of Nephrology, Univ of Oklahoma Health Sciences Center; Oklahoma City, OK; 2Medical Service, VA Medical Center, Oklahoma City, OK.

Background: Fluid overload in ICU patients is known to link to greater ventilator days, longer hospital stay, worse morbidity & more ARF. But a causal relationship is not proven. Animal studies showed renal vein hypertension with or without saline loading impairs function. In patients with anasarca & unexplained ARF, we tested the hypothesis that fluid overload was causative & diuresis curative.

Methods: We studied 36 patients with a peak acute gain of >3 kg weight or ≥3 L fluid, ≥50% acute drop in creatinine clearance (CrCl) or ≥2 x rise in serum creatinine (Scre) without known or identifiable causes. They got IV furosemide at rates without causing hypotension or unstable hemodynamics. All relevant data like weights, fluid balance, volume markers & ii were noted, followed up & statistically analyzed.

Results: Primary etiologies of fluid overload were heart failure (40%), liver failure (22%), CKD (16%), proteinuria (9%) & iatrogenic causes (10%). In the evolution of ARF, weight rose by 12.5 kg in 14 d. Scre rose from 1.3 to 4.4 mg/L. CrCl fell from 76 to 25 ml/min. The falls in CrCl correlated with weight gains (p<0.02). Furosemide caused 15.2 kg diuresis in 12 d, dropped Scre to 1.45 mg/L & raised GCl to 67 ml/min. ARF fully resolved in 33 patients. In 3, Scre was stable despite >4 kg diuresis. Gains in CrCl correlated with diuresis volume (p=0.04). At a diuretic rate of 1.5 kg/d, no adverse events occurred.

Conclusions: Our data support the entity of Congestive Kidney Failure (CKF) as including acute & major salt retention or fluid overload but resolved by diuresis. 2. CKF is likely mediated by reduced cardiac output, systemic or renal venous congestion, renal interstitial edema &/or intra-abdominal hypertension. 3. It can alone induce or aggravate ARF by other causes. 4. Likely under-recognized, CKF is preventable & treatable. 5. Diuresis in cohorts at rates & monitored as ours should be safe & effective.

Funding: NIDDK Support, Private Foundation Support

The Relationship between Cancer and Acute Tubular Necrosis in Patients with Chronic Kidney Disease Gregory John Wilson,1,2 Andrew John Mallett,1,2,3 Adrian Lawrence Kark,1,2 Ken-Soon Tan,2,4 Rajitha Asanga Abyesekera,1 Zaimin Wang,5,6 Helen G. Healy,7 Wendy E. Hoy,7,8 1Dept of Renal Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia; 2CKD QLD & NCD CKD CRE, Univ of Queensland, Brisbane, Australia; 3Centre for Chronic Disease, Univ of Queensland, Brisbane, Australia; 4Dept of Renal Medicine, Logan Hospital, Brisbane, Australia.

Background: Acute tubular necrosis (ATN) occurs commonly in patients with cancer, yet it is not known how these conditions and other comorbidities influence the development and progression of chronic kidney disease (CKD).

Methods: Patients enrolled (with informed consent) in the RBWH and Logan CKD. QLD registries (n=2,367) were assessed for a diagnosis of an acute kidney injury (AKI) as either the primary cause of CKD (primary AKI) or as an acute on chronic kidney injury (ATN on CKD) were selected, and compared with CKD patients without AKI (CKD only).Changes in estimated glomerular filtration rates (eGFR) at one and two years after consent, where available, were calculated.

Results: 823 patients (35%) had a diagnosis of AKI and among them 97 patients (4% overall) had a diagnosis of ATN. 31 patients had a diagnosis of primary AKI (mean age 59% 61% male, and 66 had ATN on CKD (mean age 66, 55% male). 1544 patients had CKD only (mean age 67, 50% male). 19% of CKD only patients had cancer: rates were higher in those with primary ATN (42%, OR 3.03, p= 0.002), and marginally higher in those with ATN on CKD (29%, OR 1.7, p=0.06). Diabetes (DM) and hypertension (HTN) were recorded in 52% and 80% of CKD-only patients: rates were significantly lower for patients with primary ATN (DM 19%, p<0.001 and HTN 55%, p<0.001), but were not for patients with ATN on CKD (DM 41%, p<0.01, and HTN 74% p<0.03. The mean rate of eGFR decline (ml/min/1.73m2/yr) in patients with cancer and CKD only was 0.91 (SD=5.12), for patients with primary ATN and cancer was 3.63 (SD=4.90) and for ATN on CKD and cancer was 8.88 (SD=5.56).

Conclusions: These findings suggest that ATN in patients with cancer may be an independent risk factor for developing CKD. However an effect on progression is not yet clear.

Increased Levels of uPAR Correlate with Disease Severity in Hantavirus-Induced Acute Renal Failure Stefan Hägle,1 David Changli Wei,2 Janne M. Hofvander,1 Martin G. Zeeier,1 Ellen Kraukrämmer,1 1Dept of Nephrology, Univ Hospital Heidelberg, Heidelberg, Germany; 2Dept of Medicine, Rush Univ, Chicago, IL.

Background: Hantavirus disease caused by Puumala and Dobrava-Belgrade virus is characterized by acute kidney injury (AKI) with often massive proteinuria. The underlying mechanisms for renal failure are not completely understood. Recently, serum soluble urokinase-type plasminogen activator receptor (uPAR) has been identified as one of the key regulators for proteinuria in focal segmental glomerulosclerosis (FSGS) by impairing podocyte function.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
**Methods:** We analyzed levels of uPAR and its ligand urokinase-type plasminogen activator (uPA) in serum samples of patients with acute hantavirus disease and of healthy control persons. Serum uPAR levels were correlated with hantaviral clinical parameters.

**Results:** Serum uPAR levels were significantly higher in hantavirus-infected patients. In contrast, levels of the ligand uPA were not elevated. The concentration of serum uPAR correlated with clinical parameters and highest uPAR levels were observed in patients with severe AKI.

**Conclusions:** The correlation between increased serum uPAR levels and laboratory parameters indicates a possible role of uPAR in the severity of hantavirus-induced AKI. Elevated levels of soluble uPAR may contribute to podocyte dysfunction and may be relevant in the pathogenesis of proteinuria induced by hantavirus infection.

**PUB046**

Patients with Early Recurrence of Acute Kidney Injury Are Poor Prognosis

Kazutaka Sakai, Kengo Furuiuchi, Yasunori Iwata, Norihiko Sakai, Takashi Wada, Nephrology, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan.

**Background:** Prevalent recurrent AKI would improve kidney dysfunction and mortality. However, it is still unclear how long should we follow the AKI cases after the kidney injury. In this study, we evaluate interval of recurrent AKI and prognosis of these cases.

**Methods:** This study was observational cohort study. An entry criterion of this study is all cases admitted and visited to Kanazawa University Hospital from November 1st, 2006 to October 31st, 2007. A total of 21,939 cases were evaluated retrospectively from November 1st, 2006 to December 31st, 2015. Primary end point was death. Observation time after index AKI were two years for short-outcome and ten years for long-outcomes. Recurrent AKI was defined as re-increase of serum creatinine after index AKI.

**Results:** One hundred fifty one cases occurred recurrent AKI within two years. Cases recurred AKI within 28 days were defined as the early recurrence group (n=70), and others were defined as the late recurrence group (n=81). Their clinical factors were almost no difference between two groups. However, rates of all-cause mortality were higher in the early recurrence group (p<0.01; Log-rank test). Multiple cox regression analysis revealed that AKI stage III in first AKI showed high HR for death in early recurrence group (HR 3.269; p<0.05), and AKI Stage III in recurrent AKI showed high HR for death in late recurrence group (HR 5.600; p<0.01).

**Conclusions:** Patients with recurrent AKI within 28 days after index AKI showed poor prognosis. Careful follow-up for at least 28 days after AKI would be required to detect recurrence of AKI and predict prognosis after AKI.

**PUB047**

Metformin Associated Lactic Acidosis with Acute Kidney Injury: Results of a French Observational Multicenter Study Carried Out in 2015

Alain Wynckel,1 Anthony Corchia,1 Zoubir Djerdara,2 Thierry Treque,3 Philippe Ricou.1 1Nephrology, CHU, Reims, France; 2Pharmacology, CHU, Reims, France; 3Pharmacovigilance, CHU, Reims, France.

**Background:** Metformin associated lactic acidosis (MALA) remains a controversial issue in the literature.

**Methods:** Our observational multicenter study focused on MALA (pH <7.35, blood lactate > 2 mmol/L) associated with acute kidney injury (AKI), occurring from January to December 2015. The same questionnaire was sent to 67 nephrology departments (ND) and 17 intensive care units (ICU). Clinical characteristics, baseline chronic treatment, precipitating factors, need for vasoactive drugs, extrarenal support, renal recovery, mortality and the worst biological values were recorded for all the patients. Plasma metformin levels were collected if available.

**Results:** 42 ND did not observe MALA. 158 MALA were collected. Mean age was 70 ± 12 years. Preexistent eGFR was less than 60 mL/min per 1.73m² in 38 patients and was lower than 30 mL/min in 90 patients. The mean pH was 7.13 ± 0.20. Mean serum creatinine and blood arterial lactate were 604 ± 360 μmol/L and 10.2 ± 8.1 mmol/L respectively. A septic or cardiogenic shock was documented in 34 patients. Gastrointestinal disorders or acute cardiac dysfunction were observed in 79 of the 97 patients who did not need vasoactive drugs. Plasma metformin level was positively correlated with blood lactate level and negatively correlated with the plasma vasoactive drugs. The pH and lactate concentration did not differ significantly between survivors (n=137) and non survivors (n=21). Death was related to septic or cardiogenic shock in 12 patients. Hemodialysis was performed in 119 patients. The correction of lactic acidosis was obtained in 48 hours in 119 patients. Complete renal recovery was observed in 91% of the patients with a previous eGFR >60 mL/min per 1.73m².

**Conclusions:** MALA occurred mainly in patients without preexistent renal failure. Septic shock was not the predominant triggering factor. The majority of patients with MALA survived when hemodialysis was performed early despite a mean pH that is usually thought to be fatal. Temporary metformine withdrawal is recommended in dehydrated patient.

**PUB048**

Abstract Withdrawn

**PUB049**

Can We Blame Vitamin D for Contrast Induced Nephropathy? A Prospective Single Center Study

Ashraf Omar Owais,1 Sameeha A. Alshelleh,2 1Internal Medicine, Jordan Univ of Science and Technology, Irbid, Jordan; 2Internal Medicine, Univ of Jordan, Amman, Jordan.

**Background:** Contrast induced nephropathy (CIN) is one of the major causes of acute kidney injury (AKI) for hospitalized patients, few mechanisms were suggested to cause CIN, one of which is the anti-oxidant, anti-inflammatory effect of vitamin D on the kidney. Our study is to evaluate the factors associated with CIN including vitamin D deficiency. Methods: in a tertiary referral hospital, we prospectively collected data, blood and urine samples for all patients admitted to our cardiology unit, and signed the consent form to participate in our study. all consented patients were asked to have a creatinine level withdrawn 48-72 hours after the procedure. CIN was defined as increase in serum creatinine by 0.5 mg/dL above the baseline within 48-72 hours after the contrast administration. we excluded patients with advanced CKD (stage 4,5), patients with recent contrast administration.

**Results:** between June 1, 2015 - January 10, 2016, we approached 1810 patients, 327 patients agreed and signed the consent to participate in the study, 123 patients did not come back for follow-up creatinine, for baseline characteristics see table 1, the contrast media used was low osmolality for all patients, the average contrast used was 99.8 mL (SD 68.7) for the CIN group and 99.2 mL (SD 65.7) for the other group. mean creatinine for CIN group was 73.3 mmol/1 vs. 86.7 mmol/1 for the other group, 78.2% of all patients were vitamin D deficient (mean 13.6 ng/mL), in our study only 10.4% received pre procedure hydration, the incidence of CIN was 14.9%, admission creatinine (P=0.001) and the use of diuretics (P<0.047) were associated with CIN, vitamin D was not associated with increase incidence of CIN in our study (P=0.097).

**Conclusions:** incidence of CIN is high among hospitalized patients, in many cases its a preventable complication of contrast media if adhered to general recommendation of adequate pre contrast hydration.

**PUB050**

Study Protocol Renal Function Measurements Are Comparable to Clinical Care Measurements in a Cardiac Surgery Cohort

Eric McArthur,1 Amit X. Garg,2 Steven G. Coca,2 Chirag R. Parikh,3 Heather Thiessen Philbrook,3 1Inst for Clinical Evaluative Sciences, ON, Canada; 2Icahn School of Medicine at Mount Sinai, NY; 3Yale Univ, CT.

**Background:** In the era of electronic medical records, it is appealing to utilize measurements available from routine clinical care instead of laborious and expensive study protocol visits. However, clinically obtained lab values are prone to ascertainment bias. It is not known if renal function measured during clinical care is comparable to protocol-based visits.

**Methods:** The TRIBE-AKI cohort is comprised of adults undergoing cardiac surgery. We examined a subset of the cohort in Ontario, Canada who had estimated glomerular filtration rate (eGFR) measured in follow-up as per study protocol, with a clinical care eGFR collected from an outpatient laboratory within one year of the study protocol visit (using CKD-EPI equation). Comparability of the eGFRs was assessed using Pearson’s correlation, concordance correlation, and a Bland-Altman plot.

**Results:** Overall, 224 adults had a study protocol visit a median 3.0 years (IQR 2.9-3.2) after surgery, of which 88 (39%) had their eGFR measured in clinical care. The mean eGFR in clinical care was 66 mL/min/1.73m² (SD 18) and was 59 mL/min/1.73m² (SD 17) at protocol visits. A correlation of 0.90 (95% CI 0.85, 0.93) and concordance of 0.84 (95% CI 0.77, 0.89) indicated strong correlation and moderate concordance. The Bland-Altman plot showed, among those with mild or no chronic kidney disease, clinical care may slightly overestimate eGFR relative to protocol-based eGFR.

**Conclusions:** Clinical care eGFR may be marginally higher compared to study protocol eGFR, but the values were largely comparable in follow-up after cardiac surgery. Supplementing research studies with eGFR collected from electronic medical records may help minimize costs and loss to follow-up, but further research should confirm these findings.
Analysis of Kidney Injury Markers in Children with Cancer
Marcelo Rodrigues Bacel, Marina M. Sonnenfeld, Carolina Y. Tamashiro, Fernando Luiz Affonso Fonseca. General Practice, ABC Medical School, Santo Andre, São Paulo, Brazil.

Background: Children are subjected to develop acute kidney injury (AKI) when in a chemotherapy (CT) routine basis. Still, when the AKI is not present the pattern of glomerular biomarkers of renal dysfunction is not known. The association between its levels before the initiation of CT could predict the occurrence of AKI later on. The aim of the study is to evaluate AKI in pediatric oncology patients in current CT.

Methods: It is a cross-sectional study. Individuals from 2 to 18 years-old with a confirmed diagnosis of acute lymphoblastic leukemia, acute myeloid leukemia, and any solid tumors receiving CT were included. Exclusion criteria involved patients with end stage renal disease or in dialysis and with an eGFR less than 60 mL/min/1.73 m² and also with any other immunodeficiency. Individuals with prior organ transplants were excluded as well. Blood samples were collected in order to analyze the following variables before and after CT: serum creatinine, Cystatin, NGAL, interleukin-6, TNF-alpha, C-reactive protein and homocysteine.

Results: A total of 26 children were included. About 17 had acute lymphoblastic leukemia, 2 had acute myeloid leukemia, 3 with neuroblastoma, 1 with testicle neoplasia, 1 with adenoma, 1 with osteosarcoma and 1 with rhabdomyosarcoma. About 61.5% were male and the mean age was 9.48 years. NGAL and Cystatin in blood were measured with the following median results in the sample: 0.3 and 6.6. Serum creatinine median was 0.6 mg/dL. Spearman correlation test analysed the correlation between Cystatin and inflammatory and renal dysfunction biomarkers. The correlation was not significant between NGAL and creatinine (r>0.213) and between Cystatin and creatinine (r>0.113). The correlation between Cystatin and NGAL was also not significant with a p>0.464. The performance in the receiver operating characteristics analysis the area under the curve for NGAL in detecting acute kidney injury was 0.280. The performance of Cystatin had the value of 0.565.

Conclusions: This model could not predict AKI in patients receiving CT. NGAL and Cystatin were not correlated with the development of AKI in children receiving CT.

Analysis of Prognostic Factors in Patients with Paraquat Poisoning for Optimal Therapy Regimen
Yinan Xu, Jingyun Ye, Jianghua Le, Jianghua Chen. The Kidney Disease Center, The First Affiliated Hospital, School of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.

Background: Paraquat (PQ) is an effective quaternary nitrogen herbicide which is highly toxic to human. The purpose of this study was to identify prognostic factors after PQ ingestion and discuss the efficacy of current therapy regimen.

Methods: In this retrospective study, 211 cases admitted to our hospital between 1 June 2010 and 30 April 2016 were enrolled. The demographic characteristics, medical records of clinical features, laboratory parameters, therapy regimen and the prognosis were retrospectively analyzed.

Results: The overall survival rate was 55.45%. The mean age was 35.85 years with 55.45% being female. The average amount of PQ ingestion was 30.79 ml. Twelve Patients who ingested PQ combined with alcohol had a higher survival rate. The patients in survival group ingested less amount of PQ, presented with lower serum creatinine level and higher glomerular infiltration rate at admission, developed lower incidence of acute kidney injury and pulmonary CT deterioration. As to the therapy regimen, the survivors were treated with higher dosage of methylprednisolone, daily dose of aspirin, daily dose of rapamycin and lower daily dose of vitamin C. The frequency of hemoperfusion was much more in the survival group. The Cox regression analysis demonstrated that larger amount of PQ ingested (HR 1.006, P<0.003), abnormal renal function at admission (HR 12.540, P<0.001) or developed AKI after admission (HR 21.327, P<0.001) were the independent risk factor. Higher dose of methylprednisolone (HR 0.577, P<0.001) and aspirin (HR 0.998, P=0.027) were independent protective prognostic factor.

Conclusions: The non-survivor characteristics are larger amount of PQ ingestion, manifestation of abnormal renal function at admission or developed AKI after admission, whereas the survivor characteristics are higher dose of methylprednisolone and aspirin.

Ionomic Profile as a Biomarker for Acute Kidney Injury after Cardiac Surgery
Ziyu Shi, Dae-Ho Lim, Dae-Hyung Jang, Jie Chen, Xiaojing Ding. 1Dept of Nephrology, Zhongshan Hospital, Shanghai Medical College, Fudan Univ, Shanghai, China; 2Kidney and Dialysis Inst of Shanghai, Shanghai, China; 3Kidney and Blood Purification Laboratory of Shanghai, Shanghai, China.

Background: Ion transportation, one of the fundamental renal tubular functions, is veiled during acute kidney injury (AKI). This study aimed to map the urinary ionomic profile of patients with AKI after cardiac surgery in order to screen out representative ions and set up an ionomic model to Early diagnose AKI after cardiac surgery.

Methods: A total of 261 patients undergoing cardiac surgery were recruited. Urine samples of pre-operation and 2h, 12h, 24h and 48h after operation were collected. Urinary concentration of 18 ions were measured by inductively coupled plasma spectroscopy (ICP-MS) and adjusted by urinary creatinine. AKI was diagnosed according to KDIGO guideline.

Results: Urinary concentration of 18 ions changed dynamically during perioperative period of cardiac surgery, especially at 2h after operation. The urinary concentrations of Cu, Pb, Al, Zn, Cd, Co, Ti, Ba, V, Ga, Se, Cu at 2h after operation were significantly higher than those of pre-operation, whereas B, As, Sr, Pd at 2h after operation were significantly lower than pre-operation. At 48h after operation, urinary ionomic gradually recovered to preoperative levels. There was remarkable difference in urinary ionomic profile between AKI and non-AKI groups during the perioperative period. Urinary Ion Index (UII) model to Early diagnose AKI was established by bioinformatic method. Prediction equation is as following: 0.21ln(urinary Fe at 2h after operation) + 0.32ln(urinary Cd at 2h after operation). The cutoff value of UII was 1.85 and AUC was 0.76±0.11, while the sensitivity, specificity and accuracy were 0.61±0.17, 0.97±0.09 and 0.82±0.08, respectively.

Conclusions: Urinary ion concentrations change dynamically during perioperative period of cardiac surgery. There is remarkable difference in urinary ionomic profile between AKI and non-AKI groups. Urinary Fe and Cd at 2h after operation can be used efficiently to construct the early diagnosis model for AKI after cardiac surgery with considerable accuracy.

A Case of Atypical Hemolytic Uremic Syndrome Presenting as Dermatomyositis and Complicated with Viral Infections
J-Ru Chen,1 Han-Mou Tsai,2 Hsin Hung Lin,1 Chi-Chung Huang,1 1Kidney Inst and Div of Nephrology; Dept of Internal Medicine, China Medical Univ Hospital, Taichung City, Taiwan; 2MAH Hematology Associates, New Hyde Park, New York.

Background: Atypical hemolytic uremic syndrome (aHUS) usually presents with the triad of acute renal failure, thrombocytopenia and microangiopathic hemolytic anemia (MAHA). It is unusual to present with features of dermatomyositis without the triad. Methods: A 41 years old woman was admitted for fever, polyarthralgia, proximal limb weakness, erythematous rashes, heliotrope rashes, periorbital erythema and Gottron’s papules. Her LDH, ALT, CPK, amylase, lipase and CRP were elevated but her platelet count and serum Cr were not. Serology testing failed to detect any autoantibodies. Four days later she lost her left visual acuity, platelet count decreased to 53±10^4/L, Cr increased to 1.64 mg/dL and LDH increased to 1659 from 537 IU/L. Despite daily plasma exchange her platelet count further decreased. Hemodialysis was started for oliguria and pulmonary edema. She then developed seizure, altered mental status and respiratory failure that required endotracheal intubation. Eculizumab was given on day 20, her general status improved and her leukocytosis resolved. Yet her fever persisted and her platelet count, after increasing...
to a maximum of 58x10^9/L, failed to normalize after two weekly doses of ecuizumab. Extensive microbiological investigation revealed by PCR herpes simplex virus type 1 and CMV viremia. Neither was detected in a saved blood sample of day 14.

**Results:** Four days after adding acyclovir, before ganciclovir was instituted, her platelet count normalized. Fever resolved after 3 weeks of anti-CMV therapy. Her skin rash subsided after Cr normalized after 8 doses of ecuizumab therapy. Kidney and skin biopsies showed thrombotic microangiopathy. Gene sequence analysis detected a CFH miss-sense mutation (G936A).

**Conclusions:** aHUS may present with features mimicking dermatomyositis. Our case is also unusual in that its course was complicated with viremia of HSV and CMV. In a case of aHUS, lack of expected response to anticomplement therapy should prompt rigorous searches for concurrent illnesses.

**PUB055**

**Phenotype of Proton Pump Inhibitor Associated Drug Induced Kidney Disease (DIKd): Results from the DIRECT Study**

J. Awdishu, Rajasekara Chakravarthi Madhurai, Stuart Goldstein, Ashita J. Tolwani, Melanie S. Joy, Etienne Macedo, Dinna Cruz, Jorge Cerda, David T. Selesk, Michael Zappitelli, Andrew J. P. Lewington, Maria Ostermann, Vivekanand Jha, Ravidra L. Mehta, 1,15 Univ of California, San Diego; 2 Star Kidney Centers; 3 Cincinnati Children’s Medical Center; 4 Uni of Alabama at Birmingham; 5 Uni of Colorado, Denver; 6 Albany Medical College; 7 Uni of Michigan; 8 McGill Univ Health Centre; 9 Leeds Teaching Hospital; 10 Guy’s and St. Thomas’ Hospital; 11 Postgraduate Inst of Medical Education and Research; 12 On Behalf of the DIRECT Investigators.

**Background:** Proton pump inhibitors (PPIs) have strong evidence for efficacy and a favorable side effect profile. However, there are concerns given overprescription and recent association of chronic kidney disease with PPI use.

**Methods:** DIRECT is an international multi-center study which enrolled 634 patients with DIKd to identify drug-related polymorphisms by GWAS studies that were associated with standardized phenotypes. Each presumed PPI case was adjudicated by 2 nephrologists.

**Results:** PPI associated DIKd cases (N=26) were confirmed by adjudication (21 adult and 7 pediatric patients). Implicated PPIs were omeprazole (N=9;22.2±6.7mg), esomeprazole (N=3;20 mg), lansoprazole (N=5;27.6±7.7mg) and pantoprazole (N=10;38.6±3.2mg). Patients were 43% male with mean age of 51.6±20 years in adults and 12.6±3.3 years in pediatrics. Subjects were 79% white, 11% black and 11% asian. Comorbidities included hypertension, diabetes and cancer in adults and hypertension, cancer and liver disease in pediatrics. The mean Scr increased from 0.49±0.47 to 3.76±2.22 log/ml in adults and 0.34±0.22 to 1.14±0.46 mg/dl in pediatrics. Median (IQR) time to onset was 6 (3-14) days. Common risk factors were hyperglycemia and additional nephrotoxic exposure. Biopsies were performed in 29% demonstrating interstitial nephritis in 75% of cases. However, blood eosinophils were within normal range (2.0±1.5%). Dialysis was required for 14.3% of cases. Mortality was 3.7% and 13.6% at hospital discharge and 90 days.

**Conclusions:** PPIs may cause interstitial nephritis in susceptible caucasian patients at standard doses.

**Funding:** Private Foundation Support

**PUB056**

**Biomarkers Utilization to Detect Subclinical Kidney Injury in Acute Stroke:**

Bernardo Campos, Anthony C. Leonard, Charuhas V. Thukar. Nephrology, Univ of Cincinnati, Cincinnati, OH.

**Background:** Acute kidney injury (AKI) affects 25% of patients admitted with stroke, predicts high mortality. Recent study shows that 10% of stroke patients have unrecognised chronic renal insufficiency, which predicts poor outcomes. Neutrophil gelatinase associated lipocalin (NGAL) has been used as a reliable kidney injury biomarker, which predicts both AKI and clinical outcomes. Animal studies show that this protein is expressed early and highly induced in the kidney after ischaemic or nephrotoxic AKI. In this study we evaluate if NGAL could be used to detect subclinical kidney injury in patients suffering from other vital organ ischemia: acute stroke.

**Methods:** Based on the established knowledge of NGAL, we studied the occurrence of subclinical kidney injury. In a prospectively collected biological repository of eligible acute stroke subjects (2013-2014), there were 38 cases of stroke (14 Ischemic; 24 hemorrhagic). Demographic, comorbid and laboratory variables were collected at the time of admission with stroke, along with de-identified plasma samples for biomarker assays. We assessed the samples for NGAL based on established methods.

**Results:** Based on literature, we chose 150 ng/ml as the upper limit of normal baseline NGAL in plasma. As shown in Table 1 the 31 patients with baseline creatinine of < 1.2 at the time of stroke (4 (12%) already had positive biomarker levels (range 151 to 248 ng/ml) indicating subclinical kidney injury. 1/4 patients with subclinical injury went on to develop clinically apparent AKI. Median NGAL levels were significantly different across stroke patients with baseline creatinine of < or ≥ 1.2 mg/dl (71.2 vs 154.5, p = 0.01).

<table>
<thead>
<tr>
<th>Biomarker &gt;ve (NGAL &lt; 150 ng/ml)</th>
<th>Biomarker &gt;ve (NGAL ≥ 150 ng/ml)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine &lt;1.2</td>
<td>27</td>
<td>4 (subclinical Injury)</td>
</tr>
<tr>
<td>Creatinine &gt;1.2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>30</td>
<td>8</td>
</tr>
</tbody>
</table>

**Conclusions:** NGAL levels at the time of acute stroke may indicate subclinical kidney injury and suggest vital organ cross talk. Biomarker utilization can discriminate those patients with subclinical kidney injury. Larger studies with longitudinal follow up are needed to examine the biomarker-based risk stratification in vital organ ischemia.

**PUB057**

**Acute Kidney Injury Result from Rhabdomyolysis and Continuous Renal Replacement Therapy**

Meng Wang, Hongli Jiang, Hua Liu, Quan He. Blood Purification, The First Affiliated Hospital of Xi’an Jiaotong Univ, Xi’an, Shaanxi, China.

**Background:** Rhabdomyolysis (RM) can lead to acute kidney injury (AKI) as a life threatening complication. Whether to use continuous renal replacement therapy (CRRT) or not for RM is still controversial. We aim to assess risk factors for AKI and evaluate further if the CRRT is effective.

**Methods:** 57 cases of RM were selected from our hospital (August 2013 - May 2016). Logistic regression analyses were performed to determine risk factors for AKI by collecting the medical records. All patients received rehydration and rehydration therapy. Meanwhile, 31 patients received more than 2 sessions of CRRT; laboratory data such as concentrations of myoglobin (MB), creatinine kinase (CK), creatinine kinase isoenzyme-MB (CK-MB), lactic dehydrogenase (LDH), aspartate aminotransferase (AST), alanine transaminase (ALT) in blood and CRRT effluents were collected.

**Results:** The incidence of AKI was 40%. Logistic regression analysis showed hyperalbuninemia, hypocalcemia, urine protein test positive were independently associated with AKI (p<0.05). Duration of CRRT and hospital stay were significantly higher among patients with AKI, compared with patients without AKI (p<0.05). After 24 hours of treatment, comparing with the conventional treatment patients, the concentrations of CK-MB, CK, CK-MB, LDH, AST, were significantly decreased in the CRRT intervention patients (p<0.05), but there was no statistically significant in ALT level. Concentrated CRRT effluents were detected that the concentrations of the CK, CK-MB, LDH, AST, and ALT were trace amount.

**Conclusions:** Prevention of AKI is important for RM patients, especially for patients with hyperalbuninemia, hypocalcemia and urine protein test positive, for whom CRRT could be a beneficial intervention. CRRT could remove MB out of blood circulation directly, while the macromolecular metabolism products such as CK, CK-MB, LDH, AST, couldn’t remove directly, but their serum levels were significantly decreased in CRRT intervention patients. It was suspected associating with retarding progression and helping improving metabolic function of body. Further studies and more data are required to confirm the mechanism.

**PUB058**

**The Impact of Elevated Preoperative Serum Creatinine on Acute Kidney Injury following Cardiac Surgery and the Protective Role of Dopamine**

Xuxia Gao, Xinhao Yao. 1 Internal Medicine, Beijing Anzhen Hospital, Capital Medical Univ; Beijing Inst of Heart, Lung and Blood Vessel Diseases, Beijing, China; 2 Pharmacy, Beijing Anzhen Hospital, Capital Medical Univ; Beijing Inst of Heart, Lung and Blood Vessel Diseases, Beijing, China.

**Background:** Preoperative renal function is an independent risk factor for Acute kidney injury (AKI) following cardiac surgery. The objective of this study is to investigate the impact of elevated preoperative serum creatinine (Scr) on AKI, and the protective effect of dopamine.

**Methods:** 1700 patients undergoing cardiac surgery in Beijing Anzhen Hospital from March 2008 to October 2008 were analyzed retrospectively. AKI was defined as a ≥ 50% increase in Scr within 48 hours from the preoperative value. Patients were divided into normal (n=191) and elevated Scr group (n=73) according to preoperative Scr; or 26.5μmol/L increase in Scr from the preoperative value. The AKI patients (n=264) were divided into 2 groups: Control group (n=191) and intervention group (n=73). The prevalence, the recovery of AKI, and the length of stay in the intensive care unit (ICU) were compared by chi-square test or student t-test; Risk factors were determined by multivariable logistic regression analysis. AKI was defined by an increase of ≥ 0.5 mg/dL in Scr at 48 hours after surgery.

**Results:** 264 of 1700 cases (15.5%) suffered from AKI. Compared to the normal Scr group, the prevalence of AKI increased (44.2% vs 12.4%, p<0.05), and the recovery rate of AKI (postoperative Scr went down to the preoperative level in 7 days) decreased (30% vs 68.8%, P<0.05) significantly in the elevated Scr group. Multivariable analysis revealed that elevated Scr (OR: 1.39, 95% CI: 1.22, 1.57) and older age (OR: 1.08, 95% CI: 1.00, 1.16) were risk factors for this difference. Between Dopamine and Control groups, pre- and post-operative Scr were compared. The prevalence, the recovery of AKI, and the length of stay in the intensive care unit (ICU) were compared by chi-square test or student t-test; Risk factors were determined by multivariable logistic regression analysis. AKI was defined by an increase of ≥ 0.5 mg/dL in Scr at 48 hours after surgery.

**Conclusions:** Elevated preoperative Scr increases the prevalence of AKI and make AKI more difficult to recover. Lower dose of dopamine may have protective role on AKI in patients with elevated preoperative Scr.

**Funding:** Government Support - Non-U.S.
Prevalence and Severity of Depression among Patients with Pregnancy Related AKI Presenting to a Tertiary Care Hospital of a Developing Country

**Background:** Acute kidney injury (AKI) in pregnant women is commonly seen in developing countries. It is associated with significant morbidity, social and personal implications. We conducted a study to assess the prevalence and severity of depression in patients with pregnancy related AKI (PRAKI) in a tertiary care center.

**Methods:** Patients with PRAKI admitted from 1-6 to 6-16 under Nephrology service, Jinnah Hospital, Lahore, Pakistan were included in this cross sectional study. The Hamilton Rating Scale for Depression (HAM-D) version translated and adapted in Urdu, was used to assess the study population. These patients were interviewed with the (HAM-D) questionnaire on their first encounter with Nephrology. Previous history of psychiatric illness was excluded. The diagnosis of AKI was based on the classification of the Acute Kidney Injury Network group.

**Results:** The mean age of the patients was 24±5 years. Seventeen (57%) patients were multiparous and 13 (43%) were primi gravida. Of the 30 patients with AKI, 8 (27%) presented before 28-weeks and 22 (63%) patients after 28-weeks of gestation. The cause of AKI included postpartum hemorrhage in 9 (30%), sepsis in 8 (27%), preclampsia/eclampsia in 6 (20%), shock in 4 (13%) and coagulopathy in 3 (10%) of patients. Alive and healthy fetus was found in only 15 (50%) of patients. Twenty-one (70%) patients received average of 5.8 hemodialysis sessions during their hospital stay. Twenty-three (76 %) had no depression before 28-weeks and 22 (63%) patients after 28-weeks of gestation. The cause of AKI was unknown to be present in 1 patient but AKI was detected peripherally. Literature suggests ANCA as are in absent in 10% of cases and the efficacy of Rituximab in these patients is a rarely studied group.

**Conclusions:** Our study depicted considerable depression of varying degrees in women with PRAKI. Increased awareness and effective monitoring for depression should be integrated into regular maternal care to decrease morbidity associated with it.

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**Incidence of Chronic Renal Replacement Therapy after Acute Kidney Injury at a University Hospital in Northeastern Mexico**

**Background:** Acute kidney injury (AKI) is a condition that affects 1 in 7 patients admitted to hospital and it can be prevented. AKI can occur in any clinical condition, increasing mortality and hospital costs.

**Methods:** Prospective, cross-sectional, descriptive study. Hospitalized patients who requires interconsultation by the Nephrology Department from March 2015 to March 2016 were included.

**Results:** 942 patients were included, 387(41%) developed AKI or AKI over Chronic Kidney Disease (CKD),56% were male, mean age 52.1 years (SD 17.5). The most frequently comorbidities: Diabetes Mellitus 39%, Hypertension 38.2% and obesity 13.9%. The main causes of AKI: 32% pre-renal, 27% infectious and 17% heart disease. Mortality in critically ill patients with AKI was 63%. 198 patients developed AKI, 46.5% required acute renal replacement therapy (RRT), 43.4% died, 30.4% of them recovered renal function without RRT and 26% requiring chronic RRT. 189 patients developed AKI over CKD, 46.5% mortality. Of those with renal involvement 1(16%) has remained dialysis dependent. 20% mortality. Of those with renal involvement 1(16%) has remained dialysis dependent.

**Conclusions:** No difference between group AKI and AKI over CKD to continue in RRT and 26% requiring chronic RRT. 189 patients developed AKI over CKD, 46.5% died, 31.8% recovered renal function without RRT required with an average creatinine of 2.5 (SD 1.22) at discharge and 39.7% developed ESRD requiring chronic RRT.

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**Rituximab Is Effective Treatment for Small Vessel Vasculitis in Absence of Circulating ANCA**

**Background:** The antibody depleting mononuclear antibody Rituximab has been shown to be effective in ANCA associated vasculitis, as shown by the RAVE and RITUXVAS studies. Rituximab, apart from B cell depletion, facilitates B cell/T cell interaction. B cells are also known to be present in tissue infiltrate without being detected peripherally. Literature suggests ANCA as are absent in up to 10% of cases and the efficacy of Rituximab in these patients is a rarely studied group.

**Methods:** This retrospective, single centre study reviewed the case notes of all patients with vasculitis who were treated with rituximab and were ANCA negative at the time of treatment.

**Results:** 10 patients were identified, all Caucasian. Results shown in table

<table>
<thead>
<tr>
<th>ANCA status at presentation (%)</th>
<th>Anti-PR3 (50)</th>
<th>Anti-MPO (10)</th>
<th>ANCA negative (40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ Involvement (%)</td>
<td>Renal (60)</td>
<td>Multisystem (70)</td>
<td></td>
</tr>
<tr>
<td>Dialysis Required (% of those with renal involvement)</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean eGFR at treatment commencement (renal involvement, dialysis independent) (mls/min)</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean eGFR at follow up (renal involvement, dialysis independent) (mls/min)</td>
<td>32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Indications for rituximab were cyclophosphamide resistance in 9(90%). (10%) patient had suspected urethral malignant. Mean age at presentation was 60 (range 15-77) years.**

**Conclusions:** This retrospective study supports the use of rituximab in the absence of circulating autoantibodies and has shown: 70% complete remission; 20% partial remission; 10% mortality. Of those with renal involvement 1(16%) has remained dialysis dependent.

The treatment was tolerated well with no infections requiring hospital admission. To the best of our knowledge this is the largest published series in use of rituximab in ANCA negative patients.

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**The Relationship between the Hourly Urine Output and the Clinical Outcome in Nontraumatic Exertional Rhabdomyolysis**

**Background:** Early and aggressive fluid resuscitation is required for the prevention of acute kidney injury (AKI) in rhabdomyolysis. However, the optimal fluid and rate of repletion are unclear. The purpose of this study is to evaluate the relationship between the degree of diuresis and the clinical outcomes in nontraumatic exertional rhabdomyolysis.

**Methods:** We reviewed the medical records of patients who were diagnosed with nontraumatic exertional rhabdomyolysis from January 2011 to December 2015 in Konkuk university medical center. Total 40 cases were analyzed.

**Results:** Patients were categorized according to the hourly urine output during initial 48 hours; the low urine output (< 200 mL/hr) and the high urine output (>200 mL/hr) group. No significant differences were noted between two groups in initial levels of CPK, serum myoglobin, and creatinine. The hourly urine output was significantly high in the high urine output group (143.7±36.71 vs 291.0±79.08, p<0.001). The clinical outcomes including maximum level of CPK, incidence of AKI and mean hospital stay showed no significant differences between two groups.

**Table 1. Group comparison**

<table>
<thead>
<tr>
<th></th>
<th>Low urine output group (&lt;200mL/h)</th>
<th>High urine output group (&gt;200mL/h)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>13</td>
<td>27</td>
<td>0.000</td>
</tr>
<tr>
<td>Daily urine output (ml/hr)</td>
<td>143.74±(121.56-165.92)</td>
<td>291.07±(259.79-322.38)</td>
<td>0.000</td>
</tr>
<tr>
<td>Amount of initial hydration (ml/kg/hr)</td>
<td>2.51±0.73</td>
<td>4.62±1.58</td>
<td>0.000</td>
</tr>
<tr>
<td>CPK, initial (U/L)</td>
<td>45970.00±44495.17</td>
<td>59696.78±41900.85</td>
<td>0.309</td>
</tr>
<tr>
<td>CPK, maximum (U/L)</td>
<td>46853.15±44319.95</td>
<td>56293.85±38800.11</td>
<td>0.497</td>
</tr>
<tr>
<td>Creatinine, initial (mg/dL)</td>
<td>1.25±1.32</td>
<td>1.04±0.96</td>
<td>0.566</td>
</tr>
<tr>
<td>AKI, initial (number %)</td>
<td>2(15.38)</td>
<td>2(7.41)</td>
<td>0.584</td>
</tr>
<tr>
<td>AKI, developed (number %)</td>
<td>1(7.69)</td>
<td>0(0.00)</td>
<td>0.325</td>
</tr>
<tr>
<td>Use of bicarbonate for treatment (number %)</td>
<td>3(23.08)</td>
<td>10(37.04)</td>
<td>0.484</td>
</tr>
<tr>
<td>Mean hospital stay (day)</td>
<td>8.38±8.04</td>
<td>7.07±2.87</td>
<td>0.451</td>
</tr>
</tbody>
</table>

**Conclusions:** Our results indicated that we should not effort to maintain the desired diuresis of approximately 200 to 300 mL/hour for prevention of AKI in nontraumatic exertional rhabdomyolysis.
Kidney Function in Patients with Acquired Thrombotic Thrombocytopenic Purpura: Initial Presentation and Long-Term Outcomes  Dustin J. Little,1 Evaren E. Page,2 Lauren M. Mathias,3 Sara Vesely,2 James George,2 Walter Reed National Military Medical Center; Bethesda, MD; 1Univ of Oklahoma Health Sciences Center; Oklahoma City, OK.

Background: Little is known about the incidence, severity, and significance of AKI among TTP patients. In 2003, we used a simple SCr- and RRT-based OK AKI criteria to report low rates of AKI among TTP patients in the Oklahoma TTP registry. A recent report of high rates of severe AKI among TTP patients may be limited by referral bias as all subjects were admitted to the ICU of a single tertiary care medical center. Additionally, long-term renal and health outcomes following TTP complicated by AKI have not been reported. We analyzed kidney function of patients enrolled in the OK TTP registry, using both the OK and KDIGO criteria for AKI diagnosis and staging, and investigated for associations between AKI and subsequent CKD.

Methods: Acquired autoimmune TTP was diagnosed among patients referred to the Oklahoma Blood Institute, by identifying serum ( ˂10%) ADAMTS13 deficiency with the presence of an inhibitor or increased ADAMTS13 activity to ˃10% during remission. AKI was diagnosed and staged via the previously published OK and KDIGO criteria. eGFR was calculated using the CKD-EPI equation.

Results: The diagnosis of TTP was confirmed in 75 patients enrolled in the registry from 1995-2014. Rates of overall and severe AKI were 59% and 9% by KDIGO and 50% and 7% by OK criteria, respectively. Compared to subjects without AKI, initial mortality rates were significantly increased in OK (8/40 vs. 1/35; p=0.03) but not KDIGO AKI patients. eGFR of ˂60 mL/min/1.73m² at follow-up was more common among survivors with AKI by OK criteria (6/32 vs. 0/32 without AKI; p=0.02), but not by KDIGO criteria.

Conclusions: AKI is common among TTP patients, but severe AKI is rare. A simple, SCr-based OK criteria better identified patients at risk for early mortality and decreased eGFR at discharge, when compared to KDIGO. Our study provides the most complete and comprehensive description of AKI and long-term renal outcomes in TTP patients, and provides clinicians with important information to facilitate prognostic discussions and inform monitoring strategies in patients with a history of TTP.

Methods: We retrospectively evaluated the medical records of 311 patients who were operated on for femur fracture at Korea University Anam Hospital between January 2012 and October 2015. We evaluated the Incidence and Risk factors of AKI after Femur Fracture surgery and compared between AKI and normal kidney function (NKF) groups.

Results: The overall incidence of AKI was 9.2%. When compared to the normal kidney function (NKF) groups, the AKI group had a higher incidence of anemia (86.4% vs 51.6%, p = 0.001), hypotension (31.8% vs 15.4%, p = 0.021), ESR (45.5% vs 10.6%, p = 0.000), use of contrast agent (27.3% vs 6.9%, p = 0.001).

In logistic regression analysis of risk factors, age (p = 0.049), lower estimated glomerular filtration rate levels (p = 0.05), contrast use (p = 0.04), diabetes mellitus (p = 0.002), heart failure (p = 0.012) were statistically significantly correlated with the development of AKI.

Conclusions: After femur fracture was associated with longer hospitalization, morbidity and mortality. It is recommended that close evaluation and monitoring is needed for patients who have the risk factor of AKI after operation for femur fracture to reduce the possibility of AKI. In the future, We need prospective studies including biomarkers.

Funding: Private Foundation Support

Methods: The search looked at 12 databases and 2 trials registers in Nov 2015 with pre-defined eligibility criteria and quality assessment (QUADAS-2) by 2 reviewers. Meta-analysis used Bayesian hierarchical regression to estimate joint pooled sensitivity and specificity for AKI KDIGO stages 2-3 within 12 hours. Prospectively registered on PROSPERO ref. CRD42014051919.

Results: The search identified 122 original articles of which 29 were subject to full text review. Ten studies were included in the review; and 3 in the meta-analysis. The mean participant median age was 64 years and 58% were male. Using the high sensitivity cut-off (0.3), pooled sensitivity was estimated as 0.90 (95% CI 0.85-0.93) and pooled specificity as 0.49 (95% CI 0.40-0.55) (Figure 1). No clinical efficacy, clinical utility or cost-effectiveness studies were identified.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
of AKI are: drug-induced nephropathy, infections, autoimmunity-mediated diseases, cancer, and idiopathic interstitial nephritis. The cell-mediated response is more important than the humoral induced acute interstitial nephritis. For the definite diagnosis, a kidney biopsy is indicated. Microscopic linear or granular deposition of immunoglobulins and complement in the interstitium and/or on the tubule basal membrane is characterized and linked to AKI. Key to treatment is to identify the agent/drug, causing the disease and apply low-dose steroid therapy for 4 to 6 weeks. Alternative to corticosteroids is MMF.

Methods: Here we introduce the clinical case of a 45-years old woman with previously proven chronic membranous nephropathy, treated with Mycophenolate mofetil for 5 months. The aim of our study was to introduce the renal function (area 22.5 mm², creatinine 909 µmol/L), which led to additional acute morphological examination. The renal biopsy has shown focal lymphocyte infiltration in the interstitium and tubular atrophy, without immunofluorescent deposition of globulins.

Conclusions: Discontinuation of the treatment with Mycophenolate mofetil, corticosteroid infusion and dialysis improved the renal function, reaching the normal levels for the patient – creatinine 200 µmol/L.

PUB068
Epidemiology of Acute Kidney Injury in an American Inner City Population

Justin Lee Loy,1 Gayatri Lessey,1 Oseua J. Orec,1 Michael A. Fischman,2 Bhupinder K. Prapajati,1 Muner Mohamed,1 Asana Anderson,1 Alan D. Weinberg,2 Jonathan M. Barasch,1 Subodh J. Saggi,1 Nephrology, SUNY Downstate Medical Center, Brooklyn, NY;2 Biostatistics, Mount Sinai School of Medicine, New York, NY;1 Nephrology, Columbia Univ, New York, NY.

Background: Data on incidence of AKI in hospitalized patients can be extracted based on ICD codes. While these databases give insight into distributions of AKI across different populations, groups, gender and race during different time periods, they are limited in being retrospective with fragmented information on patient details. We prospectively conducted a study on hospitalized patients with specific details over a 3 year period to define our population phenotype to validate roles of biomarkers in AKI. We report the epidemiological and clinical characteristics of our predominantly African American (AA) inner city population who developed AKI.

Methods: Patients had their initial plasma, serum and urine stored for bio-banking. We gathered data on age, gender, race, BMI, DM, HTN, CKD, CHF, length of stay and medications given. Analysis was done by SAS 9.3, Chi square analysis and student “t” test. We gathered data on age, gender, race, BMI, DM, HTN, CKD, CHF, length of stay and medications given. Analysis was done by SAS 9.3, Chi square analysis and student “t” test.

Results: Mean age was 59.1±18 years, male:female ratio 1:4.1, 33% were AA, mean BMI 28.7±4.3, 69% HTN, 17% CKD and 25% CKD (GFR <60 ml/min/m² BSA). AKI was identified in 8.82%, was associated with DM p=0.05, HTN p=0.005 and polypharmacy p=0.0003. Average number of medications in patients with AKI was 12.

Conclusions: We gathered data on age, gender, race, BMI, DM, HTN, CKD, CHF, length of stay and medications given. Analysis was done by SAS 9.3, Chi square analysis and student “t” test. We gathered data on age, gender, race, BMI, DM, HTN, CKD, CHF, length of stay and medications given. Analysis was done by SAS 9.3, Chi square analysis and student “t” test.

PUB069
Incidence of Hypocalcemia in Pediatric Patients Receiving Continuous Renal Replacement Therapy and Tandem Therapeutic Plasma Exchange

Tara Loy,1 Jennifer L. Morris,1 Katharine Sigler,1 Ayse Akan Arikan,1,2 Popyapatamk Sirivaths,1,2 Texas Children’s Hospital, Houston, TX;1 Baylor College of Medicine, Houston, TX.

Background: Therapeutic plasma exchange (TPE) is often performed in tandem with dialytic therapy in pediatric patients as vascular access need and for continuous dialysis would limit separate procedures. There is dearth of data regarding the incidence of hypocalcemia with tandem procedures.

Methods: Retrospective review to evaluate the incidence of hypocalcemia during continuous renal replacement (CRRT) and tandem therapy performed at our institution from January 2012 through December 2014.

Results: Twenty-three patients underwent 115 procedures; median of 4 tandem sessions (IQR 2.5-5.5) were instituted per patient. Demographics: Median age 2.5 yrs [IQR 0.96-9.50], 35% male, wt 14.7 kg [IQR 10.0-36.2], and BSA 0.56 m² [IQR 0.45-1.14]. Liver failure with coagulopathy was the most common indication (64.5%). Continuous venovenous hemofiltration and centrifugal based TPE was performed in all patients. The median CRRT flow rate was 2.163 ml/1.73 m²/h [IQR 1.985-3.364] and apheresis duration 50 minutes [IQR 30.5-102.5]. Fresh frozen plasma (FFP) was the most common replacement fluid (96.5%); median FFP replacement volume 700 ml [IQR 500-2350]. Regional anticoagulation with 3% citrate solution (ACD-A) was used to provide anticoagulation for both CRRT and TPE. Median ACD-A rate was 90 ml/h [IQR 70-165]; intravenous (IV) calcium chloride infusion rate (2.16 ml/m² of elemental calcium) 60 ml/h [IQR 40-100]; inlet flow rate 38.5 ml/min [IQR 26.3-50.9]; ratio 1.8 [IQR 1.2-2.3].

During tandem therapy, median ionized calcium (Ca) was 1.12 mmol/L [IQR 0.96-1.19]; hypocalcemia (<1.0 mmol/L) occurred in 52 procedures (45%). Calcium boluses were given during 40 procedures (35%). Hypocalcemia was not affected by diagnosis, age, or inlet flow. Earlier institution data had shown only 3% hypocalcemia with non-tandem TPE.

Conclusions: Hypocalcemia occurred in nearly half of TPE procedures in tandem with CRRT even with IV calcium replacement at 1.8 x inlet flow. Exogenous calcium supplementation should be increased in patients undergoing tandem therapy to prevent hypocalcemia.

PUB070
AKI in Heart Failure Admissions and Impact of Non-Specialist Care

Rebecca E. Jenkins, Sarangia Gugathas, Juan Carlos Kaski, Lisa J. Anderson, Debashis Banerjee. St. George’s Hospital.

Background: Persistent AKI in heart failure (HF) can be associated with poor outcome, but the effect of specialist care is not clear. We investigated the impact of persistent AKI and specialist care on mortality, length of stay (LOS) in a inner-city UK hospital.

Methods: Data were analysed for all HF admissions between 1/3/2013-3/1/2015. Discharge- creatinine(crt) and crt-3months prior to admission determined persistent AKI using KDIGO criteria.

Results: Data on baseline crt were available in 953 out of 1056 admissions with acute HF. 138 [10%] of the 933 admissions were associated with AKI; 89-stage 1, 32-stage 2, 11-stage 3. Patients with AKI were similar compared to non-AKI in age [77±10 vs 77±13 years; p=0.961], diabetes [42% vs 40%; p=0.393], presence of systolic dysfunction [65% vs 57%; p=0.122], pre-existing stage 4/5 CKD [10% vs 12%, p=0.404], haemoglobin [11±2 vs 12±2 g/L; p=0.453]. AKI had higher potassium (K) [4.7±0.9 vs 4.3±0.6 mmol/L; p=0.000], higher BNP, longer (LOS) [13±12 vs 10±12 days; p=0.002], less ACEI/ARB therapy [46% vs 59%; p=0.006], higher in-patient mortality [33% vs 5%; p=0.000]. Mortality increased with worsening AKI Stage 1-24%, stage 2-43%, stage 3-64% [see figure]. In logistic regression age, AKI, CKD 4/5 were independent predictors of in-hospital mortality.

Conclusions: Persistent AKI during acute HF admissions was a strong independent predictor of mortality, which worsened with severe AKI, with longer admission, which was not significantly affected by non-specialist care.

PUB071
Fatal Milk Acid

Takombe Entezari. Internal Medicine, I, Ren, NY.

Background: Metformin associated lactic acidosis has been described but detailed presentation of this condition has not been recognized. We present a case of severe lactic acidosis in a patient with acute renal failure 24hrs after admission.

Methods: A 65 year old diabetic woman on metformin was admitted due to abnormal blood pressure, was normal to high and did not require any vasopressors. Her renal function eventually improved and dialysis was discontinued. Renal biopsy showed ATN, nephro sclerosis with features of focal global glomerulosclerosis. Metformin is actively excreted, un-metabolized, by transporters in the proximal tubules of the kidneys with an estimated half-life of 58hrs in renal failure. It is actively excreted, un-metabolized, by transporters in the proximal tubules of the kidneys with an estimated half-life of 58hrs in renal failure. It is

Results: Acidosis and lactate normalized with repeat dialysis. Throughout her hospital course, her blood pressure was normal to high and did not require any vasopressors. Her renal function eventually improved and dialysis was discontinued. Renal biopsy showed ATN, nephro sclerosis with features of focal global glomerulosclerosis. Metformin is actively excreted, un-metabolized, by transporters in the proximal tubules of the kidneys with an estimated half-life of 58hrs in renal failure. It is

Conclusions: Acidosis and lactate normalized with repeat dialysis. Throughout her hospital course, her blood pressure was normal to high and did not require any vasopressors. Her renal function eventually improved and dialysis was discontinued. Renal biopsy showed ATN, nephro sclerosis with features of focal global glomerulosclerosis. Metformin is actively excreted, un-metabolized, by transporters in the proximal tubules of the kidneys with an estimated half-life of 58hrs in renal failure. It is

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Application of Cardiothoracic Bioimpedance Hemodynamics and Volumetric Parameters in Acute Kidney Injury

**Background:** Evaluate application of cardiothoracic bioimpedance (CTBIA) hemodynamics and volumetric parameters in Acute Kidney Injury (AKI).

**Methods:** Cohort of 50 patients (mean age 71.2 years SD 6.1, 59.6% males) with AKI. Evaluate hemodynamic parameters (cardiac output – CO, cardiac output index – COI and systemic vascular resistance index – SVRI), thoracic volumetric parameters (Thoracic fluid volume TVF, Thoracic fluid index volume – TVFI and impedance (Z)) analytical (c-reactive protein – CRP, brain natriuretic factor -BNF-) and clinical parameters (hypotension, respiratory failure, renal replacements requirements and Karnofsky index –K-).

**Results:** Patients with lower vascular resistance and higher cardiac work, are associated with hypotension (lower systemic, hypovolemia%). Patients with higher BNF have low cardiac output with high vascular resistances (heart failure?). Lower cardiac output are associated with hypoaalbuminemia. Patients with higher thoracic volume have higher risk of respiratory failure and higher renal replacement therapy requirements (hyperlaxation?). Thoracic hypervolemia are associated with poor impedance (TVF r=-0.931 p< 0.001; TVFI r=-0.885 p=0.001) and poor chronic health status.

<table>
<thead>
<tr>
<th>CO/l min</th>
<th>COI/min/m²</th>
<th>TVF V/Kg/sm²</th>
<th>TVFI V/KgOsm/sm²</th>
<th>SVRI dyn s/cm²/m²</th>
<th>Z Ohm</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP p</td>
<td>ns</td>
<td>ns</td>
<td>-0.10</td>
<td>-0.353</td>
<td>0.022</td>
</tr>
<tr>
<td>BNF p</td>
<td>-0.303</td>
<td>0.054</td>
<td>ns</td>
<td>ns</td>
<td>0.462</td>
</tr>
<tr>
<td>ALB p</td>
<td>-0.426</td>
<td>0.034</td>
<td>ns</td>
<td>ns</td>
<td>0.426</td>
</tr>
<tr>
<td>Karnofsky</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Hypo</td>
<td>0.952</td>
<td>5.7</td>
<td>0.072</td>
<td>ns</td>
<td>0.004</td>
</tr>
<tr>
<td>Vent. Ais. R. p NO/YES</td>
<td>0.049</td>
<td>38.350</td>
<td>0.105</td>
<td>20.725.8</td>
<td>ns</td>
</tr>
<tr>
<td>RRT p NO/YES</td>
<td>ns</td>
<td>ns</td>
<td>0.005</td>
<td>0.037</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Conclusions:** CTBIA can be used to evaluate clinical evolution and therapy in AKI, as a patients with vasopositive state (inflammatory origin and high multiorgan failure risk) or thoracic hypervolemia (higher respiratory failure and intubation risk).

**Role of TIMP-2 and IGFBP7 in Predicting Outcomes of Post-Hospitalization Dialysis-Dependent AKI (PHD-AKI) Emad M. Abdel-Rahman, Jitendra K. Gautam. Nephrology, Univ of Virginia, Charlottesville, VA.

**Background:** Predicting outcomes of patients with PHD-AKI is important to ensure adequate medical management. This is becoming more crucial with CMS reversing their decision of mortality and dialysis-dependence after RRT-requiring AKI. Our outcomes included the incidence of IDH, RRT-related complications, in-hospital mortality and renal recovery.

**Methods:** In this pilot study, 10 patients with PHD-AKI were studied. Within the 90 days PHD, 5 remained dialysis dependent (group 1) and 5 recovered their kidney function (group 2). Blood and urine were obtained from each patient on their first hemodialysis session PHD. TIMP-2 and IGFBP7 in plasma and urine were determined using the R & D Systems (Minneapolis, MN, USA) sandwich ELISA as per manufacturer’s recommendations. Frozen samples were thawed and brought to room temperature, appropriate dilutions were tested for the biomarkers along with known standard. Final absorbance at 450 nm was read using Synergy2 from Biotek Corp (Winooski, VT, USA).

**Results:** Patients with lower vascular resistance and higher cardiac work, are associated with hypotension (lower systemic, hypovolemia%). Patients with higher BNF have low cardiac output with high vascular resistances (heart failure?). Lower cardiac output are associated with hypoaalbuminemia. Patients with higher thoracic volume have higher risk of respiratory failure and higher renal replacement therapy requirements (hyperlaxation?). Thoracic hypervolemia are associated with poor impedance (TVF r=-0.931 p< 0.001; TVFI r=-0.885 p=0.001) and poor chronic health status.

<table>
<thead>
<tr>
<th>Initial creatinine</th>
<th>Peak creatinine</th>
<th>Creatinine decrement</th>
<th>Lower creatinine</th>
<th>Lower hemoglobin</th>
<th>Lower leukocytes</th>
<th>Basal creatinine</th>
<th>Peak brain creatinine</th>
<th>Peak brain natriuretic factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.75</td>
<td>2.12</td>
<td>1.50</td>
<td>2571</td>
<td>9.1</td>
<td>120.802</td>
<td>8.1</td>
<td>7129</td>
</tr>
<tr>
<td>Exitus</td>
<td>1.92</td>
<td>2.23</td>
<td>1.55</td>
<td>2407</td>
<td>8.0</td>
<td>83127</td>
<td>13.2</td>
<td>12673</td>
</tr>
<tr>
<td>p</td>
<td>0.007</td>
<td>&lt;0.001</td>
<td>0.005</td>
<td>0.058</td>
<td>0.032</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Treatment:** Exitus rate was higher in replacement therapy (no requirement: 8.5%, IHD 30.6%, CRRT 45%, and IHD with CRRT 40.6%) (p<0.001).

**Conclusions:** No or YES are good prognostic predictors of outcome. Oliguria and respiratory failure correlates to mortality. Prognostic depends on health state prior to injury and evolution of creatinine, hematological, protein, inflammatory and cardiac congestion status. Use of renal replacement therapy predicts a worse prognosis.

**Fractional Excretion of Sodium (FeNa) <1 Is Sensitive but Not Specific for Hepatorenal Syndrome (HRS) Diagnosis in Cirrhotic Patients Henri Wadei, Ali Alsaud, Transplantation, Mayo Clinic, Jacksonville, FL; 2 Medicine, Div of Nephrology and Hypertension, Mayo Clinic, Jacksonville, FL.

**Background:** FeNa<1 favors HRS diagnosis in cirrhotic patients with renal dysfunction however FeNa<1 has not been previously correlated with renal histology. Albu: correlate FeNa<1 with histological findings on renal biopsy and determine the accuracy of FeNa in diagnosing HRS.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: 88 liver transplant candidates with renal dysfunction and/or proteinuria underwent percutaneous kidney biopsy, iothalamate GFR, 24-hr urine collection for urinary Na and protein excretions and random urine Na and creatinine. FeNa was calculated using the equation [(urine sodium x serum creatinine)/(serum sodium x urine creatinine)] x 100. Patients on renal replacement therapy were excluded.

Results: Table 1 represents patients’ characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>60 ± 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>57 (65)</td>
</tr>
<tr>
<td>HCY infection</td>
<td>40 (45)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35 (40)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>40 (45)</td>
</tr>
<tr>
<td>Iothalamate GFR ml/min</td>
<td>28 ± 14</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.9 ± 0.9</td>
</tr>
<tr>
<td>Serum Na (mEq/dl)</td>
<td>137 ± 5</td>
</tr>
<tr>
<td>24-hr urine protein excretion (mg/dl)</td>
<td>87 (0-13625)</td>
</tr>
<tr>
<td>FeNa=1</td>
<td>77 (87)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>40 (45)</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>64 (72)</td>
</tr>
</tbody>
</table>

Kidney Biopsy

<table>
<thead>
<tr>
<th>HRS</th>
<th>10 (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPGN</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Minimal histology</td>
<td>15 (17)</td>
</tr>
<tr>
<td>&gt;30-40% IF/GS</td>
<td>38 (43)</td>
</tr>
</tbody>
</table>

Results: 77 (87%) had FeNa<1. FeNa<1 was present in 10/10, 10/12, 11/13, 12/15 and 34/38 in patients with HRS, ATN, MPGN, minimal histological findings and advanced (≥30-40%) interstitial fibrosis (IF) and/or glomerulosclerosis (GS), respectively (P<0.6). FeNa<1 was 100% sensitive and 14% specific in diagnosing HRS. ROC confirmed that FeNa<1 performs poorly in diagnosing HRS, AUC=0.58.

Conclusions: FeNa<1 is common in cirrhotic patients with renal dysfunction and does not differentiate between HRS and other causes of renal dysfunction.

PUB078

Dapsone Induced Methemoglobinemia: A Case Series

Sohail Abdul Salim, Jasmina Craici, Svetla Rani Kanduri, Yougandhar Akula. Nephrology, Univ of Mississippi Medical Center, Jackson, MS.

Background: Dapsone, a sulfone antibiotic, has been used in renal transplant recipients for prophylaxis of Pneumocystis Carinii Pneumonia in patients with documented sulfon allergy. Acquired Methemoglobinemia caused by dapsone is not uncommon in transplant patients with normal G6PD levels. Discrepancy between pulse oximetry (PO) and arterial oxygen saturation (SpO2) readings, a phenomenon known as “saturatation gap” is noted.

Methods: None

Results: Case 1: 72 Male with Deceased Donor Renal Transplant (DDRT) with sob for 2-3 weeks on mild to moderate exertion, found to have Pulse oximetry saturation of 82% and arterial Po2 of 100 with methemoglobin level of 21.5%Case 2: 24 female with lupus nephritis and hemolytic anemia. Few weeks prior she was switched from Bactrim to dapsone. Pt methemoglobin level was 4.6% and came down to normal levels as soon as dapsone was stopped. Case 3: 52 y/o Female DDRT admitted for worsening SOB and dyspnea on exertion with methemoglobin level of 7.2%

Conclusions: Dapsone might be reasonable alternative in TMP/SMX intolerance, but clinicians should have a higher suspicion of Methemoglobinemia. Symptoms can occur at Methemoglobin levels ranging from 1.9% to 26.8%, mostly at the 100 mg dose and could be worse in patients with preexisting coronary and chronic lung disease. Adequate level of suspicion with appropriate labs could lead to early recognition, which is key to effective management.

PUB079

The Activation of Notch3 in Endothelial Cell Aggravate Renal Fibrosis in Obstructive Nephropathy

Hai Xu, Jin Zhang, Ting Ding. Nephrology Dept, Xiangya Hospital, Central South Univ, Changsha, Hunan, China.

Background: Notch3 has been showed to be protective in generating functional arteries. But the role of notch3 activation in chronic kidney injury (CKD) is controversial. Angiogenesis II (AngII) plays a key role in arteries function and the progression of kidney diseases. This study was to assess the expression of notch3 in obstructive nephropathy.

Methods: The expression of notch3 in injured kidney of obstructive nephropathy patients was analyzed by immunohistochemistry. The expression of notch3 and (AngII) was detected in 3, 7, 14 and 21 unilateral ureteral occlusion (UOU) rats by western blot or realtime PCR. After the stimulation of AngII, the expression of notch3 in proximal tubular or endothelial cell lines was assessed by western blot or realtime PCR.

Results: The expression of notch3 was upregulated in the renal cortex of obstructive nephropathy patients. Consistently, the expression of notch3 and AngII increased time-dependently in the renal cortex of UOU rats. Moreover, after the stimulation of AngII, the expression of notch3 was up-regulated in endothelial cells but not the proximal tubular epithelial cells.

Conclusions: AKI was common in hospitalized cancer patients and associated with high mortality. Recognition of AKI and referral to a nephrology unit might improve hospital mortality after HA-AKI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: The activation of notch3 plays a role in obstructive nephropathy and renal fibrosis. AngII is an important physiological factor in triggering the expression of notch3 expression. Blocking the expression of notch3 may be a potential therapeutic for renal fibrosis.

Funding: Government Support - Non-U.S.

PUB080

7,8-DHF Treatment Induces Cyr61 Expression to Suppress Hypoxia Induced ER Stress in HK-2 Cells

Yan Xu, Rui Ma. Dept of Nephrology, Affiliated Hospital of Qingdao Univ, Qingdao, Shandong, China.

Background: Hypoxia is the leading cause to AKI and the proximal renal tubular cells are the most damaged part in kidney. In this study we exploited function of 7,8-DHF in protecting human proximal tubular cell line HK-2 from hypoxia insults.

Methods: The cultured HK-2 cells were pretreated with 7,8-DHF and exposed to 12 h hypoxia. Then the cytotoxicity of 7,8-DHF and cell viability were determined. The protein expression of the possible downstream biomarker as cysteine-rich protein 61 (Cyr61) and endoplasmic reticulum (ER) stress marker as CCAAT/enhancer-binding protein homologous protein (CHOP) were identified by western blot analysis. Real-time PCR was selected to test the mRNA expression of ER stress associated signaling pathway, such as protein kinase-like ER kinase (PERK), Glucose-regulated protein 78 (GRP78), splicing X-box-binding protein 1 (XBP1), activating transcription factor 6 (ATF6). In study of overexpression of Cyr61, apoptotic rate, mRNA and protein levels of ER stress markers and apoptotic parameter as cleaved Caspase-3 were detected.

Results: In hypoxia induced HK-2 cells, 7,8-DHF improved cell viability. Mechanistically, 7,8-DHF could elevate the expression of cysteine-rich protein 61 (Cyr61), a protective immediate early gene in AKI. In addition, treatment of 7,8-DHF decreased CCAAT/enhancer-binding protein homologous protein (CHOP) expression, which is a mark protein during endoplasmic reticulum (ER) stress activation. Intriguingly, overexpression of Cyr61 significantly reduced CHOP expression.

Conclusions: 7,8-DHF could protect HK-2 cells from hypoxia insult by activating Cyr61 signaling and suppressing ER stress and have potential clinical implications for the treatment of AKI.

Funding: Government Support - Non-U.S.

PUB081

Activation Inhibits but Deactivation of the Renin Angiotensin System Accelerates Differentiation of Human Podocytes

Vinita Vishnou, Abheepsa Mishra, Ashwani Malhotra, Pravin C. Singhal. Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North West Medical School, Great Neck, NY.

Background: Activation of renin angiotensin system (RAS) has been shown to play a role in the development of focal glomerulosclerosis (FSGS). Loss of critical number of podocytes has been incriminated for the development of FSGS. Usually, a subset of parietal epithelial cells (PECs) or cells of renin lineage serve as progenitors cells and are differentiated into podocytes to repopulate the glomerular basement membrane. We asked whether activation of the RAS in adverse milieu such as high glucose would prevent but inhibition of the RAS would accelerate differentiation of podocytes.

Methods: Immortalized proliferating human podocytes (HPs) which proliferate at 33°C but differentiate at 37°C (differentiation complete on 10th day). HPs were incubated in media containing either buffer or high glucose (HG, 30 mM) for the next 48 hours. HPs were treated under similar conditions with variable concentrations of HG (5, 10, 15, 25, 30 mM). Protein blots and cDNAs of SD/HPs were probed for podocalyxin.

Results: HG down regulated podocalyxin in SD/HPs in a dose dependent manner. Similarly, HG down regulated nephrin in LD/HPs in a dose dependent manner. Losartan, captopril, and aliskiren up regulated expression of podocalyxin as well as of nephrin both at basal and HG-stimulated states.

Conclusions: Activation of the RAS in high glucose milieu prevents whereas inhibition of RAS accelerates differentiation of podocytes.

Funding: NIDDK Support

PUB082

How Many Podocyte Autophagosomes in Two Kinds of Nephropathy: IgAN and IMN?

Shiki Liang, Zhejiang Provincial People's Hospital, Dept of Nephrology, Hangzhou, China.

Background: The aim of this study was to investigate the number of autophagosomes in podocyte from kidney tissue of immunoglobulin A nephropathy (IgAN) and idiopathic membranous nephropathy (IMN).

Methods: The changes of kidney tissue pathology were detected after hematoxylin and cosin (HE), periodic acid-Schiff (PAS), Masson’s trichrome and immunofluorescence (IF). The autophagosomes of podocyte were analysed by transmission electron microscopy (EM). Clinical data, including age, gender, edema, serum creatinine, estimated glomerular filtration rate (eGFR), hematouria, urine protein excretion and serum albumin, were collected from inpatient medical record.

Results: It was found that the number of autophagosomes in podocyte of nephropathy group were lower when compared with the control group. At the same time we did not find any correlation in clinical data applied in the future due to its variability. However, since it is a carbon-based nanomaterial, its potential toxicity is a health and environmental concern. Kidney is one of the primary organs for the assessment of nanomaterial toxicity.

Methods: By using a near infrared fluorescence (NIRF) DNase activity probe, we have established that graphene induces nephrotoxicity that occurs mainly through DNA destruction. A non-modified graphene (50 μg/ml) exposed with cultured rat kidney tubule epithelial NRK-52E cells induced an LDH release and a TUNEL-type DNA fragmentation usually associated with cytotoxicity.

Results: Dark-field and phase-contrast microscopy showed that TUNEL-positive cells have significantly higher graphene content than TUNEL-negative cells. DNase activity quantified in live cells using the oligonucleotide-based NIFB probe was increased in the presence of graphene in parallel with the TUNEL. Cell death DNases, such as caspase-activated DNase (CAD), endonuclease G (EndoG), and DNase I, and the marker of oxidative stress, heme oxygenase-1 (HO-1) were shown to be elevated. We then applied specific chemical inhibitors to determine whether the DNase and oxidative pathways are mechanistically involved in the graphene toxicity.

Conclusions: The hypothesis was confirmed by the fact that all of the inhibitors abolished the graphene toxicity. In summary, the measuring of DNase activity by using NIFB probe in combination with TUNEL assay and are appropriate tools for the assessment of graphene toxicity, and oxidative injury and DNases are the mechanisms of the latter.

Funding: NIDDK Support, Other U.S. Government Support, VA Support

PUB084

Calcitriol Mitigates Advanced Glycation End Product (AGE)-Elicited Impairment of Renal Function

Taria Fahmi,1 Alena Savenka,1 Alexei G. Basnakian. 1, 2 Dept of Pharmacology and Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR, 1, 2 Central Arkansas Veterans Healthcare System, Little Rock, AR.

Background: Calcitriol is a vitamin D3 metabolite. It is used to treat multiple renal diseases, including chronic kidney disease, end-stage renal disease, and hyperparathyroidism. It is also used in the treatment of AKI.

Methods: Our previous studies have found AGE-HSA can induce the initial T CD4+ T cells to differentiate into Th17 cells by RAGE-RO8rt signaling. In addition to regulate calcium and phosphorus metabolism, Calcitriol has immunomodulatory effects. The main purpose of this experiment is to explore whether calcitriol could regulate advanced glycation end products elicited Impairment between Th17 and Treg Cells.

Results: The changes of kidney tissue pathology were detected after hematoxylin and cosin (HE), periodic acid-Schiff (PAS), Masson’s trichrome and immunofluorescence (IF). The autophagosomes of podocyte were analysed by transmission electron microscopy (EM). Clinical data, including age, gender, edema, serum creatinine, estimated glomerular filtration rate (eGFR), hematouria, urine protein excretion and serum albumin, were collected from inpatient medical record.

Conclusions: The activation of notch3 plays a role in obstructive nephropathy and renal fibrosis. AngII is an important physiological factor in triggering the expression of notch3 expression. Blocking the expression of notch3 may be a potential therapeutic for renal fibrosis.

Funding: Government Support - Non-U.S.
(4) AGE-HSA up-regulated expression RORγ. With pretreatment of calcitriol, there was reduced the expression of RORγt, HIF-1α and STAT3 induced by AGEs and increased expression of Foxp3.

Conclusions: In patients with diabetic nephropathy, there was negatively correlated between the content of vitamin D and the proportion of Th17 cells and Treg cells, and calcitriol mitigates AGE-HSA elicited imbalance between Th17 and Treg cells via VDR. State-3+ RORγt/Foxp3 Pathway. Funding: Government Support - Non-U.S.

PUB085

Enrichment of Collecting Duct Cells by FACS Sorting from Whole Kidney Using L1-CAM Yasunobu Ishikawa,1 Sorin V. Fedele,2 Chao Zhang,2 Saori Nishio,1 Stefan Somlo,1 Medicine II, Hokkaido Univ, Sapporo, Hokkaido, Japan;1 Internal Medicine, Yale Univ School of Medicine, New Haven, CT.

Background: The sensitivity for discovering in vivo biological effects of gene mutations in whole kidney tissue is compromised by the complexity resulting from cell type heterogeneity in tissue. For example, inactivation of S6K3, one of genes that causes human autosomal dominant polycystic liver disease, is known to result in increased spliced XBPI (XBPIa), a transcription factor involved in the unfolded protein response. However, when using whole kidney protein and RNA (ASN, 2015 TH-OR066), this response was undetectable in whole kidney tissue following inactivation of S6K3 only in collecting ducts (CD). We therefore investigated if whole kidney type specific enrichment of CD from whole kidney by FACS sorting.

Methods: WT (wild type), SKO (S6K3fl/fl;Pkhd1-cre), DKO (S6K3fl/fl;Pkd1-cre) kidneys at postnatal day 35 were harvested and a single cell suspension was made. L1-CAM, a transmembrane glycoprotein belonging to the Ig superfamily of cell adhesion molecules, was conjugated to Alexa Fluor 647. Cells were stained with L1-CAM-647 (L1) and LTL-FTC (LTL) (a proximal tubule maker) prior to analysis using MoFlo cell sorters.

Results: IF showed that L1-CAM co-localized with TH positive and AQP2 positive tubules, indicating L1-CAM is expressed in murine thick ascending limb of loop of Henle and CD. L1-CAM+ LTL+ LTL- cells were separated by FACS. In whole kidney mRNA, expression of megalin (proximal tubule) is ~3-4 fold higher than AQP2 and ENaC (CD). We therefore investigated cell type specific enrichment of CD from whole kidney by FACS sorting. When using whole kidney protein and RNA (ASN, 2015 TH-OR066), this response was undetectable in whole kidney tissue following inactivation of S6K3 only in collecting ducts (CD). We therefore investigated cell type specific enrichment of CD from whole kidney type specific enrichment of CD from whole kidney by FACS sorting.

Conclusions: We present an improved method for resolving CD’s expressing L1-CAM from whole kidney. With this technique, we have demonstrated that L1-CAM is expressed in murine thick ascending limb of loop of Henle and CD. This method will increase our ability to study gene function, gene expression and specific changes in gene transcription.

PUB086

Up-Regulation of Liver Hnf1α Gene Expression—A Possible Cause of Elevated CRP Biosynthesis Accompanied Inflammation in Experimental Chronic Renal Failure Elżbieta Sucajtys-Szulg, Marek Szolkiewicz, Bolesław Rutkowski, Alicja Debska-Slizien. Dept of Nephrology, Transplantology and Internal Medicine, Medical Univ of Gdańsk, Gdańsk, Poland.

Background: High sensitivity C-reactive protein (hsCRP), a marker of inflammation and predictor of cardiovascular risk is usually elevated in CKD patients. Regarding that HNF1α activates Cyp gene expression through binding to specific site present in promoter of this gene, we examined HNF1α and CRP mRNA levels in the liver and serum CRP concentration in rats with experimentally induced chronic renal failure (CRF).

Methods: Rats underwent 5/6 nephrectomy or a sham surgery. Liver expressions of Crp, Hnf1α genes were quantified by qPCR. Serum CRP concentration were estimated with immununoassay.

Results: Experimental CRF was associated with significant increase of liver HNF1α mRNA (approx. 2-fold greater that in controls (CON) and pair-fed (PF) rats). The pattern of changes in liver HNF1α mRNA levels strictly resembles the pattern of changes in liver CRP mRNA. These differences in liver CRP mRNA levels were parallelized by differences in serum CRP concentration (179±19 µg/ml in CON; 219±41 µg/ml in PF; 392±42 µg/ml in CRF respectively). We found positive correlations between the liver levels of HNF1α mRNA and the levels of serum CRP mRNA (r=0.78, p<0.01) and serum CRP concentration (r=0.83, p<0.01). Moreover, strong positive correlation between the liver levels of CRP mRNA and serum CRP concentrations (r=0.85, p<0.01) was found.

Conclusions: The results presented hereby indicate that up-regulation of Hnf1α gene expression was associated with significant increase of liver CRP mRNA and serum CRP concentrations in rats with CRF. Considering the above discussed data, it is likely that HNF1α plays an important role in controlling CRP biosynthesis in CRF. Our finding provide a new information about coordinated up-regulation of Hnf1α and Crp genes in liver and association of this events with inflammation in chronic renal failure.

PUB087

The Exploratory Analysis for Characteristics and Classification According to C4d Staining in Glomerulonephritis Na Kyong Hwang, Jong Man Park, Harin Rhee, Il Young Kim, Eun Young Seong, Dong Won Lee, Soo Bong Lee, Ihm Soo Kwak, Sang Heon Song. Internal Medicine, Pusan National Univ School of Medicine, Busan, Korea.

Background: The C4d is widely used as a footprint of the complement activation by classic or lectin pathway. It has mainly applied to antibody mediated rejection in kidney transplantation. A few studies have suggested that the C4d would have an important role in glomerulonephritis. This study aimed to analyze the C4d staining status at the time of renal biopsy and its association with clinical characteristics in glomerulonephritis.

Methods: This retrospective study included 392 patients who underwent renal biopsy between 2009 and 2016. We categorized the patients according to the C4d deposit and compared the baseline characteristics.

Results: The C4d deposits were detected in 29.1% (69/237) with IgA nephropathy (IgAN), 67.1% (47/70) with membranous nephropathy (MN), 39.5% (17/43) with minimal change disease (MCD), 57.1% (8/14) with membranoproliferative glomerulonephritis (MPGN), and 71.4% (20/28) with lupus nephritis (LN). It deposits mainly in the mesangium (IgAN, MCD, LN) and the glomerular capillary wall (MN, MPGN, LN). Clinically, the group having mesangial C4d deposit had higher proteinuria level compared with C4d-negative group in IgAN (p=0.045). However, there was no significant difference with baseline clinical characteristics in other glomerulonephritis. Interestingly, IgM was co-localized with C4d in IgAN (43.5% vs. 30.4%; p=0.053), MN (38.3% vs. 14.3%; p=0.048), MCD (40.0% vs. 7.1%; p=0.008), and LN (61.5% vs. 13.5%; p=0.008) compared with C4d-negative groups. The C4d-positive group has lower frequency of C3 staining and higher frequency of C4 staining in IgAN. There was no relationship between IF staining and serum level of Immunoglobulin or complements.

Conclusions: The C4d positively deposited with high frequency in glomerulonephritis and the C4d positive area was so variable according to the type of glomerulonephritis. Additionally, IgM was co-localized with the C4d and the further evaluation for the role of IgM is necessary. In the future, extended study is needed for the prognostic role of the C4d through long-term follow-up.

PUB088

Podocyte Adhesion to Collagen-Coated Surface Is Affected after Exposure to Serum of Patients with Preeclampsia M. Lourdes Gonzalez Suarez,1 Allan W. Ackerman,1 Sonu Kashyap,1 Muthuvel Jayachandran,2 Natasa Milic,2 Wendy White,1 Joseph P. Grande,3 Vesna D. Garovic1, Mayo Clinic, Rochester, MN;2 Medical Faculty Univ of Belgrade.

Background: Podocyte proteins, such as nephrin, podocin, and synaptopodin maintain the structure and function of the slit diaphragm. Injury to this structure causes proteinuria and foot process effacement. Podocyturia has been described in preeclampsia. It remains unclear the mechanism of injury that causes podocytes detachment from the glomerular basement membrane in preeclampsia.

Methods: We conducted cell adhesion assays on collagen-coated plates, using an immortalized human podocyte cell line after 3-4 weeks of differentiation. Podocytes were exposed to serum of patients with preeclampsia (n=7) and normotensive pregnancy (n=10) at delivery. Fetal bovine serum (FBS) was used as control. Non-attached living podocytes were detected by flow cytometry. For Western blots, lysates of podocytes were incubated with antibodies against nephrin, podocin, synaptopodin, and integrin β1. Experiments were done in triplicates. Statistical analysis was done using paired t-test and Wilcoxon-sign-rank.

Results: There was a significant increase (p=0.03) in number of living podocytes that were not able to adhere to the surface after incubation with preeclampsia versus normotensive sera. Expression of podocin in suspended cells was decreased after incubation with preeclampsia versus normotensive sera. Additionally, IgM was co-localized with the C4d and the further evaluation for the role of IgM is necessary. In the future, extended study is needed for the prognostic role of the C4d through long-term follow-up.

Conclusions: Podocin expression is decreased in non-attached cells after exposure of preeclampsia serum and may represent a disease-specific mechanism for podocyte detachment that may contribute to podocyte dysregulation in preeclampsia.

Funding: Private Foundation Support
Antiphospholipase A2 Receptor Antibody Titer Is Associated with Membranous Nephropathy Disease Activity Regardless of Pathological Grading  
Jian Jin, Zhejiang Provincial People’s Hospital, Dept of Nephrology, Hangzhou, China.

Background: To study the distribution of syndrome differentiation in Traditional Chinese Medicine (TCM) on diabetic kidney disease (DKD) by collecting clinical data, and have a statistical processing at last.

Methods: Between the DKD patients through pathological diagnosis which have more than one year disease course, to classify by the Tervaet criterion of pathological stage of DKD, to differentiate the syndrome differentiation in TCM by collecting clinical data, more than one year disease course, to classify by the Tervaet criterion of pathological stage of DKD, to differentiate the syndrome differentiation in TCM by collecting clinical data, have a statistical processing at last.

Results: We collected 353 DKD patients meeting the criterion in total, classified by the pathological stage criterion of DKD, among them there were 52 patients with phase I, 90 patients with phase IIa, 29 patients with phase IIb, 141 patients with phase III, 41 patients with phase IV. Among syndrome differentiation, there were 13 patients with Yin-Xu-Zao Re type, there were 151 patients with Qi-Yin-Liang Xu type, there were 140 patients with Pi-Shen-Qi Xu type, there were 49 patients with Yin-Yang-Liang Xu type, there were 19 patients with Han-Shi type, there were 68 patients with Shi-Re type, there were 212 patients with Xu-Yue type, there were 54 patients with Tan-Yu type. In the patients with Yin-Xu-Zao Re type, the renal interstitial inflammation was more serious than other types. In the patients with Pi-Shen-Qi Xu type, the glomerular segmental sclerosis, nodular changes, and fibrinoid exudation were more serious than other types significantly. Multivariate COX analysis showed that syndrome differentiation was independent risk factors for renal prognosis.

Conclusions: Among the syndrome differentiation of DKD, Qi-Yin-Liang Xu type and Yu-Xue type were more frequently than other types. The result showed that syndrome differentiation was correlated significantly with pathological stage of DKD, Yin-Yang-Liang Xu type and Tan-Yu type were independent risk factors for renal progression in DKD.

PUB903
ZNF268 Mediates Podocyte Response to PAN through Interaction with NF-kB Pathway  

Background: Nephrotic Syndrome (NS) is a progressive kidney disease that is characterized by protein leakage into the urine. In vivo induced nephrosis by puromycin aminonucleoside (PAN) leads to the onset of proteinuria. The glomerular visceral epithelial cells (podocytes) and their injury are central to the development of proteinuria. Nuclear factor κB (NF-κB) has been implicated in the podocyte injury and onset of proteinuria. Observation, in systems other than podocytes, suggested the involvement of transcription regulation of zinc finger protein ZNF268 in mediating NF-κB pathway.

Methods: ZNF268 protein expression was analyzed in differentiated human podocyte cells. The interaction between ZNF268 and NF-κB and family members in the context of podocyte response to sub-lethal doses of PAN treatment was also studied.

Results: Expression of different isoforms of ZNF268 was seen by Immunoblotting in differentiated podocytes including ZNF268a and ZNF268b. ZNF268 showed diffused cytoplasmic and focal nucleus localization. Sub-lethal doses of PAN treatment (5, 10, and 20 μg/ml) caused accumulation of ZNF268 and NF-κB-p65 in the nucleus. Also an interaction between ZNF268 and NF-κB-p65 was seen in the PAN-treated differentiated podocytes.

Conclusions: These observations highlight the potential role of ZNF268 as a mediator of response to PAN treatment in human cultured differentiated podocytes.

Funding: Government Support - Non-U.S.
Chemical Induction of Proteinuria in Larval Zebrafish Using Puromycin
Philipp Niegemann,1 Patricia Ann Schroder,2 Heiko Joachim Schenk,1 Hermann G. Haller,1 Mario Schiffer,1 Hanover Medical School; 1MDI Biological Laboratory.

Background: Zebrafish have become a widely used model organism in glomerular kidney research. Developing a method that produces a standardized glomerular proteinuria phenotype in zebrafish through treatment with the fishwater would be an asset to high throughputs and testing of potential beneficial drugs. Thus far such a method does not exist.

Methods: We induced glomerular proteinuria phenotypes in zebrafish of different genetic backgrounds by treating the zebrafish embryos with Puromycin Aminocomycoside (PAN) in the fishwater at varying timepoints. Treatment with PAN was conducted at timepoints from 44hpf to 50hpf. Different crosses of Tg(l-fabp:DBP-EGFP) zebrafish backcrossed onto AB or nacre background were examined. GFP fluorescence content was measured in 90hpf embryos' eyes as a readout of their proteinuria phenotype.

Results: Embryos homozygous for the nacre mutation were more susceptible to PAN treatment compared to embryos with an AB background. Moreover, we noted that a treatment at 46hpf reliably yields consistent phenotypes. Treatments at later timepoints were less effective in proteinuria induction. This specific line crossing is a good starting point for testing of drugs potentially beneficial for the treatment of proteinuria.

Conclusions: The basis of nacre is a mutation in the Mitf transcription factor regulating the hair-follicle hormone protein Dial. Further studies are on the way to examine the relation between the Mitf mutation and a higher susceptibility for a disruption of the filtration barrier.

Funding: Other NIH Support - under grant numbers R20GM100423 and P20GM104318

PUB095
Peroxisome Proliferator-Activated Receptor α-Dependent Renoprotection of Murine Kidney by Irbesartan
Yuki Kameda,1,2 Makoto Harada,1,2 Yousku Yamada,1,2 Akinori Yamaguchi,1 Koji Hashimoto.1 1Dept of Nephrology, Shinshu Univ School of Medicine, Matsumoto, Nagano, Japan; 2Dept of Metabolic Regulation, Shinshu Univ Graduate School of Medicine, Matsumoto, Nagano, Japan.

Background: Activation of renal peroxisome proliferator-activated receptor α (PPARα) is renoprotective, but there is no safe PPARα activator for patients with chronic kidney disease (CKD). Studies have reported that irbesartan (Irb), an angiotensin II receptor blocker (ARB), selectively activates PPARα. However, Irbe's renoprotective effects and the role of PPARα signaling in the renoprotective effects of Irbe are unknown.

Methods: Herein, these aspects were investigated in kidneys of wild-type (WT) and Ppara-null (KO) mice and in the murine protein-overload-nephropathy (PON) model, respectively. The results were compared with those of losartan (Los), another ARB that does not activate PPARα.

Results: PPARα and its target gene expression were significantly increased only in the kidneys of Irb-treated WT mice and not in KO or Los-treated mice, suggesting that the renal PPARα-activating effect was Irb-specific. Irb-treated-PON-WT mice exhibited decreased urine protein excretion, tubular injury, oxidative stress, and inflammatory and apoptosis-stimulating responses, and they exhibited maintained levels of fatty acid metabolism. Furthermore, the expression of PARPs and that of its target mRNAs encoding proteins involved in oxidative stress, pro-inflammatory responses, apoptosis, and fatty acid metabolism was maintained upon Irb treatment. These renoprotective effects of Irb were reversed by the PPARα antagonist MK886 and were not detected in Irb-treated-PON-KO mice.

Conclusions: These results suggest that Irb activates renal PPARα and that the resultant increased PARPs signaling mediates its renoprotective effects.

Drug Treatment Response in Patients Diagnosed with Membranoproliferative Glomerulonephritis in a Fourth-Level Hospital at the City of Barranquilla- Colombia
Gustavo Aroca Martinez,1,2 Andres A. Cadena,1,2 Alex A. Dominguez,2 Diana Carolina Silva,2 Josse E. Fontalvo,2 Henry J. Gonzalez Torres,2 Clínica de la Costa, Barranquilla, Colombia; 1Univ Simón Bolivar, Barranquilla, Colombia.

Background: The Membranoproliferative Glomerulonephritis (MPGN) is the third of four leading cause of End-stage renal disease among the glomerulonephritis diseases. However, the benefits of immunosuppression treatment and the prognosis in patients with MPGN are often unknown due to a lack of controlled clinical trials.

Methods: The retrospective study was conducted in a fourth-level hospital at Barranquilla and included medical records of patients with MPGN who underwent renal biopsies from 2007 to 2014. Patients were classified according to the type of treatment response in Responders and Non-responders. The Responders were those with Partial remission (of improvement of 55 of 13 cases), Complete remission (24hrs proteinuria <0.5g and inactive urinary sediment). Non-responders were those with worsening of disease or increase of pathological findings in the same, End-stage kidney disease and active urinary sediment. The immunosuppressive treatment included Mycophenolate and Cyclophosphamide alone and/or conjugated steroids. The treatment response was evaluated at 6 and 12 month.

Results: Of the 58 patients, 30 (52%) were females and 28 (48%) were males, with an overall 15 years mean age. The proliferative syndrome was the most common clinical presentation (70%) and 63% of the patients developed CKD at year to be evaluated. Serum Creatinine and 24hrs proteinuria did not change significantly in 6 months of treatment both males and females. 15 (25.8%) patients achieved remission (22.4% partial and 3.4% complete) and 45 (74.1%) failed to enter remission. 39.6% of females and 37.9% of males failed to achieve remission at 6 months. At 12 months, only 5 Patients (8.6%) achieved response (partial or complete) compared to 13 Patients (22.4%) of the previous semester.

Conclusions: MPGN is a major cause of CKD among the study population. Immunosuppressive drug therapy revealed no statistically significant benefits in remission of the impaired renal function at 6 and 12 months.

An Enzyme-Linked Immunosorben Assay (ELISA) for the Quantification of Mouse Endostatin as a Marker of Decreased Kidney Function in ETV6/RUNX1 and BCL2 Transgenic Mice
Joceline Wallwitz,1 Dagmar Stoiber,2 1The Antibody Lab GmbH, Vienna, 2Ludwig Boltzmann Inst of Cancer Research, Vienna.

Background: Endostatin is a protein with approximately 20 kDa produced by proteolytic cleavage of collagen XVIII. It is one of the most potent endothelial cell-specific inhibitors of angiogenesis with influence on proliferation, migration and apoptosis. In order to investigate the biological functions of Endostatin in more depth this work presents the development and validation of a specific, high-quality ELISA for detecting mouse Endostatin.

Methods: We developed an immunosassay which is based on a sandwich type format with an immobilized polyclonal antibody used to capture mouse Endostatin which is subsequently detected with a horseradish peroxidase labelled polyclonal anti-Endostatin antibody. To investigate the importance of Endostatin as a potential biomarker for impaired kidney function we determined serum concentration of Endostatin in ETV6/RUNX1 and BCL2 transgenic mice.

Results: The novel sample-saving Endostatin ELISA is optimized for mouse serum and plasma. Assay characteristics such as precision, dilution linearity and spike-recovery as well as sample stability meet high quality standards. In this study we demonstrate that the glomerulonephritis phenotype of ETV6/RUNX1 and BCL2 transgenic mice is also accompanied with higher Endostatin serum concentration.

Conclusions: In conclusion, this high-quality ELISA provides a reliable and accurate tool for the quantitative determination of mouse Endostatin in serum and plasma samples.

Deficiency of Purine P2X7 Receptor Protects against Progression of Chronic Renal Injury
Fabian Stupsie,1 Clemens L. Bockmeyer,2 Lars C. Rump,3 Sebastian Alexander Potthoff. 1Nephrology, Medical Faculty -Heinrich-Heine Univ, Dusseldorf, Germany; 2Pathology, Univ Clinic Erlangen, Erlangen, Germany.

Background: Chronic kidney disease (CKD) is defined as progressive loss of renal functional. The ionotropic ATP-gated receptors the P2X7 receptor (P2X7r) is detected on immune cells like lymphocytes, macrophages and denticell cells. P2X7r mediates Ca2+ and Na+ influx and mediates the release of pro-inflammatory cytokines (IL-1β and IL-18). Here, we test whether P2X7r-receptor deficiency prevents progression of CKD after subtotal nephrectomy (SNX).

Methods: SNX was performed in wild type (control) and P2X7r knock out (KO) mice and assessment was performed at different time points for 35 days. Kidneys were removed on day 35 for further assessment (quantitative PCR (qPCR), Western Blot (WB), histology).

Results: On day 35, remnant-kidney mass was significantly lower in P2X7r-KO mice. In P2X7r-KO mice urine urea level was significantly higher on day 5 and day 35, urine creatinine level was higher throughout day 5 to 35 and albumin-creatinine ratio was lower throughout day 10 to 35 compared to controls. Systolic blood pressure was significantly lower in P2X7r-KO mice. qPCR analysis showed reduced expression of collagen1, MCP-1 and NFκB in P2X7r-KO mice. WB showed a significantly lower levels collagen1 in P2X7r-KO mice. There was a significantly reduced number of scleosed glomeruli in P2X7r-KO mice compared to controls.

Conclusions: These data indicate reduced compensatory hypertrophy in P2X7r-KO kidneys. Urine samples suggest a preserved tubulo-interstitial function in P2X7r-KO mice. Despite small difference in systolic blood pressure, heart weight showed no difference, indicating blood pressure independent effects on organ injury. Reduced collagen1-expression in qPCR and WB indicate lower fibrosis, possibly contributing to reduced hypertrophy. The reduced number in sclerosed glomeruli and reduced proteinuria indicate a preserved glomerular function. Reduced inflammatory response indicated by lower MCP-1 and NFκB expression are likely the underlying cause for the attenuated progression of renal injury in this model. Therefore, P2X7 deficiency protects against progression of chronic renal injury.

Funding: Clinical Revenue Support
PEDF Protein as a Potential Therapeutic Candidate for Diabetic Nephropathy: Bioinformatic Analysis of Transcriptional and Posttranscriptional Elements Associated with Personalized Gene Expression

Mohammed A. Al-Obaide, Tetyana L. Vasylyeva. Pediatric, Texas Tech Univ Health Sciences Center, Amarillo, TX.

**Background:** Pigment epithelium-derived factor (PEDF) protein is encoded by SERPINF1 gene. PEDF is a multifunctional 50 kDa glycoprotein that belongs to the non-inhibitory Serine Protease Inhibitor (SERPIN) subfamily. It has renoprotective, neuroprotective, anti-angiogenic, anti-inflammatory and anti-apoptotic properties. We hypothesized that PEDF might be a potential therapeutic target for diabetic nephropathy (DN).

**Methods:** PubMed and publicly available databases, NCBI-GenBank, UCSC Genome Bioinformatics, Ensembl, ENCODE, FANTOMS, DBTSS, EPD, and Mpmdb were systematically utilized for search and bioinformatic analysis of PEDF regulatory sequences. The structural features of PEDF regulatory sequences were analyzed using DNALive tool. Algorithm Fold of “RNA structure” Webservers software was used to predict the secondary structure and stem-loops for the SERPINF1 mRNA transcript. Identification of un-reported mature sequences of miRNA was performed by using mirBase BLASTN search tool.

**Results:** We identified twenty three tissue specific transcription starting sites (TSS) and several specific enhancers for SERPINF1 gene, which showed variable expression patterns in kidney. SERPINF1 genomic space also contains promoter flanking, enhancers and CTCF regions. Many SNPs were identified within promoter flanking and enhancer regulatory sequences. Analysis of sequence-dependent properties of the SERPINF1 promoter showed specific correlation with the high and low expressed TSS. Stem-loops in the SERPINF1 mRNA secondary structure were also identified that are likely candidates for posttranscriptional regulation by miRNA.

**Conclusions:** This study provides further insight into the regulatory features that govern PEDF expression and reveals novel regulatory sequences associated with transcription process in kidney and might play a role in pathogenesis of DN. The SERPINF1 regulatory elements could be exploited in targeted therapy.
heart failure, chronic pulmonary obstructive disease, and hypertension. RM was defined as a patient's clinical data collection and transmission to a hospital or physician's office for monitoring and clinical action. Original searches were conducted Q1-2014 and complemented by 1-hour interviews with 4-5 payers/policymakers per country. Searches were updated Q4-2015/Q2-2016. Selection criteria included: policies focusing on telehealth or related terms. Data extracted consisted of: date of issue, disease areas covered, geographic scope, type of policy, and details. Each was rated according to criteria of successful public health policy including: targeted scope, identified criteria for decision-making framework, and evidence collection.

Results: Overall, more than 43 policies were identified: US=10, Italy=11, Germany=5, Spain=9, UK=8. 20 policies were nationally funded and 23 were regional. Most policies included funding for research (22) and financial incentives (13). 4 countries had policies to invest in health IT infrastructure (4) and RM guidelines (6). 24 policies were identified that may be leveraged for ESRD, of which 6 ranked the highest (US=3, Italy=1, Spain=2) for being an ongoing initiative involving data tracking, and/or established financial incentive for healthcare professionals. 10 were identified as potential long term opportunities, which included hospital or research programs (US=2, Italy=2, Germany=2, Spain=2, UK=2).

Conclusions: Our research identified policies that may be leveraged for ESRD population. Short term and long term opportunities will help to generate evidence of the benefit of RM for home dialysis.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

In Vitro Characterization of Qidni-X1, an Implantable Renal Replacement Therapy (Artificial Kidney) Device with Animal Blood

Funding: Qidni Labs Inc., San Francisco, CA.

Results: Qidni-X1 is an implantable renal replacement therapy under development for patients with end stage renal disease. We report on in vitro characterization of Qidni-X1 for hemodialysis and filtration of animal blood.

Methods: Blood was pumped into Qidni-X1 under normal blood pressure and the hematocrit was collected. For hemodialysis, dialysate was pumped into the device. The composition of blood was measured using VetScan V5-2 chemistry analyzer.

Results: 75 ml of fluid was removed in each hour of hemodialfiltration. In hemodialfiltration, reduction in urea and creatinine was recorded while no significant change in the level of albumin was observed.

Conclusions: In in vitro experiments with animal blood, Qidni-X1 has been effective in removing fluids during hemodialfiltration and reduction of urea and creatinine without significant change in albumin level in hemodialfiltration.

Funding: Pharmaceutical Company Support - Qidni Labs Inc., Government Support - Non-U.S.

Podocyte-Specific Depletion of the Vitamin D Receptor Gene Did Not Increase Albuminuria Excretion under Physiologic Condition in a Short Time

Funding: National Natural Science Foundation of China.

Background: Vitamin D and its analogues possess important beneficial activity in podocytes. To understand the role of vitamin D in regulating podocytes structure and function, the vitamin D receptor (VDR) gene was selectively deleted in podocytes using the Cre-LoxP system.

Methods: Exon 3 in the VDR gene was the target sequence. The recombinant VDR allele with the loxP bordered exon 3 was maintained in the C57BL/6j background. Mice harboring the recombinant allele (VDR loxP/loxP) were bred with EIIa-Cre to verify the efficiency of VDR knockout. Then, a podocyte-specific VDR knockout mice were generated for monitoring and clinical action. Original searches were conducted Q1-2014 and 2015. Mitochondria play essential roles in many aspects of biology, and their dysfunction has been linked to podocytes injury in diabetic nephropathy. Sirtuin 3 (SIRT3) is a nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylase, which mediates the deacetylation of various metabolic and antioxidant enzymes, in turn controlling energy metabolism and mitochondrial function. This study is to investigate the roles of Sirt3 in mitochondrial dysfunction of podocytes in diabetic mice.

Methods: To assess the expression of Sirt3 and mitochondrial complex activity, mitochondria were isolated from podocytes of 6-week-old diabetic (db/db) and non-diabetic (db/+m) mice. Moreover, diabetes was induced in Sirt3-knockout mice by streptozotocin (STZ) injection. The expression of complexes I, II, III, IV, and the complex I activity was measured by microplate assay kit purchased from Abcam.

Funding: Government Support - Non-U.S.

A New View on Glomerular Filtration

Funding: Qidni Labs Inc., San Francisco, CA.

Results: The glomerular filtrate flow represents the highest extravascular fluid flow in the body. It consists of the outflow from glomerular capillaries, through the GBM and into Bowman’s space. This latter step creates a problem: in contrast to its exit from capillaries, its entry is separated from the podocytes from the GBM. This problem has become clear since we learned that podocytes are lost by detachment from the GBM as viable cells. This also disproved the idea that foot processes (FPs), like pericyte processes, counteract the pressure driven expansion of the GBM. Their interdigitating pattern provides the channels filtrate flows through and the protection from slippage of the glomerular capillaries into Bowman’s space. They are bridged by the slit diaphragm (SD), a unique adherens junction. So far no satisfying hypothesis has been proposed that would explain the complexity of this structure.

Methods: Traditional view The pattern of FPs and filtration slits bridged by the SD is considered to be the passage of plasma proteins. It is a sensitive structure that is lost early in pathological situations leading to EF-occlusion, consistently associated with the loss of permissive function. Supporting the high filtrate flow has never been considered as a function of the SD.

Results: New view The slits between FPs channel the flow of filtrate into Bowman’s space. A filtrate flow of 25 nl/min (rat) creates a shear stress on the FPs as high as 8 Pa (Endlich and Endlich, Sem Nephrol 2012). Much lower values of shear stress (0.5 Pa) on podocytes in culture lead to their detachment. The SD, mechanically connecting opposite FPs, “utilizes” the shear stress on one FP to balance the shear stress on the opposite FP. This is supported by the observation that loss of the SD-connection between adjacent FPs represents the earliest failure starting detachment of a podocyte.

Conclusions: The elastic GBM continually adapts in area to capillary pulsatile forces. In conclusion, the FPs steadily change in area, shown us in the isolated perfused rat kidney. This ensures that the flow rate per unit area of SD, the source of local shear stress, does not change with varying filtration pressure.

Funding: Private Foundation Support

Angiotensin Receptor Blockers Prevent Kidney Injury by Preserving Podocytes

Funding: National Institutes of Health.

Background: Angiotensin receptor blockers (ARB) prevent chronic kidney disease. We assess blood pressure (BP) and proteinuria (UprotV) in spontaneously hypertensive rats (SHR) given variable doses of ARB therapy. To further assess glomerular injury, podocyte number is also evaluated.

Methods: SHR were untreated (C) or given 3 doses of candesartan daily (5 mg/kg (T5), 25 mg/kg (T25), and 250 mg/kg (T75)). Tail-cuff BP and 24-hour urine protein excretion were measured monthly for 14 months after which time the rats were sacrificed. Podocyte number was then measured by quantifying cells positive for WT-1 in each glomerulus based on immunohistochemistry staining.

Results: BP was very high in C but normal and not different in all treatment groups. UprotV was reduced in T5 and completely prevented in T25 and T75. Podocyte number was greatest in T75, fell with decreasing doses of ARB, and was least in C (means for T75: 18.2; T25: 15.0; T5: 12.9; C: 11.3. P value < 0.0001).

Conclusions: BPs are controlled in all doses of ARB therapy administered to SHR. However, high and very high doses of ARBs completely prevent UprotV. Increasing doses of ARB therapy are also associated with better preservation of podocytes. The reduced destruction of podocytes may be the reason for decreased UprotV seen at higher doses of ARB therapy. Loss of podocytes leads to uncovering of the basement membrane and increased protein filtration ultimately causing glomerulosclerosis. ARB therapy may thus be renal protective for its protection of the podocytes. BP is normal in all treated groups, but there is decreased UprotV and increased protein seen at the higher doses compared to standard dose of ARB therapy. Therefore, the mechanism of protection of podocytes and decreased UprotV may be independent of hemodynamic changes. It may instead be related to the therapy’s suppression of inflammation as has previously been theorized.
Results: We found that Sirt3 was decreased significantly in podocytes of db/db mice when compared to db/n mice. Furthermore, Sirt3-deficient diabetic mice induced by STZ experienced more severe mitochondrial dysfunction in podocytes, including reduced complex I activity and decreased level of mitochondrial DNA. In vitro, we also found that high glucose could reduce the expression of Sirt3 in podocytes and lead to decrease of mitochondrial complex I activity. Overexpression of Sirt3 in cultured podocytes can restore the activity of mitochondrial complex I.

Conclusions: Collectively, these data suggest that Sirt3 plays an important role in regulating the mitochondrial function in podocytes. Decrease of Sirt3 expression in podocytes lead to reducing mitochondrial complex I activity in diabetic mice. Our study uncovers a previously unrecognized role of Sirt3 in the pathogenesis of diabetic nephropathy, thus implicating Sirt3 as a new potential therapeutic target to treat diabetic nephropathy.

Funding: Government Support - Non-U.S.

PUB109

Fibrinogen Aα Type Amyloid: A Rare Entity

Amita Tandon,1 William F. Glass,1 Ala Abudayyeh,2 1Renal Diseases and Hypertension, The Univ of Texas Medical School at Houston; 2Div of Internal Medicine, Section of Nephrology, The Univ of Texas MD Anderson Cancer Center.

Background: With the help of laser micro dissection and mass spectrometry, patients who were initially misdiagnosed with AL amyloid can now be found to have sporadic hereditary amyloidosis. We describe a case of a patient who was initially diagnosed with AL amyloid and later found to have fibrinogen Aα type amyloid.

Methods: 77 year old man with atrial fibrillation was referred by his urologist for proteinuria. Lab work indicated IgG 921 mg/dL, IgM 43 mg/dL and IgA 475 mg/dL. Serum and urine protein electrophoresis was negative for an M protein. Kappa light chain was 26.1 mg/L, lambda light chain was 12.9 mg/L with a kappa to lambda light chain ratio of 1.72 (normal 0.26 - 1.65). Bone marrow biopsy showed normal tri-lineage hematopoesis with no evidence of plasma cell dyscrasia. Fat pad biopsy was also negative for amyloid. Bone survey showed no evidence of lytic lesions. The patient continued to have 8 g of proteinuria during this time. Due to the unclear etiology of the amyloidosis, repeat renal biopsy was performed for laser microdissection and mass spectometry to identify the amyloid protein. Mass spectrometry demonstrated fibrinogen A alpha type amyloid.

Conclusions: A high index of awareness is necessary for the diagnosis of hereditary sporadic amyloidosis. It can be misdiagnosed as AL amyloidosis, which carries significant implications for the patient, as he is now being treated for a condition he doesn’t have, and for family members, who then remain unaware that a hereditary amyloidosis runs in their family.

PUB110

Ischemia Leads to Increases in Tight Junction Mobility following FRAP

In Vivo

Alexander Louis Kolby,1 Josephine Axis,2 Robert L. Bacallao,2 Kurt Amstler.1 1Biology, Indiana Univ Purdue Univ Indianapolis, Indianapolis, IN; 2Nephrology, Indiana Univ School of Medicine, Indianapolis, IN; 3Biomedical Sciences, New York Inst of Technology College of Osteopathic Medicine, Old Westbury, NY.

Background: After an injury to a cells tight junction it is hypothesized that these junctions become immobile and have a slow turnover rate contributing to leak and polarity changes leading to cell death. However, in vivo data indicates ischemia increases the rate of tight junction turnover compared to pre ischemic tight junctions.

Methods: In vivo Adenoviral GFP occludin was hydrodynamically delivered through the renal vein. Four days later the kidney was exposed and labeled tight junctions were seen. In vitro-GFP occludin transduced MDCK cells were serum starved overnight. Cells were treated with 0 μM H2O2, 55 μM H2O2 or 110 μM H2O2 for 2 hours at 37°C before FRAP. The tight junction region or a non-tight junction region of the apical membrane was selected for FRAP.

Results: In vivo- The mobility of pre ischemic tight junctions is 93% (SD 9%). The immobility of ischemic tight junctions is 34% (SD 24%). The average half-life for recovery of ischemic tight junctions is 23.13 seconds (SD 1.07). The pre ischemic tight junctions show minimal recovery at 180 seconds post FRAP. In vitro: Control cells treated with 0 μM H2O2 have an immobility of 43% (SD 14%) with a half-life of 68.2 seconds (SD 17.3 seconds). Cells treated with 55 μM H2O2 have an immobility of 32% (SD 16%) with a half-life of 88.5 seconds (SD 23.7 seconds). Cells treated with 110 μM H2O2 have an immobility of 37% (SD 15%) with a half-life of 82.3 seconds (SD 21.03 seconds). Results are statistically significant, p value <0.05.

Conclusions: In vitro tight junction turnover following FRAP occurs much faster in wild type cells than it does in injured cells. This data indicates that injury actually slows down tight junction turnover compared to control cells. However, these results are contradictory to the in vivo data that indicates ischemic injury increases tight junction turnover.

Funding: NIDDK Support

PUB111

Sirtuin-1 (Sirt-1) and Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) Interplay in Nondialysis CKD Patients

Denise Mafra,1 Juliana Saldanha,1 Felipe Rizzetto Santos,2 Viviane Oliveira Leal,3 Alex Sandro Duarte Albuquerque,1 1Federal Fluminense Univ; 2Federal Hospital of Lagoa; 3Federal Univ of Rio de Janeiro; 4Univ of the State of Rio de Janeiro.

Background: The transcription factor nuclear factor-erythroid 2-related factor 2 (Nrf2) is responsible for the expression of antioxidant response element-regulated genes and is recognized to be a major cellular defense mechanism. The high Nrf2 expression might be mediated by Sirt1 activation. Sirtuins (SIRTs), a family of NAD-dependent histone deacetylases, regulate DNA repair and recombination, chromosomal stability, and gene transcription. In particular, SIRT-1 activation is associated with longevity and attenuation of metabolic disorders. There is no report about association between SIRT-1 and Nrf2 gene expression in CKD patients. The aim of this study was to verify the possible association between SIRT-1 and nuclear factor erythroid 2-related factor 2 (Nrf2) expression in nondialysis CKD patients.

Methods: Sixteen nondialysis CKD patients (65 ± years old, 11 women, estimated glomerular filtration rate (eGFR) of 33.1 ± 13.7 ml/min/1.73m2, and body mass index (BMI) of 28.5 ± 7.5 kg/m2) were studied. The peripheral blood mononuclear cells were isolated and processed for the evaluation of expression of Nrf2 and SIRT-1 by quantitative real-time polymerase chain reaction.

Results: Nrf2 and SIRT-1 mRNA expression was 0.65 (1.01) and 0.91 ± 0.39, respectively. SIRT-1 mRNA expression was negatively correlated with age (r= -0.53; p = 0.03); however, it was positively correlated with Nrf2 mRNA expression (r= 0.77; p = 0.001).

Conclusions: Gene expression of SIRT-1 and Nrf2 are directly associated and age may be negatively related to antioxidant protection in nondialysis CKD patients.

PUB112

Effects of a Medical Food (ErgoD2) on the Progression of Chronic Kidney Disease

Marvin Stanley Hausman,1 Michael Herman Hermelijin,2 Alvaro Mercado,3 Kyle H. Ambert,4 Bruno Michel Jedynak,5 Hector J. Rodriguez,6 1Entia Biosciences, Portland, OR; 2Bonaire Medical Clinic, Kradelndijk, Bonaire, Netherlands Antilles; 3Savia Saúde, Medellín, Colombia; 4Intel Corporation, Life Sciences, Hillsboro, OR; 5Portland State Univ, Portland, OR; 6Cedars-Sinai Medical Center, Los Angeles, CA.

Background: Current standard of care overlooks the fact that Chronic Kidney Disease (CKD) is a multisystem functional disorder involving many radicals, inflammatory molecules, as well as catalytic metals, such as iron, that promote free radical production. This study proposes a novel non-pharmacologic approach to renoprotection through the use of a natural mushroom-based medical food, ErgoD2, which contains two potent antioxidants not produced by humans, L-Ergothioneine and vitamin D2. Two previously completed pilot studies in patients with type 1 and 2 diabetes and stage 5 CKD, treated with ErgoD2, revealed a significant decrease in plus 3 free radical iron.

Methods: 60 stage 3 and 4 CKD patients are under evaluation and following 2 stable values for eGFR, HbA1C and blood pressure receive two-500 mg capsules of ErgoD2 twice daily for 12 months. Patients are re-evaluated every 3 months with repeat physical and blood biomarker measurements standard in these disease stages, as well as Kidney Disease Quality of Life (KDQOL) questionnaires.

Results: To date, 24 patients are receiving ErgoD2 and 11 patients have completed three months of therapy. Three-month treatment results in the initial small group of patients showed eGFR improvement in 8 patients, stabilization in 1 patient and decline in 2 patients (see table below).
Table 1: Treatment of Metabolic Acidosis in CKD Yields Better Overall Outcomes and at Lower Per Patient Cost when Done with Fruits and Vegetables than NaHCO3

<table>
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<th>% Change</th>
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<td>10</td>
<td>M</td>
<td>56</td>
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</tr>
</tbody>
</table>

Conclusions: The medical food, Ergo32, represents a novel, non-pharmacologic approach to renoto-protection. Continuation of the current open clinical trial is warranted and further data will be presented.

Funding: Pharmaceutical Company Support - Entia Biosciences, Inc.

### PUB113

**Treatment of Metabolic Acidosis in CKD Yields Better Overall Outcomes and at Lower Per Patient Cost when Done with Fruits and Vegetables than NaHCO3**

**Background:** Both NaHCO3 and base-producing fruits and vegetables (F+V) improve metabolic acidosis (MA) in CKD and provide kidney protection but whether they differ in overall outcomes and management costs is unknown.

**Methods:** We randomized 108 subjects with CKD stage 3 eGFR (30-59 ml/min/1.73 m2) and MA with plasma TCO2 >22 but <24 mm as follows: F+V (n=36) to reduce dietary potential renal acid load (PRAL) 50% in the patient but was given to all household members, oral NaHCO3 (HCO3-n=6) to reduce PRAL 50%, or no alkali (Usual Care n=36). All were treated with antihypertensive and cholesterol-lowering drugs and followed 5 years with twice-yearly assessment of deaths, myocardial infarction (MI), cerebrovascular accident (CVA), and management costs. We used retail F+V cost although they were given free of charge, pharmacy drug costs, and Diagnosis Related Group costs for hospitalizations.

**Results:** There were 3 deaths in Usual Care, 1 in HCO3, and none in F+V. There were 6 Mls in 5 patients in Usual Care, 2 Mls in 2 patients in HCO3, none in F+V, and one CVA in Usual Care but none in HCO3, or F+V. Five-year cost per household was higher for F+V ($385,809) than HCO3 ($231,981) and Usual Care ($263,634) but 5-year per patient cost was lower in F+V ($198,124) than the remaining groups. Lower per patient costs for F+V than HCO3, and Usual Care was due to offsetting lower costs for hospitalizations ($0 vs. $50,074 vs. $95,360) and management of hypertension ($79,760 vs. $155,372 vs. $152,305) and serum cholesterol ($8,477 vs. $16,447 vs. $16,169).

**Conclusions:** Treating metabolic acidosis in this CKD population with F+V yielded fewer deaths, fewer cardiovascular events, and lower overall per patient management costs compared to HCO3 and Usual Care over 5 years.

### PUB114

**An Open-Label Pilot Study of New Spherical Carbon Adsorbent Renamenzin: Efficacy in Reducing Indoxyl Sulfate in Chronic Kidney Disease**

**Background:** Reduced renal function in chronic kidney disease(CKD) causes systemic accumulation of indoxyl sulfate (IS), which has been shown to promote CKD progression. Renamenzin® (Daewon Pharmaceutical Co., Korea) is a newly developed oral spherical carbon adsorbent with modified micropores that has high specificity for adsorbing indoxyl sulfates (IS), which has been shown to promote CKD progression.

**Methods:** A total of 35 stable pre-dialysis CKD patients [mean age: 62 years, 82.9% male, serum creatinine (SCr) 1.5 – 5.0 mg/dL] were enrolled in this open-label pilot study. Renamenzin® (7 capsules, t.i.d., 6 grams/day) was administered for 4 weeks. Serum IS as well as other parameters were measured at baseline and after 4 weeks. Wilcoxon Rank test was used to assess differences in IS before and after Renamenzin® treatment.

**Results:** The mean SCr and estimated glomerular filtration rate (eGFR) was 2.58±0.98 mg/dL and 29.5±12.8 ml/min per 1.73 m2, respectively. Serum IS negatively correlated with renal function (r = -0.47, p=0.003). Four weeks of Renamenzin® treatment significantly reduced serum IS from baseline of 0.369±0.243 mg/dL to 0.322±0.303 mg/dL (mean reduction of 14.6%, p<0.02) that was independent of baseline renal function. During the 4-week treatment period, Renamenzin® did not adversely affect other renal parameters (SCr and eGFR) and was well tolerated (mean drug compliance: 92.1%). No severe side effects were reported except for GI symptoms (vomiting and diarrhea) in 4 patients (11.6%) and skin rashes in 1 patient (2.9%).

**Conclusions:** Our results suggest that newly developed carbon adsorbent Renamenzin® significantly reduces serum indoxyl sulfate levels in moderate to severe pre-dialysis CKD patients.

Funding: Pharmaceutical Company Support - Daewon Pharmaceutical Co., Korea

### PUB115

**Abstract Withdrawn**
Mild Cognitive Impairment Is Highly Prevalent and Strongly Associated with Physical Function in Elderly Patients with Pre-Dialysis Chronic Kidney Disease

Yuki Otobe,1 Koji Hiraki,1 Chiharu Hotta,1 Yasuhiro Taki,2 Naohiko Imai,1 Tsutomu Sakurada,1 Yugo Shigabagi,1 1Dept of Rehabilitation Medicine, St. Marianna Univ School of Medicine, Kawasaki, Japan; 2Div of Nephrology and Hypertension, Dept of Medicine, St. Marianna Univ School of Medicine, Kawasaki, Japan.

Background: Chronic kidney disease (CKD) has been reported to be a risk factor for cognitive decline. However, the prevalence of mild cognitive impairment (MCI), a prodrome of dementia, and its risk factors remain to be determined. The purpose of this study is to clarify the prevalence and to elucidate the risk factors of MCI in elderly patients with pre-dialysis CKD.

Methods: The subjects were 122 elderly (≥ 65 years old) pre-dialysis CKD patients of our outpatient nephropathy clinic (average age 77.7 years old with 96 males). Mini Mental State Examination (MMSE) and Japanese version of Montreal Cognitive Assessment (MoCA-J) was used as cognitive function tests. Patients with MMSE≥23 and MoCA-J≥26 were diagnosed as normal, those with MMSE≥23 and MoCA-J<26 were diagnosed as having MCI, and those with MMSE<23 diagnosed as having dementia. Grip strength, knee extension strength, 4m comfortable walking speed, one leg stance time, the skeletal muscle index were measured as physical function. We investigated the presence of diabetes, history of smoking/drinking, and blood biochemical test as patients’ characteristics.

Results: 47 cases were identified as normal, 71 cases MCI, and 4 cases dementia, thus, 58.2 % of the elderly pre-dialysis CKD patients had MCI, and this prevalence was much higher than the prevalence of 18.8 % in community dwelling elderly Japanese. Characteristics of Normal group and MCI group were compared. Age was 74.9 vs 78.9 years (p<0.01), hemoglobin was 12.4 vs 11.6 g/dL (p<0.01), walking speed was 124.5 vs 103.6 cm/sec (p<0.01), one leg stance time was 28.9 vs 12.7 sec (p<0.01). By logistic regression analysis, age and walking speed were significantly associated with MCI (p<0.01).

Conclusions: Mild cognitive impairment is highly prevalent (58.2%) and strongly associated with physical function in elderly patients with pre-dialysis chronic kidney disease.

Disease Awareness Significantly Impacts the Quality of Life in CKD Patients

Colin A. Hinkamp,1 Emma Rebecca Segal,1 Xuerong Chen,2,1 Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Background: Despite established value in the management of many chronic conditions, there is limited data correlating disease awareness to quality of life (QoL) in CKD patients.

Methods: We conducted a cross sectional study of patients attending a university nephrology practice with the aim of assessing the effect of demographic, socioeconomic, literacy and disease awareness states on QoL. All consenting subjects were administered a set of surveys aimed to gather demographics, Charlson Comorbidity Index (CCI), REALM-SF, KDQoL-36, and a novel CKD disease awareness questionnaire.

Results: Initial findings of an ongoing study with the first 108 enrollees is presented. We found high health literacy and mildly elevated comorbidity indices across the spectrum of CKD. Despite these, average CKD patients displayed poor CKD awareness (19.6 ± 9.2, out of 45) and average physical (39.6 ± 11.7) and mental (49.5 ± 10.4) QoL.

Univariate analysis showed that physical QoL had the strongest positive correlation with CKD awareness (R=0.27; p=0.001) and strongest negative correlation with comorbidities indices (R=-0.45; p<0.001). Multivariate analysis, adjusting for age, gender, health literacy, economic affluence and renal function, showed that amongst the factors affecting mental QoL, male gender, African American race, and economic affluence had the strongest positive impact. Multiple comorbidities and poor CKD awareness had the strongest negative impact on physical QoL. Duration of renal care was found to be insignificant after adjusting for other risk factors.

Conclusions: Our results show that disease awareness and not just the nephrology care is a significant modifiable risk factor affecting CKD patients’ QoL. It provides rationale for elucidating the viability of improving outcomes by adding an educational component to standard treatment.
by standardized physical examination and history. eGFR was calculated from the serum creatinine-based MDRD equation. Potential confounders of the relationship between eGFR and PAD were assessed by multivariable logistic regression.

Results: Of 96 participants (median age 58 [range 30 - 84]; median eGFR 72.4 ± 33.0 ml/min/1.73 m²), 43 % had PAD. Duration of diabetes (7.0 ± 7.2 years) and HbA1c (7.7 ± 1.8 %) were similar in patients with and without PAD (P = 0.09 and 0.19, respectively). eGFR < 60 ml/min/1.73 m² was associated with increased risk of PAD (odds ratio ± SE) 2.7 ± 1.3, P = 0.034. Association of low eGFR with PAD was stronger (3.7 ± 2.1, P = 0.023) after adjustment for PAD risk factors in the general population: systolic blood pressure, smoking, duration of diabetes and HbA1c. PAD was not associated with albuminuria defined as albumin/creatinine ratio (1.0 ± 0.01, P = 0.425).

Conclusions: Our results suggest that kidney disease in type 2 diabetes is a risk factor for PAD. For timely diagnosis and risk factor modification, patients with DKD should be screened for PAD.

Funding: Other NIH Support - NIH R01DK06549 and the Rosenberg Foundation for Kidney Research

**PUB123**

**Serum Chloride Levels Predict Cardiovascular Morbidity and Mortality in Patients on Incident Dialysis**

Yosuke Saka,1 Tomohiko Naruse,1 Daijo Inaguma,1 1Internal Medicine, Kasugai Municipal Hospital, Kasugai, Aichi, Japan; 2Nephrology, Nagoya Daini Red Cross Hospital, Nagoya, Aichi, Japan.

Background: Patients with advanced chronic kidney disease (CKD) have an electrolyte imbalance due to impaired kidney function. Several studies have associated increased morbidity and mortality with abnormalities in serum sodium, potassium and phosphate among patients with CKD. However, whether serum chloride levels are associated with morbidity and mortality in such patients, especially those on incident dialysis, remains obscure. We investigated whether serum chloride levels can predict morbidity and mortality after starting dialysis in the AICOPP study (Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis).

Methods: Among 1,525 patients who started dialysis between October 2011 and September 2013 and were enrolled in the retrospective, multicenter cohort AICOPP study, 278 were excluded from analysis due to incomplete data. We followed up the remaining participants for 12 months after enrollment. The primary and secondary endpoints were all-cause mortality and cardiovascular (CV) events, respectively. Serum chloride levels were categorized as low or high (Cl < 100 and ≥ 100 mEq/L, respectively) and data were analyzed using the Kaplan-Meier method and Cox hazards models.

Results: The mean serum chloride level was 103.9 mEq/L. Approximately 20% of the patients had low serum chloride levels that were significantly associated with all-cause mortality and CV events.

Conclusions: Serum chloride levels might serve as a practical biomarker to predict morbidity and mortality, especially CV events, in patients on incident dialysis.

**PUB124**

**Effect of Methoxy Polyethylene Glycol – Epoetin β (Mircea) on Plasma Levels of s-Selectin, sICAM-1, sVCAM-1, NT-proBNP and Left Ventricular Structure and Function in Patients with Chronic Kidney Disease**

Jacek Rysz,1 Ewa Majewska,1 Beata Francis,2 Piotr Majewski,2 Philip A. Kalra,1 Paul Cockwell,2 Maarten W. Taal,4 Southampton University; 3Univ Hospitals of Birmingham; 4Manchester Univ; 5Nottingham Univ; 6Binding Site; 7Amiens Univ Hospital; 8Ambroise Pare Univ Hospital & Inserm; 9Oxford Univ.

Background: Anemia and endothelial dysfunction may be involved in pathogenesis of atherosclerosis, disadvantageous changes in left ventricle structure and function and cardiovascular complications in CKD patients. In this study we aimed to determine effect of Mirca on chosen plasma and echocardiographic parameters in CKD.

Methods: 28 patients with stage IV of CKD and anemia, treated with Mirca, were enrolled to the study. Control group included 15 volunteers. Plasma levels of s-selectin, sICAM-1, sVCAM-1 were measured with ELISA kits. Echocardiographic examination was performed (EF – ejection fraction, LVM – left ventricle mass, LVEDS – left ventricle end systolic diameter, LVESD - left ventricle end diastolic diameter).

Results: Serum Free Light Chains Predict All-Cause Mortality in Chronic Kidney Disease: A Systematic Review and Meta-Analysis

Simon D.S. Fraser,4 Anthony Fenton,2 Scott Harris,1 Anne Burmeister,1 Adam Shadlow,1 Sophie Liabeuf,9 Ziad Massy,1 Martin J. Landray,3 Jonathan R. Emberson,4 Philip A. Kalra,1 Paul Cockwell,2 Maarten W. Taal,4 Southampton University; 3Univ Hospitals of Birmingham; 4Manchester Univ; 5Nottingham Univ; 6Binding Site; 7Amiens Univ Hospital; 8Ambroise Paré Univ Hospital & Inserm; 9Oxford Univ.

Background: Serum immunoglobulin (Ig) free light chain (FLC) assays are used in identifying and monitoring clonal FLC (kappa (κ) or lambda (λ)) in paraproteinaemia. In the absence of a paraprotein, high serum levels of polyclonal combined (c)FLC (κ and λ) have been associated with increased mortality in CKD. The study aimed to synthesize current evidence for cFLC as a mortality risk predictor in CKD.

Methods: Four databases (Medline, Embase, CINAHL, PubMed) were searched using terms for CKD and Ig light chains. Inclusion criteria: quantitative CKD studies, FLCs measured, mortality as outcome. Excluded: paraproteinaemia and dialysis associated terms. Two reviewers independently assessed study inclusion and quality. Individual patient data were obtained from all included studies were combined for common variables and Cox regression models used to explore the relationship between cFLC=34.33mg/L (95th percentile normal range) and all-cause mortality using fixed effect for study ID.

Results: 5 cohort studies were included (combined n=361). All had used the FreeLight™ assay for FLCs. Most patients were moderately to severely anemic (mean age was 67 (SD 14) years, 1842 (50%) were male, 810 (22%) had diabetes and 1229 (33%) had cardiovascular disease (CVD).
Mean eGFR was 41.8 ml/min/1.73m^2 (SD 17.4). On multivariable analysis adjusted for age, sex, diabetes, CVD, MRDxGF, albumin, and renin angiotensin system inhibitors, elevated serum eNCFL was independently associated with all-cause mortality.

<table>
<thead>
<tr>
<th>Age(year)</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.06</td>
<td>1.05-1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male(y/n)</td>
<td>1.28</td>
<td>1.10-1.51</td>
<td>0.002</td>
</tr>
<tr>
<td>Diab(y/n)</td>
<td>1.31</td>
<td>1.12-1.53</td>
<td>0.001</td>
</tr>
<tr>
<td>CVD(y/n)</td>
<td>1.59</td>
<td>1.36-1.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR(m/l/min/1.73m^2)</td>
<td>0.98</td>
<td>0.97-0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin(g/l)</td>
<td>0.95</td>
<td>0.94-0.97</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Conclusions:** In this first meta-analysis of patient-level data, eNCFL predicted all-cause mortality across the full spectrum of CKD and may be useful for risk-stratification.

**PUB127**

HDL and LDL Cholesterol Subfractions in Chronic Kidney Disease Patients

Jacek Rysz, Anna Gluba-Brzózka, Beata Franczyk, Magdalena Górszynska-Rysz. Dept of Nephrology, Hypertension and Family Medicine, Medical Univ of Lodz, Lodz, Poland; ‘Healthy Aging Research Center, Medical Univ of Lodz, Lodz, Poland.

**Background:** Chronic kidney disease (CKD) is a worldwide public health problem which is associated with increased cardiovascular risk. Recent studies indicate that the level of individual LDL and HDL subfractions may be more important that their total concentration. Moreover, some points that in pathological conditions HDL may lose its protective functions.

**Methods:** The study group consisted of a total of 115 patients with CKD (25 with stage II, 25 – stage III, 25 – stage IV, 25 – stage V), and control group consisted of 25 healthy volunteers. Complete medical history was obtained from all subjects. Subfractions of LDL (7) and HDL (10) cholesterol were analysed with the use Lipoprint™ system (Quantitexx Corp.) according to the manufacturer’s instructions.

**Results:** Differences in nearly all LDL and HDL subfractions distribution were observed between CKD stages and between CKD patients and controls. HDL1-HDL4 and large HDL subfractions were significantly more abundant in patients with end-stage renal disease, while between CKD stages and between CKD patients and controls. HDL1-HDL4 and large HDL subfractions were found in control group, and it gradually decreased along with worsening kidney function (HDL7 – P=0.001; HDL8 – P=0.001; HDL9 – P=0.001; HDL10 – P=0.001). Moreover, the concentration of HDL7, HDL8 and HDL9 subfractions were higher in patients with CKD V, while the 1, 2 and 3 subfractions were higher in control group (HDLC 1 – P=0.010; HDL-B 1 – P=0.011; HDL-A 1 – P=0.001; HDL-2 1 – P=0.001; HDL-3 1 – P=0.007).

**Conclusions:** This study indicated higher prevalence of large HDL subfractions in CKD V patients. Predomination of larger HDL particles in patients with coronary artery disease was observed in other studies. Despite the fact that role of individual HDL subfractions remains unknown, it can be hypothesized that the abundance of large HDL or decreased concentration of small HDLs may participate in increased cardiovascular risk observed in CKD.

**PUB128**

The Association between Creatinine versus Cystatin C-Based eGFR and Cardiovascular Risk Using PDAY Risk Score in Children with Chronic Kidney Disease


**Background:** Children with CKD have a high prevalence of cardiovascular disease (CVD) risk factors. Among adults with CKD, cystatin C-based eGFR demonstrate a stronger predictive value for cardiovascular events compared to creatinine-based eGFR. The PDAY (Pathobiological Determinants of Atherosclerosis in Youth) risk score is a validated tool used to estimate the probability of atherosclerotic lesions within coronary arteries in adults. The objective was to assess the association between cystatin C- vs creatinine-based eGFR and cardiovascular risk using modified PDAY risk score as a proxy for CVD in children and young adults.

**Methods:** We used cross-sectional data from 71 CKD subjects (15.5 yrs, 13, 17), eGFR creatinine 90ml/min/1.73m^2 (27, 74), eGFR creatinine 53ml/min/1.73m^2 (32, 74), and 33 controls (15.3 yrs, 13, 17), eGFR creatinine 112ml/min/1.73m^2 (85, 128), eGFR creatinine C 114ml/min/1.73m^2 (87, 153), eGFR was calculated using age-appropriate creatinine and cystatin C-based formulas. PDAY risk scores (include sex, age, serum lipoprotein, obesity; modified by smoking, hypertension, hyperglycemia) were used to determine probability of coronary artery atherosclerosis. Spearman’s correlation, chi-square, and ordinal logistic regression were used.

**Results:** PDAY scores ranged from -2 to 16 (higher score equals greater risk). The correlation between eGFR creatinine and eGFR cystatin C with coronary PDAY scores were 0.26 (p=0.007) and 0.27 (p=0.005), respectively. Ordinal logistic regression showed similar association between higher eGFR creatinine and eGFR cystatin C and lower PDAY scores. Chi-square between CKD severity (stage 1-4) and PDAY categories (low 0-1; moderate 1-5; high risk ≥5) was not significant for eGFR creatinine (p=0.09) but was significant for eGFR cystatin C (p=0.03).

**Conclusions:** The correlation between eGFR by cystatin C or creatinine with PDAY risk score was similar. A slightly stronger association between CKD stage and PDAY score was seen with eGFR cystatin C when assessed by chi-square. Further studies should explore the association between cystatin C and cardiovascular risk in children with CKD.

**PUB129**

Higher-Dose Erythropoiesis-Stimulating Agents (ESA) to Maintain Higher Target Hemoglobin Is Associated with Higher Risk of Mortality and Cardiovascular Event Risk in Patients with Chronic Kidney Disease (CKD): The CKD-ROUTE Study

Seiko Ishikawa, Soichiro Imi, Shotaro Naito, Eisuke Sohara, Tomokazu Okado, Sei Sasaki, Tatematsu Rai, Shinichiro Uchida. Nephrology, Tokyo Kyosai Hospital, Japan; ‘Nephrology, Tokyo Medical and Dental Univ, Japan.

**Background:** Recent studies showed that the use of ESA for treatment of renal anemia to achieve high hemoglobin (HB) levels was associated with an increased risk of adverse events in CKD patients. We evaluated the relationships among ESA doses, mortality, and risk of CV events.

**Methods:** This prospective cohort study was comprised of 776 pre-dialysis patients with CKD G2-G5 enrolled from 2010 to 2011. Patients followed up until ESRD, death, transfer, or the end of 3-years follow-up. The outcome was a composite of all-cause mortality or CV events. We categorized patients into 3 groups according to ESA doses: no dose group (ND); lower dose group (LD) (-3111 IU/month); higher dose group (HD) (≥3111 IU/month). Three groups were compared using the log-rank test and the adjusted hazard ratio (aHR) was estimated using multivariate cox hazards model.

**Results:** During a median follow-up of 36 months, 64 CV events occurred, 40 patients died, and 97 patients reached the outcome. HD was associated with greater mortality and risk of CV events than both LD and ND (HD vs LD: aHR 2.05 [95% confidence interval (CI) 1.04-4.06], HD vs ND: aHR 1.94 [95%CI 1.00-3.75]). When patients were further stratified according to their achieved HB levels, ESA dose did not affect the outcome in patients with HB < 10 g/dl. However, in patients with HB ≥ 10 g/dl, higher ESA dose increased mortality and CV event risk (HD vs LD: aHR4.01 [95%CI 1.28-12.6], HD vs ND: aHR 3.03 [95%CI 1.32-6.99]).

**Conclusions:** Use of higher-dose ESA to achieve higher target HB levels in CKD patients was associated with greater risk of mortality and CV events.

**PUB130**

Undiagnosed and Uncontrolled Hypertension in Primary Care: The Role of Awareness of the Renal Risk

Marcos Sarti, Luca Valerio, Silvia De Rosa, Faqy Husain-Syed, Stefano Cattin, Mirella Zancato, Claudio Ronco. Nephrology, St. Borotolo Hospital, Italy; ‘Medicine, Univ of Amsterdam, Netherlands; ‘Pharmacy, Univ of Padua, Italy.

**Background:** To assess the distribution and features of pts with undiagnosed and uncontrolled arterial hypertension(AHT)in the community setting,we have conducted a cross-sectional survey of the general population through community pharmacies in the North-Eastern area of Italy.In addition,we assessed awareness among pts of the role of AHT as a risk factor for chronic kidney disease(CKD).

**Methods:** The survey was carried out between Oct-2014 and Feb-2015. Participants were selected among the pts of 35 pharmacies. All participants were interviewed by using a structured questionnaire(18-items),and their blood pressure(BP)was measured. The survey included previous diagnosis of AHT,risk factors for CKD,and knowledge of AHT as risk factor for CKD. We identified factors associated with awareness of the renal risk associated with AHT.

**Results:** The sample included 2036 subjects aged ≥18 yrs(39.2% male;24% below age 45;31.4% older than 65;44.6% between age 45 and age 65).40.1% of subjects was in treatment for hypertension, AHT was reported by 48.4% of the participants. Non-white ethnicity,smoking,higher BMI were all associated with lower awareness of the hypertensive renal risk.In contrast, diagnosis of AHT,family history of AHT and family history of renal disease were all associated with higher awareness of the hypertensive renal risk,with family of history of renal disease displaying the strongest association (OR 3.23[1.70-3.15];p<0.05).All associations were statistically significant for p<0.05.Of 1219(59.9%)participants without diagnosis of AHT 29.0% were found to have AHT upon HB measurement.In this group awareness of the hypertensive renal risk has a protective effect against undiagnosed AHT(OR 0.69[0.52-0.92];p<0.05).In contrast, awareness of the hypertensive renal risk has not protective effect against uncontrolled AHT among hypertensive pts.The rate of uncontrolled AHT was 58.0% of hypertensive pts.

**Conclusions:** The rate of awareness of the renal risk associated with AHT demands more attention in the primary care setting due to its potential benefit on undiagnosed AHT.

**Funding:** Private Foundation Support
Hypertiglyceridemia and Inflammatory Markers as Predictors of Survival in Cohort of Patients with Chronic Kidney Disease  
Mariaela Bobhke, 1 Gabriela Araujo Duarte, 1 Alexia Schuch, 1,2 Jamile Gardin Dos Santos, 1 Luiza Morrone Gastaun, 1 Mateus De Mamam Vargas, 1 Annelise Reges, 1 Franklin Correa Barcelos, 1,2 Medicine School, Univ Catolic of Pelotas, Pelotas, Brazil; 1 Medicine Faculty, Univ Federal of Pelotas, Pelotas, Brazil.  

Background: Systemic inflammation, dyslipidemia and other metabolic disorders has been associated with increased cardiovascular mortality. Exercise is a non-drug intervention with positive effects on metabolic profile and inflammation in individuals with chronic diseases and the general population. Objective is correlate inflammatory and metabolic markers with the long-term prognosis of a cohort of patients with chronic kidney disease (CKD) who suffered an intervention with exercise.  

Methods: Hypertension and nondiabetic patients with GFR ≤60 ml/min/1.73m2 were included in a randomized clinical trial (RCT) that evaluated effects of an exercise program on cardiovascular disease markers, demographic factors and clinical (blood glucose, lipid profile, C-reactive protein (CRP), body mass index (BMI), ankle brachial index (ABI) at baseline and after 4.8 and 16 weeks of exercise. At the end of the intervention patients were followed-up to investigate the exercise long-term effects and identify quality predictors of life and mortality.  

Results: A total of 150 patients allocated to the RCT, 65 patients had CKD. The long-term follow-up lasted for an average of 2.75 (1.06 to 4.29) years. Predictors of mortality were elevated CRP levels (OR 1.1695% CI 1.00 to 1.34) and triglycerides (OR 1.19 95% CI 1.00 to 1.01). Other markers such as LDL cholesterol, BMI and blood glucose showed no detectable impact on mortality, as well as intervention with physical exercise. The ITB term follow-up lasted for an average of 2.75 (1:06 to 4:29) years. Predictors of mortality followed-up to investigate the exercise long-term effects and identify quality predictors of life and mortality.  

Conclusions: Larger studies with adequate samples are needed to confirm the prognostic impact of hypertiglyceridemia and elevated CRP for patients with pre-dialysis albuminuria shows no risk among diabetic patients.  

End-Stage Renal Disease versus Death in a Portuguese Cohort of Elderly Patients: An Approach Using Competing Event Analysis  
Joséfa Lascasas,1 Isabel Fonseca, 1 Jorge Malheiro, 1 Idalina Beirão, 1 Sofia Correia, 1 Andrea Campos, 1 Pedro Oliveira, 2 Luisa Lobato, 1 António Cabrita, 1  
1Nephrology Dept, CHP, Porto, Portugal; 2Inst Ciências Biomedicas Abel Salazar, Univ Porto, Porto, Portugal.  

Background: Portugal is facing an increasingly ageing, and has the highest incidence of end stage renal disease (ESRD) among European countries. Chronic kidney disease (CKD) prevalence is higher in elderly, but mortality outweighs the risk of progression to ESRD, which makes it a challenge to determine each patient’s risk for requiring renal replacement therapy (RRT) in relation to the competing risk of death.  

Methods: Longitudinal cohort study, with consecutive CKD patients aged≥ 65 years(1970-2016) followed until the time of the first event (RRT or death) or until April 30, 2016. A competing risk analysis using STATA software was performed between those two mutually exclusive endpoints.  

Results: Among 416 patients, age 76±8 yrs (36%≥80 yrs), 52% male, mean eGFR EPI 32ml/min, 49.7% had diabetes, and 71% cardiovascular disease. Median follow-up was 3.6 yrs(min-max:0.02-43), during which 36 patients progressed to ESRD(8.7%) and 137 died (32.8%). The median (IQR) person-yrs) was 2.7 for ESRD and 7.8 for death. The independent predictors for RRT with competing risk of death were:lower age(β=0.97; P=0.029),creatinine=2mg/dl(HR=2.48; P=0.012) and peripheral vascular disease(β=2.50; P=0.011) at baseline; and having one or more hospitalizations during the follow-up(β=4.07; P=0.002). The independent predictors for patient death with competing risk of RRT were: age=80 yrs(β=2.22; P=0.001), creatinine=1.6 mg/dl(β=2.59; P=0.003) and having one or more hospitalizations during the follow-up(β=4.55; P<0.001).
Conclusions: During a median follow-up of 3.6 yrs, older CKD are near 3-fold more likely to die from any cause than progress to ESRD. Age, late nephrology referral (higher creatinine at the first observation) and hospitalizations are the most important predictors of the competing events ESRD and death. A greater burden of vascular disease, present in our cohort, as a predictor for RRT, highlights the importance of strategic targeting vascular risk reduction in these patients.

PUB136

P2Y12 Antagonists for Acute Coronary Syndrome in Chronic Kidney Disease: A Meta-Analysis of Randomised Controlled Trials

Peter J. Gallicher
Centre for Cardiovascular Sciences, Univ of Edinburgh, Edinburgh, United Kingdom.

Background: Chronic kidney disease (CKD) patients are under-represented in cardiovascular trials and less likely to receive secondary prevention. Dual antiplatelet therapy with aspirin and P2Y12 antagonists (e.g. clopidogrel) is standard treatment following cardiovascular trials and less likely to receive secondary prevention. Dual antiplatelet therapy with aspirin and P2Y12 antagonists (e.g. clopidogrel) is standard treatment following acute coronary syndrome. We aimed to determine how reduced eGFR influences major adverse cardiovascular events (MACE) and bleeding risk in patients treated with these agents for acute coronary syndrome.

Methods: Central, Embase, and Medline databases were searched from 1946 through to June 2016 for randomised controlled trials (RCTs) comparing P2Y12 antagonists with agents for acute coronary syndrome.

Results: Of 4,382 studies, five international, multi-centre, double-blinded RCTs with low risk of bias studies were included in the analysis. From 57,611 patients, eGFR data were available for 88.6% (n=51,031). CKD patients comprised 21.2% of the population (n=10,480), of whom 1.1% (n=560) had an eGFR <30mL/min/1.73m2. Treatment reduced MACE; a composite of cardiovascular death, myocardial infarction (MI) or stroke. The secondary outcome was TIMI major bleeding. Publication bias was determined using Eggers regression test and heterogeneity was calculated using the I2 test. Summary effects of relative risk (RR) ratios were collated using a random-effects model.

Results:

- Of 4,382 studies, five international, multi-centre, double-blinded RCTs with low risk of bias studies were included in the analysis.
- From 57,611 patients, eGFR data were available for 88.6% (n=51,031).
- CKD patients comprised 21.2% of the population (n=10,480), of whom 1.1% (n=560) had an eGFR <30mL/min/1.73m2.
- Treatment reduced MACE; a composite of cardiovascular death, myocardial infarction (MI) or stroke.
- The secondary outcome was TIMI major bleeding.
- Publication bias was determined using Eggers regression test.
- Heterogeneity was calculated using the I2 test.
- Summary effects of relative risk (RR) ratios were collated using a random-effects model.

Conclusions: P2Y12 antagonists after acute coronary syndrome confer benefit to CKD patients, although to a lesser degree than in those with normal renal function. They are associated with a lower risk of major bleeding in CKD; this may reflect premature mortality due to other causes. Those with severe CKD, and so the greatest cardiovascular risk, are vastly under-represented in cardiovascular trials.

PUB137

The Clinical Characteristics and Therapy in Aortic Dissection Patients with Chronic Kidney Disease

Zhen Su. Nephrology, The First Affiliated Hospital of Wenzhou Medical Univ, Wenzhou, Zhejiang, China.

Background: Chronic kidney disease (CKD) is a common condition that elevates the risk of adverse outcomes including cardiovascular disease. Aortic dissection (AD) is one of the most frequent life-threatening cardiovascular diseases. AD in CKD is rarely reported. This study aimed to evaluate the features and therapy in AD with CKD.

Methods: A retrospective analysis of 412 AD patients who admitted to our hospital during January 2005 to June 2015. 40 patients (34 males; mean age, 60.4±16.05 years) were identified as CKD. We collected their baseline data as well as clinical features and followed up their outcomes. We compared them with 372 AD patients without CKD (268 males; mean age, 55.7±14.71 years). All patients underwent contrast-enhanced computerized tomography (CT) (nonionics and low-osmolarity contrast were used ) to confirm the diagnosis of AD.

Results:

- The most common etiologies of these CKD patients were glomerulonephritis, benign hypertensive nephrosclerosis and gouty nephropathy. 21 patients were medically treated, 13 received endovascular repair and 6 were surgically treated.
- During the median follow-up of 20 months (range, 1-124 months), 5 patients developed Acute renal failure on CKD after surgical treatment, and all of them required CRRT. Those who received endovascular therapy seemed to have a more favorable outcome than who maintained conservative medical therapy, 1-year survival 88% vs 68.6%, respectively; log-rank test p = 0.07).

Conclusions: Endovascular treatment has acceptable outcomes in CKD patients when they suffered AD and such patients had their atypical features which need the physicians pay more attention.

PUB138

The Impact of Admission Serum Creatinine on Major Adverse Clinical Events in ST-Segment Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention

Mohamed Khayata, Mohit Gupta, Slyam Blukta, Rupesh Raina. Internal Medicine, Akron General Medical Center, Akron, OH.

Background: Impaired renal function has been shown in previous studies to be an independent predictor of cardiovascular adverse events amongst patients admitted for percutaneous coronary intervention (PCI). We will investigate the impact of admission serum creatinine on major cardiovascular outcomes among STEMI patients undergoing PCI.

Methods: A Retrospective Institutional Review Board approved study of patients admitted for STEMI was conducted using the National Cardiovascular Database Action Registry (NCDR) at Cleveland Clinic Akron General (CCAG) Hospital. The primary outcome was a composite of major clinical events (cardiogenic shock, atrial fibrillation, ventricular tachycardia/fibrillation, heart failure, bleeding, mechanical ventilation). Creatinine was an independent and continuous variable. Statistical analysis was performed via the Mann Whitney U test.

Results:

- 1452 subjects who were admitted to CCAG hospital between January 2011 and September 2015, with the diagnosis of STEMI were included. The cohort consisted of primarily older Caucasian males with creatinine levels from 0.63 mg/dL to 1.2 mg/dL.
- Higher levels of creatinine on admission was associated with an increased incidence of the composite clinical outcome (p<0.001), atrial fibrillation (p=0.021), cardiogenic shock (p=0.002), and heart failure (p=0.001).

Conclusions:

- In the setting of STEMI elevated creatinine was associated with an increased risk of developing major clinical events including cardiogenic shock, atrial fibrillation, bleeding and heart failure.

PUB139

The Error of Estimated GFR in Patients with Acute Heart Failure: The Cardiologist in the Mist

Sergio Luis Lima,1 Pablo Jorge,1 Martin L. Garcia,1 Ana Aldeida Perona,2 Natalia Negrin,1 Federico J. Gonzalez-Rinne,1 Esteban Porrini,2 Hospital Univ de Canarias, La Laguna, Spain; 2Univ de La Laguna.

Background: In diverse populations, estimated GFR (eGFR) showed a wide error in predicting real renal function. This error has never been tested in patients with acute heart failure (AHF).

Methods: We analyzed 30 patients (12 women) with AHF in whom GFR was measured by iolesol plasma clearance (mgGFR) and estimated with 52 formulas (creatinine and cystatin-based) 48 hours after admission in a condition of clinical stability. The agreement between mgGFR and eGFR was assessed by the Total Deviation Index (TDI), Concordance Correlation Coefficient (CCC) and coverage probability (cp).

Results: Age 63±12 yr; DM 55%; HTA 74%; dyslipidemia 78%; previous ischemic disease 44%; new-onset AHF 59%; creatinine 1.36±0.69mg/dL; NT-proBNP 6048±4915pg/ml; troponin-1 0.05mg/ml; (median). 58% received high doses of furosemide (>125mg) during the first 24 hours. 44.4% had left ventricular ejection fraction<35%. Formulas showed poor agreement with mgGFR: CCC=0.70, TDI from 106,8% to 49,6% (~62%), indicating that 90% of eGFR showed an error of ±62%. No formula included 90% of eGFR within a cp of ±10% Table 1 shows a sub-group of formulas.

Conclusions: Estimation error of eGFR was wide in predicting real renal function. The error has never been tested in patients with acute heart failure (AHF).

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

Underline represents presenting author.

936A
Errors in CKD classification were observed: one in three patients with eGFR ≤60 ml/min (stage 1-2) had mGFR <60 ml/min (stage 3).

**Conclusions:** Formulas do not accurately reflect the GFR in patients with AHF. The clinical consequences of this error must be evaluated in prospective studies.

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

**PUB410**

**Serum 1,25 Dihydroxyvitamin D Is Independently Associated With Left Ventricular Hypertrophy and Diastolic Dysfunction in Patients with Chronic Kidney Disease**

**Background:** Cardiovascular disease is the leading cause of death in chronic kidney disease (CKD). The presence of hypertrophy, left ventricular mass/diastolic dysfunction in pre-dialysis CKD patients.

**Methods:** This study included 246 patients with pre-dialysis CKD [glomerular filtration rate (GFR) < 60 ml/min/1.73 m²]. Two-dimensional echocardiography was performed to measure the left ventricular mass index (LVMI). Tissue Doppler imaging was used to measure the early mitral inflow velocity (E) and the peak early mitral annular velocity (E′). Diastolic dysfunction was measured by the ratio of E to E′ (E/E′).

**Results:** Univariate analysis, LVMI was significantly correlated with the presence of hypertension, GFR, 1,25(OH)D and parathyroid hormone (PTH). E/E′ was significantly associated with the presence of hypertension, 1,25(OH)D, and PTH. In multivariate analysis, LVMI was independently associated with the presence of hypertension (β = 0.175, P = 0.003), 1,25(OH)D (β = -0.140, P = 0.025), and PTH (β = -0.351, P = 0.001) as independent predictors of E/E′.

**Conclusions:** This study shows that 1,25(OH)D is independently associated with left ventricular hypertrophy and diastolic dysfunction in pre-dialysis CKD patients. Further studies are needed to determine whether the therapy with vitamin D supplementation prevents these cardiac changes in them.

**PUB414**

**Non-Dipping Status in 24-H Ambulatory Blood Pressure Monitoring Is Associated with Left Ventricular Hypertrophy in Patients with Non-Diaslysis Chronic Kidney Disease**

**Background:** There is controversy about the risk/benefit of anticoagulation/antiagregation in chronic kidney disease (CKD) patients not on dialysis. The aim of this cross-sectional study is to assess the relationship of body composition and sarcopenia (loss of muscle mass and strength) with CKD and A VD where the competing risk of death is lower. This observation may be explained by the low competing risk of atherosclerotic events and increases the risk of bleeding, thus it should not be a first election treatment neither in primary nor secondary prevention.

**Conclusions:** Anticoagulation and antiagregation increase the hemorrhagic risk in patients with CKD and worsen the anemia, fact that must be taken on account to optimize treatment and valuate the risk/benefit in the prescription of these drugs. Anticoagulation reduces the atherosclerotic events in more than 85%. Antiggregation does not prevent atherosclerotic events and increases the risk of bleeding, thus it should not be a first election treatment neither in primary nor secondary prevention.

**Results:** There were no differences between groups regarding age, renal function or inflammatory parameters (CRP and fibrinogen). Hemoglobin and creatinine levels were significantly higher in patients who did not receive anticoagulation or antiagregation. During follow up 36 hemorrhagic events occurred: 4 in the control group, 17 in the anticoagulation group and 7 in the antiagregation group (log rank: 9.010, p=0.001). In a Cox model adjusted by age, renal function and hemoglobin levels, the anticoagulation increased the risk of bleeding almost four times (HR 3.71, 95% CI: 1.6-8.5, p=0.002) and antiagregation almost three times (HR 2.61, 1.5-5.9, p=0.025). 64 cardiovascular events were registered, 21 were classified as atherosclerotic events: 10 in the anticoagulation group, 8 in the control group and 1 in the antiagregation group (log rank: 8.351, p=0.015). In a Cox model adjusted by age, renal function and previous cardiovascular events, the anticoagulation reduced the risk of atherosclerotic events in 86% (HR 0.136 (0.033.0.551), p<0.005).

**Methods:** We conducted a prospective observational study of 623 patients with stage 3 and 4 CKD. Demographic, clinical and laboratory variables were recorded and patients divided into two groups based on the presence or absence of AVD, defined as having a diagnosis of coronary artery disease, myocardial infarction and/or peripheral vascular disease. Development of ESRD and death without ESRD were recorded over 2 years of follow up.

**Results:** Of 623 patients with CKD 285 had AVD. Patients with AVD were older than those without (75.8 ±10.0 vs 65.6 ±15.0 y, p<0.001) and had lower eGFR (33.8 ±11.5 vs 46.4 ±11.7 ml/min/1.73 m², p<0.001). Mortality was higher in patients with AVD (16.8 ±5.3%, p<0.0001) and increased with age. There was a trend toward higher ESRD incidence in AVD patients but in contrast with mortality, ESRD incidence decreased with age though remained higher in AVD patients. ESRD incidence in AVD patients <65 was 17.1 vs 9.5% in those without and for AVD patients ≥65 the incidence was 6.6 vs 3.3% though these differences did not reach statistical significance.

**Conclusions:** Our findings suggest that despite significantly higher mortality rates in patients with CKD who have AVD, they may also experience an increased risk of development of ESRD. This effect may be especially pronounced in younger patients with CKD and AVD where the competing risk of death is lower. This observation may be helpful in decision making such as planning for renal replacement therapy in patients with CKD and AVD and suggests that pathophysiological mechanisms contributing to both cardiovascular death and progression of CKD to ESRD.

**PUB414**

**Fracture Risk Assessment (FRAX) in Chronic Kidney Disease (2-5ND)**

**Background:** A higher risk fractures has been well recognized among patients with chronic kidney disease (CKD).FRAX is a well-accepted tool for fracture risk assessment in the general population.In CKD many pts are frail and prone to falling which predispose to suffer a fracture.Bone changes in CKD are over imposes to normal aging evolution, as sarcopenia.The aim of this cross-sectional study is to assess the relationship of body composition and sarcopenia in CKD (2-5ND) pts with FRAX.

**Methods:** 411 pts ≥70 y were enrolled, (mean age 75 y, 40% diabetic status, 44.4% female) from our CKD unit. (Stage 2 19%, Stage 3A 39%, Stage 3B 37%, Stage 4 25% and Stage 5 5%) Spanish FRAX was use to calculate the 10-year probability of a major osteoporotic fracture. Vertebral score was >10 at 10 yr and hip fractures risk score >3% as at risk.Body composition assessment was performed with vectorial bioelectrical impedance (FEG, Akern FL. ITA and multifrequency Bioimpedanza 920, Maltron,London UK). Handgrip and walking in both arm and hand muscle force with (Handgrip-Akern FL. ITA) biochemical markers of CKD-MB, nutrition,renal function (CKD-EPI & ACR),inflammation and CV risk were performed.

**Results:** 170 pts (39.8%) were in risk of hip & vertebral fractures and 256 pts (61%) in risk of hip fracture alone.In bivariate analysis female (p=0.001) and older (p<0.001) evidenced high risk of fractures.

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

Underline represents presenting author.
**PUB145**

**Muscle-Kidney Crosstalk through microRNA-29a in Mice with Chronic Kidney Disease**

Daiqing Zhang, Haidong Wang, Bin Fang, Faten Hamam, Xiaoxian H. Wang.

**Methods:** UO was induced by left ureteral ligation. A NanoSight instrument was used to quantify exosomes. A miR deep sequencing array and qPCR were used to identify microRNA. We used Adeno-Associated Virus (AAV) for miR overexpression. Immunohistochemistry (Mason Trichrome) identified renal fibrosis.

**Results:** We found that serum-derived exosomes from UO mice are larger than control exosomes. miRNAdeep sequencing showed that miR-29a-5p was significantly increased in serum exosomes but decreased in skeletal muscle and kidney tissue of UUO control exosomes. MiRNAdeep sequencing showed that miR-29a was significantly overexpressed in skeletal muscle not only attenuated skeletal muscle atrophy but also ameliorated UUO-induced renal fibrosis through exosome-mediated muscle-kidney crosstalk.

**Conclusions:** FRAX is a useful tool to predict fracture risk in CKD pts. Our study reflects bone-muscle cross talk. Importance of physical exercise should not be underestimated.

**Funding:** Other NIH Support - SERGAS

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**PUB146**

**Childhood IgA Nephropathy Presenting Acute Nephritic Syndrome at Onset**


**Methods:** Serum creatinine, serum albumin, serum C3, C4, urine protein, urine albumin, urine protein/creatinine ratio, urine red blood cells/urine creatinine ratio, serum IgG4, and antinuclear antibodies were measured.

**Results:** 27 patients were included. The mean age of the patients was 14.8 years (range: 1.5 to 25.0 years). The mean duration of follow-up was 6.3 years (range: 1 to 17 years). The mean eGFR at presentation was 46.2 ml/min/1.73m² (range: 20 to 90 ml/min/1.73m²).

**Conclusions:** The prognosis of childhood IgA nephropathy is significant. The mortality rate is high, and the stage of kidney damage progresses rapidly. The treatment is mainly supportive. The prognosis is directly related to the patient's age at presentation. Early diagnosis and treatment can improve the prognosis of the disease.

**Funding:** No financial support was received for this study.

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**PUB147**

**A “Mini- Epidemic” of Anti-GBM Disease: Epidemiological, Clinical and Immunological Study**

Umeshia Lingaa, 1,2

**Background:** Anti-GBM disease is a rare and severe glomerulonephritis caused by the deposition of antibodies against the GBM. The disease is characterized by rapidly progressive glomerulonephritis and is associated with a high mortality rate. The aim of this study was to investigate the epidemiological, clinical, and immunological characteristics of a “mini-epidemic” of Anti-GBM disease.

**Methods:** We conducted a retrospective analysis of all cases of Anti-GBM disease diagnosed at our institution between 2005 and 2015. The demographic, clinical, and immunological data of all patients were collected and analyzed.

**Results:** A total of 8 patients were identified as having Anti-GBM disease. The mean age of the patients was 45 years (range: 23 to 74 years). The mean duration of symptoms before diagnosis was 2 months (range: 1 to 6 months). All patients had a history of smoking and smoking was found to be a risk factor for the development of Anti-GBM disease.

**Conclusions:** Anti-GBM disease is a rare but serious condition that can have a significant impact on patient outcomes. Early recognition and treatment are crucial for improving patient outcomes.

**Funding:** This study was supported by grants from the National Science Council of Taiwan.

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**PUB148**

**Are We Slowly Increasing the Rate of CKD Progression in Children?**

Isabel Roberti, Shefali Vyas, BernieRaghunath Children's Kidney Center, Barnabas Health Medical System, West Orange, NJ.

**Methods:** We conducted a retrospective analysis of all cases of CKD progression in children diagnosed between 2000 and 2015. The demographic, clinical, and immunological data of all patients were collected and analyzed.

**Results:** A total of 8 children were identified as having CKD progression. The mean age of the patients was 12 years (range: 5 to 17 years). The mean duration of symptoms before diagnosis was 18 months (range: 6 to 36 months). All patients had a history of smoking and smoking was found to be a risk factor for the development of CKD progression.

**Conclusions:** Anti-GBM disease is a rare but serious condition that can have a significant impact on patient outcomes. Early recognition and treatment are crucial for improving patient outcomes.

**Funding:** This study was supported by grants from the National Science Council of Taiwan.

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**PUB149**

**The Evaluation of the Associations between Measures of Kidney Dysfunction and Oral Health Status**

Seonam Catholic Univ of Korea, Seoul, Republic of Korea; 2Internal Medicine, Seonam Univ Myongji Hospital, Goyang, Republic of Korea.

**Background:** Urinary incontinence was considered an important part of the physician’s diagnosis. The purpose of the present study was to investigate the association between urinary symptoms and urinary tract function and urinary symptoms/urine specific gravity and oral health behavior using naturally representative data.

**Methods:** Data from the Korea National Health and Nutrition Examination Survey conducted between 2008 and 2010 were used; the sample analyzed in this study consisted of total of 15,013 respondents over 19 years old who had no missing values for the urinary tract function and urinary symptoms/urine specific gravity and oral health behavior.

**Conclusions:** The present study found a significant association between urinary symptoms and urinary tract function and urinary symptoms/urine specific gravity and oral health behavior. This relationship was consistent across different age groups and was stronger in women than in men.

**Funding:** This study was supported by grants from the National Science Council of Taiwan.

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

**Underline represents presenting author.**

938A
Results: Urinary sodium level was significantly lower in females (P<0.05). The rate of hypertension and diabetes was significantly lower in females (P<0.05). Adjusted odds ratios of urinary sodium and their 95% confidence intervals in relation to the frequency of tooth brushing (≤1, 2, and ≥3 times per day, respectively) were 1, 0.963 (0.794, 1.168), and 0.897 (0.741, 1.086) for males (P<0.05) and 1, 0.898 (0.704, 1.145), and 0.734 (0.573, 0.937) for females (P<0.05). Adjusted odds ratios and their 95% confidence intervals of urinary sodium regarding the number of secondary oral hygiene products used per day (0, 1, and ≥2, respectively) were 1, 0.986 (0.839, 1.158), and 0.766 (0.542, 1.081) for males (P<0.05) and 1, 0.851 (0.735, 0.985), and 0.798 (0.63, 1.01) for females (P<0.05).

Conclusions: Poor oral hygiene behavior was associated with higher sodium consumption in females. This association between sodium uptake and oral health behavior was independent of various potential confounding factors such as age, body mass index, smoking, drinking, exercise, diabetes, hypertension, and metabolic syndrome. Oral hygiene behavior may be considered an independent risk indicator for high urinary sodium level in Korean females.

PUB152
Low Serum Uric Acid Level Is a Risk Factor for 5-Year Mortality in Incident Hemodialysis Patients
Yoshiko Nishizawa,1 Sonoo Mizuiri,2 Mariko Asai,3 Kyoko Ono,1 Kazuomi Yamashita,1 Kenichiro Shigemoto,1 Takao Masaki,1
1Division of Nephrology, Ichikyokai Harada Hospital, Hiroshima, Saeki-Ku, Japan;
2Nephrology, Hiroshima Univ Hospital, Hiroshima, Minami-ku, Japan.

Background: 'J-shaped' association between uric acid and mortality has been controversial in maintenance hemodialysis patients. However, low serum uric acid (UA) level at the initiation of dialysis has not been fully clarified as a risk factor for mortality.

Methods: A retrospective study was conducted on 252 consecutive incident hemodialysis (HD) patients who started HD between 2005 and 2010. Data collection was terminated either at the 5-year observation of the study or at the time of death. Age, sex, presence of diabetes mellitus (DM), hemoglobin (Hb), serum uric acid (UA), creatinine (Cr), blood urea nitrogen (BUN), creatinine-protein (CRP), albumin (Alb), phosphate (P), albumin-adjusted calcium (Ca), phosphate, and geriatric nutritional risk index (GNRI) at the initiation of dialysis were recorded. The cumulative 5-year survival rate was estimated in each UA quartile group. The hazard of survival rate between the each group was also evaluated by Cox regression analysis. For 5-year all-cause mortality and the lowest UA quartile (Q1:≤5.9 mg/dl), risk factors including age, sex, DM, Hb, UA, Cr, BUN, CRP, Alb, Ca, P, and GNRI were assessed by univariate and multivariate logistic regression analysis.

Results: The cumulative 5-year survival rate of the patients in Q1 (45.5%) was significantly lower than those of the patients in Q2 (59.7-7.2 mg/dl, 68.3%), Q3 (7.2-8.3 mg/dl, 68.7%), and Q4 (≥8.3 mg/dl, 67.8%). Comparing with UA in Q4 as a reference group, the hazard ratio of patients with UA in Q1 was 2.3 (P<0.01). Age (P<0.05), BUN (P<0.001), UA (P<0.01), Cr (P<0.01) and Alb (P<0.05) were associated with 5-year all-cause mortality. The lowest UA quartile (Q1) was significantly associated with age (P<0.01), sex (P<0.05), Cr (P<0.01), BUN (P<0.01), P (P<0.05), and GNRI (P<0.05) in univariate logistic regression analysis. In the multivariate model, Cr (P<0.05) was detected.

Conclusions: Low serum uric acid (≤5.9 mg/dl) level at the time of initiation of dialysis is a risk factor for 5-year mortality.

PUB153
Median Nerve Thickness Related to Renal Impairment in Inflammatory Arthritis
Suad Ma Hannawi1, Issa A.L. Sulmi2
1Internal Medicine, Ministry of Health, Dubai, United Arab Emirates; 2Rheumatic Medicine Dept, The Royal Hospital, Muscat, Oman.

Background: Autoimmune processes, contribute to the burden of kidney disease. The reported kidney disease prevalence patients in rheumatoid arthritis (RA) is 5-15%. Subclinical decreased kidney function has been identified as an independent risk factor for CV events with increased mortality in RA. On the other hand, both RA and renal impairment associated with increase prevalence of carpal tunnel syndrome. This study aims to establish the relation of the to the median nerve thickness to the renal function in RA.

Methods: 120 RA patients recruited through a specialized rheumatology clinic. 8–16 MHz linear array transducer probe was used. The median nerve was examined at the entrance of the carpal tunnel, between the pisiform bone and the tubercle of the scaphoid bone, where the distal volar crease is an external pisiform landmark. The cross-sectional area of the median nerve was calculated directly by the software of the US equipment. Each median nerve was measured three times, and the mean value was used for further analyses. GFR calculated used MDRD formula. The average median nerve thickness was used when exploring bivariate correlations to the renal variables (Pearson's correlation coefficients). All statistics were performed using STATA program.

Results: The mean (SD) age of participants was 49 (13) years and female were 82%. The average median nerve thickness was 9.7±2.6 mm2 (Range 1.5–22.25). The average GFR was 122 ± 20 ml/min/1.73 m2. Thickness of the median nerve was positively associated with the age of the participants (P=0.03, Cl0.0.08), body mass index (P=0.04, Cl0.0.21), uric acid level (P=0.03, Cl0.00, 0.01), & urine microalbumin (P=0.04, Cl0.00, 0.01) showed no significant correlation to the renal variables. The median nerve thickness was positively correlated to the level of microalbumin and uric acid. Whether sonographic examination of the median nerve would be helpful in anticipating who is going to have a deteriorated renal function need to be explored in a larger study.

Funding: Government Support - Non-U.S.
Long-Term Exposure to Tenofovir Is Not Linked with Increased Risk of Renal Dysfunction: A Propensity Score-Matched Analysis

Minoru Ando,1,2 Kumiko Momoki,2 Ken Tsuschiya,2 Kosaku Nitta.1 1Dept of Medicine, Fuchu Medical and Welfare Center, Tokyo, Japan; 2Dept IV of Internal Medicine, Tokyo Women's Medical Univ, Tokyo, Japan; 1Dept of Nephrology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan.

Background: Tenofovir disoproxil fumarate (TDF) has nephrotoxicity; however, it has not been validated in the clinical setting for HIV care. A retrospective cohort study with a propensity score (PS)-matched analysis is considered comparable to randomized control trials.

Methods: A retrospective cohort study was performed in 661 HIV-infected patients receiving antiretroviral therapy from 2008 to 2014. PS matching using a multivariable logistic regression model was performed to match each TDF user with TDF non-user in a 1:1 fashion, and 214 patients (107 in each) were eligible for analysis. Baseline covariates that would relate significantly to the decision to use or not to use TDF were chosen in the PS scoring. A decline in eGFR was defined as an eGFR decline ≥30% from baseline. The difference in proportion of eGFR decline between the PS-matched groups was analyzed by McNemar test. A multivariable Cox proportional hazards model was constructed to calculate hazard ratio (HR) with its 95% confidence interval (CI) of TDF use for eGFR decline. Cumulative incidence of eGFR decline over time was drawn by Kaplan-Meier method.

Results: eGFR decline developed in 8 and 7 in the TDF users and the non-users, respectively; moreover, the proportions were not significantly different between the groups (7.48% versus 6.54%; p = 0.7889). The Kaplan-Meier estimates were not different between the groups.

Conclusions: Long-term exposure to TDF is less likely to develop renal dysfunction.

Dialysis Therapy and Conservative Management of Advanced Chronic Kidney Disease: A Meta-Analysis

Paweesa Susantiphong,1 Supakanya Wongrakpanich,2 Wikrom Chaiwatcharayut,2 Suramath Isaranuwatchai,3 Jirat Jirat,4 Somchai Maoliosa,1 Natanong Komagome,1 Brenda Jaber,5 Maria Miranda Cam,1 Nephology, Hospital Clinico San Carlos, Madrid, Spain; Nephology, Hospital Clinico San Carlos, Madrid, Spain; Hospital Clinico San Carlos, Madrid, Spain.

Methods: A systematic literature search was conducted in MEDLINE, Scopus, Cochrane, and ClinicalTrials.gov to identify cohort studies examining the association of dialysis vs conservative management of stage 5 CKD with clinical outcomes. Random-effect models were used to compute the pooled adjusted hazard ratio (HR) for association of dialysis vs. conservative management of stage 5 CKD with clinical outcomes. Descriptive statistics were utilized in order to calculate the prevalence of proteinuria among these populations.

Results: The records of 326 patients were examined. In this population, 201 did not have urine dipstick performed and therefore were excluded from analysis. Among those examined, proteinuria (1+ or higher) was found in 7 of 33 patients with carbon monoxide poisoning (21%), 31 of 67 patients with non-healing soft tissue infection or osteomyelitis (46%), 9 of 33 patients with a history of cancer of the head and neck (27%), and 8 of 11 patients with radiation cystitis (73%).

Conclusions: To our knowledge, this is the largest study to date examining proteinuria in patients who are undergoing hyperbaric oxygen therapy. Our results indicate that there is a higher than expected rate of proteinuria in these patients, particularly in those with carbon monoxide poisoning and history of cancer of the head and neck. The reasons for this are unclear and require further research. A prospective study measuring proteinuria prior to and after sessions of hyperbaric oxygen therapy has been approved by the IRB at the University of Iowa and is forthcoming.

Gluomerular Filtration in Patients with Advanced Chronic Kidney Disease by Berlin Study Initiative Equation

Marisol Poma Tapia,1 Fernando Tornero,1 Jose A. Herrero,1 Jose Maria Bautista,1 Amir Shabaka,2 Marta Calvo,1 Virginia Lopez de la Manzanara Perez,2 Fabio Proccacini,1 Mauricio Alejandro Miranda Cam.1 Nephology, Hospital Clinico San Carlos, Madrid, Spain; Nephology, Hospital Clinico San Carlos, Madrid, Spain; Nephology, Hospital Clinico San Carlos, Madrid, Spain.

Methods: We estimate the glomerular filtration rate (eGFR) using formula based on serum creatinine (Cockcroft-Gault, MDRD and CKD-EPI). These equations are poorly developed in the elderly population. Recently described new equations specifically designed in this population as the Berlin Initiative Study (BIS 1). Our goal is to assess the difference in measured GFR by CKD-EPI and BIS1 in patients in advanced chronic kidney disease (CKD).

Results: We studied 182 patients, 117 over 70 years old and 65 under of the advanced chronic kidney disease program with eGFR <20 ml/ min according to CKD-EPI equation. We compare the difference between CKD-EPI and BIS 1 equations. The mean age of patients over 70 years was 80.88 +/- 5.98 (66 males, 51 females) and under 70 was 58.84 +/- 5 (39 men, 26 women). The eGFR measured by CKD-EPI was similar in both groups (15.92 +/- 0.5 ml/ min in patients over 70 years VS 16.2 +/- 0.8 ml/ min in younger, p NS). However, when we use the BIS1 equation older patients have a significantly lower GFR that younger (19.6 +/- 0.4 ml/ min vs 24.16 +/- 1.0 ml/ min; p <0.001). When equate both equations CKD-EPI gives lower values of eGFR in 96.5% of patients with lower levels (16.03 +/- 0.45 ml/ min vs 21.3 +/- 0.50 ml/ min; p <0.001). If we analyze the difference between the two equations by the age we note that CKD-EPI gives lower values in patients under 70 years, being the difference between the two equations off 7.94 +/- 0.45 ml/ min for under 70 years and -3.67 +/- 0.16 ml/ min for over 70 years (p <0.011).

Conclusions: The eGFR by BIS1 equations in patients over 70 years gives higher than estimated by CKD-EPI equations, although it is more correlated than younger patients. Patients over 70 years, being the difference between the two equations of 7.94 +/- 0.45 ml/ min for under 70 years and -3.67 +/- 0.16 ml/ min for over 70 years (p <0.011).

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

Underline represents presenting author.

Methods: Participants included adults ≥18 years with access to a computer and Internet, high-speed Internet service, and were recruited from the following groups: patients with non-dialysis CKD, their caregivers, CKD health care providers, or CKD health policymakers. 56 participants were randomized to a wiki-inspired modified NGT that occurred over 3 weeks vs. a one-day in-person NGT workshop, informed by James Lind Alliance methodology, to develop and rank the top 10 CKD-related research priorities. The primary outcome was the pairwise agreement between the two groups’ final top 10 ranked priorities, evaluated using Spearman’s correlation coefficient. Secondary outcomes were participant engagement and satisfaction and wiki tool usability.

Results: Spearman’s rho for correlation between the two lists was 0.139 (95% CI -0.543 to 0.703, p=0.71), suggesting low correlation between the top 10 lists across the two groups. Both groups ranked the same item as the top research priority, with 5 of the top 10 priorities ranked by the wiki group within the top 10 for the in-person group. In comparison to the top 10 CKD-related research priorities. The primary outcome was the pairwise agreement between the two groups’ final top 10 ranked priorities, evaluated using Spearman’s correlation coefficient. Secondary outcomes were participant engagement and satisfaction and wiki tool usability. Before it can be considered an alternative to an in-person workshop for engaging patients in research prioritization.

PUB159
Clinical Predictors of Maternal and Fetal Outcomes in Pregnancy of Chronic Glomerulonephritis Patients Yuyueh Li,1 Jiajuan Lv,2 Nephrology, Beijing Tsinghua Changgung Hospital, Medical Center of Tsinghua Univ, Beijing, China.

Background: Analyzing the predictors of maternal and fetal outcomes in pregnancy of chronic glomerulonephritis (CGN) patients is helpful to acknowledge the effects of proteinuria on chronic kidney diseases. Decreased kidney function, uncontrolled hypertension and serious proteinuria are unfavorable pregnancy outcomes observed in some cohorts, but not enough studies on outcomes of pregnancies in CGN patients. The aim of the study was to define the predictors of adverse maternal and fetal outcomes in CGN patients. Methods: Maternal and fetal outcomes in 60 pregnancies of CGN patients from Jan 2006 to Jan 2016 were retrospectively analyzed. Descriptive analyses, laboratory data, medication and outcomes before and during pregnancies of these patients were analyzed by univariate and logistic regression. Results: CGN patients were associated with more adverse pregnancy outcomes. The gestational ages were shorter, the incidences of preeclampsia and gestational hypertension were increased. The rates of premature delivery and low birth weights were higher. 2 Prenatal proteinuria (1.8±2.1 g/d vs 0.6±0.8 g/d, P=0.032) and blood pressure (11.7% vs 3.3%, P=0.001) significantly increased compared with pre-pregnancy stage. 3 Proteinuria ≥1.0 g/d (OR 12.22, 95%CI 7.31–16.47, P=0.001) was the predictor of adverse maternal outcomes. Blood pressure ≥140/90 mmHg (OR 3.97, 95%CI 1.69–4.73, P=0.010) and uric acid ≥363 umol/l (OR 7.35, 95%CI 1.88–28.76, P=0.004) were the predictors of adverse fetal outcomes. Conclusions: Maternal-fetal risks are increased in pregnancies of CGN patients. Proteinuria ≥1.0 g/d is the predictor of adverse maternal outcomes. Blood pressure ≥140/90 mmHg and uric acid ≥363 umol/l are the predictors of adverse fetal outcomes.

PUB160
Specialists’ Perspectives on the Management of Patients with Systemic Lupus Erythematous - A Mixed-Methods Study David J. Tunnicliffe,1,2 Davinder Singh-Grewal,1 Jonathan C. Craig,1,2 Shilpa Jesudason,1 David Sumpton,1 Allison Tong,1,3 Uni of Sydney; 1Centre for Kidney Research, Children’s Hospital at Westmead; 1,2Central and Northern Adelaide Renal and Transplantation Service; Royal Adelaide Hospital.

Background: Different specialists are involved in the management of patients with systemic lupus erythematosus (SLE) but uncommon variation in practice remains unexplored. We aimed to describe specialists’ attitudes and perspectives on the management of SLE.

Methods: Immunologists, nephrologists and rheumatologists (n=43) caring for adult systemic lupus erythematosus (SLE) patients were given an online likert-like tool to rank 10 research questions associated with research topics, and 5) healthcare specialties, and discussed the reasons for their choices. Descriptive statistics were calculated for qualitative and quantitative data was analyzed thematically.

Results: From the 26 participants, there was an undifferentiated allocation of votes to research topics and associated research questions. They allocated their votes towards medical and mental health specialities in the management of SLE, whilst fewer votes were given to allied health. Seven themes underpinned participants’ priorities: improving standardized practice, research topic shortfalls, strengthening well-being, ensuring cost efficacy, minimizing family/community burden, severity of comorbidity or complications, reducing lifestyle disruption, and fulfilling future goals.

Conclusions: Young patients with SLE value comprehensive care, in particular relating to nephrology, and mental health. Research on improving psychological health and self-management of symptoms may improve treatment satisfaction and health outcomes for adolescents and young adults with SLE.

PUB161
Healthcare and Research Priorities of Adolescents and Young Adults with Systemic Lupus Erythematosus - A Mixed-Methods Study David J. Tunnicliffe,1 Davinder Singh-Grewal,1,3 Jonathan C. Craig,1,2 Martin Howell,2,3 Ming-Wei Lin,1 Angelique F. Ralp,1 Allison Tong,1,3 Uni of Sydney; 1Centre for Kidney Research, Children’s Hospital at Westmead; 2Dept of Rheumatology, Sydney Children’s Hospital Network; 3Faculty of Medicine, Univ of New South Wales; 4Dept of Immunology, Westmead Hospital.

Background: The care of adolescents and young adults with systemic lupus erythematosus (SLE) is particularly challenging. The disease may be severe, adolescent patients have complex medical and psycho-social needs, and they must navigate the transition to adult services. To inform patient-centered care, we aimed to identify the healthcare and research priorities of adolescents and young adults with SLE and describe the reasons underlying their priorities.

Methods: Face-to-face, semi-structured interviews and focus groups were conducted with patients with SLE, aged from 14 to 30 years, from five centres in Australia. In five allocation exercises, participants allocated ten tokens (i.e. votes) to 1) research topics (topics: treatment, symptom management, psychological morbidity, lifestyle factors, comorbidities), 2) health research questions associated with research topics, and 5) healthcare specialties, and discussed the reasons for their choices. Descriptive statistics were calculated for qualitative and quantitative data was analyzed thematically.

Results: From the 26 participants, there was an undifferentiated allocation of votes to research topics and associated research questions. They allocated their votes towards medical and mental health specialities in the management of SLE, whilst fewer votes were given to allied health. Seven themes underpinned participants’ priorities: improving standardized practice, research topic shortfalls, strengthening well-being, ensuring cost efficacy, minimizing family/community burden, severity of comorbidity or complications, reducing lifestyle disruption, and fulfilling future goals.

Conclusions: Young patients with SLE value comprehensive care, in particular relating to nephrology, and mental health. Research on improving psychological health and self-management of symptoms may improve treatment satisfaction and health outcomes for adolescents and young adults with SLE.

PUB162
Impact of an On-Line Course for Primary Health Care Physicians on Patients at Risk for Chronic Kidney Disease (CKD) Maria Alejandra Guzman,1 Alfonso M. Cueto-Manzano,1 Cristina Chavez,2 Hector Martinez Ramirez,1 Jorge Lopez-Leal,1 Roxana Marquez-Herrera,1 Norma Palacios,1 Enrique Rojas-Campos,1 Unidad Investigación Medicina en Enfermedades Renales, HE-CMNO IMSS, Guadalajara, Mexico; 1ISN-Fellowship Program, ISN; 2Coordinacion Nacional de Educacion en Salud, IMSS, DF, Mexico.

Background: On-site education increases clinical competence of family physicians (FP) working in diverse renal populations of early CKD patients. On-line learning might have higher impact, however, this has not been probed. Aim: to assess the impact of an on-line course for FP on patients at risk for CKD.

Methods: Fifty FP from 2 Family Medicine Units were registered in an on-line course implemented during Aug-Oct/2015. One-hundred forty-seven patients attended by those FP registered, with diagnosis of diabetes mellitus and/or hypertension, were retrospectively studied (from medical charts). Patients were divided in 2 groups: those whose physician approved the course (G1), and those whose physician did not approve (G2).

Results: Main results are shown in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group G1 (n=40)</th>
<th>G2 (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP advice to improve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet(%)</td>
<td>37</td>
<td>58*</td>
</tr>
<tr>
<td>Physical activity(%)</td>
<td>32</td>
<td>52*</td>
</tr>
<tr>
<td>Excretion management(%)</td>
<td>5</td>
<td>31*</td>
</tr>
<tr>
<td>Referral to diuretics(%)</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Referral to self-help(%)</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Creatinine request(%)</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>GFR estimation(%)</td>
<td>27</td>
<td>40</td>
</tr>
<tr>
<td>Urinalysis request(%)</td>
<td>33</td>
<td>35</td>
</tr>
</tbody>
</table>

* p<0.05 vs baseline same group; ** p<0.05 vs group 1 same evaluation.
Conclusions: FP who successfully completed the on-line course significantly increased advice to patients to improve diet, physical activity, emotional management, levels of systolic blood pressure and glucose. Although kidney function remained clinically stable in both groups, FP who successfully completed the course tended to request serum creatinine and estimate GFR more frequently than the others.

PUB163
Impact of an On-Line Course about Prevention, Diagnosis and Treatment of Early Chronic Kidney Disease (CKD) in the Primary Health-Care
María Alejandra Guzman,1,2 Alfonso M. Cueto-Manzano,1 Cristina Chavez,1 Héctor Martínez Ramirez,1 Jorge Lopez-Leal,1 Roxana Marquez-Herrera,1 Norita Padilla.1,2 Project Coordinators.1 ‘Programa de Investigación Médica en Enfermedades Renales, HE-CMNO IMSS, Guadalajara, Mexico; 2 ISN Fellowship Program, ISN; 3 Coordinación Nacional de Educación en Salud, IMSS, DF, Mexico.

Background: The Mexican Institute of Social Security (IMSS) is the major health care provider. On-site education increases clinical competence of family physicians (FP) and preserves better renal function of early CKD patients; on-line learning might have higher impact, however, this has not been proved. Aim: to report the experience in implementing an on-line course on early CKD in primary health care.

Methods: An on-line course was developed in collaboration with IMSS Educational Experts. It was focused on early CKD, containing 5 units: General Aspects, Prevention, Diagnosis, Treatment, and Follow-up/Referral to Nephrologist. Each unit contained relevant information, clinical cases, homework, summary, and final test; all the latter together with a final course evaluation, had to be approved to obtain credits. The course was implemented in Aug-Oct/2015.

Results: One hundred eight FP from 3 Family Medicine Units (FMU No. 53, 78, and 171) of Guadalajara city, were initially registered; roughly, one third of physicians belonged to each FMU. Forty-four FP never started (terminal efficiency 58%), half of them were male, and their age was 45±9 yrs. At the end of Unit 1, 1 FP dropped out (70%), 2 (10%) at the end of Unit 2, 3 (15%) at Unit 3, and 1 (5%) at Unit 5; 43% were male and age was 45±8 yrs. Forty-four FP completed the course, and all of them finally approved it (modified terminal efficiency 100%); these latter subjects were younger 43±8 yrs (p=0.008), and tended (NS) to have more men (68%) in the group than those who did not approved.

Conclusions: An on-line course about early CKD was successfully developed and approved by the majority of FP. A sufficient proportion of physicians dropped out before starting; however, those physicians who finally approved the course, Terminal efficiency was adequate; however, it is needed to implement strategies to increase it in order to improve tools against kidney disease.

PUB164
CKD-QLD: Management of Chronic Kidney Disease through Tele-Health in Queensland, Australia
See Krishna Venuthurupalli,1,2 Andrea Rolfe,3 Anne Cameron (Salisbury),1,2 Zainim Wang,1 Wendy E. Hoyo,1,3 NHMRC CKD CRE and CKD QLD, Brisbane, Queensland, Australia; ’School of Medicine, Univ of Queensland, Brisbane, Queensland, Australia; ’Renal Services, Darling Downs Hospital and Health Service, Toowoomba, Queensland, Australia.

Background: In some areas of Australia, access to specialists is limited by geographical location and resources. We explored a Tele-health program for management of chronic kidney disease (CKD) patients in rural, regional and remote Queensland.

Methods: Patients were among those attending renal clinics in Toowoomba Hospital, but living at some distance. Their first review was at Toowoomba Hospital to ascertain their clinical profile and to discuss the process. Tele-health clinics in Kingaroy & Cherbourg were coordinated by the renal nurse practitioner. Other hospital locations were managed by local nursing personnel. At each clinic the patients’ health records and relevant investigations are assembled in advance. Consultations are conducted through Queensland Health (QH) facilities.

Results: 151 patients were seen between November 2011 and May 2016, with over 400 consultations. Total distance traveled by all patients to specialist clinics at Toowoomba for their first consultation was 55,619 kilometers (range 63.5 to 672). Mean age was 64.0 (SD13.9) years, median 67 yr, and 48.3% were males. A quarter (27.8%) were Aboriginal. Major risk factors include hypertension (94%), smoking (current or former) (64.2%), diabetes (58.2%) and obesity (58.2%). Diabetic nephropathy (40.7%) was the dominant CKD. They are critical partners in kidney research, and feel a sense of hope in the partnership effective partnership in research. In their qualitative feedback, patient partners expressed that they were empowered in their involvement, while allowing peer support and giving back.

Conclusions: More knowledge about organ transplantation can be transformed into better attitude which can lead to increased number of organ donations. More and more people should be educated and made aware of the importance of organ donation.

PUB166
Patient Partnership as the Core of a National Patient-Oriented Kidney Research Network: Can-SOLVE CKD
Helen Chiu,1 Mila Tang,1 Heather A. Harris,1 Adeera Levin,1 Braden J. Manns.1,2 PHCRI; 1Dept of Medicine, UBC; BC Renal Agency; 2Dept of Medicine & Community Health Sciences, U of Calgary, AB, Canada.

Background: Patient-oriented research (POR) focuses on priorities that matter to patients, seeking to engage them throughout the research process, and to generate results that can rapidly advance improvements in health and care. The Canadians Seeking Solutions and Innovations to Overcome (Can-SOLVE) CKD Initiative embraces a national partnership strategy with patients across Canada to transform kidney research and care.

Methods: The James Lind Alliance method was adopted to discern top research priorities with patients and families with CKD. Patient partners, researchers and policy-makers developed in workshops research proposals and various components in Can-SOLVE CKD. A national Patient Council was formed to lead all aspects of Can-SOLVE CKD. The extent and impact of patient engagement is continually assessed with surveys and testimonials.

Results: The priority-setting workshops identified research questions for early and advanced CKD, resulting in a 3-themed research program in Can-SOLVE CKD (early identification, access to novel therapies, and models of care). A diverse representative Patient Council of >30 members is a key strength, secured federal funding support and has become the core driver of the research agenda. Quantitative and qualitative survey results demonstrated that the patient partners are highly engaged and appreciative of having a voice in research, along with concrete insights on needs for training and other supports for effective partnership in research. In their qualitative feedback, patient partners expressed that they were empowered in their involvement, while allowing peer support and giving back.

Conclusions: Patients are making a unique and important contribution to Can-SOLVE CKD. They are critical partners in kidney research, and feel a sense of hope in the partnership in transforming kidney care and therapy. Meaningful engagement with patients enables a new era in kidney research to co-create better kidney health and care with researchers and policy-makers across Canada.

PUB167
Development of an Automated CKD Risk Management System
Naveed Tangri,1 Eleanor Herriman,1 Medicine, Seven Oaks Hospital, Winnipeg, MB, Canada; ‘Views Inc., Sunnyvale, CA.

Background: CKD is managed according to gFR based stages rather than risk of progression, resulting in variable and suboptimal care. Here we describe the development of an automated system that achieves the highly accurate (very Failure Risk Equations (KFRE) via a practical, automated clinical solution.

Methods: We defined a four-step protocol based on the KFRE that recommends referral to nephrologist, multidisciplinary care enrollment, dialysis discussion and education and patient/primary care communication. We conducted a systematic review to identify risk factors at all stages. Utilizing the Views Inc. platform (Figure 1), we automated the input of patient’s lab results and demographic information and calculation of the KFRE algorithm. A series of dashboards was created to enable primary care and nephrologist clinicians, as well as program managers to track patient

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 942A
results, protocol recommendations, and required actions. Finally, custom patient education reports were automatically created, which detail individual risk of renal failure and care recommendations, designed to reduce anxiety and better engage patients in their care.

Results: Our solution is a cloud-based, HIPAA compliant, end-to-end program which reconciles the risk score prediction for clinical adoption and improved CKD management. It comprises a lab and EMR integration platform, personalized risk prediction for renal failure, automated and integrated care management recommendations for primary care physicians and nephrologists, and customized patient education reports.

Conclusions: This program accurately predicts the risk of progression from CKD to ESRD for at least five years, and its integration into practice allows for more appropriate care and improved outcomes. Total annual cost savings to an ACO with a population of 25,000 covered lives was estimated at $2 million as a result of delaying stage 3 progression, reclassifying stage 4s, and providing earlier nephrologist care for patients with a high risk of progression.

Funding: Pharmaceutical Company Support - Viewics Inc.

PUB168

Incidence of Cisplatin-Induced Nephrotoxicity among Patients Using Saline Hydration, Potassium Chloride, Magnesium Sulfate and Mannitol

Minoru Nomura,1, Maria Kristina Tran,2, Kenji Masuda,1,2, Akira Kugimiya,1, Erito Iwahashi,1 Kenji Yokoyama,2 Terumasa Hayashi,2

Background: Cisplatin is the standard drug for treating solid-organ malignancy however, can cause tubular toxicity, decrease in GFR, and increase creatinine causing AKI, interstitial injury and probably CKD. To prevent nephrotoxicity that can lead to CKD, maintenance of adequate hydration and replacement of electrolytes are necessary but no standardized hydration protocols available. Determination of the incidence of cisplatin-induced nephrotoxicity using isotonic saline, KCl, MgSO4, and mannitol can help improve the hydration regimen for the prevention of nephrotoxicity.

Methods: A retrospective study evaluating the incidence of nephrotoxicity among patients using cisplatin-based chemotherapy hydrated with isotonic saline, KCl, MgSO4, and mannitol from January 2011-2015. Estimated GFR was calculated using CKD-EPI. Nephrotoxicity is defined as lower GFR, higher creatinine, and reduced magnesium and potassium levels. Descriptive statistics were done. Any associated p-values <0.05 will be considered statistically significant.

Results: Total of 53 patients were analyzed which showed an increasing trend in creatinine and decreasing trend in eGFR until 3 months after chemotherapy. The baseline creatinine, eGFR, and serum electrolytes compared with the results 3 months post-chemotherapy were found to be significantly different.

The incidence of decreased renal function after 3 months from the last chemotherapy cycle was 33% (n=18).

Conclusions: Despite judicious hydration, Cisplatin therapy may induce permanent nephrotoxicity with an incidence of 33% three months after 3 chemotherapy cycles. Cisplatin induces nephrotoxicity as evidenced by electrolyte imbalance, increased mean serum creatinine and decreased estimated GFR.

PUB169

Urinary Procollagen Type-III Amino Terminal Propeptide (PiIIINP) Predicts End Stage Kidney Disease (ESKD) and All-Cause Death in Non-Dialysis CKD Patients

Hiroki Yonishii,1 Akira Suzuki,1 Shihomi Mueda,1 Aiko Kugimiya,1 Erito Iwahashi,1 Kenji Yokoyama,2 Terumasa Hayashi,2

Background: Tubulointerstitial fibrosis is the final common pathway to ESKD. Since urinary PiIIINP is correlated significantly with the severity of fibrosis in renal biopsy, it could be a marker of progressive kidney diseases. Recent cross-sectional study demonstrated that the urinary PiIIINP was correlated with the progression of CKD in the community based population. In this prospective study, we investigated whether urinary PiIIINP was associated with renal outcome and mortality in predialysis advanced CKD patients.

Methods: A total of 132 CKD patients were recruited from January 2011 to December 2014. Patients with liver disease, lung fibrosis, and malignancies were excluded. Urinary PiIIINP was measured using the radioimmunoassay at baseline. Multivariate Cox regression analysis and log-rank test were adopted using urinary PiIIINP/Cr as the explanatory variable and initiation of RRT and all-cause death as the primary composite endpoint.

Results: The study population included 71, 51, and 10 patients with CKD stage 3, 4, and 5, respectively. The mean age of the overall patients were 68 years and 70.5% were male sex. Forty-four patients (33.3%) had diabetes. A total of 14 patients (11%) started RRT and 8 patients died during the follow-up period (mean, 40.1 months) The patients were stratified into two groups based on the cut-off value of urinary PiIIINP/cr determined by the ROC analysis. The Kaplan-Meier survival curves showed that the patients’ group with urinary PiIIINP had significantly poorer outcomes (p = 0.000). Furthermore, multivariate Cox regression analysis revealed that higher urinary PiIIINP was significantly associated with increased risk of RRT and all-cause death adjusted for the age, gender, the etiology of diabetes, blood pressure, eGFR, and urinary protein. (HR: 3.177, 95%CI; 1.018-9.915, p = 0.046).

Conclusions: Urinary PiIIINP in predialysis and advanced CKD patients might be a novel prognostic marker for ESKD and all-cause death.

PUB170

Neck Circumference Predicts Renal Function Decline in Overweight Men and Women: A Community-Based Prospective Cohort Study

Youn Kyung Kee, Chang-Yun Yoon, Changhwan Seo, Hae-Ryong Yun, Dae-Suk Han. Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Upper body subcutaneous fat, commonly estimated by neck circumference (NC), has recently been noticed as the main determinant of systemic free fatty acid concentrations in overweight patients. Therefore, the association between upper body subcutaneous fat, represented by NC, and incident chronic kidney disease (CKD) was explored.

Methods: The data was retrieved from the Korean Genome and Epidemiology Study (KoGES) cohort. Overweight was defined as body mass index ≥23 kg/m², and subjects were followed for a 2-year interval from 2003 to 2012. Incident CKD was defined as the composites of estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² or development of proteinuria. A total of 35,709 cohort subjects were screened. After exclusion, 2,268 overweight subjects were eligible for final analysis.

Results: The mean age was 36.3±9.0 years, and 1,285 patients (56.7%) were male. The subjects were divided into two groups according to the median value of NC in male and female subjects, respectively. High NC showed significantly high prevalence of hypertension (male, P=0.001, female, P=0.009) and diabetes (male, P=0.002, female, P=0.001), while eGFR was significantly low only in male subjects with high NC (male, P=0.001, female, P=0.167). In multiple Cox analysis, higher NC values were independently associated with incident CKD development in female subject after adjusting for multiple confounding factors (NC, 1 cm increase; male; hazard ratio (95% confidence interval)=0.989 (0.89-1.01), P=0.841, female; 1.159 (1.02-1.31), P=0.019). However, a significant relationship was not found in male subjects.

Conclusions: NC is independently associated with the incidence of CKD in overweight female subjects. Upper body subcutaneous fat, chiefly represented by NC, could be considered as a practical risk factor for CKD.

PUB171

Early Emergence of Proteinuria Portends Subsequent Development of Kidney Function Decline or Nephrotic Syndrome after Stem Cell Transplantation in Patients with Nephrotic Syndrome

Kumiko Kogure,1 Minoru Ando,2 Masaki Hara,2 Akihito Ohta,1 Masamitsu Uba,1 Kosaku Nitta. 21 Div of Nephrology, Dept of Medicine, Tokyo Metropolitan Komagome Hospital, Bunkyo-ku, Tokyo, Japan; 2Dept IV of Internal Medicine, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan; 3Dept of Medicine, Tokyo Metropolitan Fu-chu Medical and Welfare Center, Fu-chu-shi, Tokyo, Japan.

Background: Stem cell transplantation (SCT) places a heavy burden on the kidneys. New proteinuria after SCT may portend the subsequent development of kidney insults.

Methods: A total of 83 patients who received allogeneic SCT between August 2004 and July 2015 were surveyed. Excluding those with prior kidney disease and those who were not followed over one year, 251 were eligible for the study. A historical cohort study was conducted.

Results: The mean age was 36.3±9.0 years, and 1,285 patients (56.7%) were male. The subjects were divided into two groups according to the median value of NC in male and female subjects, respectively. High NC showed significantly high prevalence of hypertension (male, P=0.001, female, P=0.009) and diabetes (male, P=0.002, female, P=0.001), while eGFR was significantly low only in male subjects with high NC (male, P=0.001, female, P=0.167). In multiple Cox analysis, higher NC values were independently associated with incident CKD development in female subject after adjusting for multiple confounding factors (NC, 1 cm increase; male; hazard ratio (95% confidence interval)=0.989 (0.89-1.01), P=0.841, female; 1.159 (1.02-1.31), P=0.019). However, a significant relationship was not found in male subjects.

Conclusions: NC is independently associated with the incidence of CKD in overweight female subjects. Upper body subcutaneous fat, chiefly represented by NC, could be considered as a practical risk factor for CKD.
performed. Dickkopf proteinuria ≥1 within one year after SCT with persistence at least for 3 months was defined as ‘incident proteinuria’, and subsequent persistence of an eGFR of < 60 mL/min/1.73 m² for 3 months or longer was defined as ‘incident CKD’. Additionally, kidney-biopsied tissue was investigated in all patients who developed nephrotic syndrome.

**Results:** The mean duration of follow-up was 3.4 (1.7-5.7) years [median (interquartile range)], and 34 patients (13.5%) developed incident proteinuria. Sixty-six of 251 (26.3%) developed incident CKD, and 9 (3.6%) developed nephrotic syndrome due to membranous nephropathy in 8 (89%) or minimal change disease in one (11%). The incidence of such kidney disease was extremely greater in patients with incident proteinuria than those without (61.8% vs 20.7% in incident CKD, and 26.5% vs 0% in nephrotic syndrome).

**Conclusions:** Patients who manifest incident proteinuria are more predisposed to incident CKD or nephrotic syndrome thereafter. Dickkopf urinary protein test is a simple measure to predict the ensuing emergence of kidney disease that should be treated by nephrologists.

**PUB174**

*Blockade of P2X7 Receptor Is Protective in the Adriamycin Model of Chronic Kidney Disease*

**Authors:** Yuan Min Wang, Geof Yu Zhang, Andrew Sawyer, Jianheng Zhou, Min Hu, Guoping Zheng, Qi Cao, Yi Ping Wang, Simon C. Robson, David C. Harris, Stephen I. Alexander. 1Centre for Nephrology Research, The Children’s Hospital at Westmead; The University of Sydney, Sydney Medical School, Australia; 2Centre for Transplantation and Renal Research, Univ of Sydney, Westmead Inst of Medical Research, Sydney, NSW, Australia; 3Transplant Inst, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

**Background:** Extracellular purines have both protective and damaging effects on the immune system and on the kidney. ATP is released from injured tissues via its major receptor P2X7 (P2X7R) to induce inflammation and release pro-inflammatory cytokines, such as interleukin-1β. Extracellular ATP and P2X7 appear to be involved in early stages of damage in nephritis. A804598 (A8) is a potent competitive P2X7R antagonist. Blockade of P2X7 by A8 could potentially limit kidney injury. The aim of the study is to evaluate the role of extracellular ATP and P2X7R in Adriamycin Nephropathy (AN, a toxin-induced model of proteinuric kidney disease) by increasing extracellular ATP or blockade of P2X7R.

**Methods:** AN was induced with Adriamycin (ADR) in three groups: ADR, ADR+ATP and a normal control group. ATP or A8 was injected prior to and 24 hours after ADR injection, followed by a further 4 weekly injections. Four weeks after AN induction, renal function and histology were assessed. Serum cytokines were measured using Cytometric Bead Array (CBA) and apoptosis was assessed by TUNEL assay in primary tubular cells.

**Results:** Mice receiving P2X7R antagonist A8 had significantly less kidney injury with reduced proteinuria and serum creatinine, less gliomerulosclerosis and tubular damage than mice receiving ATP or ADR alone. ATP in vivo TUNEL assay showed that proapoptotic effects of ATP on renal tubular cells with apoptosis peaking at 2 hours with 3mM ATP. There was significantly less apoptosis in tubular cells exposed to P2X7R antagonist A8 after ATP treatment.

**Conclusions:** P2X7R blockade protects against kidney injury through inhibition of tubular cell death by ATP in Adriamycin Nephropathy.

**PUB175**

*High-Intensity Exercise Did Not Adversely Affect the Renal Function or Proteinuria in Stable Patients with IgA Nephropathy after the Initial Treatment*

**Authors:** Tatsuyuki Inoue, Hitoshi Sugiyama, Masashi Kitagawa, Jun Wada. Dept of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ, Okayama, Japan.

**Background:** IgA nephropathy (IgAN) often occurs in young adults. In IgAN, proteinuria and hypertension are the main risk factors for end-stage kidney disease and can be caused by lifestyle-related diseases. Although patients with stable IgAN are generally younger than middle-aged with a high level of daily activities, the actual lifestyle of these patients has not been explored, particularly with respect to their exercise regimen.

**Methods:** We surveyed the outpatients with IgAN at Okayama University Hospital via a questionnaire about their lifestyle. The degree of exercise was evaluated using the method of “Category Range” of the American College of Sports Medicine. We also investigated the kind of each exercise and further analyzed the relationships between the subjects’ lifestyle and data extracted from the medical record. The severity of IgAN was determined by the Japanese clinical and histological grading system.

**Results:** We obtained valid responses from 81 patients, including 57 with stable IgAN who were not taking corticosteroids. Males accounted for 46% if the subjects, the mean age was 43.7 years old, the mean estimated glomerular filtration rate (eGFR) was 68.7 ml/min/1.73 m², and the mean daily protein excretion was 0.28 g/day. 91% practiced some form of diet therapy, usually salt restriction (79%). Most (54%) engaged in moderate exercise (category 4). A significantly positive correlation was noted between daily proteinuria at diagnosis and exercise intensity (r = 0.18, p < 0.01). However, this correlation had disappeared at the final observation. We did not observe any relationships
between exercise intensity and daily proteinuria, change in the protein excretion, or the eGFR at the final observation. Some (34%) felt that their quality of life had been increased by the improvement in their diet after the diagnosis. 

Conclusions: This study showed that stable IgAN patients are conscious of their risk of developing lifestyle-related diseases. High-intensity exercise during the period when initial treatments for IgAN are essential did not appear to affect patients with stable IgAN adversely.

Funding: Government Support - Non-U.S.

PUB178

An Association between Remodeling of Large Arteries and Arteriosclerosis of Small Renal Arteries in Chronic Kidney Disease

Kentarō Kohagura,1,2 Tsuyoshi Miyagi,2 Ryo Zamami,1 Yusuke Ohya,1,2 Dialysis Unit, Univ Hospital of the Ryukyu, Nishihara-cho, Okinawa, Japan; 3Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyu, Nishihara-cho, Okinawa, Japan.

Background: Remodeling of large arteries may promote organ damage by leading to arteriosclerosis of small arteries. In the present study, we examined the association between arteriosclerosis of small renal arteries and remodeling of large arteries in patients with chronic kidney disease (CKD).

Methods: A total of 174 consecutive patients who underwent renal biopsy at our department between 2010 and 2013 were enrolled. We excluded patients with vasculitis etc., leaving us with 102 patients. Using pathological specimens, the intimal thickening of the renal small arteries (RSA-IT) was semiquantitatively evaluated. Remodeling of large arteries and endothelial function were assessed by brachial-ankle pulse wave velocity (ba-PWV) and percentage flow-mediated dilation (%FMD) of the brachial artery.

Results: The mean values for age, blood pressure, and estimated glomerular filtration rate (eGFR) were 40.4 ± 7.4 years, 72.5 ± 11.7 mmHg, and 94.4 ± 12.6 ml/min/1.73m², respectively. There was a positive correlation between the Log RSA-IT score and Log ba-PWV and a negative correlation between %FMD and both Log RSA-IT and ba-PWV. Patients with high ba-PWV, which was defined as a ba-PWV score equal to or more than the median value, were characterized by older age, higher incidence of comorbidities such as hypertension and diabetes mellitus, higher high-sensitive C-reactive protein (hs-CRP), lower %FMD, and higher RSA-IT score. We conducted multivariate logistic analysis for high RSA-IT, which was defined as a score equal to or more than the median value. High ba-PWV was significantly associated with high RSA-IT independent of age, sex, eGFR, and comorbidities such as hypertension. However, its significance disappeared upon additional adjustment with hs-CRP. Subgroup analysis revealed that patients with a combination of high RSA-IT and ba-PWV had relatively high urine protein.

Conclusions: Remodeling of large arteries may lead to the development of CKD because arteriosclerosis of the small renal arteries is promoted in association with inflammation.

PUB179

Monocyte Count and the Risk of Incident Chronic Kidney Disease and Progression to End Stage Renal Disease

Benjamin Charles Bowes,1,3 Yan Xie,1,4 Rick C. J. Dean,1,2 Zaizid Al-Aly,1,2,3 Clinical Epidemiology Center, Research and Education Service, VA Saint Louis Health Care System, St. Louis, MO; 2Dept of Biostatistics, College for Public Health and Social Justice, Saint Louis Univ, St. Louis, MO; 3Div of Nephrology, Dept of Medicine, VA Saint Louis Health Care System, St. Louis, MO; 4Dept of Medicine, Washington Univ School of Medicine, St. Louis, MO.

Background: Experimental evidence suggests a role for monocytes in the biology of kidney disease progression; however, whether monocyte count is associated with risk of acute CKD, CKD progression, and ESRD has not been examined in large epidemiologic studies.

Methods: We built a cohort of 1,594,700 United States Veterans and used survival models to examine the association between monocyte count and risk of incident CKD and risk of CKD progression (defined as doubling of serum creatinine, eGFR decline ≥ 30%, or the composite outcome of ESRD, dialysis or renal transplantation). Monocyte count was categorized into quintiles (Q1: <0.00 to <0.40, Q2: ≥0.40 to <0.55, Q3: ≥0.55 to ≤0.70, and Q4: ≥0.70 k/cm³).

Results: Over a median follow up of 9.16 years (IQR: 8.26-9.42), in adjusted models, there was a graded association between monocyte counts and risk of renal outcomes. Compared to Q1, Q4 was associated with increased risk of incident eGFR<60 ml/min/1.73m² (HR=1.13; CI:1.12-1.14) and risk of incident CKD (HR=1.15; CI:1.13, 1.16). Q4 was associated with increased risk of doubling of serum creatinine (HR=1.22; CI:1.20-1.24), ≥30% eGFR decline (HR=1.18; CI:1.17-1.19), and the composite renal endpoint (HR=1.19; CI:1.16-1.22). Cubic spline analyses of the relationship between monocyte count levels and renal outcomes showed a linear relationship where risk was increased with higher monocyte count.

Conclusions: Our results demonstrate a significant association between high monocyte count and risks of incident CKD and CKD progression.

Funding: VA Support

PUB180

Toll Like Receptors, Cytokines, and Catheleinidin as a Complex Inflammatory Mechanism in HD and PD Patients

Caren Cristina Grabulosa,1 Jacqueline Ferritto Rebelló,2 Beata Maria Redublo Quinto,1 Marcelo Costa Batista,1,2 Maria Dalboni,1,2 Medicine, Univ Federal de Sao Paulo, Sao Paulo, Brazil; 3Medicine, Univ Nove de Julho, Sao Paulo, Brazil; 4Medicine, Hospital Israelitico Albert Einstein, Sao Paulo, Brazil.

Background: It has been reported that Toll-like receptors (TLR) expression on neutrophils and monocytes are associated with increase cytokines synthesis and may result in inflammation. However, the TLRs expression, catheleinidin on PMN

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
was significant in all regions; (ii) female gender was significant only in Africa, South Asia and South East Asia; (iii) hypertension was significant only in South East Asia and South America; (iv) diabetes was significant in Western Europe / North America, Eastern & Central Europe / Middle East, South Asia, China and South East Asia.

Conclusions: We report an overall RI prevalence rate consistent with previous studies, but significant regional variations in prevalence and risk factors.

PUB183

Predictors of Rapid Progression in Women with X-linked Alport Syndrome
Michelle N. Rheault, 1 Shelley Dunn, 2 Paul C. Gritti, 3 Jacqueline Blem, 4 Michael Huang, 2 Clifford E. Kashtan. 1 Univ of Minnesota, 2 Regulus Therapeutics, Inc

Background: Females with X-linked Alport syndrome (AS) have a wide variability in disease course. Predictors of rapid kidney disease progression in this population are unknown.

Methods: ATHENA (NCT02136862) is a non-interventional, global, multicenter study enrolling patients with CKD due to AS. Urine and plasma biomarkers and estimated GFR (eGFR) were assessed at baseline and every 12 weeks thereafter. P-values for categorical variables were calculated based on Fisher’s Exact test. P-values for continuous variables were based on t-tests.

Results: We analyzed 28 women with X-linked AS enrolled to date with at least 3 eGFR values. Women were categorized as a slow progressor if eGFR slope declined <5ml/ min/1.73m2 per year and a rapid progressor if eGFR declined ≥5ml/min/1.73 per year. Proteinuria, genotype, urea biomarkers, blood loss, or hypertension were not predictive of rapid progression.

Funding: Pharmaceutical Company Support - Regulus Therapeutics, Inc

PUB184

Hormone Therapy and Urine Protein Excretion: A Systematic Review and Meta-Analysis
Andrea G. Kattah, 1 M. Lourdes Gonzalez Suarez, 2 Natasa Milic, 2 Vesna D. Garovic. 1 Nephrology & Hypertension, Mayo Clinic, Rochester, MN; 2 Inst for Medical Statistics & Informatics, Univ of Belgrade, Serbia

Background: Animal models suggest estrogen has a renoprotective effect, but human studies have had variable results.

Methods: We performed a systematic review and meta-analysis of observational studies and randomized controlled trials (RCTs) that evaluated the association of hormone therapy (HT) and urine protein excretion (albuminuria/proteinuria) in post-menopausal women. We searched Medline, Embase, Cochrane Register of Controlled Trials and Scopus. Two reviewers screened all abstracts/texts and assessed quality. Dichotomous (odds ratios (ORs)) and continuous measures (mean differences) of the association between HT and urine protein excretion were converted to standardized mean differences (SMDs).

Results: We identified 1088 abstracts - 143 full texts were reviewed and 12 studies were included. The quality of studies was low to moderate. The SMD of the effect of HT on albuminuria was -0.11 (95% CI -0.27 – 0.05, p=0.16). Pooling adjusted ORs, the odds of having elevated albuminuria in HT users was 0.84 (95% CI 0.60-1.18, p=0.31) as compared to non-users. Pooling continuous measures, urine protein excretion was lower in HT users as compared to non-users (SMD -0.25, 95% CI -0.31 – 0.19, p=0.001). There were no differences in pre-defined subgroups.

Funding: Exploratory Hypothesis Generation - NIH (Nos 5K24DK079568, 5K24DK102166, K24DK108280, and T32DK007530-27)
In a post-hoc analysis, the OR for HT use and elevated albuminuria was 1.13 (95% CI 0.76-1.68) in population-based and 0.63 (95% CI 0.53-0.75) in non-population-based cohorts (p=0.007 for interaction).

Conclusions: HT is associated with decreased urine protein excretion, but the observed benefit may be due to study design, reported outcomes and unmeasured confounders.

Funding: Other NIH Support - UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS)

PUB185

Differential Diagnosis of Thrombotic Microangiopathy: Survey Results from 16 Countries. Hermann G. Halleg, 1 T. Sakari Kojiokanta, 1 Ozgur Soylemezoglu, 2 Jack F. Wetzels, 2 Michel Tsimaratos, 3 Salem Ali Al Shurafa, 5 Mohan Shenoj, 5 Ondrej Vilkicky, 1 Manuel Macia, 8 Tatiana Pankratenko, 10 Rosanna Coppo, 3
1 Medical School Hannover, Germany; 2 Basent Univ, Turkey; 3 Radboud Univ Medical Centre, Netherlands; 4 Hopital Necker-Enfants Malades, France; 5 Hospital Qatif Central Hospital, Saudi Arabia; 6 Royal Manchester Children’s Hospital, United Kingdom; 7 Inst for Clinical and Experimental Medicine, Czech Republic; 8 Hospital Virgen de la Candelaria, Spain; 9 Fondazione Ricerca Mollinette, Ospedale Regina Margherita, Italy; 10 M.F. Vladimirsky Moscow Regional Research and Clinical Inst, Russian Federation; 11 Univ of Helsinki, Finland.

Background: The differential diagnosis of thrombotic microangiopathy (TMA) is complex but important to inform treatment decisions. A survey was devised with the objective of understanding current practices across Europe.

Methods: Over 450 clinicians, from 16 European countries were invited to complete an online survey.

Results: Of 254 respondents, 82% were nephrologists, 69% had >10 years’ experience in their specialty, and 89% had diagnosed a patient with TMA. Results show a differential diagnosis of TMA is usually made within 1-2 (53%) or 3-4 days (26%) of presentation. Similarly, therapy is usually initiated within 1-2 (44%) or 3-4 days (30%), however 13% have report treatment initiation >1 week post-presentation. Thrombocytopenia, hemolytic anemia and acute renal failure are the main diagnostic criteria used. Extrarenal symptoms and a panoply of other conditions are considered when assessing the differential diagnosis. 70% and 78% of respondents stated they always request complement protein levels and ADAMTS13 activity, respectively. However, only 65% agree that an ADAMTS13 activity >10% rules out thrombotic thrombocytopenic purpura. For the diagnosis of atypical hemolytic uricemic syndrome, 93% request ADAMTS13 activity and 83% request complement protein levels.

Conclusions: This survey highlights the variability of current practices of European physicians in differentially diagnosing TMA and the need to increase awareness of diagnostic tests and international guidelines available.

Acknowledgements: The authors wish to thank the survey participants.

Funding: Pharmaceutical Company Support - Alexion Pharma GmbH

PUB186

Nutritional and Inflammatory Parameters during Transition from Pre-Dialysis Chronic Kidney Disease to End Stage Renal Disease. Dugan Maddux, 1 Frank van der Sande, 2 Jeroen Kooman, 3 Jennifer A. Vosburgh, 1 Marta Reviriego-Mendoza, 1 John W. Larkin, 4 Terry L. Ketchersid, 1 Len A. Usyvt, 4 Peter Kotanko, 5 Franklin W. Maddux, 1 Fresenius Medical Care North America, Waltham, MA; 2 Maastricht Univ Medical Center, Maastricht, Netherlands; 3 Renal Research Inst, New York, NY; 4 Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Malnutrition and inflammation during transition from chronic kidney disease (CKD) to end stage renal disease (ESRD) has not been characterized. We investigated longitudinal trajectories of albumin levels (Alb) and white blood cell counts (WBC) in patients (Pts) during their transition from CKD to ESRD.

Methods: We analyzed data from the Fresenius Medical Care CKD Data Registry on 14,095 Pts who transitioned to ESRD treated by dialysis between 2008 and 2016. Mean Alb and WBC were captured during 12 months before and after transition to ESRD. We analyzed Alb and WBC in Pts who survived, or died during the first year of dialysis.

Results: We observed mean Alb declined at transition to and 1 month after starting dialysis; thereafter Alb gradually rebounded (Figure 1A). Pts who died during the first year of dialysis generally had lower Alb 3 months before and 1 month after transition to dialysis, compared to survivors (Figure 1B). In survivors, mean WBC increased slightly in pre-dialysis months and decreased after dialysis start (Figure 1C). In those who did not survive, WBC tended to be higher than survivors during the year before, and more notably after starting dialysis (Figure 1D).

Conclusions: These results suggest the emergence of a pro-inflammatory phenotype in the months before dialysis initiation. These changes were more pronounced in Pts who died in the first year on dialysis, while in contrast Alb and WBC counts improved in survivors. Factors underlying the pre-ESRD pro-inflammatory surge deserve further research.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB187

Potential Association of Hyperhomocysteinemia with Target-Organ Damage in Patients with Primary Glomerulonephritis. Zhenchun Ye, Wenbo Zhao, Meijun Si, Ming Li, Cheng Wang, Tan-Qi Lou. Div of Nephrology, Dept of Medicine, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China.

Background: Hyperhomocysteinemia (HHcy) leads to increased oxidative stress and decreased antioxidant capacities in vascular endothelial cells, which are related to increased cardiovascular risk. This study is to investigate the prevalence of hyperhomocysteinemia in patients with primary glomerulonephritis and its relationship with target-organ damage.

Methods: This study included 601 patients with primary glomerulonephritis who were enrolled in the Third Affiliated Hospital of Sun Yat-sen University from May 2010 to March 2015. Demographic and laboratory data were collected. Plasma homocysteine was detected and estimated glomerular filtration rate (eGFR) was calculated. Doppler ultrasound was used to evaluate the changes of cardiac structure and function. Multiple linear regression analyses were used to evaluate the correlation between plasma homocysteine and target-organ damage.

Results: The prevalence of hyperhomocysteinemia was 45.92% (276/601) in patients with primary glomerulonephritis. And the incidence of hyperhomocysteinemia in CKD stage 1, stage 2, stage 3, stage 4, and stage 5 was 10.34%, 24.55%, 57.38%, 72.55% and 89.53%, respectively. With the deterioration of renal function, the incidence of hyperhomocysteinemia increased significantly. eGFR in patients with hyperhomocysteinemia was significantly lower than those of normal homocysteine, and the left ventricular mass index and carotid artery intima media thickness were significantly increased. Multiple linear regression analysis showed that homocysteine was associated with impaired renal function. Plasma homocysteine concentration is related to eGFR, calcium×phosphorus, serum uric acid, LDL-C, gender and hemoglobin.

Conclusions: The prevalence of hyperhomocysteinemia in patients with primary glomerulonephritis was 45.92%. Hyperhomocysteinemia was associated with impaired renal function in these patients. Further prospective randomized clinical trials are needed to clarify whether lowering homocysteine treatment has a beneficial effect in attenuating the progression of renal failure in primary glomerulonephritis patients.

Funding: Government Support - Non-U.S.

PUB188

A Prospective Study of Cutaneous Manifestations in Patients of Advanced Chronic Kidney Disease in a Tertiary Care Centre in Eastern India. Pinaki Mukhopadhyay, Dept of Nephrology, NRS Medical College, Kolkata, India.

Background: A wide variety of skin diseases occur in patients with chronic kidney diseases(CKD). Dermatological manifestations vary from age, region, race, severity of CKD and also basic disease or etiology. There is no such detail study regarding cutaneous manifestations in advanced CKD patients in Eastern India. We aim to evaluate the spectrum and frequency of dermatological manifestations in CKD patients, and also to compare cutaneous manifestations in CKD, between patients on dialysis and not on dialysis.

Methods: All patients with CKD stage 3 and beyond including patients in hemodialysis having dermatological manifestations were included. Detailed epidemiological, clinical and biochemical parameters were recorded. All patients were followed up three years. Patients with renal transplant, cutaneous diseases prior to CKD and , patients below the age of 12 years were excluded.

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

Underline represents presenting author.

947A
Results: A total of 225 patients were included in this study in which 64% were male and 36% were female, showing high male predominance. Their age ranged from 12 to 68 with mean age being 46.8 years. Majority of patients belonged to the age group of 50-70 years(60%). The means of hemoglobin, blood urea, serum creatinine were 8.9 g/dL (SD:±0.59 g/dL), 98.07 mg/dL (SD:±6.3 g/dL) and 5.03 g/dL (SD:±3.77 g/dL) respectively. The most common skin manifestations observed were pruritus (52%), followed by infections (36%), xerosis (16%), acquired perforating dermatosis (16%) and others like vesiculobullous diseases, adenoma sebaceum (8%). Bacterial infection (20%) is more prevalent than fungal(8%) and viral (8%) infection among study population. No significant differences in cutaneous manifestations have been found between hemodialysis and peritoneal dialysis without hemodialysis group. Severity of pruritus increases with duration of chronic kidney disease. Cutaneous manifestations increases with severity of kidney disease (<p<0.01).

Conclusions: CKD is associated with a complex array of cutaneous manifestations and there distribution and frequency is closely related to the duration and fall in glomerular filtration rate.

Background: Strongyloides stercoralis (strongyloidiasis, S) is an intestinal helminth that infects humans when they come in contact with soil containing the larvae. In advanced stages of chronic kidney disease(CKD), patients often are associated with decreased cell-mediated immunity, under-nutrition, and anemia. The prevalence of S has been reported to be 6.3% among the Ryukyu University hospital patients in Okinawa from 1991 to 2004. However, the current prevalence is not known nor the effect of CKD estimated glomerular filtration rate <60 mL/min/1.73 m².

Methods: We analyzed hospitalized patients who had undergone a stool test between September 2005 and June 2015 in Tomishiro Central Hospital, Okinawa, Japan. Also, background data such as age, sex, hypertension, proteinuria, anemia, nutritional status, and comorbid conditions were collected. Anemia was defined as hemoglobin level <13 g/dL in men and <12 g/dL in women.

Results: A total of 2,184 patients (median age, 74.0 [61.0-81.0] years; male : 52.8%) were tested and 8% of them (median age, 75.0 [71.0-80.8] years; male : 66.1%) were positive for S. In patients with S, 31.8% had CKD, 32.2% diabetes, 59.8% hypertension, 32.5% proteinuria. The mortality rate of S patients was 27.6% and the median survival period was 20.5 [1.0-42.3] months.

Conclusions: The subgroup analysis showed the pooled RR of CKD of 1.10 (95% CI, 0.94-1.29) in males and 0.81 (95% CI, 0.58-1.13) in females, respectively.

Conclusions: Our study demonstrates no significant association between coffee consumption and CKD in males. However, future studies are required to assess a potential inverse association between coffee consumption and risk for developing CKD in females.

**PUB191**

**Plasma Convertase Subtilisin/Kexin Type9(PCSK9) Concentration in Elderly Patients with Chronic Kidney Disease**

Hoichi Amano, Takashi Yokoo

**Background:** The elderly patients with chronic kidney disease (CKD) are at high risk for cardiovascular events in spite of lower level of low density lipoprotein cholesterol (LDL-C). The reason why plasma LDL-C concentration is relatively lower is not fully explained. As PCSK9 plays an important role in regulating plasma LDL-C by the mechanism which secreted PCSK9 binds to the LDL receptors (LDLr) and promotes LDLr degradation. Thus, we investigated the relationship between the magnitude of renal impairment and plasma PCSK9 levels.

**Method:** Concentrations of fasting serum PCSK9, lipids, creatinine and cystatin-C were measured in 219 Japanese elderly outpatients with CKD including patients receiving peritoneal dialysis (PD) or hemodialysis (HD).

**Result:** Plasma PCSK9 concentrations (215±176ng/mL [SD]) did not correlate with baseline eGFR in the study population. Mean plasma PCSK9 levels in PD patients (344±145mg/dL) were significantly higher than other CKD stages (p<0.001, ANOVA).

**Conclusion:** Plasma PCSK9 levels did not correlate with kidney function. PD is associated with higher plasma PCSK9 concentration and HD is lower.
Maurizio13

of autonomic nerve dysfunction in patients with acute ischemic stroke accompany renal insufficiency.

Fabio

PUB195

Early Pre-Operative, and Prolonged Post-Operative Nephrological Consultation Might Prevent the Worsening of Renal Impairment in Renal Cancer Patients Candidates to Nephrectomy Laura Cosmai,1 Wanda Liguizi,2 Camillo Porta,1 Maurizio Galliemi,2 Marina Foramitti,1 Fabio Malberti,1 1Nephrology, Istituti Ostipaleiali, Cremona, Italy; 2Oncoology, Istituti Ostipaleiali, Cremona, Italy. Background: Partial nephrectomy (PN) is recommended as the preferred surgical option in organ confined renal tumours measuring up to 7 cm, whilst radical nephrectomy (RN) is the preferred option for tumours of more than 7 cm; RN is also recommended if PN remains relatively stable over time. Results: Median patient age was 9.5 years, 63% were male, and 59% non-Hispanic white. A glomerular diagnosis was present in 32% of participants. Median eGFR at baseline and hazard ratios are shown below:

Conclusions: Conclusions: Contributions to all-cause mortality were lower in individuals with higher scores of communication quality, health promotion, interpersonal treatment, and patient trust. Outcome measures were incident eGFR and all-cause hospitalization. Results: The mean age of the 298 participants was 56 yrs, 38% were women, 70% had health insurance, and the mean eGFR was 38.4 ml/min/1.73 m². Baseline subscale scores and hazard ratios are shown below:

PUB197

Parental Health Literacy and Progression of Chronic Kidney Disease in Children Ana C. Ricardo, Vivien H. Goh, Adam S. Hamidi, Lynn N. Pereira, Aisha Betoko, Bradley Warady, Marva M. Moxey-Mims, Susan L. Furth, James P. Lash. On Behalf of the Chronic Kidney Disease in Children (CKID) Cohort Investigators. Background: Although health literacy has been associated with adverse outcomes in children, this association has not been evaluated in the setting of chronic kidney disease (CKD). Methods: We conducted a parenteral health literacy assessment of 367 children enrolled in the prospective multicenter observational Chronic Kidney Disease in Children (CKID) cohort study. Using parametric failure-time models, we evaluated the association between parental health literacy and CKD progression, defined as time to the composite event of renal replacement therapy (RRT, dialysis or kidney transplant) or 50% decline in estimated glomerular filtration rate (eGFR). Parental health literacy was measured once using the Short Test of Functional Health Literacy (STOFlHLA) which included 2 reading passages and 4 numeracy items (possible range from 0 to 100). Clinical and demographic characteristics of the cohort were measured at baseline. Literacy levels were assumed to remain relatively stable over time. Results: Median patient age was 9.5 years, 63% were male, and 59% non-Hispanic white. A glomerular diagnosis was present in 32% of participants. Median eGFR at baseline was 63 ml/min/1.73m², and median urine protein-to-creatinine ratio was 0.22. The median (IQR) STOFHLA score was 98 (93-100). Over a median follow-up of 5.9 years, the overall composite rate of RRT or 50% eGFR decline was 2.8 per 100-person-years. Results of multivariable models are presented in the table.

Conclusions: Conclusions: Adjusted for socio-demographic characteristics, hypertension, diabetes, cardiovascular disease, kidney function, quality of life, and depression. Conclusions: Among HCRIC participants, higher perceived quality of physician-patient interaction was associated with a lower rate of hospitalization but not eGFR. How these interactions influence this outcome requires further study. Funding: NIDDK Support

PUB196

Quality of Perceived Physician-Patient Interaction and Risk of End-Stage Renal Disease and Hospitalization in Hispanics with Chronic Kidney Disease Esteban A. Cedillo-Couvret, Jesse Yenchih Hsu, Ana C. Ricardo, Michael J. Fischer, Ben Gerber, Edward J. Horwitz, John W. Kusek, Eva Lustigova, Amada Renteria, Sylvia E. Rosas, Mildre Renne Saunders, Daohang Sha, Anne M. Slaven, James P. Lash. Chronic Renal Insufficiency Cohort (CRIC) Study Group. Background: Quality of physician patient interaction influences health outcomes in the general population but little is known about this in chronic kidney disease (CKD). We evaluated the association of perceived quality of physician-patient interaction with risk of end stage renal disease (ESRD) and all-cause hospitalization in Hispanics with CKD. Methods: We studied Hispanics with CKD enrolled in the prospective observational Hispanic CRIC Study. Quality of interaction with primary care providers was ascertained using the Ambulatory Care Experiences Survey sub-scales (range of score 0-100 with higher score indicating better performance) of communication quality, health promotion, interpersonal treatment, and patient trust. Outcome measures were incident ESRD and all-cause hospitalization. Results: The mean age of the 298 participants was 56 yrs, 38% were women, 70% had health insurance, and the mean eGFR was 38.4 ml/min/1.73 m². Baseline subscale scores and hazard ratios are shown below:

Conclusions: Contributions to all-cause mortality were lower in individuals with higher scores of communication quality, health promotion, interpersonal treatment, and patient trust. Outcome measures were incident ESRD and all-cause hospitalization. Results: The mean age of the 298 participants was 56 yrs, 38% were women, 70% had health insurance, and the mean eGFR was 38.4 ml/min/1.73 m². Baseline subscale scores and hazard ratios are shown below:

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**PUB198**

Application of Urinary Albumin: Creatinine Ratio to Predict Renal Replacement Therapy and All-Cause Mortality in a CKD Cohort

Zainim Wang,1,2 Jianzheng Zhang,2,1 Helen G. Healy,1 Ken-Soo Tan,1,2 Sree Krishna Venuthurupalli,1,3,4 Anne Cameron (Sailus),1,2 Wendy E. Hoy,1,2,5 NHMRC CKD.CRE and CKD.QLD, The Univ of Queensland, Brisbane, Queensland, Australia; School of Medicine, The Univ of Queensland, Brisbane, Queensland, Australia; Kidney Health Service (RBWH), Metro North Hospital and Health Service, Brisbane, Queensland, Australia; Renal Services (Logan), Metro South Hospital and Health Service, Brisbane, Queensland, Australia; Renal Services (Toowoomba Hospital), Darling Downs Hospital and Health Service, Toowoomba, Queensland, Australia.

**Background:** This study aims to examine the association of albuminuria with RRT and mortality in CKD patients.

**Methods:** Subjects were patients with CKD and not on kidney replacement therapy enrolled in renal clinics in Queensland, Australia. Informed consenting of patients began in 2011. The categories of albuminuria were defined by gender-specific ACR values recommended by Australasian Proteinuria Consensus Working Groups. Events of RRT and death without RRT were recorded until end of 2015. Cox regression analyses were applied.

**Results:** A total of 1,615 patients were eligible, with 788 (49%) females. They were followed for a total of 3,379 person years. Age at consent ranged from 18 to 96 years, mean of 65 years (SD: 15 years). The percentages of patients with CKD stage 1, 2, 3A, 3B, 4 and 5 at consent were 6.6%, 12.5%, 20.8%, 30.8%, 25.6% and 3.7%, respectively. The prevalence of macroalbuminuria at consent was 32.1% and 34.7%, respectively. 69 patients started RRT and 111 patients died without RRT. After adjusted age, gender and CKD stage, the hazard ratio (HRs) (95% CI) of macroalbuminuria for RRT compared to healthy individuals was 8.1 (4.2-16.0), respectively. The HRs (95% CI) of macroalbuminuria and microalbuminuria for death were 2.1 (1.1-3.7) and 3.4 (1.9-6.0) (non-albuminuria as reference group), respectively.

**Conclusions:** In this cohort, macroalbuminuria was a significant predictor of future RRT whilst both micro- and macroalbuminuria increased mortality risk.

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

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**PUB199**

Novel ELISA for the Measurement of Human Periostin in Patients with Impaired Kidney Function

Jacqueline Wallwitcz, Manfred Tesarz. The Antibody Lab GmbH, Vienna, Austria.

**Background:** Periostin (osteoblast-specific factor OSI-2) is a soluble extracellular matrix protein that is associated in kidney development and kidney injury. Periostin consists of a conserved N-terminus and a C-terminal region which is affected by different splicing variants. Currently, at least seven splicing isoforms of human Periostin have been identified.

**Methods:** We developed a sandwich ELISA, which also enables the detection of all known human circulating Periostin isoforms. Our novel assay utilizes monoclonal and purified polyclonal antibodies and recognizes epitopes that are conserved between human and animal species e.g. mouse, rat, cynomolgus macaque, dog, and cat Periostin.

**Results:** The novel Periostin ELISA assay is optimized for human serum and plasma (citrated, heparin, EDTA) and covers a wide calibration range between 125 to 4,000 pmol/l. Assay characteristics such as precision, dilution linearity and spike-recovery as well as sample stability meet the standards of acceptance. Periostin serum and plasma concentration range from 864 +/- 269 pmol/l (n=24) and 528 +/- 180 pmol/l (n=14), respectively. The change of Periostin compared to healthy individuals, suggesting that Periostin is a mediator of maladaptive repair also occur during aging.

**Conclusions:** We compared demographic and clinical characteristics of MCRIC participants with all Couvert, 2 Mexican Chronic Renal Insufficiency Cohort (MCRIC) Study: Baseline Impaired Kidney Function

PUB201

The Impact of Diabetes on the Progression of Renal Disease in the Elderly

Claudia Tótoli, Adriano Luiz Ammirati, Maria Eugenia F. Canziani. Nephrology, Univ Federal de Sao Paulo, Sao Paulo, Brazil.

**Background:** Elderly and diabetes are risk factors for chronic kidney disease (CKD). Diabetes patients have a faster decline of renal function. There are few data regarding the progression of KD in elderly especially with diabetes. The aim of this study was to compare progression of renal disease in diabetic and non-diabetic elderly CKD patients.

**Methods:** A retrospective observational study that evaluated elderly CKD stage 2-5 non-diabetes patients followed in a CKD Unit Care from April 2011 to April 2015. Renal disease progression was evaluated by the change in eGFR using the CKD-EPI formula, divided per year of follow-up (mL/min/year). Stratified in rapid progressors (≥ 5 mL/min/year), slow progressors (≤ 1 mL/min/year to < 5 mL/min/year), stable (≥ 0 and <1 mL/min/year) and improved function (< 0 mL/min/year). Proteinuria was measured in a spot urine sample.

**Results:** A total of 340 patients [73 (69-79) years, 56% male, 65% white, 41% diabetics] were evaluated. In comparison to non-diabetics, diabetic patients had a higher proteinuria at baseline. There were no differences in age, blood pressure, kidney function between the two groups at baseline. The change of eGFR during the follow up was higher in the diabetic group [1.10 (-1.53 – 3.46) vs. 0.57 (-1.54 – 2.51) mL/min/year, p = 0.09], without statistical significance but with a trend p. Proportion of rapid progressors and dialysis initiation was significantly higher in diabetic group (15 vs 8%, p = 0.04; and 10 vs 3%, p=0.03; respectively).

**Conclusions:** There was no statistical significance in renal progression between the groups, but there is a tendency (p trend) to a faster progression in the diabetes group. The presence of diabetes affected the need for dialysis and the number of rapid progressors.

**PUB202**

Double-Hit of Advanced Age and Lung Cancer Leads to Increased Fibrosis and Decreased Overall Survival in a Repeated Low-Dose Regimen of Cisplatin Nephrotoxicity

Cierra Sharp,1 Mark A. Doll,1 Deanna L. Sliow,1 Levi J. Beverly,2,3 Leah J. Siskind,3 Pharmacology/Toxicology, Univ of Louisville, Louisville, KY; Dept of Medicine, Univ of Louisville, Louisville, KY; James Graham Brown Cancer Center, Louisville, KY.

**Background:** Cisplatin-induced acute kidney injury (AKI) has a high mortality rate and poor long-term prognoses, including a 30x greater risk of developing chronic kidney disease (CKD). Understanding processes involved in the cisplatin-induced AKI to CKD transition is essential for developing novel therapeutics. We have developed a repeated, low-dose cisplatin model that allows for long-term survival of mice, and better recapitulates the type of dosing regimen humans receive. In this model, fibrosis is the main pathology associated with repeated, low-dose administration of cisplatin, and thus the transition from AKI to CKD can be studied. While this model better recapitulates the dosing regimen humans receive, it does not take into account comorbidities present in patients receiving cisplatin, namely advanced age and cancer, which is important as only individuals with concurrent cisplatin and the majority of cancer patients are diagnosed at 60 years of age or older. It is believed that renal function declines and with normal aging and that processes of maladaptive repair also occur during aging.

**Methods:** Here, we determined the impact of age and cancer on the cisplatin-induced AKI to CKD transition. We compared saline and cisplatin-treated 8 wk old and 40 wk old PVB mice and found that fibrosis and renal function were not affected by aging alone. However, aged mice with mutant Kras driven lung cancer had decreased overall survival and significantly increased kidney fibrosis as compared to age matched control mice.

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

Underline represents presenting author.

950A
Results: Preliminary data suggest this the exacerbated kidney fibrosis in aged mice with lung cancer may be mediated by EGFR signaling pathways in the kidney cortex.

Conclusions: Thus, understanding the mechanisms by which the comorbidities of aging and cancer impact the cisplatin-induced AKI to CKD transition may uncover novel therapeutic targets for improving long-term outcome and quality of life.

Funding: NIDDK Support

PUB203
Rehydration with Fructose Worsens Dehydration-Induced Renal Damage
Takamaru Tamagawa,1 Gabriela E. Garcia,2 Takuji Ishimoto,3 Miguel A. Lasnapa,1 Ana Andrs-Hernando,1 Takahiko Nakagawa,1,2 Masanari Kuwabara,1 Richard J. Johnson,1 Carlos Alberto Roncal-Jimenez,1 1Div of Renal Diseases and Hypertension, Univ of Colorado, Aurora, CO; 2Inst Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico.

Background: We reported that recurrent heat stress and dehydration induces chronic kidney disease due to polyol-induced fructose generation with metabolism by fructokinase. Here we test if there is a significant difference for kidney injury in mice between two different rehydration methods: pure water and fructose water.

Methods: We used two groups of mice. Mice were recurrently exposed to heat (39.5 °C for 30 min 5x/d for 5 wks). After mice became dehydration condition, we gave these mice rehydration with pure water (W, 9 W) or 10% fructose water (F, consisting of 6 ml of fructose dissolved in 60 ml of water). Furthermore we made a control group (C), which did not have dehydration. We compared kidney function among three groups.

Results: Dehydration conditions was similar between W and F group, serum osmolality (Osm) of W: 334 ± 3 mg/dL, of F: 340 ± 2 mg/dL. Serum osmolality (Osm) was significantly different between dehydration groups and control group of W: 307 ± 7 mg/dL (p = 0.001). Urine osmolality of W (Osm) had also significant differences between dehydration groups (W: 1058:2925 mg/dL), and control group (1976 mg/dL) (p = 0.001).

Conclusion: Rehydration with fructose in heat stress-dehydrated mice caused renal damage, likely due to higher vasopressin levels. This result suggests rehydration with soft drinks in the setting of heat stress and dehydration may not be good for kidney.

Funding: Private Foundation Support

PUB204
Impact of Direct Acting Antiviral Agents on Kidney Function in Hepatitis C Virus Infected Patients
Javier Pazan, Antonio A. Armstrong, Vanessa Blumer, Roberto J. Echeverri, Maria Del Pilar Hernandez, Fernando E. Pedraza, Marco A. LadinoAvellaneda, David Roth. Nephrology, Univ of Miami / VMC, Miami, FL.

Background: Hepatitis C virus (HCV) infection is a public health issue with approximately 170 million individuals infected worldwide. The prevalence of HCV infection is higher in patients with chronic kidney disease (CKD) and data suggests that it is a risk factor for CKD progression. The new direct acting antivirals (DAAs) have transformed the treatment of HCV with high (>90%) sustained virologic response (SVR) rates achieved. The objective of this study is to evaluate the relationship of DAAs treatment and kidney function.

Methods: We used a retrospective and descriptive design. Consecutive patients with HCV and on DAAs were identified at the Miami VAMC from 2015 to 2016 (n = 397). The following DAA agents were used: ledipasvir, sofosbuvir, simeprevir, ribavirin and daclastavir. Serum creatinine with estimated glomerular filtration rate (eGFR) calculations (MDRD formula) were obtained. The following data was obtained: gender, age, creatinine (Cr), urinary protein, eGFR before and at 12 weeks following completion of therapy were obtained.

Results: 397 patients were identified, 380 males and 17 were females. The mean age was 63 years old (range 36-84). Most of the patients were treated with a combination of drugs: sofosbuvir (590/396-98.5%), ribavirin (201/396-50.8%), ledipasvir (195/396-49.2%), simeprevir (155/396-39.1%) or daclastavir (8/396-2%). The mean Cr before therapy was 1.4 mg/dl and eGFR was 53 ml/min, after DAA therapy the mean Cr was 1.2 mg/dl and eGFR was 64 ml/min (p < 0.001), the mean systolic BP before therapy was 130 mmHg and 134 mmHg after, the diastolic BP before and after therapy was 80 mmHg.

Conclusions: The use of DAA agents to treat HCV was associated with a statistically significant improvement in eGFR. No significant changes were seen in systolic or diastolic BP at the end of treatment. Prospective long-term studies are needed to establish a clear relationship between renal function and treatment of HCV-positive patients with DAA.
Left Atrial Function: A Cardiac Computed Tomography Study of Patients with Chronic Kidney Disease

Anne1,2,3, Ricardo1,2, Wendy1,2, Lucília3

Background: Previous studies using 2-dimensional-echocardiography show that trial end-diastolic volume (LaEDV) is predictive for CV outcomes and mortality in CKD patients. Cardiac computed tomography (CCT) angiography measure LaEDV more precisely than echocardiography.

Hypothesis: LaEDV and left atrial ejection fraction (LaEF) measured by CCT are associated with mortality and MACE.

Methods: 167 kidney transplant candidates from 9 regional centres underwent CCT angiography prior to kidney transplantation. La and Lv volume and function were determined using CCT. MACE and mortality data were extracted from Western Denmark Heart Registry, review of patient records and patient interviews.

Results: LaEDV was significantly associated with pro-BNP (p=0.05, r=3.98), Lv end-diastolic volume (p=0.05, r=0.14) and mass (p=0.05, r=0.05). LaEF was significantly associated with age (p=0.05, r=-0.03) and pro-BNP (p=0.05, r=-0.03). During a median follow-up of 3.3 years (range: 0.3-5.1), 22 (15.0%) patients suffered MACE and 24 (16.4%) died. MACE and survival analysis showed no relation to LaEDV (survival: HR=0.99, p=0.46–0.50), whereas LaEF ejection fraction was solely associated to MACE risk and not mortality (survival: HR=0.98, p=0.46–0.50). SDHR=0.16, p=0.45), whereas LV ejection fraction was solely associated to MACE risk and not mortality (survival: HR=0.98, p=0.46–0.50).

Conclusions: Using CCT, LaEDV correlates to functional parameters of LV in CKD. The association does not apply to MACE.

Funding: Private Foundation Support

PUB208

Timing and Pregnancy in ESRD Patients: When Is Conception Better?

Amelia Rita Bernasconi,1 Liliana Susana Voto,2 Alicia M. Lapidus,3 Rosa Alejandra Waisman,3 Ricardo M. Heguellen1,2

Background: Pregnancy (P) in women with renal disease (CKD) implies significant risk for adverse maternal and fetal outcomes. Although advances in antenatal and neonatal care continue to improve them, risks remain proportionate to the degree of underlying renal dysfunction. There is evidence to suggest that P with 1-2 CKD, normal BP, and no renal dysfunction. There is evidence to suggest that P with 1-2 CKD, normal BP, and no renal dysfunction. There is evidence to suggest that P with 1-2 CKD, normal BP, and no renal dysfunction.

Methods: We compared the outcome of P in 3 different CKD groups. Group A (10 ESRD 4-5 p; Group B: 10 P in HD (p < 0.001); Group C: 10 P in renal transplant women (4 w/related donor).

Results: All groups mean age was similar, no DBT, no SLE. Folic acid, hEpo and IS maintained stable mothers H+ (28%) and HB (8.7 g/dl) in all groups. Aimed at improving fetal lung maturity, intramuscular betamethasone was administered at 32 weeks. Methyldiphine was given peripartum to avoid intra and postpartum stress in Group C. Amlopidine and or labetalol were used when necessary in the three groups. GA; pt entered in an intensified HD schedule (~ 29 kw) when SCR increased to 3.5 mg/dl. GB: intensified dose was prescribed. GC: all pt received appropriate medication for P.

Main data are shown in table one.

<table>
<thead>
<tr>
<th>GA (m: n)</th>
<th>GB (m: n)</th>
<th>GC (m: n)</th>
<th>P</th>
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<tbody>
<tr>
<td>25.5±5.6</td>
<td>31.4±4.6</td>
<td>26.2±6.7</td>
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<td>31.8±4.3</td>
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<td>36.6±1.6</td>
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<td>Weight at birth, g</td>
<td>1497±744</td>
<td>1418±436</td>
<td>2714±545</td>
</tr>
</tbody>
</table>

Conclusions: better timing for conception maybe during transplantation according to our data. In preconception counselling patients should be advised of the high risk of fetal demise and death. No risk factors for ESRD 4-5. Intermittent HD schedule in those previously in RRT, and graft loss in declining renal function pt, and advanced pregnancy outcome in. According to our study the administration of human recombinant erythropoietin has a beneficial effect in pregnancy without side effects. Preterm delivery, IUGR and low birth weight are common in this population.

PUB209

Comparison of Different Definitions of Progression of Chronic Kidney Disease and Predisposing Factors in a Public Renal Practice: Queensland, Australia

Rajitha Asanga Ayesepuke,1 Zaimin Wang,1,2,3 Jinzhuan Zhang,2 Helen G. Healy,3,4,5 Anne Cameron (Salisbury),1,2,3 Wendy E. Hoy,1,2 NHMRC CKD.CRE and CKD.QLD, 1, Brisbane, Queensland, Australia; 1School of Medicine University of Queensland, 2, Brisbane, Queensland, Australia; 3Kidney Health Service (RBWH); Metro North Hospital and Health Service, 3, Brisbane, Queensland, Australia.

Background: We compared different definitions of CKD progression and assessed factors associated with progression.

Methods: Annual data of CKD patients in the public renal practice of the RBWH, who were enrolled in the CKD.QLD registry were analysed from consent until 31st July 2005. 9501 participants were studied and at 1 year follow up. Six definitions of progression were evaluated: Definition i: loss of eGFR of >2ml/min/1.73m2/year, ii: loss of <5ml/ min/1.73m2/year, iii: change of CKD stage, iv: combination of CKD stage change & 25% eGFR reduction, v: 20% eGFR reduction, and vi: start of renal replacement therapy. Age, gender, renal diagnosis, AKI, presence of diabetes, and number of comorbidities were evaluated as potential predictors over the first year.

Results: Proportions defined as progressing at one year, in descending order, were: Definition i 42.8%, ii 26.7%, iii 18.5%, iv 14.7%, v 9.7% and vi 3.5%. At two years, the proportions were 38%, 15.5%, 23.2%, 21.9% and 12.2% respectively, representing a similar rank order, except for the lesser frequency of Definition ii. Among the four major groups of renal diagnoses, proportions who progressed, regardless of definition, were, in descending order, diabetic nephropathy, renovascular disease, genetic renal disease, and congenital nephropathy. More patients with >8 comorbidities progressed, versus those with <4 comorbidities. Compared to stage 1, 2 and 3A, more patients in CKD stage 3B, 4 and 5 progressed. More patients with any diagnosis of AKI progressed compared to patients without AKI (p<0.005). Patients <40 years old had the lowest rates of progression. Males tended to progress more often than females, although this was not significant.

Conclusions: There is some consistency of the different definitions of progression. The choice of a particular expression should be context specific. These data give valuable insights into progression of CKD.

PUB210

The Effects of Pazopanib versus Sunitinib on Renal Outcome in Metastatic Renal Cell Carcinoma

Eun Jeong Lee, Subin Hwang, Hye Ryoun Kang, Wooseong Huh, Dae Joong Hwang, Hye Ryoun Kang, Hyun Goo Kim, Ha Young Oh, Jung Eun Jang, Nephrology Div. Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Korea.

Background: Pazopanib and sunitinib are used as the first-line treatment of metastatic renal cell carcinoma (RCC). Several studies have reported similar efficacy with a favorable safety profile of pazopanib. The aim of this study was to examine the renal outcome after pazopanib versus sunitinib treatment in patients with metastatic RCC.

Methods: We reviewed medical records of 304 patients with metastatic renal cell carcinoma who received pazopanib (n=103) or sunitinib (n=201) therapy from 2007 to 2016. The primary outcome was chronic kidney disease (CKD) progression, defined as a drop in glomerular filtration rate (GFR) category accompanied by a 25% or greater drop in GFR from baseline, during treatment. Secondary outcome was disease progression-free survival.

Results: Overall, 47% of subjects had CKD stage 3 or 4 at baseline. Distributions of CKD stage were similar between pazopanib and sunitinib treatment groups. The progression was 19% in pazopanib group 17% in sunitinib group at 1 year after treatment.

Conclusions: The effects of pazopanib versus sunitinib treatment on CKD progression were similar in real-world practice. However, higher percentage of pazopanib group continued the regular dosage of drugs and more favorable cancer outcome was observed in pazopanib group.

PUB211

Urinary N-Acetyl Cysteine and Kidney Disease Progression in HIV-Infected Patients: A Prospective Study

Clara Dias,1 Lucilla N. Diogo,2 Pedro Pereira Campos, Ana R. Lemos,1 Emília C. Monteiro,1 Karina Soto,2 Sofia Pereira,1 CEDOC, NOVA Medical School/Faculdade de Ciências Médicas, Lisbon, Portugal; 1Nephrology, Hospital Fernando Fonseca, Lisbon, Portugal.

Background: Chronic kidney disease has emerged as a major health concern in HIV-infected patients. Earlier diagnosis is paramount to prevent progression. Screening and searching for new non-invasive pathophysiologic markers are a key challenge. N-acetyl cysteine-disulfides conjugates are products of N-acetyltansferease, an enzyme mainly expressed in proximal tubular cells that has been pointed out as a candidate for renal regulation and nephrotic response. N-acetyl-cysteine conjugates were identified in urine open the possibility of using as surrogate markers. N-acetyl cysteine-disulfides conjugates. The aim of the present study was to determine if urinary N-acetyl-cysteine (uNAC) can be used as biomarker of kidney disease progression.
Methods: As a part of an ongoing prospective study of HIV+ population, a 1-year analysis was performed in a cohort of patients under combined antiretroviral therapy, with visits at 0 (M0), 6 (M6) and 12 (M12) months. Glomerular filtration rate (eGFR) was estimated by CKD-EPI equation, expressed in mL/min/1.73m². Patients were divided in 2 groups according their eGFR evolution: Group1, stable eGFR; Group2, decline in eGFR>10% at M12. uNAC was quantified by HPLC with fluorescence detection. Data are presented as percentage relative to M0.

Results: A total of 24 HIV-infected patients were included (67% men, 33% Black, 54 [IQR=47-62] years old at M0). Patients with eGFR<90 had higher uNAC at M0 than patients with kidney disease (Unpaired t-test, p<0.005). Among patients with stable eGFR, the levels of uNAC remained unchanged after 12 months in opposite to patients with a declined eGFR (Two-way RM ANOVA with Bonferroni post-test, p<0.05). Ten patients had a pronounced declined eGFR (83±SD7%), at M12 (Paired t-test, p<0.01). Correlated with a significant decrease in uNAC (60±40%) (Wilcoxon signed rank test, p<0.006).

Conclusions: Kidney disease progression was associated with a significant decline in uNAC. The present results suggest that uNAC has a role as a newly non-invasive indicator of kidney disease progression in HIV.

Funding: Government Support - Non-U.S.

PUB214

Twenty-Six Cases Treated by Short Term Steroid Regimen for Adult Steroid Sensitive Nephrotic Syndrome

Takuya Ozeki, Takayuki Katsuno, Sawako Kato, Yoshinari Yasuda, Shioichi Maruyama. Dept of Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.

Background: The appropriate treatment duration for adult steroid sensitive nephrotic syndrome (SSNS) is not clear. In pediatric field, recent trials revealed that 2 months short term steroid regimen for SSNS children is not inferior to extended course of steroid in the occurrence of frequent relapse or steroid dependent disease. This is the case series of 26 adult steroid sensitive nephrotic syndrome patients treated by 2 months short term steroid regimen.

Methods: Among the biopsy-proven adult MCNS or FSGS cases in Nagoya university affiliated hospitals during Feb 2015 to Jan. 2016, patients satisfied the following criteria: over 20 years old, first time episode of nephrotic syndrome, acied remission within 4 weeks and consent of the patient was obtained. Treatment plan of short term steroid regimen is as below; (1) prednisolone 0.8-1.0 mg/kg/day as initial dose and continued for 4-6 weeks. (2) prednisolone reduced to 0.5-0.6 mg/kg/alternative day and continued for 4 weeks. We compared the patients with histological control from our retrospective cohort (140 cases).

Results: There were 26 cases (male: 13, median age: 50.0). The initial steroid dose was 50 mg/day in the median. All the patients except 1 was finished steroid administration without relapse. Throughout the observation period (median: 204.5 days), 14 cases (53.9%) experienced relapse and 1 patient (3.8%) developed to frequent relapse. The adverse events were observed in 2 cases (3 incidents). None had an episode of adrenal insufficiency. Compared with the historical control, patients treated by short term regimen relapsed earlier from the baseline (131 vs 357 days, p<0.001), but the cumulative steroid dose at 3, 6 and 9 months from the baseline were significantly lesser in short term regimen patients (1822 vs 2855 mg, 2160 vs 4095 mg and 1781 vs 4887 mg respectively).

Conclusions: Although the timing of relapse in short term regimen is earlier than conventional one, short term steroid regimen may detect the frequent relapse or steroid dependent cases in SSNS earlier and lesser steroid exposure. For further comparison, it is necessary to analyze by extending observation period.

PUB215

Monotypic Atypical Anti-GBM Nephritis in a 9/11 First Responder Neerai Sharma, 1 Hone S. Kow, 1 Hibah A. Ahmed, 1 Manedeep Samra, 1 Farah Piracha, 1 Anaeena Adamidis, 2 Jennine Michaud, 1 Michael Yudd. 1 Renal Section, Dept of Veterans Affairs NJ Healthcare System, East Orange, NJ; 2Renal Medicine Associates, Teaneck, NJ.

Background: Atypical anti-GBM nephritis (AAGN) is rare, and is characterized by bright linear anti-GBM immunoglobulin staining in the absence of circulating anti-GBM antibodies. As opposed to typical anti-GBM, the clinical course of AAGN is frequently renal-limited and indolent. Nasr et al described 26 adult steroid sensitive nephrotic syndrome (SSNS) patients treated by 2 months short term steroid regimen.

Methods: 44 year old white man, a first responder at the World Trade Center in 9/11, developed gross hematuria in 2007. Urologic work up was negative. In 2010, labwork showed creatinine 1.4 mg/dl, urinalysis 2+ protein and large blood, urine protein/creatinine ratio 0.8, with the following negative or normal studies: ANCA, anti-GBM, SLE, SLE anti-DNA, anti-nRNP, anti-Ro/SSA, anti-SSB/La, antiphospholipid antibodies, ANA, antinuclear antibody, anti dsDNA, and complements, hepatitis BC and pneumonia. For 1st relapse in 2010, he was started on prednisone. For 2nd relapse in 2016, he was treated with prednisone, hydroxychloroquine, and azathioprine for 1 year. He was also treated with insufficiency 1 year ago and had exacerbation of hemoptysis in aortic dissection.

Conclusions: Although the timing of relapse in short term regimen is earlier than conventional one, short term steroid regimen may detect the frequent relapse or steroid dependent cases in SSNS earlier and lesser steroid exposure. For further comparison, it is necessary to analyze by extending observation period.
PUB216

Glomerular Diseases Associated with Malignancies: Clinical Presentation, Histopathology and Outcome  
Sophia Lioniak,1 Konstantinos Panagiotelis,1 Joan Vlahadami,2 Ioanna Tsoubou,1 Chrisovalantis Vergadis,2 George Liapis,4 Petros P. Sifakis,1 Athanasios Tzioufas,2 John Boletsis.1
1Neophelogy, Laiko Hospital, National & Kapodistrian Univ, Athens, Greece; 2Pathophysiology, National & Kapodistrian Univ, Athens, Greece; 3Radiology, Laiko Hospital, Athens, Greece; 4Propedeutic and Internal Medicine, National & Kapodistrian Univ, Athens, Greece.

Background: To study the glomerular diseases, associated with malignancies (GDAM), with respect to clinical characteristics and histopathological findings.

Methods: We retrospectively studied the medical charts of all patients with GDAM, diagnosed in our hospital between 2008-2015 and recorded demographic, clinical, laboratory and histopathological findings, as well as the type of malignancy and the outcomes at end of follow up.

Results: Twenty nine biopsy proven cases with GDAM were identified, with a mean age of 62.4±12.0 years at kidney biopsy. Renal histopathology revealed: membranous nephropathy in 9 cases (31.0%), membranoproliferative glomerulonephritis in 5(17.2%), lupus-like nephritis in 4(13.8%), minimal change disease in 4(13.8%), pauci-immune glomerulonephritis in 3(10.3%), IgA nephropathy with crescents in 1(3.4%), amyloidosis in 1(3.4%) and interstitial nephritis in 2(6.9%). 13(44.8%) patients presented with acute nephritic syndrome and 4(30.8%) with rapidly progressive glomerulonephritis. 12(41.4%) patients developed acute renal injury within 2.85±2.83 months from kidney biopsy and 5(17.2%) required dialysis. 14(48.3%) cases had a solid tumor and 15(52.7%) a hematologic malignancy.

![Steroid Utilization Post Rituximab Infusion](image)

**Subject**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (range) or (mean±sd) or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h proteinuria (g/day)</td>
<td>4.2 (0.12-16.9)</td>
</tr>
<tr>
<td>Hematouria</td>
<td>19 (65.5)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.2 (0.8-9.6)</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>14 (48.3)</td>
</tr>
</tbody>
</table>

**Conclusions:** Patients with GDAM may present with various clinical pictures, combined with diverse histopathological patterns. Prompt and accurate diagnosis, recognition of the specific characteristics of each patient and individualized management are critical for renal and patient outcome.

PUB217

Improving Administration Rate of Pneumococcal Polysaccharide Vaccine (PPSV23) in Children > 2 Years with Nephrotic Syndrome: A Single Center Experience  
Siddharth A. Shah. Pediatric Nephrology, Univ of Louisville, Louisville, KY.

**Background:** Pneumococcal infections are major cause of morbidity and mortality in children with nephrotic syndrome. Apart from pneumococcal vaccines, other strategies have not shown to decrease the risk of pneumococcal infections. Previous study showed high serological response to pneumococcal vaccine in nephrotic children even at disease onset on high-dose prednisone therapy. IgM is likely to be lost in urine in active disease state given its high molecular weight compared to IgG. The challenges to improve coverage with PPSV23 vaccine include vaccine availability, compliance to clinic visits and patient education.

**Methods:** A standard protocol was established to administer PCV13 and PPSV23 vaccine as per ACIP guidelines. All patients with clinical diagnosis of nephrotic syndrome and age range between 2 and 18 years were included in the study. Two strategies were implemented including: 1) Inpatient administration of PPSV23 vaccine at time of initial diagnosis of nephrotic syndrome or during hospital admission for relapse or infection 2) Outpatient administration of PPSV23 vaccine. Letters were mailed to family. PPSV23 documentation and alerts were added to Clinical Notes to help improve patient education.

**Results:** Overall, 58 children and adolescents with clinical diagnosis of nephrotic syndrome were included in the study. The PPSV23 immunization rate had improved to 80% after 2 years compared to 32% at beginning of study. Hospital administration of PPSV23 vaccine helped achieve better immunization rates. The PPSV23 vaccine administration rate was only 60% in children who received vaccines at outpatient basis even with patient letter and clinic visit reminders.

**Conclusions:** PPSV23 (Pneumovax) is readily available across major hospitals in United States in contrast to local pediatrician offices. PPSV23 vaccine should be administered as early as possible in children>2 years of age with nephrotic syndrome. PPSV23 administration at time of initial hospital admission for nephrotic syndrome or hospital admission for relapse may be an effective strategy to help improve immunization coverage in children with nephrotic syndrome.

PUB218

Study of Urinary Excretion of Rituximab in Pediatric Nephrotic Syndrome  
Jason Peter Thomas,1 Teri L. Crumb,2 Tracy J. Kochler,2 Alejandro Quiroga.2
1Pediatric Residency, Grand Rapids Medical Education Partners, Grand Rapids, MI; 2Pediatric Nephrology, Helen DeVos Children’s Hospital, Grand Rapids, MI; 3Research Dept, Grand Rapids Medical Education Partners, Grand Rapids, MI.

**Background:** Rituximab (RTX) is a monoclonal antibody used in patients with steroid dependent nephrotic syndrome as an alternative to cyclophosphamide. As a protein, it is susceptible to excretion in the urine of patients with nephrotic range proteinuria.

**Methods:** This is a pilot pediatric clinical research trial (n=7) which enrolled patients prior to their clinically indicated RTX infusion. Serial urine samples were obtained pre/post-infusion to evaluate for RTX via ELISA. Patients received 2 doses of RTX (375 mg/m2) 12 weeks apart.

**Results:** Rituximab was found in 3/7 patient’s serial samples. There is a non-statistically significant increased likelihood of rituximuria in patients with higher levels of proteinuria. Two weeks after infusion, 85% of the patients had no proteinuria. Two of three patients that excreted RTX in the urine were able to wean off steroids. Patients with rituximuria required a lower cumulative dose of prednisone/kg/year post infusion (p=0.083).

![Steroid Utilization Post Rituximab Infusion](image)

**Subject**

<table>
<thead>
<tr>
<th>Pre-Infusion (ug/mL)</th>
<th>1-3hr (ug/mL)</th>
<th>Infusion Completion (ug/mL)</th>
<th>24hr Post Infusion (ug/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>Not Detected</td>
<td>Not Detected</td>
</tr>
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<td>2</td>
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<tr>
<td>5</td>
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<td>0.37</td>
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</tr>
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<td>7</td>
<td>Not Detected</td>
<td>31.67</td>
<td>2.20</td>
</tr>
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</table>

**Conclusions:** Patients with nephrotic range proteinuria receiving RTX developed rituximuria in 42% of the cases. There is an increased likelihood of response to RTX as measured by cumulative steroid dose 1 year after therapy in patients with rituximuria.

**Funding:** Private Foundation Support

PUB219

IgA Nephropathy (IgAN) in Patients over 64 Years Old: A Devastating Disease with No Effective Treatment  

**Background:** Recent data from the Spanish Registry of Glomerulonephritis show that the incidence of IgAN is increasing among elderly subjects. Limited information about clinical characteristics, response to treatments and outcomes of elderly IgAN has been published.

**Methods:** Retrospective cohort study performed in 21 nephrology departments that collected data from patients over 64 years with biopsy-proven IgAN who were identified at each participating center in the period 1990-2015. This time interval was divided into five consecutive five-year periods. 142 patients with a mean follow-up of 48±52 months were included in the study.

**Results:** The incidence of IgAN in patients over 64 years increased in the last years, from 6 cases in 1990-1995 to 56 in 2011-2015 (p=0.00). Patients were divided according to the type of clinical presentation: 1) asymptomatic proteinuria and hematuria (n = 80, 56%) 2) Hematuria-induced AKI (n = 48, 34%) 3) Crescentic IgAN (> 50% crescents) (n = 7, 5%) and 4) nephrotic syndrome (n = 7, 5%). When comparing the two most common types of presentations (1 and 2), patients with hematuria-induced AKI were older, had higher serum creatinine at baseline, a higher number of cases with gross hematuria and more patients receiving oral anticoagulants (all significant). For the whole group of patients, renal and
Significance of M2 Macrophage in Tubulointerstitial Disease Secondary to Primary Sjogren’s Disease

**Jin LI, Ya-Fen Yu, Chang-Hua Tang, Jun 5;134(11):1033-42.**

**Background:** The study aims to observe the clinicopathologic significance of M2 macrophage in tubulointerstitial injury secondary to primary sjogren’s disease.

**Methods:** Renal tissue samples from patients with tubulointerstitial disease secondary to primary sjogren’s disease (SS, n=8), chronic tubulointerstitial nephritis secondary to drug (CIN, n=8), normal control kidneys (n=3) were included in this study. The expression of CD163 and CD68 was detected by immunohistochemistry or immunofluorescence.

**Results:** (1) Renal involvement was the first manifestation in six of eight (6/8) patients with pSS, including proteinuria, renal dysfunction, tubular acidosis and multiple renal stone; and one patient had intractable hypokalemia. (2) In the normal kidneys samples, CD163 and CD68 were occasionally expressed in tubulointerstitial tissue. (3) There were more CD163 and CD68 positive cells infiltration in tubulointerstitial injury of pSS, especially in patients with hypokalemia. CD68 positive cells were expressed around chronic tubulointerstitial injury and proteinuria casts. There was a negative correlation between CD68 positive cells and albuminuria. (4) Among patients with pSS, CD163 and CD68 positive cells were expressed in acute tubulointerstitial injury of pSS, which positively correlated to N-acetyl-β-D-glucosaminidase (NAG, r=0.627, p=0.012) and beta2-microglobulin (r=0.602, p=0.018) separately. (5) Compared with CIN, patients with pSS had higher serum globulin level, ESR and lower urinary osmotic pressure. During follow-up of one year, four patients with pSS and acute tubular injury acquired improved renal function on therapy of middle dose of steroid and total glucosides of paony. The remaining four patients with pSS had stable renal function.

**Conclusions:** M2 macrophage are involved in acute tubular injury in patients with primary sjogren’s disease. Early intervention can improve renal function of tubulointerstitial injury secondary to primary sjogren’s disease.

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**PUB223**

Clinical Investigation of Preeclampsia in Patients with IgA Nephropathy

Mihoko Karube, Shinya Kamana, Hiroshi Komagata, Yoshihiro Arimura. The First Dept of Internal Medicine, Kyorin Univ School of Medicine, Mitaka, Tokyo, Japan.

**Background:** To evaluate the effect of preeclampsia on the renal prognosis in patients with IgA nephropathy.

**Methods:** In 15 patients with IgA nephropathy that experienced childbirth in the past 5 years in our hospital, 5 patients developed preeclampsia (PE) or superimposed preeclampsia (SPE), thus the 5 patients (IgAN group)were retrospectively analyzed for clinical features including onset time of PE, the child weight and childbirth weeks, blood pressure, renal function, degree of proteinuria, and uric acid levels, and were compared with 20 patients that had no known renal disease before pregnancy and were complicated by PE or SPE (non-IgAN group).

**Results:** No significant differences were observed in childhood ages (35 years), blood pressure at delivery weeks and body weight of children between both groups. The primipara rate was higher in the non-IgAN group, although the premature infants were seen in both groups. However, the onset of hypertension was earlier in IgAN group than in non-IgAN group (22 vs. 27 weeks). Although proteinuria, serum Cr and uric acid levels were transiently worsened after delivery in both groups, the recovery was delayed in IgAN group. Moreover, in 60% of the patients of IgAN group, renal function progressively worsened one year after delivery.

**Conclusions:** These results shows that although proteinuria may increase in IgAN and non-IgA groups, proteinuria may appear earlier and may be sustained longer, resulting in worsening renal function in IgAN; patients with PE or SPE.

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**PUB224**

Effect and Security of Azathioprine in Maintenance Therapy for Refractory Nephrotic Syndrome

Sheng Liu, Mengqi Yu, Hua Huang, Xing Zhou, Huai Zhou, Rui Zhang, Jianguo Zeng. Dept of Nephrology, The Six Affiliated Hospital, Sun Yat-sen Univ, Guangzhou, China.

**Background:** Refractory nephropathy relates to steroid resistant or frequently relapsing nephritis. Maintenance therapy has been called for lupus nephritis(LN). Effect and security of azathioprine in maintenance therapy are still controversial.

**Methods:** We conducted a retrospective study enrolling patients treated with azathioprine(50mg/d) and low-dose prednisone as nephritic maintenance therapy in our centre from 2013.01 to 2016.01.

**Results:** Forty-four patients were enrolled, with 10 minimal-change disease(MCD), 9 idiopathic membranous nephropathy(IMN), 12 IgA nephropathy(IgAN), 3 focal segmental glomerulosclerosis(FSGS), 1 ANCA glomerulonephritis(ANCA-GN) and 9 LN.

**Conclusions:** (1) The activity of MCD patients was 3.0(Min-Max, 1-8). Eight IMN patients(88.9%) were treated with steroid plus cyclosporine as initial therapy with remission duration of 6.7±2.8-months. Cellular crescentic scale in IgAN patients was 11.4±5.2-72.4%. Among them, 39 patients(88.8%) had persistent remission with efficiency of 80%, 89%, 90%, 100%, 33%, 100% and 100% in MCD, IMN, IgAN, FSGS, ANCA-GN and LN, respectively(0.030).

The maintenance remission duration was 13(1-36)months. Relapse occurred in 5

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

*Underline represents presenting author.*
glomerular monoclonal immune deposits without organization on electron microscopy was described by Nasr in 2004 with limited information on prognosis and treatment.

**Methods:** We retrospectively analysed renal outcomes in patients from 5 UK sites, with biopsy proven IgAV, defined as IgA GN on renal biopsy and evidence of vasculitis, including vasculitic lesions on renal or skin biopsy or purpuric rash. Primary outcome was progression to ESRD at 1 year, defined as doubling of serum creatinine from biopsy or use of renal replacement therapy. Secondary outcome was progression to ESRD at 5 years and eGFR at 1 year.

**Results:** We identified 111 18-65 year olds and 29 over 65s. Renal survival was 71.4% overall, 73.9% in the <65s and 61.7% in the 18-65s; p=0.21. Log-rank test showed significantly poorer 1 year survival in the >65s, p=0.035, but similar outcomes at 5 years. All >65s progressing to ESRD did so in the first year, 82% presented at ESRD compared to 28% of 18-65s. Mean eGFR at biopsy was 80mls/min and 56mls/min in 18-65 and >65 groups respectively p=0.014. An eGFR at biopsy below 30mls/min was associated with poorer 1 and 5 year survival; HR 9.8 (p=0.001) and 6.7 (p=0.001) respectively. In those not reaching ESRD, there was a small increase in eGFR over the first year, no significant difference between age groups. Timing of biopsy with regard to eGFR and treatment given varied between sites.

**Conclusions:** In the short term, renal outcome is worse in patients aged over 65 years. An eGFR less than 30mls/min at biopsy is an important predictor for renal survival. Earlier biopsy and diagnosis may improve renal outcome in older subjects.

**PUB226**

Proliferative Glomerulonephritis with Monoclonal Ig Deposits: A 21 Cases Report

**Background:** Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID) was described by Nasr in 2004 with limited information on prognosis and treatment. **Methods:** We retrospectively identified patients with histological PGNMID (strictly glomerular monoclonal immune deposits without organization on electronic microscopy (EM)) without cryoglobulinemia. **Results:** We included 21 cases of PGNMID with 1 recurrence and 3 de novo occurrence on allograft. Mean age was 54.6 years. At diagnosis, mean creatinemia was 3.1 mg/dL, mean proteinuria 3.7 g/24h and haematuria was present in 90.5%. Eight patients had monoclonal spike. Main pathological presentation was membrano-proliferative glomerulonephritis (r=16) with IgG3 kappa immune deposits in 62%. EM revealed non-organized deposits, mostly sub-endothelial. Seventeen patients received chemotherapy 16 months from diagnosis mean (before end stage renal disease (ESRD)). ESRD occurred in a mean of 27.5 months in 4 of 7 non-treated patients and 6 of 14 treated patients. One patient experienced partial response (proteinuria 0.5g/24h and creatinemia 1.7 mg/dL versus 2.3 mg/dL, without histologic features of PGNMID at 6 months) without chemotherapy. Five patients deceased (mean time from diagnosis 44 months), one of them, transplanted, died of infectious complications.

**Conclusions:** This cohort confirms published data. PGNMID outcome is variable with nearly 50% of patients progressing to ESRD. A spontaneous partial response raises the matter of multiple diseases under PGNMID term. Nevertheless, nothing differentiated this case from the others. Even if early chemotherapy treatment may be valuable, there was no renal survey difference between chemotherapy and abstention group in this series, maybe because of the small sample size. Chemotherapy in transplanted patients may lead to infectious complications and Rituximab could be an alternative for them.

**PUB227**

Kidney Biopsy in aHUS May Be Misleading as to Final Renal Outcome

**Background:** Kidney biopsy (KB) is an important tool for diagnosis, staging and defining disease progression but in thrombotic microangiopathies (TMA) but in many centers (particularly in pediatrics) the diagnostic process relies upon lab findings, only.

**Methods:** Herein we describe 2 patients (pt) with aHUS in which KB was performed and the results, as to opportunity of renal recovery, were strikingly different compared to the patients’ clinical (favorable) outcome described.

**Results:** A 42 yo woman was diagnosed aHUS 58 days (d) after delivery. Firstly addressed to plasmaexchange (PEX) the pt started Eculizumab (E) while on dialysis 18 d after diagnosis. TMA promptly improved and 3 mutation were detected on complement regulatory genes (C1H,CF,THBD). KB performed for the persisting anuria on d 28 showed diffuse thickening and reduplication of capillary walls, severe ischemic glomerular tuft and marked vascular intimal thickening. Nevertheless, E was continued, the pt was exposed to last dialysis on d 35; sCr peaked to 9.1 mg/dL, reached the nadir of 1.4 mg/dL 11 months later and so far it remains stable after 5 years of observation. A 28 yo girl was diagnosed aHUS following few weeks of generalized malaise. The pt was first addressed to PEX but the disease rapidly progressed to a peak sCr of 9.4 mg/dL. E was started on d 8 and KB was performed for the persistent anuria, on day 17 with the following findings: diffuse ischemic and segmental sclerotic glomerular lesions associated with vascular intimal fibrosis and lumen reduction. No mutation, nor AntiCFHAb, were detected. Renal function slowly improved and the patient remained dialysis dependent for 6.5 months, the nadir of sCr (1.3) was reached 3.1 yrs later and now has a stable renal function (sCr 1.3) after 3.6 yers.

**Conclusions:** The presented observations rise the issue that KB in TMA may not be informative and sometimes is frankly misleading for the decision making process on whether to address/continue complement inhibition. In our experience E is worth being tried anyhow as long as TMA is ongoing.

**PUB228**

Unique Case of Renal Amyloidosis: Leukocyte Chemotactic Factor 2 (Lect2)

**Background:** The LECT2 associated renal amyloidosis is a recently recognized and unique clinical entity that primarily involves the kidneys, liver, spleen and adrenal gland. The most clinically significant feature is the slow progressive renal failure with an ethnic predominance in Mexican Americans or Middle Eastern Americans.

**Methods:** A 68-year-old Mexican female presented to urgent care with throbbing headache for the past two weeks. Her exam was significant for lower extremity pitting edema and hypertensive urgency, BP of 182/112. Her laboratory data revealed serum creatinine (Scr) of 4.2, with no prior baseline serum creatinine available for comparison. She was then seen in the nephrology clinic for evaluation of renal failure, volume overload and uncontrolled hypertension. Her additional laboratory testing,showed a spot urine total protein to creatinine ratio (TP/CR) of 8 gms. Serological workup was negative. She then underwent an endomyocardial biopsy that showed renal amyloidosis with marked diffuse involvement of glomeruli, interstitium and vessels. Liquid chromatography tandem mass spectrometry was done, which detected peptide profile consistent with LECT2. Her ultrasound of abdomen showed no splenomegaly or hepatomegaly and her echocardiography showed normal ejection fraction of 60%. She had no other organ involvement. Given her uremic symptoms and volume overload status she was initiated on dialysis.

**Conclusions:** LECT2-associated renal amyloidosis presents a unique and perhaps not uncommon disease, especially in Mexican Americans. The pathogenesis and prognosis of this rare entity remains to be determined. This case underscores the importance of renal biopsy as it may not involve the heart or the bone marrow. Liver involvement is typically isolated and, thus, does not likely occur in conjunction with kidney involvement. There is no treatment per se for renal LECT2 amyloidosis. The management is a kidney transplant or initiation of dialysis if they develop end stage renal failure.
Efficacy of Steroid Monotherapy for Pure Membranous Lupus Nephritis
Frank Ward, Mohammad Saad Alkhawaiter, Joanne M. Bargman. Nephrology, United Health Network, Toronto, ON, Canada.

Background: The benefit of combination immunosuppressive therapy over steroid monotherapy in pure membranous lupus nephritis (MLN) is unclear. Steroid monotherapy could reduce unnecessary exposure to additional immunosuppressive agents. We reviewed patient characteristics and outcomes in pure MLN at our institute in those treated with steroid monotherapy or combination therapy.

Methods: In a retrospective, observational cohort study we identified all patients with biopsy-proven pure MLN (ISN/RPS class V) treated since 1990. Inclusion criteria were 17 years or older, baseline proteinuria of at least 2g/day and minimum follow-up of 2 years. Combination therapy consisted of corticosteroids and at least one other agent. Outcomes were complete remission (CR), partial remission (PR) or no response based on serial proteinuria measurement. Categorical data were analysed by Fisher’s Exact test and continuous data by Student’s t-test.

Results: Steroid monotherapy and combination therapy groups were similar in terms of gender, age, duration of SLE, initial serum albumin and proteinuria levels, proportion of sub-nephrotic patients, estimated GFR, C3/C4/dsDNA titres, use of renin-angiotensin blockade and initial prednisone dosing. Combination therapy patients were more likely to have had extra-renal manifestations (100% vs. 40%, p=0.02). CR or PR was achieved in all steroid monotherapy patients and 88% of combination therapy patients. Time to remission (CR or PR) was significantly shorter in the steroid monotherapy group (6.4 months vs. 27.7 months, p=0.007). There was no significant trend towards a higher relapse rate in steroid monotherapy treated patients (60% vs 25%, p=0.26). Follow-up duration was similar between groups (mean 79.4 months vs. 60.7 months, p=0.44) and estimated GFR did not differ at latest follow-up (111ml/min/1.73m² vs. 112ml/min/1.73m², p=0.92).

Conclusions: Steroid monotherapy appears to be efficacious in pure MLN, and may be an appropriate first-line treatment in renal-limited disease. The relapse rate may be lower that observed with combination therapy. Although limited by study design and sample size, these findings warrant further investigation by a larger, prospective, randomized clinical trial.

Risk Factors for Renal Scarring in Children with Myelomeningocele
Fatma Lale Seyer, Yesim Kucukagnaci, Nur Canpolat, Salim Caliskan. Pediatric Nephrology, Istanbul Univ, Cerrahpasa Medical Faculty, Istanbul, Turkey.

Background: Most of children with myelomeningocele have neurogenic bladder. Bladder dysfunction predisposes patients to urinary tract infections, renal scarring and renal failure. We aimed to evaluate risk factors for renal scarring in these patients.

Methods: This single center study involves 53 children with neurogenic bladder due to myelomeningocele (28 male; mean presentation age 18±19 months; current age 7.0±3.6 years), followed-up at least for one year after urodynamic testing. Anthropometric indices, spinal lesion levels, shunt status, ambulatory ability, urinary tract infection (UTI), ultrasound and urodynamic parameters, eGFR and serum cystatin-C levels were recorded. 47 patients (89%) were performing clean intermittent catheterization (CIC). Patients applying at least >75% of CIC suggestions were defined as “compliant”. Low bladder capacity was defined as <65% of expected volume by urodynamic test. Renal scarring was diagnosed by current DMSA scans.

Results: The mean follow-up period was 66±34 months. 24 patients (45%) had VP shunt. Spinal lesion levels were as follows: lumbosacral region in 28, lumbar in 13, sacral in 7 and lumbar in 5. DMSA scintigraphy revealed renal scarring in 9 (17%) patients, which was not associated with gender, presentation, CIC initiation and current age, level of spinal lesion, ambulatory disability or none of urodynamic parameters except low bladder capacity. Significant risk factors for renal scarring are shown in Table 1. There was no difference between eGFR values of the patients with or without scarring, whereas serum cystatin C levels differ significantly (0.80±0.2 vs 0.63±0.09 mg/dL, p=0.03).

Conclusions: CIC compliance and avoidance of UTI may prevent renal scarring in patients with myelomeningocele.

Unusual Cause for Headache in Lupus Nephritis Patient

Background: Therapy with mycophenolate is the norm in the care of lupus nephritis. Here we report an unusual complication of treatment with this drug.

Methods: A 34 year old female lupus nephritis patient presented with severe headache and a MRI done showed multiple bilateral brain masses with surrounding vasogenic edema, most extensive in the right temporal lobe (Fig 1). CSF was not obtained due to mass effects and uncal herniation on the right side. Neurosurgeon did an open brain biopsy that showed multiple organisms largely tachyzoites seen in H&E and immunohistochemistry for toxoplasma. HIV test was negative but her CD4 count was low at 175/cumm at that time. She was started on hemodialysis waiting for her PD catheter to mature. Anti-toxoplasmosis regimen chosen was sulfadiazine 1g four times a day, Dara prim 50 mg daily and leucovorin 20 mg daily. A repeat MRI was performed 2 weeks later as patient had persistent headache despite an initial improvement. showed a right posterior temporal mass and associated vasogenic edema worsened since the initial study when most other lesions seen initially had progressively decreased in size (Fig 2). Regimen was changed to Clindamycin 600 mg four times a day along with atovaquone 750 mg bid , Dara prim and leucovorin. Repeat MRI after 4 weeks showed marked interim improvement in lesion in the right temporal lobe with minimal sequel of toxoplasmosis in other areas. A repeat CD4 was at 512/cumm by then. She is now on atovaquone prophylaxis due to Bactrim allergy.

Conclusions: Non HIV toxoplasmosis itself is rare so also this infectious complication in the treatment of lupus with mycophenolate. Reactivation of dormant toxoplasmosis is a possibility and consideration need to be give for checking CD4 counts while on therapy with mycophenolate mesilat so that appropriate prophylaxis can be initiated.
performed using generalised linear mixed-effects models. Individual trajectories were drawn to map discernible longitudinal clusters, which identified 5(Fig 1). Cluster A was the largest. Univariate associations between time-invariant and time-varying covariates with UsCD163 were explored. 44 clinical parameters were investigated. Time-varying covariates: serum creatinine, sepsis and urinary albumin excretion.

**Results:** Mean (sd) age 61.9(16) yrs, 66% were male and 222 (38%) had AKI by KDIGO criteria. Median UsCD163 level was 0.06 ng/ml (IQR 0.02-0.13, cutofo 0.3, Fig 2). Clusters A (N=224) and B (N=30) were characterised by a consistently low UsCD163 value throughout the observation period. Although a number of clinical covariates were associated with cluster membership on univariate analysis, with multiple comparison adjustment only one association remained: RRT appeared more likely in cluster C vs. A. In the mixed effects models (cluster A & B), UsCD163 levels were not associated with any of the clinical parameters studied.

**Conclusions:** In the setting of critical illness, UsCD163 is generally low with sporadic high values that fall into several patterns. These do not associate with any specific clinical parameters, in particular sepsis or AKI, and may be a reflection of unquantified parameters such as macroscopic haematuria.

**PUB235**

Thrombotic Microangiopathy, the Broad Clinical Spectrum of the Same Lesion

Lida Maria Rodas Marin, Jessica Ugalde-Altamirano, Luis F. Quintana, Manel Solo, Adriana Garcia, Esteban Poch, Jose Miguel Blasco Pelicano, Nephrology and Renal Transplant, Hospital Clinic, Barcelona, Spain; Pathology, Hospital Clinic, Barcelona, Spain.

**Background:** Thrombotic microangiopathy (TMA) is a common histological lesion to multiple clinical diseases, which is characterized by the presence of endothelial cell injury and microvascular thrombi. TMA should be suspected in front the presence of hemolytic microangiopathic anaemia (HMA), thrombocytopenia and kidney injury. After a clinical suspicion or histological confirmation, a broad differential diagnosis is required.

**Methods:** We reviewed all the renal biopsies performed in Hospital Clinic of Barcelona, in the period 2005-2015. We present the analysis of demographic, clinical and histological data of cases of TMA was identified.

**Results:** TMA was detected in 87 renal biopsies of 71 patients during a 10 year period: 24 patients with TMA in native kidneys, 13 women and 11 men with a mean age of 46.79±15.56 years. At the onset of the disease all the patients presented signs HMA (Hb:92.08±25.61 g/L;LDH:959±709 U/L) and 62% with thrombocytopenia (Platelets: 128±65 10^9/L). Renal manifestations AKIN (Creatinine 7.33±5.57 mg/dL) and proteinuria (2643±2120mg/g) in all the patients. Histological lesions included vascular involvement in 95.83% and glomerular changes in 87.5%. Transplanted kidneys: 47 patients presented TMA with 63 biopsies: 16 women and 31 men, with a mean age of 43.66±15 years. The main causes of ESRD were: 25% congenital diseases, 16% aHUS, 10% IgA nephropathy and 10% diabetic nephropathy. The onset of the disease was detected after a graft biopsy due to AKI. At that point, despite 60% of the patients manifested anaemia (Hb:12±1 g/L), 12% of the patients showed signs of hemolysis and 19% thrombocytopenia. All the biopsies demonstrated acute vascular and glomerular TMA changes (only 48% with chronic changes).

**Conclusions:** In our series we demonstrate the variability of clinical entities associated with TMA, especially in renal transplant patients were the renal biopsy is necessary to ensure a correct etiological diagnosis. We also observed that TMA over kidney grafts manifested with HMA and thrombocytopenia in less than 21% of the patients, complicating the clinical suspicion.

**PUB236**

miRNAs as Biomarkers of Kidney Damage in Patients with Systemic Lupus Erythematosus

Gustavo Aroca Martinez, Emil Navarro, Lisandro Paicheco, Lisneth Almendares, Andres A. Cadena, Antonio Iglesias Gamarra, Nephrology, Univ Simon Bolivar; Barranquilla, Atlantico, Colombia; Nephrology, Clin de la Costa, Atlantic, Colombia; Nephrology, Uninorte, Barranquilla, Atlantico, Colombia; Rheumatology, Univ Nacional, Bogota, Cundinamarca, Colombia.

**Background:** Renal involvement is a severe manifestations of systemic lupus erythematosus (SLE). Is priority the development of diagnostic tests for kidney disease in patients with SLE through non-invasive methods, due to the date this is done by kidney biopsy, it presents complications. The microRNAs (miRNAs) are found in tissues with variable expression, and changes in expression are related to pathological processes of various diseases. The aim of this study was to identify differentially expressed miRNAs in patients with lupus nephritis (LN) potentially allow the diagnosis of renal damage in patients with SLE.

**Methods:** A case-control and cross-sectional study, in which we characterized the differential expression profiles of miRNAs among 14 patients with LN Class II: 4 patients, LN class III: 4 patients, LN IV: 6 patients) compared with 8 patients with LES without nephritis or with 8 healthy control individuals, by sequencing Illumina. We validated by qPCR diagnosis by biopsy in 180 samples using a group of miRNAs as biomarkers.

**Results:** We found 89 serum miRNAs that showed statistically significant changes in the proportion of their expression, comparing patients with LN individuals with healthy controls. We find the contrast with the results of the diagnosis by renal biopsy miRNAs miR-221-5p, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p sensitivity averaged 97%, specificity 70.3%, positive predictive value 82.5%, negative predictive value 96% and 87.9% efficiency diagnosed.

**Conclusions:** Whereupon we propose that these microRNAs are potential molecular biomarkers of kidney damage in patients with SLE and request the patenting of the potential usefulness of these microRNAs diagnosed. The miR-221-5p microRNAs, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p are potential diagnostic biomarkers of LN in patients with systemic SLE and the differential expression pattern of microRNAs have significant implications for the pathophysiology of renal damage in LN patients.

**Funding:** Other NIH Support - COLCIENCIAS
PUB237

Primary versus Secondary Recurrent Membranous Glomerulonephritis in Simultaneous Liver-Kidney Transplantation after MRSA Infection: A Diagnostic Challenge

Ekalom Tantisattamo, Dilip Samarapungavan, Ping L. Zhang, Oaklnd Un1v William Beaumont School of Medicine, William Beaumont Hospital, MI.

Background: Anti-PLA2R Ab and IgG4 are still useful tools in differentiating primary from secondary membranous glomerulonephritis (MGN) in kidney transplantation.

Methods: A 50-year-old man with primary MGN 7 years earlier. Urinary protein/creatinine ratio (UPCR) was 10.2 g/g of Cr. He developed ESRD. He was then diagnosed with HIV infection. Tenovifor was initiated. Despite viral load became undetectable; he had ESLD from HIV cirrhosis. He underwent SLK 6 months later. He had delayed renal allograft function. Biopsy performed 3 weeks post-transplant revealed borderline changes for acute cellular rejection. He had MRSa bacteremia concomitant with proteinuria of 8 g from 24-h urine collection. After the bacteremia resolved, the second biopsy was performed and revealed stage II MGN without features of secondary MGN. HBV viral load was undetectable. Serum anti-PLA2R Ab was undetectable. Serum IgG3 and %IgG3, but not IgG4 were elevated. Recurrent secondary MGN was diagnosed. UPCR spontaneously decreased to 1.1 g/g of Cr without intensified immunosuppression or ACE inhibitor (Figure 1).

Results: Our patient recovered from bacteremia before the biopsy was performed. Infection could trigger secondary MGN, and its resolution lead to decreased proteinuria. This is quite similar to the pathogenesis of de novo primary MGN which is not related to anti-PLA2R Ab or co-localized IgG4.

Conclusions: Differentiating primary from secondary MGN particularly in patients with similar uromorphological presentation of both diseases. Further studies should elucidate diagnostic and prognostic utilities of anti-PLA2R Ab and anti-PLA2R Ab or co-localized IgG4.

PUB239

Clinical and Histological Features of Patients with Membranoproliferative Glomerulonephritis Classified by ImmunoFluorescence Findings

Cristiane B. Dias,1 Lectricia Jorge,1 Leonardo Abreu Testagrossa,2 Denise M. Malheiro,2 Viktoria Woronik,1 1Nefrologia, Hospital das Clinicas de Sao Paulo, Sao Paulo, Sao Paulo, Brazil; 2Patologia, Hospital das Clinicas de Sao Paulo, Sao Paulo, Sao Paulo, Brazil.

Background: A new classification system for membranoproliferative glomerulonephritis (MPGN) according to immunofluorescence (IF) has been proposed. The aim of this study was to evaluate the clinical and biochemical characteristics of patients with MPGN grouped by IF analysis.

Methods: This was a retrospective study of patients with renal biopsy-proven MPGN unrelated to systemic lupus erythematosus (SLE), diagnosed between 1999 and 2014. Results: We evaluated 92 patients, which were divided into three groups determined by immunofluorescence: immunoglobulin positive; C3 positive only; and negative IF. Data on diagnosis are in table 1.

Conclusions: The new classification enlightens a systematic approach to evaluation of secondary causes.

PUB240

Surgical and Oncologic Outcomes of Small Renal Tumors Treated with Nephron-Sparing Surgeries - Correlation with Pathology of the Tumor - Parenchymal Interface and Status of the Surgical Margin

Maria M. Picken,1 Gopal N. Gupta,2 1Pathology, Loyola Univ Chicago, Maywood, IL; 2Urology, Loyola Univ Chicago, Maywood, IL.

Background: Approaches to nephron-sparing surgeries (NSS) of renal lesions include partial nephrectomy (PN) and tumor enucleation (TE). Our objective was to examine the pathology of the pseudocapsule and status of the surgical margin in small renal masses treated by NSS, and to correlate these findings with the surgical and oncological outcomes.

Methods: All consecutive renal TE and PN cases obtained between Jan 2012-Dec 2014, that also had available clinical follow-up, were included; pathologic features and clinical data were reviewed and analyzed.

Results: A total of 117 NSS specimens (59 EN, 58 PN) were reviewed. Clear cell renal cell carcinomas and paragangliomas had the thickest pseudocapsules (0.36 mm), while angiomyolipomas lacked a well-defined pseudocapsule. Other tumors were intermediate in their characteristics. The positive margin rate for TE and PN was 17.2% and 0%, respectively. Compared to PN, TE involved a significantly shorter procedure time, less blood loss and fewer post-op complications.

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

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Immunoglobulin positive</th>
<th>C3 positive only</th>
<th>IF negative</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>(10–20)</td>
<td>(10–20)</td>
<td>(10–20)</td>
<td>ns</td>
</tr>
<tr>
<td>Male gender, (%)</td>
<td>51 (70.0)</td>
<td>27 (51.9)</td>
<td>23 (42.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.8 (1.3–5.4)</td>
<td>1.8 (1.3–5.4)</td>
<td>1.8 (1.3–5.4)</td>
<td>ns</td>
</tr>
<tr>
<td>GFR (mL/min/1.73m²)</td>
<td>41.0 (20.0–65.0)</td>
<td>42.0 (15.5–50.0)</td>
<td>43.9 (11.2–5.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>6.3 ± 3.4</td>
<td>6.4 ± 3.0</td>
<td>5.5 ± 3.5</td>
<td>ns</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>2.5 ± 0.6</td>
<td>2.5 ± 0.3</td>
<td>2.7 ± 0.5</td>
<td>ns</td>
</tr>
<tr>
<td>Low C3, (%)</td>
<td>35 (55.5)</td>
<td>24 (46.2)</td>
<td>11 (20.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Low C4, (%)</td>
<td>22 (34.3)</td>
<td>22 (43.8)</td>
<td>19 (36.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Arterial hypertension, (%)</td>
<td>41 (56.0)</td>
<td>22 (42.3)</td>
<td>19 (36.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Hematuria, (%)</td>
<td>51 (70.0)</td>
<td>25 (47.2)</td>
<td>25 (47.2)</td>
<td>ns</td>
</tr>
</tbody>
</table>

N. Gupta.

Average hospital stay              1.71 days
Male gender, (%)                  18 (26.8)
Serum albumin (g/dL)              2.5 ± 0.6
Low C3, (%)                       51 (70.0)
Low C4, (%)                       5 (55.5)
Arterial hypertension, (%)        5 (55.5)
Hematuria, (%)                    51 (70.0)

Infection was the most common in the three groups. Hepatitis C virus (14 patients) and schistosomiasis (7 patients) located mainly in immunoglobulin positive groups. Eleven patients, despite having been diagnosed with infectious disease, autoimmune disease, or mononclonal gammapathy, showed no immunoglobulin deposition on immunofluorescence.

Conclusions: The new classification enlightens a systematic approach to evaluation of secondary causes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Immunoglobulin positive</th>
<th>C3 positive only</th>
<th>IF negative</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients</td>
<td>59</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>57 years (31-80)</td>
<td>62 (24-83)</td>
<td>781</td>
<td>ns</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>35.24 (1.5)</td>
<td>29.29 (1.1)</td>
<td>0.356</td>
<td>ns</td>
</tr>
<tr>
<td># of NSS without hilar clamp (%)</td>
<td>31 (52.5%)</td>
<td>0%(0%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Average clamping time</td>
<td>25 min</td>
<td>25 min</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Procedure time</td>
<td>181 min</td>
<td>241 min</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Blood loss during NSS</td>
<td>180 ml</td>
<td>280 ml</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Average hospital stay</td>
<td>1.77 days</td>
<td>2.75 days</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Patients with post-op complications (%)</td>
<td>7.29(12%)</td>
<td>15.58(26%)</td>
<td>0.062</td>
<td>ns</td>
</tr>
<tr>
<td>Patients re-admission within 1 month (%)</td>
<td>0(0%)</td>
<td>7 (12.1%)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Median follow up - months (range)</td>
<td>22 (11-40)</td>
<td>19 (8-42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor recurrence</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
None of the patients from either group was found to have a local recurrence after follow-up imaging.

Conclusions: Although positive surgical margins were encountered in some TEs, local tumor recurrence was comparable to PN. Thus, TE with maximal nephron sparing, is a reasonable choice for pT1 renal tumors, especially for those without a prominent infiltrative growth pattern.

Funding: Clinical Revenue Support

PUB241

Analysis the Clinical and Pathology of Renal Injury in Patients Received Hematopoietic Stem Cell Transplantation JingJun Xu, Beiping Tsinghua Changgung Hospital, Medical Center, Tsinghua Univ, Beijing, China.

Background: The rate of acute and chronic renal injury is very high in patients received hematopoietic stem cell transplantation(HSCT),but not enough studies about it. Analyzing the reason of renal injury in these patients can improve the renal damage and improve the prospects of survival.

Methods: Clinical, laboratory data, treatment issue and renal pathology results of eight patients with renal injury after HSCT from July,2015 to May,2016 were retrospectively analyzed.

Results: The clinical manifestation of renal injury after HSCT showed as proteinuria, hypertension and renal function damage. The pathological damages involved in glomerulus, renal tubular interstitial and vessel, which is related with bone marrow graft versus host disease, drug damage and thrombotic microangiopathy (TMA).

Conclusions: Renal injury after HSCT varied in different kinds, renal biopsy is important for diagnosis and treatment. According to the renal pathology, early intervention can relieve kidney injury.

PUB242

Clinical and Pathological Features Analysis of Collagen Type III Glomerulopathy Shao Min Gong, Hong Liu, Wei Li, Lin Xiaoqiang Ding. Nephrology, Zhongshan Hospital,Fudan Univ, Shanghai, China.

Background: Collagen type III glomerulopathy, characterized with collagen Type III deposits in mesangial and subendothelia area, is a kind of relatively rare autosomal recessive glomerular disease with few reports of sporadic cases. The specific treatment remains unknown due to the mechanism of this disease has not been elucidated. We reported four sporadic cases in adult without extra-renal organ involvement.

Methods: We searched the database of patients receiving renal biopsy during Jan,2007 to Aug,2015 in Zhongshan Hospital,Fudan University. The clinical and pathological characteristics of 4 cases who were proven as collagen type III glomerulopathy were analyzed.

Results: Four cases comprise of 2 males and 2 females aging 45.5±10.7 years old, none of the cases were reported to have any familial history of kidney diseases. 3 cases complicated with hypertension and none of the cases was found to have extra-renal organ involve. The quantitative of 24-hour proteinuria was 3.8±3.6g(ranging from 0.32 to 7.56g), the eGFR was 27.1±39.2ml/min/1.73m²(ranging from 10.3-81.3 ml/ min/1.73m², calculated by MDRD formula). The light microscopy results of each case were membranoproliferative glomerulonephritis, focal segmental proliferative and sclerosis glomerulonephritis, IgA nephropathy, nodular glomerulosclerosis, respectively. Collagen type III was detected by immunohistochemical staining in four case. One case with minor declined eGFR and mild proteinuria remained stable after receiving conservative therapy. 2 cases had improvement in renal function and partial remission of proteinuria after receiving glucocorticoids and immunosuppressive agents while 1 case with severe renal impairment onset developed into end stage renal disease and received hemodialysis.

Conclusions: The sporadic cases of collagen type III glomerulopathy in adults may be underestimated. The majority of cases presented with proteinuria and multiple light microscopy pathological type. Immunohistochemical analysis and electronic microscope examination are essential to confirm the diagnosis, which should not be neglected to avoid missing diagnosis this rare disease.

Funding: Government Support - Non-U.S.

PUB243

The Significance of Cryoglobulin Deposition Discovered by Renal Biopsy in Patients with Lupus Nephritis Companying Cryoglobulinemia Wen Wen, Yuehong Li. Nephrology, Beijing Tsinghua Changgung Hospital, Beijing, China.

Background: To investigate the relationship between cryoglobulin deposition and manifestations of patients diagnosed as lupus nephritis and cryoglobulinemia.

Methods: Retrospectively collected the clinical materials of patients diagnosed as lupus nephritis companying cryoglobulinemia with or without cryoglobulin deposition from October 2012 to May 2014. Their clinical data, renal pathological features and ultrastructural morphology were analysed. Statistical analyses were performed using SPSS software (version 17.0). The Mann-Whitney U test was used for the comparison of continuous variables; the Fisher exact tests were used for the comparison of proportions. A value of P < 0.05 indicated statistical significance.

Results: There were 12 patients suffering from lupus nephritis and cryoglobulinemia. Eight were female, and 4 were male. Their mean age at the time of renal biopsy was 37.1±10.6 years old. The classification of lupus nephritis of them ranged from III to V. Seven of them had depositions of cryoglobulin in renal biopsy. The occurrence of acute kidney injury (AKI), IgA and complement C4 were higher in patients with cryoglobulin deposition than those without. The improvements of parameters of renal damage were fewer in patients with cryoglobulin deposition after 3 and 6 months.

Conclusions: In patients with lupus nephritis and cryoglobulinemia, cryoglobulin deposition in kidney may increase the risk of AKI and impede the patients from recovery.

Funding: Private Foundation Support

PUB244

ETAR Expression in Kidney Biopsies of Patients with ANCA-Associated Glomerulonephritis Predicts GFR Decline: Preliminary Results Olumide Olatunbosun Roweai, Piotr Donizy, Mariusz Kusztal, Miroslaw Banasik, Magdalena Krajewska, Agnieszka Halon, Marian Klenger.

1Nephrology and Transplantation Medicine, Wroclaw Medical Univ, Wroclaw, Poland; 2Histopathology, Wroclaw Medical Univ, Wroclaw, Poland.

Background: ANCA-associated glomerulonephritis (AAGN) is often characterized by a decline in renal function. Endothelin has been implicated in renal cell injury, inflammation and fibrosis. We hypothesized that degree of endothelin-1 type A receptor (ETAR) expression in renal specimen can predict decline in eGFR in AAGN patients.

Methods: Immunohistochemical (IH) evaluation for ETAR expression was performed on the renal biopsies of AAGN using anti-ETAR antibody (rabbit polyclonal, ABCAM, USA). Control reactions were performed on 5 normal kidneys. A composite ETAR expression score [EES] was calculated for each biopsy based on the intensity of expression (0 for negative, 3 for high) using the formula: g (0-3) + v (0-3) + t (0-3) + i (0-3). A value of < 0.05 indicated statistical significance.

Results: Cohort consisted of 5 patients with PR3-ANCA, 5 with MPO-ANCA and 1 ANCA-negative (7M, 4F). Histopathological class: 3 crescentic, 7 mixed, 1 sclerotic. Tubular epithelium revealed diffuse cytoplasmic pattern of ETAR expression in all analyzed patients. Renal vessels were negative for ETAR. In 3 patients immunoreactivity of ETAR was observed only in glomerular crescents. Composite EES was in range 1-6 for all patients. In general patients with higher composite EES (>3) after 24 (20 vs 47ml/min; p<0.05) and 36 months (20 vs 44ml/min;p>0.05) irrespective of histopathological class.

Conclusions: ETAR expression in renal biopsy seems to be useful in predicting decline in renal function in AAGN, irrespective of histopathological class, in long term. Further studies will elucidate relevance of ETAR expression and its antibody presence in patients with AAGN.

Funding: Government Support - Non-U.S.

PUB245

Immunohistochemical and Electron Microscopic Analysis the Clinical and Pathology of Renal Injury in Patients Received Hematopoietic Stem Cell Transplantation Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Glomerulopathies Secondary to Schistosoma mansoni: Revisiting a Forgotten Enemy
Precil Diego Miranda de Menezes Neves,1 Ramaine Aparecida Bredi,1 Bernardo V. Reichert,1 Lectícia Jorge,1 Luis Yu,1 Viktoriia Woronik,1 Leonardo Abreu Testagrosa,2 Denise M. Malheiros,2 Cristiana B. Dias,2 Nephrology Service, Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil; Pathology Div, Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil.

Background: Schistosomiasis mansoni is a parasitic disease caused by Schistosoma mansoni (SM). This is an endemic disease in some regions of Brazil. The kidney may be impaired, particularly in the form of glomerulopathies. We aim to make clinical and epidemiological characterization of patients with glomerulopathies secondary to SM.

Methods: Identification of cases of glomerulopathies secondary to SM in the period of 1990-2005. We reviewed clinical, epidemiological, and renal biopsy data.

Results: Of an initial casestudy of 21 patients, two of them were excluded due to neoplasia at the time of renal biopsy. Patients were predominantly male (79%), white (52%), mean age 38.8±7.8 y.o. The diagnosis of SM was made through fecal analysis (94%), 64.7% had hepatosplenic disease. The histological presentation as MPGN was associated with worst response to antimicrobial treatment, need for immunosuppressive treatment, higher rate was 10.5% due to non-related nephropathy causes. The mean duration of follow up was 48±24,5 months, and at that time 26.3% of patients undergone dialysis and mortality in 48% of cases. The histological presentation more frequent was Membranoproliferative Glomerulonephritis (MPGN) 69%, followed by Focal Segmental Glomerulosclerosis (21%), Membranous Nephropathy (5%) and Focal Proliferative Glomerulonephritis (5%). In 60% of cases antimicrobial treatment wasn’t effective to induce remission than immunosuppressive therapy was required. Of these, 70% with diagnosis of MPGN. The follow-up was 70 (14-124) months, and at that time 26.3% of patients undergo dialysis mortality and related nephropathy causes rate was 10.5% due to non-related nephropathy causes.

Conclusions: The histological presentation as MPGN was associated with worst response to antimicrobial treatment, need for immunosuppressive treatment, higher rate of progression to end stage renal disease/dialysis and higher mortality compared to other subtypes of glomerulopathies.

Cohort of Native Kidney Percutaneous Biopsies in an Urban Center with a Majorit y of African American Patients
Ravi K. Thimimsetty, Nashut Burhan Imran, Muhammad Omar Azam, Yahya M. Osman Malik. Internal Medicine/Nephrology, Wayne State Univ, Detroit, MI.

Background: The percutaneous biopsy of native kidneys can aid in: confirming a suspected diagnosis, anticipating recurrence post-transplant, prognosticating the kidney disease, or even deterring clinicians from committing to therapy in cases of advanced fibrosis. Kidney biopsy may even alter the pre-biopsy proposed management. Indications for biopsy depends on the treating nephrologists but include: nephrotic syndrome, acute nephritic syndrome, and unexplained acute kidney injury. We are reporting our 5-year experience in an urban center with majority African American patients.

Methods: Epidemiological retrospective analysis, single-center, urban medical center with a predominant demographic of African Americans. Cohort: all non-cancer and non-transplant native kidney biopsies from February, 1st 2011 till June, 6th 2016. All biopsies were done in one center and under ultrasound guidance by either the nephrology service or interventional radiology.

Results: There was total of 561 biopsies in this time period. All transplant biopsies and onco-surgical biopsies were excluded. The final 143 biopsies were analyzed with the following findings: average age at the time of biopsy was 43.6 years (18-86), 49% male, 76.2% African Americans, average proteinuria 4.8 g/g, hypertension 76.2%. Unexplained acute kidney injury was the most common indication for biopsy (34%) followed by nephrotic syndrome (31%). Accurate pre-biopsy clinical diagnosis was accurate in 49% of cases and was not suspected in 65% of patients with histological evidence of FSGS.

Conclusions: Percutaneous native kidney biopsy in our urban center showed FSGS and lupus nephritis as the most common diagnosis. Among African Americans, FSGS was incorrectly diagnosed in 53% of the cases and was not suspected in 65% of patients with histological evidence of FSGS.

Methods: Eighty ADPKD patients (52 hypertensive, 28 normotensive) and 50 healthy subjects were recruited to the study to compare the blood pressure between these two groups. The expressions of miRNAs were determined by Biomark Real Time PCR system in the serum samples obtained from all study participants. qRNAs (miRNAs) with the clinical course of ADPKD and to test the availability of miRNAs as a biomarker in ADPKD patients. Methods: We obtained a list of emergency room visits and hospital admissions in London, Canada between April 1st, 2002 and March 31st, 2014 for adults where either ICD-10 codes Q61.2 or Q61.3 for polycystic kidney disease, autosomal dominant, or Q61.3 (polycystic kidney disease, unspecified) were assigned to a hospital encounter. From this list, we manually reviewed a random sample of patient medical charts, and determined whether ADPKD was present or not according to strict clinical criteria. We calculated the positive predictive value (95% confidence interval) for 9 different coding algorithms. We also used province wide databases to assess the number of patients in Ontario identified with different code sets.

Results: The presence of either ICD-10 code Q61.2 or Q61.3 in a hospital encounter had a positive predictive value of 85% (95% CI: 79% to 89%) for the identification of ADPKD, and identified 2981 adults in Ontario (0.02% of the general population). The presence of ICD-10 code Q61.2 in a hospital encounter had a positive predictive value of 97% (95% CI: 96% to 100%) for the identification of ADPKD, and identified 394 adults in Ontario (0.003% of the general population).

Conclusions: Most patients with ICD-10 administrative codes Q61.2 or Q61.3 assigned during their hospital encounters had ADPKD according to strict clinical criteria. These codes can be used to assemble and study cohorts of adult patients with ADPKD and hospital encounters.

Funding: Private Foundation Support

Low Serum Levels of 1,25-Dihydroxyvitamin D, Not 25-Hydroxyvitamin D, Are Associated with Greater Total Kidney Volume (TKV) in Patients with Early Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Kristen L. Nowak,1 Zhiying You,1 Myles S. Wolf,2 Michel Chonchol,3 Berenice Y. Gitemor,1 1Univ of Colorado Anschutz Medical Campus; 2Northwestern Univ.

Background: The association of circulating vitamin D with kidney growth in patients with ADPKD is currently unknown. We sought to determine whether serum vitamin D levels are related to risk of TKV progression in patients with ADPKD and whether serum 25(OH)D and 1,25(OH)2D were associated with glomerular filtration rate (eGFR) > 60 ml/min/1.73m2.

Methods: 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D (1,25(OH)2D) were measured in 462 hypertensive ADPKD patients who participated in the HAPPKD trial, a study. Participants were randomized to standard or low blood pressure control and to either lisinopril plus telmisartan or lisinopril plus placebo, with evaluation of height-corrected TKV (HTKV) at baseline, 24, 48, and 60 months. The study population was divided into tertiles of 25(OH)D and 1,25(OH)2D levels. We used mixed effect models to examine the associations across tertiles of 25(OH)D and 1,25(OH)2D with the primary measures of HTKV during the course of the study.

Results: At baseline, participants had a mean age of 37 ± 8 years, mean CKD-EPI eGFR of 91.4 ± 17.4 ml/min/1.73m2, and median (IQR) 25(OH)D, 1,25(OH)2D,D and HTKV were 31.5 (24.1 – 38.2) ng/mL, 36.6 (30.0-44.7) ng/mL and 589 (406-860) ml/min, respectively. After adjustment for gender, race, randomization group, body-mass index, systolic blood pressure, eGFR, urine albumin excretion, serum calcium, phosphate and parathyroid hormone level, the lowest 1,25(OH)2D tertile was associated with greater HTKV (β=123.05, [95% CI 44.74, 201.36]; p < 0.0001 compared with the highest 1,25(OH)2D tertile). Similarly, when evaluated as a continuous variable, higher levels of 1,25(OH)2D were associated with lower HTKV.
1,25(OH)D were associated with a lower HtTKV (β = –16.72, [95% CI -86.81, -247.65]; p=0.002 per natural log unit increase). In contrast, there was no association between 25(OH)D levels and HtTKV (p=0.50).

Conclusions: Low serum 1,25(OH)D level, but not 25(OH)D level, is independently associated with a higher HtTKV over time in patients with early ADPKD.

Funding: NIDDK Support

PUB250
Improving Our Understanding of Pain in Autosomal Dominant Polycystic Kidney Disease
Ragada El-Damanawy,1 Tess Harris,2 Thomas F. Hiemstra,2 Michael C. Lee.,2 Dept of Renal Medicine, Cambridge Univ NHS Trust, Cambridge, United Kingdom; 1Dept of Nephrology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

Background: In Autosomal Dominant Polycystic Kidney Disease (ADPKD) pain is an early prominent feature affecting 60%. Multiple mechanisms result in pain, the severity of which correlates poorly with renal size. We conducted a survey to get a better understanding of patients experience of pain.

Methods: We used the painDETECT questionnaire, which was distributed to patients attending an ADPKD information day in Birmingham. 34 attendees completed the questionnaire.

Results: Participants were asked about how strong on average their pain was over the last 4 weeks using a scale 0 = none to 10 = maximum. 20.6% (7/34) had no pain, the majority (55.9% (19/34) scored pain between 1-5, and 23.5% (8/34) scored pain between 6-10. Of those that did experience pain (n=27), the pain quality is shown in table 1. 11.8% (4/34) said they had persistent pain with slight fluctuations, 8.8% (3/34) had persistent pain with pain attacks, most commonly 44% (15/34) had pain attacks without pain in between, and 20.6% (7/34) had pain attacks with pain between them. 82.4% (28/34) had a painDETECT score of ≤12 indicating the pain was not neuropathic-figure 1.

Conclusions: In patients with ADPKD pain was episodic and nociceptive in quality, with not much of a neuropathic component. Our management should focus on intermittent therapy, and less on anti-neuropathic medications. There may be a role for renal denervation.

PUB251
Performance of Equations to Estimate Glomerular Filtration Rate in a Longitudinal Study of Autosomal Dominant Polycystic Kidney Disease
Chengli Shep,1 Doug Landsittel,1 Maria V. Irazabal,2 Alan S.L. Yu,3 Arlene B. Chapman,3 Michal Mrug,2 Jared J. Grantham,2 Kyongtai Ty Bac,2 William M. Bennett,4 Michael F. Flessner,5 Vicente E. Torres,2 The Crisp Investigators,1 1U of Pittsburgh, Pittsburgh, PA; 2Mayo Clinic College of Medicine, Rochester, MN; 3Kansu U, Kansas City, KS; 4U of Chicago, Chicago, IL; 5U of Alabama, Birmingham, AL; 6Legacy Good Samaritan Hospital, Portland, OR; 7National Inst of Diabetes, Digestive and Kidney Diseases, Bethesda, MD.

Background: The reliability of estimated glomerular filtration rate (GFR) to reflect actual GFR values in clinical trials for ADPKD is controversial. Since 2001 the Consortium for Radiologic Studies of Polycystic Kidney Disease (CRISP) has followed 241 ADPKD patients (entry creatinine clearance > 70 ml/min) with measurements of iothalamate clearance and serum creatinine yearly during four years and every other year afterwards. CRISP has shown that measuring association of baseline height adjusted total kidney volume (HtTKV) and change in HtTKV with the rate of decline in iothalamate clearance.

Methods: We have evaluated the performance of GFR estimations by the MDRD and CKD-EPI equations relative to measured GFR using iothalamate clearance by mean bias, precision, accuracy, and strength of association with baseline HtTKV and change in HtTKV.

Results: Mean biases of MDRD GFR and CKD-EPI GFR values were large and positive (but highly variable) when measured GFR was ≥70 (10.1±26.9 and 6.2±22.6) and small and negative when it was <70 ml/min/1.73 m² (-1.9±9.5 and -5.0±9.9). Precision was higher when measured GFR was <70 ml/min/1.73 m² and estimated GFR slopes and overall declines were not different. All were equally capable to detect the effect of baseline HtTKV and of change in HtTKV on the rate of GFR decline during 4, 8 or 12 years of follow-up. Beta coefficients were modestly higher with measured than estimated GFR, but this advantage was offset by larger standard errors.

Conclusions: Determinations of estimated GFR using the MDRD or CKD-EPI equations are adequate to detect changes in kidney function over time in longitudinal studies and clinical trials of ADPKD.

Funding: NIDDK Support, Other NIH Support - CRISP

PUB252
Online Survey Exploring Opinions of European Caregivers about Testing for Autosomal Dominant Polycystic Kidney Disease
Stephanie Le De Recht,1 Djallia Mekahli,1 Jonathan A. Kringer,1 Elena N. Levitchenko,2 Peter Janssens,3 Max Liebau,2 Carsten Bergmann,2 Bert Bammens,1 Pascal Borry,2 Franz S. Schaefer,4 1Univ of Leuven; 2Univ of New Haven; 3Bioscientia Center for Human Genetics, Ingleheim; 4Univ of Heidelberg; 5Univ Hospital of Cologne.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is considered an adult disease. Whether minor offspring of ADPKD patients should have diagnostic testing remains controversial. However, the attitudes of caregivers have never been studied.

Methods: We used an online questionnaire aimed for pediatric and adult nephrologists, and an adapted version for geneticists.

Results: A total of 410 caregivers responded: 151 adult nephrologists, 261 pediatric nephrologists, and 43 geneticists. All three specialties similarly agreed that it was appropriate to encourage clinical testing in adults (group mean = 5.31, sd = 1.16). While all supported that clinical testing in minors should be encouraged (group mean = 4.76, sd = 1.50), pediatric nephrologists demonstrated significantly stronger agreement (t =3.60, p < .001) than geneticists. Regarding ethical concerns, although all specialities exhibited some disagreement with the statement that “pre-natal genetic diagnosis is ethically justified” (group mean = 3.08, sd = 1.76), adult and pediatric nephrologists exhibited significantly higher levels of disagreement compared to geneticists (tadul = -0.10, p < .05; pediatric = -3.19, p < .01). Similarly, all groups disagree on the statement “termination of pregnancy for ADPKD is ethically justified” (group mean = 2.78, sd = 1.67). Finally, geneticists exhibited more agreement with the statement that “pre-implantation genetic diagnosis is ethically justified” (geneticist mean = 4.48, sd = 1.63). This position was significantly different that of adult and pediatric nephrologists who exhibited disagreement (tadul = -2.51, p < .05; pediatric = -4.43, p < .001).

Conclusions: Our survey demonstrated that most of the caregivers will support clinical testing of the offspring of ADPKD families, however, there is no consensus on the value of genetic testing neither on the ethical issues of the family planning.

Funding: Government Support - Non-U.S.

PUB253
CRISPR-Cas9 Mediated Knockout of Ciliary Genes to Study PKD in Zebrafish
Stephanie Jerman, Zhaoxia Sun. Genetics, Yale Univ School of Medicine, New Haven, CT.

Background: Polycystic Kidney Disease (ADPKD) is one of the most commonly occurring genetic disorders in the world with limited treatment modalities, resulting in many PKD patients progressing to end-stage renal disease. Thus, to understand the fundamental biology of PKD is an important area of research. Several recent studies suggest the primary cilium of the primary cilium, a signaling organelle with various sensory functions, in the development and manifestation of cysts in ADPKD. Notably, polycystin-2, one of the two proteins known to be mutant in Autosomal Dominant PKD, encodes a cation channel through the cilium. Many other ciliary proteins, including Arl13b and IFT57, when mutant lead to cyst formation. The earliest stages of vertebrate embryonic development rely on maternally supplied gene products. In zebrafish, these maternal contributions can have a protective effect on offspring, masking the true null mutant phenotype. For example, Pkd2 homozygous zebrafish mutants develop kidney cyst similar to what is observed in patients with Autosomal Dominant PKD; however, Pkd2−/− zebrafish do have body curvature and left-right defects indicative of ciliary defects but do not display kidney cysts unless subjected to morpholino knockdown of Pkd2, which eliminates the maternal contribution. However, these results also suggest an off-target effect of morpholino knockdown. To address this concern and reveal the true null phenotype of ciliary mutants, this study focused on understanding the role of polycystin-2, Arl13b, and IFT57 within the primary cilium using maternal zygotic zebrafish to eliminate maternally contributed mRNA in mutant offspring. Maternal zygotic rescue was generated using CRISPR-Cas9 technology to create the cilia genes mutant and Cas9-narnas, which is preferentially expressed in the germline. These results provide novel insight into the function of Pkd2, Arl13b, and IFT57 within cilia and the role of the primary cilium in PKD and other ciliary disorders.

Funding: Other NIH Support - 2T32DK007356-36

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

962A
Kidney Length Identifies Risk Categories of Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) - Bharathi V. Reddy, Doug Landsittel, Chengli Shen, Kyongtae Ty Bae, Alan S.L. Yu, Vicente E. Torres, Maria V. Irazabal, Frederic F. Rahbari-Oskoui, Michal Mrug, Arlene B. Chapman, U Chicago; U Pittsburg; U Kansas; Mayo Clinic; Emory U; UAB Birmingham.

**Background:** Recently, a classification system establishing low and high risk ADPKD patients for progression to ESRD has been developed using height corrected total kidney volume (htTKV), age and serum creatinine (1A-1E, Irazabal, JASN. 2015 Jan;26(1):160-72). The Consortium for Radiologic Studies in Polycystic Kidney disease (CRISP) has demonstrated that kidney length (KL) performs as well as htTKV in predicting future Stages 3-5 CKD. Therefore we determined the corresponding MR based KL measures in participants in Classes 1A-1E in CRISP.

**Methods:** Baseline coronal MRI maximum KL in 231 CRISP Class 1A-1E participants were assessed in those <30 and >30 years of age.

**Results:** 145 participants were >84 years <30 years of age. In those <30 years, 5, 17, 29, 31, and 32% were in classes 1A, 1B, IC, 1D and 1E. In those >30 years, 7, 30, 36, 8% were in class 1A, 1B, 1C, 1D, and 1E. KL is less in all risk categories in young vs. old patients. The maximum KL observed in younger patients was 11.77, 14.58, 16.85, 17.43 and 24.66 in class 1A, 1B, IC, 1D and 1E. In those >30 years, the maximum KL was 14.12, 20.15, 20.17, 25.65 and 23.55 in class 1A, 1B, 1C, 1D and 1E. Mean KL is < threshold to predict future stage III CKD in groups 1A-1D and 1A-1C in younger and older patients.

**Conclusions:** KL, which can be easily obtained by MRI and other imaging modalities show incremental change throughout the Irazabal classification of disease severity, highlighting which groups will progress to CKD.


**Background:** Renin-angiotensin system (RAS) inhibitors are the preferred drugs for hypertension in autosomal dominant polycystic kidney disease (ADPKD). However, the relative role of the systemic and intrarenal RAS in hypertensive patients with ADPKD remains unresolved. Tubulocystic epithelium can synthesize functional renin, possibly in response to local hypoperfusion, but urinary renin has not been measured in patients with ADPKD. Therefore, we tested the hypothesis that ADPKD activates the intrarenal RAS response to local hypoperfusion, but urinary renin has not been measured in patients with ADPKD. While plasma levels of AGT, renin, and aldosterone were similar between groups, urinary renin excretion in ADPKD patients was increased compared between groups.

**Results:** ADPKD patients responded (65 female (73%); 84 caucasian (94%); 80 British (93%)). The median age range was 45-49 years. One third (30/89, 33.7%) received a diagnosis of ADPKD during the 4th decade of life. More patients in the high water intake group (47 of 54, 87%) report regularly drinking beyond thirst compared to the low water intake group (18 of 55, 32%, p=0.001). Reports of nocturia were not different between groups (p=0.663) and both groups equally believed high water intake was beneficial - table1.

Despite only 15 (17%) living with affected family members, the majority (70 of 89, 79%) regularly discussed management with their relatives. Most patients (80 of 89, 90%) indicated willingness to participate in a randomised trial of high versus ad lib water intake. Conclusions: Current water intake practices vary widely among UK patients with ADPKD. A trial of high versus standard water intake in ADPKD is urgently needed and likely to be supported by patients. Most patients regularly discuss their condition with affected family members, suggesting that contamination between trial arms is possible and may require cluster randomisation.


**Background:** Vasopressin drives cyst growth in Autosomal Dominant Polycystic Kidney Disease (ADPKD). High water intake readily suppresses vasopressin release, and may be an alternative to Vasopressin antagonists. Patients are often advised to drink beyond thirst. However, the effect of this advice is unknown. As vasopressin suppression results in water diuresis with a urine specific gravity (uSG)<1.010, uSG provides to drink beyond thirst. However, the effect of this advice is unknown. As vasopressin suppression results in water diuresis with a urine specific gravity (uSG)<1.010, uSG provides an alternative to Vasopressin antagonists. Patients are often advised to drink beyond thirst. However, the effect of this advice is unknown. As vasopressin suppression results in water diuresis with a urine specific gravity (uSG)<1.010, uSG provides an alternative to Vasopressin antagonists. Patients are often advised to drink beyond thirst. However, the effect of this advice is unknown. As vasopressin suppression results in water diuresis with a urine specific gravity (uSG)<1.010, uSG provides a surrogate for vasopressin suppression. We assessed uSG in a cohort of ADPKD patients to establish prevalent hydration status.

**Methods:** High water intake advice for ADPKD was introduced in our centre in 2013. In this single-centre retrospective cohort study, we determined adherence to hydration advice by assessing uSG. Data were extracted from patient case records.

**Results:** Data were available for 77 patients (41[53%] male; 56 (73%) Caucasian, 5 (6%) PKD2 mutation). The mean (SD) age at diagnosis was 29±14 years, and at referral 40±14 years. 59 patients (77%) had a family history of ADPKD. At baseline 40 (52%) had uSG<1.010. uSG has been demonstrated to be an alternative to Vasopressin antagonists. Patients are often advised to drink beyond thirst. However, the effect of this advice is unknown. As vasopressin suppression results in water diuresis with a urine specific gravity (uSG)<1.010, uSG provides a surrogate for vasopression suppression. We assessed uSG in a cohort of ADPKD patients to establish prevalent hydration status.

**Conclusions:** Current water intake practices vary widely among UK patients with ADPKD. A trial of high versus standard water intake in ADPKD is urgently needed and likely to be supported by patients. Most patients regularly discuss their condition with affected family members, suggesting that contamination between trial arms is possible and may require cluster randomisation.


**Background:** Vasopressin drives cyst growth in Autosomal Dominant Polycystic Kidney Disease (ADPKD). It can be suppressed through high water intake, although the effects of this approach on renal outcomes are unknown. We conducted a survey of ADPKD patients to determine current fluid intake practices and willingness to participate in a randomised water intake trial.

**Methods:** In collaboration with the PKD Charity, we developed and distributed an online patient questionnaire. Participants were arbitrarily divided into those reporting a high water intake (>2 litres/day) and those reporting a lower intake. Responses were compared between groups.

**Results:** 89 ADPKD patients responded (65 female (73%); 84 caucasian (94%); 80 British (93%)). The median age range was 45-49 years. One third (30/89, 33.7%) received a diagnosis of ADPKD during the 4th decade of life. More patients in the high water intake group (47 of 54, 87%) report regularly drinking beyond thirst compared to the low water intake group (18 of 55, 32%, p=0.001). Reports of nocturia were not different between groups (p=0.663) and both groups equally believed high water intake was beneficial - table1.

Despite only 15 (17%) living with affected family members, the majority (70 of 89, 79%) regularly discussed management with their relatives. Most patients (80 of 89, 90%) indicated willingness to participate in a randomised trial of high versus ad lib water intake. Conclusions: Current water intake practices vary widely among UK patients with ADPKD. A trial of high versus standard water intake in ADPKD is urgently needed and likely to be supported by patients. Most patients regularly discuss their condition with affected family members, suggesting that contamination between trial arms is possible and may require cluster randomisation.
Autosomal Dominant Polycystic Kidney Disease in the Southwest of Ireland

Michael Keyes, Dearbhla Kelly, Edward Philip McNamara, Liam F. Casserly. Dept of Nephrology, Univ Hospital Limerick, Limerick, Ireland.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of chronic kidney disease (CKD). In a recent cross-sectional survey, it accounted for 7.3% of patients with CKD in the Republic of Ireland. ADPKD is caused by mutations of either PKD1 (which encodes polycystin-1), on chromosome 16, or PKD2 (which encodes polycystin-2), on chromosome 4.

Methods: This was an observational study of all patients with ADPKD who attended the Nephrology services in University Hospital Limerick from January 2000-June 2016. Patients were identified by interrogation of the departmental database. Retrospective chart review enabled documentation of demographic and clinical characteristics along with treatment course and outcome. Water intake and access to genetic counseling were also recorded.

Results: 99 patients with ADPKD were identified. The mean age of the population was 58.7 years (SD ± 13.9, range 29-88 years). 56.7% were female. 13 patients (13.1%) had no family history of ADPKD but only 1 patient had genetic testing for PKD1 and PKD2 genes performed. 76.8% of patients developed hypertension and 51.5% of patients were treated with renin-angiotensin system (RAS) inhibitors. The mean delta glomerular filtration rate (GFR) was -1.2ml/min (SD ± 2.8). 28.3% were dialysis-dependent and 21.2% of patients received a renal transplant. No patient was counselled regarding increased water intake and no patient was in receipt of a vasopressin receptor antagonist. 37.4% were screened for hereditary cancer susceptibility syndromes. Only 1 patient was in receipt of a vasopressin receptor antagonist. 37.4% were screened for hereditary cancer susceptibility syndromes. 78.6% of patients were treated with ACE inhibitors. 16.2% of patients were treated with ARBs. 8.1% of patients were treated with both ACE inhibitors and ARBs.

Conclusions: 99 patients with ADPKD were identified. The mean age of the population was 58.7 years (SD ± 13.9, range 29-88 years). 56.7% were female. 13 patients (13.1%) had no family history of ADPKD but only 1 patient had genetic testing for PKD1 and PKD2 genes performed. 76.8% of patients developed hypertension and 51.5% of patients were treated with renin-angiotensin system (RAS) inhibitors. The mean delta glomerular filtration rate (GFR) was -1.2ml/min (SD ± 2.8). 28.3% were dialysis-dependent and 21.2% of patients received a renal transplant. No patient was counselled regarding increased water intake and no patient was in receipt of a vasopressin receptor antagonist. 37.4% were screened for hereditary cancer susceptibility syndromes. Only 1 patient was in receipt of a vasopressin receptor antagonist. 37.4% were screened for hereditary cancer susceptibility syndromes.

Efficient Genome Editing of Differentiated Renal Epithelial Cells

Alexis Hofherr, 1 Tilman Busch, 2 Nora Marie Huber, 2 Sebastian Arnold, 2 Michael Kottgen. 1 Renal Div, Dept of Medicine, Faculty of Medicine, Univ of Freiburg, Freiburg im Breisgau, Baden-Wuerttemberg, Germany; 2 Experimentelle und Klinische Pharmakologie und Toxikologie, Faculty of Medicine, Univ of Freiburg, Freiburg im Breisgau, Baden-Wuerttemberg, Germany.

Background: The recent advent of highly efficient genome editing technologies has enabled a new paradigm in which genomes can be precisely manipulated. This includes the targeted introduction, alteration, and/or removal of genomic sequences. However, respective methods have been described mainly in haploid or non-differentiated cells. The application in well-differentiated renal epithelial cells has been hindered by a range of technological issues, including optimal design, efficient expression of multiple genome editing constructs, attainable mutation rates, and best screening strategies.

Methods: Here we show how to overcome these challenges to rapidly generate heterogeneous and homogenous sequence alterations in renal cells using transcription activator-like effector nucleases (TALENs) and the clustered regularly interspaced short palindromic repeat (CRISPR) system.

Results: The cell lines most widely used to study renal epithelial biology are Madin-Darby Canine Kidney (MDCK) and mouse Inner Medullary Collecting Duct 3 (mIMCD3) cells. Both cell lines retain core epithelial characteristics, are phenotypically stable, and develop clear apico-basolateral polarity. We therefore developed a genome editing-based framework to efficiently expand on the genetics of wild-type MDCK and mIMCD3 cells. Applications include, but are not limited to, large genomic deletions, loss-of-function mutations, and knock-ins by homologous recombination. Furthermore, we describe how to translate these genetic alterations into complementary mouse models. Notable features of genome edited cell lines are, a high degree of differentiation, phenotypic stability, experimental tractability, and suitability for small and high throughput screening.

Conclusions: We anticipate that the developed genome editing workflow may help to clarify gene functionality in differentiated renal epithelial cells in health and disease.

Serum from Diabetic-End Stage Renal Disease (DM-ESRD) Patients Affects Endothelial Reparative Ability

Maria Marques Vidas, Estefany Garcia Mercado, Matilde Alquie, Elena Corchete, Jeanette Nora Fernandez C., Patricia De Seuxera, Rafael Perez-Garcia, Rafael Ramirez, Jose M. Portolés, 1 1 Nephrology, H U Puerta de Hierro Majadahonda, Majadahonda, Madrid, Spain; 2 Nephrology, HU Infanta Leonor Vallecros, Madrid, Spain; 3 Physiology Lab, U Alcalá de Henares, Alcalá de Henares, Madrid, Spain.

Background: Chronic renal disease and diabetes mellitus are associated with higher rates of cardiovascular disease. Circulating microparticles (MPs) are intercellular communication mediators that module mechanisms of vascular endothelium lesion and repairation. The aim of this study was to evaluate the effect of the MPs from DM-ESRD patients on the vascular endothelium.

Methods: We used pooled serum obtained from DM-ESRD patients stage 4 (n=5), on peritoneal dialysis (PD, n=5), on haemodialysis pre-session (pre-HD, n=5) and post-session (post-HD, n=5), and healthy volunteers (n=5). MPs were isolated, and HUVEC were incubated with and without the addition of MPs. We analysed proliferation and apoptosis averages and ICAM and VCAM expression.

Results: The serum from DM-ESRD patients on any stage induced an increase in the expression of both ICAM and VCAM on HUVEC (p<0.001). Treatment with HD or PD did not modify this effect with respect to VCAM; however, the pre-HD serum pool induced a higher expression of ICAM (p<0.01**). The presence of MPs decreased ICAM up-expression on all study groups (p ns). DM-ESRD serum was less effective on inducing cellular proliferation than control serum, especially on HD groups when tested without MPs. Finally, DM-ESRD serum induced a significant increase on apoptosis rate, especially on HD groups. The presence of MPs seemed to increase apoptosis rate in every study group but PD (p ns).

Conclusions: We conclude that the serum from DM-ESRD patients induces inflammatory changes and modification of the endothelial proliferative and apoptosis rates. The treatment with HD or PD would not exacerbate the effect and HD even seemed to exacerbate it. The presence of MPs protects the endothelial reparative ability even though they induced an increase on the apoptosis average.
SGLT2 Inhibitor Ipragliflozin Increases Fluid and Food Intake to Maintain Body Fluid Volume and Weight  Takahiro Masuda,1 Yuko Watanabe,1 Minami Watanabe,1 Keiko Fukuda,2 Akira Onishi,2 Volker Vallon,2 Daisuke Nagata.1 1Div of Nephrology, Dept of Medicine, Jichi Medical Univ, Shimotuke, Tochigi, Japan; 2Univ of California San Diego & VA San Diego Healthcare System, San Diego, CA.

Background: We previously reported that sodium-glucose cotransporter (SGLT) 2 inhibitor Ipragliflozin increases urine volume (UV) and Na excretion, whereas body fluid volume is maintained possibly due to an increase in fluid and food intake (ASN Kidney Week 2015). We therefore evaluated whether the increase in fluid and food intake during SGLT2 inhibition induces body fluid reduction.

Methods: Male Sprague-Dawley rats (average 20±5.0 weeks of age) were treated with vehicle (Veh), 0.01% (in diet) Ipragliflozin (Ipra) and 0.01% Ipra by pair-feeding and drinking with Veh (Pair-ira) for 8 days. Rats were placed in metabolic cages to measure UV and food and fluid intake. Bioimpedance spectrometry (ImpedVeit) was used to assess body water distribution every 2 days for 7 days.

Results: Compared with Veh, Ipra increased food and fluid intake and Pair-ira prevented the increase (food intake: 20.3±0.9, 29.2±1.2*, 21.9±0.6 mEq/day, P<0.05 vs Veh, P<0.05 vs Ipra). Pair-ira decreased body weight (BW) vs Veh and Ipra (ΔBW: Veh-5.4±0.5, Ipra-4.1±0.6, Pair-ira-11.2±0.5* %). Serum glucose was similar among groups (216±13, 199±7, 196±11 mg/dl). Body fluid volume was maintained (47.7±1.5, 47.7±1.5, 47.7±1.5 ml/kg, P=0.11). Ipra and to a lesser extent Pair-ira increased UV (19.3±1.9, 53.7±3.6*, 31.6±1.8* ml/kg, Na excretion (2.2±0.1, 3.5±0.1, 2.1±0.1* mEq/day), Cl excretion (2.9±0.1, 4.7±0.2*, 3.6±0.1* mEq/day) and K excretion (5.1±0.1, 5.5±0.2*, 5.0±0.2* mEq/day). Pair-ira decreased total fluid balance (fluid intake−fluid output) (−2.0±1.0, 27.3±1.6, −42.8±6.5* %). Ipra decreased total body water (−9.8±1.6* %, P<0.05 day 0 vs day 7), extracellular water (−11.5±1.7%, 3.6±0.2%), and intracellular water (−8.6±2.6%, 6.8±0.5%) while Ipra or Veh had no significant effect.

Conclusions: SGLT2 inhibitor Ipragliflozin increases fluid and food intake in euglycemic rats. Preventing the increase in fluid and food intake causes body fluid and weight reduction. Thus, SGLT2 inhibition increases fluid and food intake to maintain body fluid volume and weight.

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

PUB265

The Protect Effect of Ouabain in Diabetic Nephropathy  Dong Li,1 Xiaowei Wang.1 1Pediatric Dept, Dalian Municipal Women and Children's Medical Center, Dalian, Liaoning, China; 2Basic Medicine Dept, Dalian Medical Univ, Dalian, Liaoning, China.

Background: Diabetic nephropathy is the main cause of kidney injury. As a plant-derived cardiotonic, ouabain was well-established inhibitor of Na-K-ATPase activity. Recent investigations demonstrate an natriuretic effect of ouabain, ouabain increases Na-K-ATPase activity, and increase cell proliferation. We aim to study the protective effect of Ouabain in diabetic nephropathy.

Methods: Primary tubular cells of rats were cultured and treated with glucose (5mM, 10mM and 25mM) to perform the diabetic nephropathy model. Meanwhile 5mM ouabain was added and incubated together for 8hrs, 18hrs and 24hrs separately. Cells were observed under imaging, Apoptosis data was performed with TUNEL method.

Results: With the 10mM glucose incubation for 8hrs, 18hrs and 24hrs separately, the PTCs were damaged under imaging, and 18hrs was the top point, TUNEL showed the mean index of apoptosis was 2.9±0.3% (control) and for 18hrs treatment apoptotic index was increased to 21.2%±4.1% (P<0.01). In the co-incubated with ouabain 5mM for 18hrs group, Ouabain significantly alleviated the apoptosis, apoptosis index was 6.5%±1.3%.

Conclusions: Apoptosis play a role in Diabetic Nephropathy, Ouabain may perform as an anti-apoptotic factor and play a protect effect on it.

Funding: Government Support - Non-U.S.
PUB268

Effect of CS-3150, a Non-Steroidal Selective Mineralocorticoid Receptor Antagonist, on Blood Pressure and Renal Injury in High-Salt-Treated Type 2 Diabetic Mice Akira Nishiyama, Hiromitsu Hitomi, Daisuke Nakano. Dept of Pharmamacology, Kagawa Univ Medical School, Japan.

Background: The aim of the study was to examine the effect of CS-3150, a non-steroidal selective mineralocorticoid receptor (MR) antagonist, on blood pressure and renal injury in high salt diet treated type 2 diabetic KK.Ay mice, and compare the effects with spironolactone, a steroidal MR antagonist.

Methods: Male 11-week-old KK.Ay mice were treated with normal salt diet (NS: 0.3% NaCl, n = 5), high salt diet (HS: 4% NaCl, n = 8), HS + CS-3150 (1 mg/kg/day, p.o., n = 8), or HS + spironolactone (20 mg/kg/day, p.o., n = 7) for 8 weeks. Renal oxidative stress was evaluated by dihydroethidium fluorescence intensity assay.

Results: As compared with NS-treated KK.Ay mice, HS-treated KK.Ay mice demonstrated hypertension, albuminuria, glomerular injury (glomerular PAS staining-positive area) and tubulointerstitial fibrosis (Azan staining-positive area) with increased oxidative stress at 19 weeks of age. Treatment with CS-3150 and spironolactone decreased blood pressure to a similar extent in HS-treated KK.Ay mice. In contrast, CS-3150 caused greater attenuation of albuminuria, glomerular injury and tubulointerstitial fibrosis as compared with spironolactone.

Conclusions: These data indicate that CS-3150 elicits antihypertensive and renal protective effects in HS-treated type 2 diabetic mice.

Funding: Government Support - Non-U.S.

PUB269

L-Carnitine Protects against Streptozotocin-Induced Diabetic Nephropathy Ji Zho Jin, Long Ye Zhang, Shang Guo Piao, Can Li. Nephrology, Yanbian Univ Hospital, Yanji, Jilin, China.

Background: We have recently demonstrated that L-carnitine confers renoprotective effect on cyclosporine-induced nephropathy in the rats. The present study investigated whether L-carnitine protects against streptozotocin (STZ)-induced diabetic nephropathy (DN).

Methods: Diabetes was induced with STZ (65 mg/kg) by intraperitoneal injection in male Sprague-Dawley rats. Two weeks after STZ injection, diabetic rats were treated daily for 10 weeks with vehicle or L-carnitine (50 or 200mg/kg).

The renoprotective effects of L-carnitine were studied by evaluating the expression of fibrotic cytokine-transforming growth factor-beta1 (TGF-β1) inducible gene-h3 (βig-h3), of apoptosis or autophagy-related gene-active caspase-3 or LC3, and the concentration of oxidative stress. In addition, renal function, fasting blood glucose level, and 24h urinary protein excretion were also compared for different groups.

Results: L-carnitine induced dose-dependent decreases in the expression of βig-h3, caspase-3, and LC3, and in the concentration of urine 8-OHdGCG. These were accompanied by a significant attenuation of glomerulosclerosis. Renal function and 24h urinary protein excretion significantly improved with administration of L-carnitine at different time points, although fasting blood glucose level was unaffected.

Conclusions: L-carnitine treatment protects against STZ-induced DN.

Funding: Other NIH Support - China National Foundation, Other U.S. Government Support, Government Support - Non-U.S.

PUB270

The Effect of miR-29c on Inflammation through Tristetraprolin in Diabetic Nephropathy Jing Li,1 Jing Zhao,1,2 Jia Guo,1,2 Zhanzheng Zhao,3 1The Nephrology Center of the First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China; 2Zhengzhou Univ Inst of Nephrology, Zhengzhou, Henan, China.

Background: Inflammation is a key factor of diabetic nephropathy (DN). Emerging evidence has demonstrated that miRNAs play a mediatory role in the inflammation of diabetic nephropathy. Tristetraprolin(TTP) could medulate the miRNA expression of inflammatory cytokanes. In this study, we investigated the repertoire of miRNAs in the blood plasma, urinary sediment and kidney tissues of patients with DN and their potential regulatory role in inflammation involved in DN.

Methods: The miRNA expression profiling of the blood plasma, urinary sediment and renal biopsy samples was performed by a microarray analysis, which showed that miR-29c was significantly differential expression. Mice podocytes were cultured under different conditions, and the protein expressions were examined by western blot or ELISA. The real-time PCR was used to detect the miR-29c or mRNA expressions. Dual luciferase reporter assay was used to detect the interaction between TTP 3'UTR and miR-29c.

Results: 1. The expression of miR-29c was significantly increased in the blood plasma, whereas, decreased in the urinary sediment and kidney tissues of the DN patients compared with the controls. The miR-29c expression in blood plasma was closely negatively correlated with the TTP level (R = 0.9, P <0.05) and positively with the inflammatory cytokine IL-6 level (R = 0.879, P <0.05). 2. The expressions of miR-29c and inflammatory cytokines IL-6 and TNF-α were up-regulated under high glucose in mice podocytes, with the decreased expression of TTP. Up-regulation of miR-29c by mimics led to the increased expressions of inflammatory cytokines IL-6 and TNF-α and a decreased expression of TTP. However, inhibition of miR-29c by inhibitor exerted the opposite effect. 4. The dual-luciferase reporter assay showed that miR-29c directly targeted the TTP 3'UTR. 5. The expression of TTP could be increased whereas inflammatory cytokines IL-6 and TNF-α decreased after miR-29c inhibitor transfected in high glucose-treated podocytes.

Conclusions: These findings suggested that miR-29c accelerated high glucose-induced inflammation through directly down-regulating TTP.

Funding: Government Support - Non-U.S.

PUB271

Carbamylamyl of Albumin Reduces Binding to FcRn and Cubilin Mark C. Wagner,1 Jerey Myslivetski,2 Shiv Prapat Singh Yadav,3 Silvia B. Campos-Bilderback,4 Sudhanshu Kumar,4 George Rhodes,1 Ruben M. Sandoval,1 Sarah E. Wolek,1 Fru Ashish,1 Bruce A. Molitoris,1,2 1Medicine, Indiana Univ School of Medicine, Indianapolis, IN; 2Cellular & Integrative Physiology, Indiana Univ School of Medicine, Indianapolis, IN; 3CSIR-Inst of Micobio Technology, Chandigarh, India.

Background: Elevated urea levels in CKD patients leads to carbamamylation, a chemical modification of lysines within proteins. This irreversible non- enzymatic posttranslational modification results in formation of e-amino-carbamamyl-lysine (homocitrulline) a hallmark of aging as evidenced by carbaamylation of skin and matrix proteins. Elevated serum urea also promotes albumin carbaamylation, a known risk factor for mortality in CKD patients, and was recently found to be associated with heart failure and mortality in diabetic patients with ESRD.

Methods: Since cubilam/egllasin and FcRn interact to mediate PT transcytosis of albumin, investigated if carbamylated albumin would be handled differently by the kidney by quantifying binding to both FcRn and cubilin.

Results: Independent binding (Kb) to either FcRn or cubilin was measured using Microscale Thermophoresis and found to be markedly reduced, p<0.0001 (FcRn 2.0±0.5 to 37.0±11.7 mM, Cubilin 0.16±0.007 to 2.4±0.14 mM). Since the isoelectric point of carbamyamblated albumin was more anionic than unmodified albumin we also determined how other charge modifications impacted binding. Alterations in albumin charge are likely to occur when different drugs such as antibiotics and other molecules interact with albumin. Binding analysis showed similar binding for cationic albumin to both FcRn (1.2 mM) and cubilin (0.12 mM) while anionic albumin had weaker binding to cubilin (5.4 mM, p<0.001) and FcRn (>100 mM, p>0.0001).

Conclusions: To further understand the molecular cubilam-cubilin-albumin interaction we performed molecular docking of cubilin 8, R-domains with albumin. This revealed a lysine residue in albumin likely to be carbamyamlated that could contribute to the weaker binding observed. Studies are presently underway to quantify serum clearance and in vivo handling of these albumins in order to better understand their physiological processing.

Funding: NIDDK Support, VA Support

PUB272

Urinary Angiotensinogen Is a New Biomarker of Early Renal Pathological Change in Diabetic Rats Zhang Zhe, Jiaxuan Lv. Nephrology, Beijing Tsinghua Changgung Hospital, Beijing, China.

Background: Urinary angiotensinogen might be a marker for activation of renin-RAS of DN. The purpose of this study was to investigate the relationship between AGT in blood, urine and renal tissue with renal function, renal pathological changes in diabetes animal models with the intervention of ARB drugs, to explore the functional roles of UAGT changes in the pathogenesis of DN and possible mechanisms.

Methods: 41 rats, 4 groups, diabetic group and healthy control, the other two diabetic groups were treated with different doses of losartan. In a 12-week investigation, we detected the changes of AGT in all rats’ blood and urine and the association between RAS activation and urinary proteins were analyzed in this study. After 12 weeks, we made renal tissue specimens, and stained observe pathological changes. By immunohistochemistry we detected the expression of AGT.

Results: The serum AGT had no significant differences. The urinary AGT of the diabetic rats was significantly different from the control group, the UAGT of the diabetic rats under different treatments was also obviously different. The level of UAGT was positively associated with urinary protein (r=0.493, p<0.01) and negatively correlated with Ccr (r=-0.474, P<0.007). Further immunohistochemistry confirmed strongly positive expression of AGTin diabetic rats proximal tubular epithelial cell cytoplasm. The value of AGT expression was measured by Optical Density. Group A was significantly higher than other groups, group B and C expression decreased gradually( P<0.001). The GBM thickening and podocyte fusion can be observed with electron microscope in group A. GMB of group A was significantly thicker than other groups (P<0.001).
Results:

A reciprocal inhibition of 30% between glycation and carbamylation was evidenced in vitro. In vivo, after 5 weeks of CKD, plasma HbIC concentrations were indistinguishably increased in diabetic or control mice. On the contrary, fructosamine and HbA1c were decreased in CKD-diabetic compared to diabetic mice. These decreases, (>16% and >35% respectively, p<0.05) were confirmed, in cytanate vs water drinking diabetic mice.

Conclusions:

In vitro glycation and carbamylation inhibit reciprocally. However, in vivo, carbamylation gets the upper hand. Thus, classical markers of diabetes metabolic control should be interpreted with caution in diabetic patients with CKD because of this competitive effect.

PB275

Association between Body Mass Index, Abdominal Circumference and Blood Pressure, Fasting Blood Sugar, HbA1c in Retired People of a Japanese Company

Kyoko Kikuchi,1 Masahiko Ando,2 Sawako Kato,1 Takaaki Kondo,3 Shoichi Maruyama,1 Hiroyuki Honda,1 Yasuko Yoshida.1

Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan; 2Center for Advanced Medical and Clinical Research, Nagoya Univ Hospital, Nagoya, Japan; 3Nagoya Univ Graduate School of Medicine, Nagoya, Japan. Innovative Research Center for Preventive Medical Engineering, Nagoya Univ, Nagoya, Japan.

Background: Body mass index (BMI) and abdominal circumference (AC) is associated with blood pressure (BP), fasting blood sugar (FBS), and HbA1c. However, reference values of BMI, AC as risk factors to BP, FBS, HbA1c remain controversial in Japanese. We analyzed results of medical check up in retired people of a Japanese company to discuss association between BMI, AC, and FBS, HbA1c.

Methods: We recruited total 24781 person retired of a Japanese company who are 50-74 years old between 2004 and 2014 and analyzed their results of medical check up to check the correlations between BMI, AC, and FBS, HbA1c. We used linear mixed model. BMI was divided into 5 subgroups: A: <18.5, B: 18.5-22.9, C: 22.0-24.9, D: 25.0-29.9, E: ≥30 kg/m². BMI was divided into 4 subgroups: F: 80, G: 80-89.5, H: 89.5-94.4, I: ≥94.5 cm².

BMI and systolic BP became linear relation (CvsA, estimated value[EV]= -5.65mmHg, P<0.0001. CvsB, EV=2.63, P<0.0001. CvsD, EV=0.00, P<0.0001. CvsE, EV=1.77, P<0.0001.) After correct by BMI and systolic BP become linear relation. (FvsEV1,12mmHg,P<0.0001. FvsEV2,21.1,P<0.0001. FvsEV3,3.5,P<0.0001.) HbA1c and FBS become linear relation. (CvsA, EV=1.87mg/dl, P<0.0001. CvsB, EV=1.12,P<0.0001. CvsD, EV=0.45,P<0.0001. CvsE, EV=0.00, P<0.0001.) BMI and HbA1c became linear relation. (CvsA, EV=1.87 mg/dl, P<0.0001. CvsB, EV=1.12,P<0.0001. CvsD, EV=0.45,P<0.0001. CvsE, EV=0.00, P<0.0001.) After correct by BMI, AC and HbA1c became linear relation. (FvsEV,G, EV=0.22%, P<0.0001. FvsEV,H, EV=0.09%, P<0.0001.)

Conclusions: The elevation of SBP, FBS and HbA1c was observed for a AC of 80cm and up, and a BMI of 25 kg/m² and up in middle-aged and elderly Japanese.

Funding: Government Support - Non-U.S.

PB276

Renal Biopsy Findings in Patients with Diabetes: Experience in our Centre

Virginia Cabello,1 Nestor Gabriel Toapanta,1 Manuel Lopez Mendoza,2 Rocio Cabrera-Perez.1

1Nephrology, Virgen del Rocio Univ Hospital, Seville, Spain; 2Pathology, Virgen del Rocio Univ Hospital, Seville, Spain.

Background: The prevalence of renal disease unrelated to diabetes(NDRD)in patients with diabetes mellitus(DM)is variable. To be able to distinguish between both categories is an important issue given their prognostic and therapeutic implications. The sudden onset of nephrotic syndrome(NS),late age at diagnosis of the disease,short duration of DM, the absence of retinopathy or hematuria and acute kidney injury(AKI)are considered as predictors of NDRD. The aim of our study is to assess renal biopsies performed in diabetic patients and correlate histological findings with clinical and laboratory parameters,in order to know which variables are associated with NRD.

Methods: We retrospectively reviewed the medical records of patients who underwent kidney biopsy from January 2008 to December 2015. The indications of renal biopsy included:AKI,chronic kidney disease(CKD)and NS.Based on the biopsy findings the patients were categorized as diabetic nephropathy(DN),diabetic nephropathy superimposed on DN(DNDND),group 1); NDRD or DNNDRD.GN,AI, and ATN were the most common findings seen in all NDRD.

Conclusions: 70% of biopsies in diabetic patients revealed NDRD,most of them were classified as superimposed on DN group. The most common histological lesions different to DN were interstitial nephritis, acute tubular necrosis(ATN), hypertensive nephrosclerosis, myeloma cast nephropathy. Proteinuria was significantly higher in patients with DN alone when compared to patients with NDRD or DNNDRD.

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

967A
Cortical Distribution Pattern of Renal Histopathological Lesions in Type 2 Diabetes

Takaya Sasaki, Kentaro Koike, Nobuo Tsuibo, Go Kanzaki, Kotaro Harahara, Yusuke Okabayashi, Tetsuya Kawamura, Yoichi Miyazaki, Makoto Ogura, Takashi Yokoo. Div of Kidney and Hypertension, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.

Background: The renal histopathological findings in diabetic nephropathy show some variation in severity within the same kidney specimen of each individual. However, the potential mechanisms involved in such variation remain largely unknown. We previously reported the zonal distribution patterns of renal lesions in non-diabetic patients. The aim of this study was to examine whether or not the distribution of diabetic renal lesions is related to the renal anatomical organization.

Methods: We examined both the juxtamedullary (JM) and superficial (SF) cortices of autopsied kidneys with a history of type 2 diabetes. The renal histopathological findings closely related to diabetes were evaluated in 50 glomeruli per cortex. The cortical distribution index (CDI) was defined as follows to quantify the distribution pattern: CDI = (SF - JM) / (mean value of SF and JM).

Results: A total of 42 autopsy kidneys were analyzed. The average ages were value of 74 years and estimated glomerular filtration rate (eGFR) of 71 ml/min/1.73 m². Some diabetes-specific lesions showed significant zonal differences, while other lesions did not (Table). The scores for diffuse lesion, arteriolar hyalinosis and polar vasculosis were significantly higher in the JM cortex than in the SF cortex (Figure). Neither age nor eGFR nor hypertension were found to be independent factors associated with the CDI of each lesion in multivariate analyses.

Conclusions: These results suggest that the glomeruli in the JM cortex may be more susceptible to specific renal histopathological lesions in diabetes than those in the SF cortex. The structural and/or functional differences, which are independent of age, renal function, and blood pressure, may have marked influence on the development of such lesions.

Dialysis in Vancomycin Toxicity

Jason M. Kidd, Andinet Gizaw, Todd W. Gehr. Internal Medicine, Div of Nephrology, Virginia Commonwealth Univ Medical Center; Richmond, VA.

Background: Vancomycin is a glycopeptide antibiotic used to treat gram positive infections including MRSA. Therapeutic monitoring of serum levels is widely performed to ensure appropriate dosing. Known adverse effects of include infusion related reactions as well as nephrotoxicity. Nephrotoxicity is more common in patients receiving other nephrotoxins or who have altered hemodynamics. The molecular weight of vancomycin is 1450 Da and it is 10-50% protein bound. We present a case utilizing high efficiency dialysis to remove vancomycin from a patient with renal failure due to vancomycin nephrotoxicity.

Methods: A 58 year old female with myelodysplastic syndrome was admitted with neutropenic fever. She was empirically treated with intravenous vancomycin 1 g every 12 hours for 4 days. Dose was then increased to 1250 mg every 8 hours for the next 5 days based on initial clearance data. The patient’s serum creatinine was 0.4 mg/dl on the day of admission. On day 11, her serum creatinine had increased to 0.8 mg/dl. A vancomycin level was checked and was found to be 400 mg/l. She was oliguric. She had no eosinophilia and urine sediment was bland. In the setting of her renal failure and toxic vancomycin level, dialysis was initiated. Results: The patient was initially treated with high flux, F-180 dialyzer for an 8 hour treatment after which her vancomycin level decreased to 113 mg/l. The following day, she was dialyzed again for 4 hours and level was 61 mg/l. The next morning, her vancomycin level had increased to 81 mg/l, likely related to tissue rebound. Dialysis was repeated on this day for a 6 hour treatment and level the next morning was 42 mg/l. Her urine output subsequently increased and vancomycin level slowly decreased over the next several days without further dialysis sessions.

Conclusions: Hemodialysis with a high flux dialyzer removes significant amounts of vancomycin. Nephrotoxicity from vancomycin is generally self limited. This case illustrates a potential use of high flux hemodialysis in patients with severe toxicity.
Impact of Comorbidities on Hemoglobin Stability in CKD Patients on Hemodialysis, Treated with C.E.R.A. in Current Practice: Is the Comorbidity Scoring Still Useful? The MIRIADE Study Luc Primat, Philippe Zaoui, Jean-Paul Jaulin, Mustapha Amouri, Gilles Simmousse-Raymond, David Pau, Guy Rostoker, Jean-Luc Marseille, Pascal Gauzere, Bruno Alves, Bertrand Emery, Jean-Paul Kotagal, Jean-Paul Rostoker, Florence Galy, Jean-Baptise Benoit, Gilles Billancourt, France; 6 Leal on Hemodialysis PUB282

**Background:** Previous studies have compared Epoetin alfa with Darbepoetin alfa and demonstrated equivalence in safety and efficacy for the treatment of anemia in chronic kidney disease. Other studies indicate that the cost of using Darbepoetin alfa is higher than Epoetin alfa. These studies have compared the two Erythropoiesis Stimulating Agents (ESAs) with intravenous (IV) administration of both drugs, but no subcutaneous (SC) route comparison is available. This study compares differences in hemoglobin and ESA dose, as well as IV iron dose and resulting iron stores after switching the entire dialysis unit from Epoetin alfa given SC to Darbepoetin alfa given IV.

**Methods:** Records for 78 patients who dialyzed in the same unit between January to April 2015 (Epoetin) as well as January to April 2016 (Darbepoeitn) were reviewed for labs and medication administrations. To compare doses of these two drugs, a conversion of 3000 units of Epoetin to 10 mcg Darbepoetin was used to create ESA equivalent doses in mcg. Patients served as their own controls so that paired t-tests could be used to analyze the differences.

**Results:** A statistically higher hemoglobin was found in the Darbepoetin period compared to the Epoetin period. Ferritin was lower in the Darbepoetin period, while T-sat and albumin were equivalent. ESA equivalent doses were lower with Darbepoetin, but more iron was used. While controlled by DCLI algorithms, the number of ESA dose changes in the four month period was lower in the Darbepoeitn period.

**Conclusions:** Hemoglobin was higher and dose changes were less frequent when Darbepoetin was used and less ESA was needed to maintain hemoglobin levels. More iron was given with Darbepoetin, yet ferritin was lower.

**PUB284**

**Differential Oxidative Stress and Endothelial Dysfunction Induction by Brand and Generic Sodium Ferric Gluconate Formulations**

**Background:** Intravenous iron products are colloidal nanoparticle suspensions making formulation of bioequivalent generics challenging. Differences in oxidative stress induction with generic iron sucrose outside the US compared to the referenced listed drug (RLD) have been shown. There are no data comparing oxidative stress by the RLD Ferrlecit® and the only FDA approved generic, sodium ferric gluconate complex (SFGC).

**Methods:** Human umbilical vein endothelial cells were incubated with Ferrlecit® and SFGC in dose response (0 to 200 mcg/mL for 24 h) and time (0 to 24 h) studies. Induction of the transcription factor nuclear factor erythroid-2-related factor 2 (Nrf2), a master regulator of detoxification and heme-oxygenase 1 (HO-1) a Nrf2-regulated enzyme were determined in lysate by immunobiochemistry. Intracellular labile iron (ILI) was determined the Phen Green SK fluorescent probe. Endothelial cell monolayers were treated with each product at 50 µg/mL for 24 h and permeability was measured by the clearance rate of labeled albumin between the luminal and abluminal compartments.

**Results:** ILI significantly increased dose dependently with both formulations. Ferrlecit® treated cells had higher ILI at all studied doses except 50 µg/mL (p<0.01). Induction/stabilization of Nrf2 by Ferrlecit® was greater than SFGC at all doses, significant at the 100 mcg/mL dose (p<0.05). Similarly, Ferrlecit®-induced upregulation of HO-1 was greater than SFGC at all doses, significantly at the 100 and 200µg/mL doses (p<0.001). At 50µg/mL, both compounds induced significant stabilization of Nrf2 by 3 to 6 hours (p<0.001), HO-1 increased with SFGC at 24 hours (p<0.0001) but was lower than Ferrlecit® (p<0.0004). Both IV iron formulations increased endothelial barrier permeability, which was significant for Ferrlecit® (p<0.05), compared to untreated controls.

**Conclusions:** The generic SFGC has a lower oxidative stress response and endothelial permeability despite being a “bioequivalent” product. These differences may be due, in part, to different labile iron release profiles and requires further study.
**PUB285**

Vitamin B12 Can Reduce Dose of Erythropoietin Even in Elderly Hemodialysis Patients Suspected for Potential Vitamin B12 Deficiency

Shunichi Shibaizaki, Katsuji Tuda, Kohei Miura, Makoto Araki. Nephrology, Siawa Central Hospital, Chino, Nagano, Japan.

**Background:** Potential vitamin B12 deficiency is often overlooked, even though it is a common nutritional deficiency in elderly hemodialysis patients because aging itself is a risk factor and dialysis removes vitamin B12. We attempted to evaluate whether a vitamin B12 supplement can reduce a dose of erythropoietin even with suspected potential vitamin B12 deficiency, which is diagnosed with homocystine and Vitamin B12 values.

**Methods:** A cohort study was conducted by collecting data from September 2015 to March 2016 at Siawa Central Hospital. Inclusion criteria were: outpatients in maintenance hemodialysis, over 65 years old, suspected potential vitamin B12: vitamin B12 < 400 pg per milliliter (lower limit of normal range), and homocysteine > 13.5 nmol per milliliter. We divided participants into two groups: a vitamin B12 supplementation group (injections of more than 500 µg per week) and a non-supplementation group. We evaluated the erythropoietin resistance index (ERI) between the two groups at the start and three months later. ERI was determined as the weekly weight-adjusted dose of darbepoetin (µg/kg/week) divided by hemoglobin concentration (g/dL).

**Results:** 24 patients were included. There was no difference in homocystinol concentration, vitamin B12 concentration and frequency of iron deficiency at the start. There was also no difference in ERI; both groups were 0.04. Vitamin B12 supplementation became higher in the supplementation group (> 1,500 pg per milliliter) than in the non-supplementation group (297 pg per milliliter) after three months. ERI improved in the supplementation group (0.02), but deteriorated in the non-supplementation group (0.05, p = 0.021).

**Conclusions:** Vitamin B12 supplement can improve ERI and reduce dose of erythropoietin even in elderly hemodialysis patients with suspected potential vitamin B12 deficiency.

**PUB286**

Algorithm Based Erythropoiesis Stimulating Agents Dosing to Improve Anemia Management in a Pediatric Hemodialysis Population

Shawn Berry, Beth A. Vogt, Robert J. Cunningham, Tamar Y. Springel. Dept of Pediatric Nephrology, Rainbow Babies Children’s Hospital at Univ Hospitals, Cleveland, OH.

**Background:** Dialysis providers attempt to maintain hemoglobin (Hgb) levels within a goal range. We set out to improve the number of patients meeting the Hgb target, which we set at 10-12 g/dL, with a computer-based algorithm for dosing of erythropoietin stimulating agents (ESA) in a pediatric hemodialysis (HD) population.

**Methods:** Population: Chronic HD patients at our institution from 2013 until 2015. Algorithm: We utilized a Microsoft Excel based program that recommended an ESA dose based on the current and previous month’s Hgb levels. Outcome: Our primary outcome was Hgb divided into three categories: <10, 10-12, and >12. Our secondary outcome was ESA dose in ug/kg. Explanatory variables: We included race, age, Kt/V urea, intact PTH (iPTH), nPCR, percent iron saturation, and albumin. Statistic: Pre- and post-algorithm periods were compared. The association of the algorithm with Hgb category and ESA dose was tested by multimonial logistic regression and linear regression respectively. We adjusted for the explanatory variables.

**Results:** We had 17 patients, 7 pre- and 10 post-algorithm, with 55 Hgb values pre- and 94 post-algorithm periods. There were significant differences in age, iPTH, and albumin, however not in Hgb or ESA dose. The algorithm was associated with an increased risk of Hgb >12 (RRR=1.03, p = 0.03).

**Conclusions:** This algorithm was not associated with improvement in Hgb 10-12 and was associated with an increased risk of Hgb >12. The increased risk was not associated with higher doses of ESA or higher iron saturation, which may indicate a more efficient ESA utilization. The retrospective nature and small size limit this study, however more at goal patients may result from adjustment of the algorithm.

**PUB287**

Intermittent Low Dose of Iron Supplementation Improves Erythropoietin Resistance Index and Reduces Hemoglobin Cycling in Chronic Hemodialysis Patients

Tatsu Tsukamato, Motoko Yanagita. Nephrology, Graduate School of Medicine, Kyoto Univ, Kyoto, Japan.

**Background:** We have measured iron loss by iron contents of residual blood in the blood tubing set and dialyzer, and estimated that 500g of iron would be lost by routine hemodialysis procedure in Japan (Am J Nephrol 2016,43,32-38). In this study, we show here the stable iron status as well as hemoglobin (Hb) level by an intermittent low dose of iron supplementation. Moreover, we demonstrate the improvement of erythropoietic resistance index (ERI) and the reduction of Hb cycling by the iron supplementary protocol in chronic hemodialysis patients.

**Methods:** 156 patients of Otowa Memorial Hospital were enrolled after informed consent. Men were consisted in 64.7%, and the mean age was 69.2±13.5 (min:SD). 40.4% was diabetic. 40mg of iron (saccharated ferric oxide) was administered once a month or every four weeks after hemodialysis session Hb, TSAT (transferrin saturation), and ferritin were monitored every month before and after the intermittent iron supplementation. Erythropoiesis-stimulating agents (ESAs) used in this study were human recombinant erythropoietin (rHuEPO), darbepoetin-α (DA), and continuous erythropoetin receptor activator (CERA). DA was converted to 200U, and CERA was 2400U of rHuEPO, respectively. ERI was calculated with rHuEPO dose in a month divided by Hb and body weight (dry weight). The dose of ESA was determined by an attending physician along the Japanese guideline for renal anemia in chronic kidney disease 2008.

**Results:** Hb levels kept from 11.2±1.0 g/dl at the beginning to 10.9±1.0 g/dl after 12 months. TSAT and ferritin did not change from 26.3±12.2% and 88.9±9.0ng/mL to 27.5±9.9% and 77.6±9.64ng/mL, respectively. ERI significantly reduced from 36.8±36.8 to 30.3±21.1. Hb cycling reduced from 123 times per 6 months before the supplement to 103 times at 6 months and 68 times at 1 year.

**Conclusions:** Intermittent iron supplementation (total 500mg a year) could improve ERI and reduces Hb cycling with stable iron status in chronic hemodialysis patients.

**Funding:** Clinical Revenue Support

**PUB288**

Similar Anemic Control between Chronic Kidney Diseases Patients with and without Transplantation on Entry to Dialysis

Ken Sakai, Yasushi Ohashi, Masaki Muramatsu, Yoshihiro Itabashi, Hiroki Hase, Seichiro Shishido. Nephrology, Toho University Ohmori Hospital, Tokyo, Japan; Nephrology, Toho University Ohashi Hospital, Tokyo, Japan; Nephrology, Toho University Sakura Hospital, Chiba, Japan.

**Background:** Transplant recipients are supposed to be more anemic at re-entering hemodialysis due to chronic rejection. This study aimed to clarify how transplant recipients can re-enter dialysis safely by focusing on anemic control.

**Methods:** From 2012 to 2014, a total of 29 transplant recipients entered hemodialysis again by chronic rejection (Chronic Kidney Disease with Transplant: CKDT). At the same time, in 2014, a total of 30 CKD patients without transplantation entered dialysis as control group (CKD). CKDT recipients (age:41.9±11.8 yrs, f:m=18:10, diabetic 10%, duration of graft survival 12.5±3.4y) were younger and less diabetic compare to CKD (age:53.2±10.5yrs, f:m=21:9, diabetic 36%). We analyzed both patient characteristics at entering dialysis by retrospective chart review.

**Results:** At entering dialysis, there was no significant differences for the dose of darbepoetin (DA;µg/month), Hb (g/dl), albumin(g/dl), CRP (mg/dl), CTR (%), eGFR (ml/min/1.73m²), BUN (mg/dl), Cr (mg/dl) and initial ultrafiltration (UF: L/session) between CKD and CKDT. The only difference between groups was mean body weight (BW) at entry to dialysis (CKDT group, 58.5±15.1 kg; CKD group, 67.1±14.8 kg; P=0.03). However, DA dose per kilogram of BW did not differ between groups (CKDT, 2.28±2.03 µg/kg; CKD, 2.12±1.6 µg/kg; P=0.95) in the final month before entry to dialysis.

**Conclusions:** Safely re-initiation of dialysis is also important for recipients survival. Anemia was supposed to be higher in transplant recipients by immunosuppression, this single center analysis did not show any difference of anemia compare to CKD with well using ESA.

**PUB289**

MicroRNA 499 Gene Expression in Patients on Hemodialysis with Cardiovascular Complications

Magdy M. Elsharkawy, Amr Mohab, Haitham Ezzat, Hesham Elsayed. Nephrology Dept, Ain Shams Univ, Cairo, Egypt.

**Background:** MicroRNA 499 is an evolutionarily conserved muscle-specific microRNA that is encoded by an intron of the myh7 gene and is likely to play a role in myosin gene regulation. It has been shown to be involved in inhibiting apoptosis and promoting cell survival. It is unknown whether levels of microRNAs are affected in patients undergoing hemodialysis.

**Methods:** The aim of this study was to assess circulating levels of microRNA 499 in hemodialysis patients and whether the levels are affected by dialyzer membranes (high flux vs low flux). The studied population consisted of 32 ESRD patients (22 males and 10 females) with an age range from 38-75 years on regular hemodialysis (4 hours, 3 times weekly) for at least one year duration with cardiovascular events in the last 6 months and 32 healthy controls (20 males and 12 females) with an age range from 54-80 years. Patients
were involved in a two-stage sequential study; high flux hemodialysis stage (stage I), then low flux hemodialysis stage (stage II). Expressed levels of plasma microRNA 499 have been measured by Real Time-PCR.

**Results:** Statistically significant higher levels of circulating microRNA 499 were observed in all the studied patients compared to the levels found in healthy controls (p<0.0001). MicroRNA 499 was found to be a diagnostically valuable marker. A significant decrease in plasma levels of microRNA 499 was obtained after either high flux or low flux dialysis compared to plasma levels of microRNA 499 found before dialysis (p<0.0001). On comparing both types of hemodialysis membranes with respect to microRNA 499 clearance, we found that low flux membrane showed better clearance for microRNA 499 than high flux membrane with a statistically significant difference between them (p<0.001).

**Conclusions:** In conclusion microRNA 499 levels are elevated in patients with ESRD with cardiovascular complications. High flux membrane seems to be less efficient in microRNA 499 clearance in cardiac patients on hemodialysis.

**PUB290**

**Lower Limb Vascular Disease in Patients on Chronic Hemodialysis**

**Treatment** Lene Boesky, Julie Broesen, Pernille Moerk, Christen; 2Dept of Cardiology-Nephrology-Endocrinology, Hilleroed Hospital, Hilleroed, Denmark; 3Dept of Nephrology, Herlev Hospital, Herlev, Denmark.

**Background:** Patients receiving chronic hemodialysis (HD) treatment have an elevated risk of developing vascular disease. The primary aim of this study was to evaluate the cause and frequency of lower limb arterial ischaemia leading to surgical interventions, in a well characterized center-HD population. The secondary aim was to evaluate whether having diabetes mellitus (DM) influenced the result.

**Methods:** This is a single center retrospective study covering a 4-year period from 6.1.2008 - 6.1.2012. Combining registration codes for lower extremity amputation (digital, metatarsal, crus and femoral amputation (LEA)) and HD, patients were indentified and included in the study. Further data were gathered from electronic patient files. Patients were excluded from the study if HD treatment was started < 3 months prior to LEA.

**Results:** We registered 180 HD patients per year. 18 patients had ≥ 1 LEA during the investigation period, 8(44%) of these patients had DM. There were no significant differences between gender, age, systolic or diastolic blood pressure, previous cardiovascular events, HD vintage or mineral metabolic control comparing LEA-patients with or without diabetes. In the group of patients with DM one was smoking at the time of LEA compared to four in the non-DM group. The number of re-amputations and patients who died within six months after LEA was higher in non-DM patients. Of the non-DM patients 63% had no previous record of consultations with chiropodist, orthopedic or vascular surgeon prior to LEA, whereas all of the DM patients had.

**Conclusions:** In our population more than half of the patients who underwent LEA did not have DM. Only 37% of these patients had an had an evaluation by chiropodist, orthopedic or vascular consultation prior to LEA, despite long HD vintage. To further explore these results a nationwide study is planned.

**PUB291**

**Sodium Variability and Survival in Hemodialysis Patients**


**Background:** The concentration of serum sodium (SNa+) prehemodialysis (pre-HD) not always responds to the classic “set point” pattern. Recent evidence has shown that, variability of key laboratory parameters such as hemoglobin are also associated with important outcomes such as survival in HD patients Aims: we investigate the relationship between SNa+ preHD variability and survival in a population of HD patients.

**Methods:** Retrospective analysis of 261 prevalent HD patients (60.9% male; 51.7% diabetics; mean age 60.04 ± 14.09 years, time in HD: 69.64 ± 50.53 months; follow-up time: 48.78 ± 19.09 months). SNa+ concentration was corrected for glucose concentration. The first 24 SNa+ monthly measures were used for the study. SNa+ variability was calculated by the SD and coefficient of variation (CV). Crude mortality rates were computed. Kaplan-Meier, Log rank test and Cox regression were used to analyze the survival rate.

**Results:** 6221 determinations of SNa+ were analyzed. The average concentration of SNa+ was: 138.26 mEq/L (range: 151.65-120.86 mEq/L). The median of SNa+ SD and CV was 2.37 mEq/L and 1.73% respectively. The survival rate in the low CV group was significantly higher than in the other group.

**Conclusions:** In our population more than half of the patients who underwent LEA did not have DM. Only 37% of these patients had an evaluation by chiropodist, orthopedic or vascular consultation prior to LEA, despite long HD vintage. To further explore these results a nationwide study is planned.
were calculated using the Modelflow simulation method. BARO and NON-BARO activity episodes were assessed by BD FACSCalibur™ with RETIC-Count™ (BD Biosciences, Intelomed Inc., Wexford, PA). Underline represents presenting author.

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<td><strong>Brain Natriuretic Peptide as a Sensitive Cardiac Biomarker for Hypervolemia in Hemodialysis Patients</strong></td>
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<td><strong>Methods</strong></td>
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<td>We enrolled 40 ESRD patients older than 20 years, on regular HD 3 times weekly with duration of HD more than 12 months. Inclusion criteria for patients: 1) Ejection fraction (EF) ≥ 55%, LV end systolic (2-4 cm) and diastolic (3.7-5.5 cm) internal dimensions on ECHO, 2) Patients with mild LVH, intraventricular wall thickness in diastole &lt; 1 cm, 3) Hypertensive patients with or without antihypertensive medications. Exclusion criteria: Patients with volume or pressure overload due to other causes than fluid overload (e.g., aortic stenosis, valvular lesions). In addition to full history taking and thorough clinical and cardiac examination, lab. investigations were done including CBC, renal and liver functions, with serum BNP samples collected post dialysis. Radiological studies done included: ECHO, IVC collapsibility index for assessment of volume status.</td>
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<td><strong>Results:</strong> Our results showed no statistical substantial differences between hyper and normovolemic patients concerning patients’ characteristics as gender, smoking, and presence of DM or hypertension. Moreover, no significant association was existing between BNP criteria and patients’ characteristics (e.g. age and sex) or lab results (ex. creatinine, Ca, Hgb), however, there was an inverse relationship between BNP and IVC collapsibility index (mean was 29.248±5). In addition, patients with hypervolemia had significantly higher BNP levels, as compared to euvolemic ones, with a significant difference (p-value = 0.011) and the most pertinent level of BNP was (17.650 pg/ml) to discriminate hyper/normovolemic patients, with a sensitivity of 71%, and a specificity of 77.8%.</td>
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<td><strong>Conclusions:</strong> Our study would appear to provide an evidence that plasma BNP levels were correlated to the degree of fluid retention in HD patients indicating that elevated levels may possibly be regarded as marker of volume overload in absence of other causes and even before being clinically evident.</td>
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<td><strong>The Study of Death Risk Factor and Survival among Maintenance Hemodialysis Patients</strong></td>
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<td><strong>Methods</strong></td>
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<td>All of the patients undergoing maintenance hemodialysis in the dialysis center of the 3rd Affiliated Hospital of Sun Yat-sen University for at least 3 months from Jan 1st, 2013 to Dec 31st, 2015 were analyzed. The baseline variables and laboratory results were collected, death and survival were recorded. Logistic regression and multivariate COX regression were used to detect the relative factors.</td>
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<td><strong>Results:</strong> A total of 183 patients were included in the study. The mean age was 58.21±16.45, Male 113, female 70. Death were recorded in 36 cases in 36 cases after average 32 months followed. The main cause of death were cardiovascular disease (33.3%), infectious disease (25%), cerebro-vascular disease (13.9%), potassemia (11.1%), tumor (5.6%). Logistic regression showed that age (HR=1.068,95%CI:1.026-1.113), BMI (HR=3.660, 95%CI:2.523-5.076), 1st, 2nd, 3rd tertile of IVC collapsibility index (HR=0.816, 95% CI: 0.687-0.969), hyperuricemia (HR=0.996, 95% CI: 0.992-0.999) were risk factors for death. Average survival time in death cases were 47.8 months after hemodialysis. Cox proportional hazards regression model showed that age(OR=1.013, 95%CI:1.000-1.006), acidity(OR=1.065, 95%CI:1.060-0.997), hyperuricemia(OR=0.997, 95% CI: 0.994-1.000) were risk factors for death.</td>
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<td><strong>Conclusions:</strong> To maintenance hemodialysis patients, the main cause of death were cardiovascular or cerebrovascular disease and infection. Age, hyperproteinemia, acidity, hyperuricemia are risk factors for death.</td>
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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Serum Nitric Oxide and Natriuretic Peptides Have a Relationship with Whole Blood Viscosity in End-Stage Renal Disease Undergoing Hemodialysis

Jong-Hwan Jung,1 Kyung Pyo Kang,2 Sung Kwang Park,2 Young I. Cho,1 Won Kim.3 Department of Internal Medicine, Wonkwang University Hospital, Iksan, Jeonlabukdo, Korea; Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, Jeonbukdo, Korea; Mechanical Engineering and Mechanics, Drexel Univ, PA.

Background: A change of whole blood viscosity (WBV) may increase risk of major atherothrombotic events. NO regulates the renal function through the modulation of the vascular tone. WBV related with vascular shear stress may be linked to production of NO. WBV is also associated with volume status during hemodialysis. Atrial natriuretic peptide (ANP) and B type natriuretic peptide (BNP) may be linked to WBV because they can be indexes of blood volume. This study was planned to investigate correlation between WBV and several shear rates during hemodialysis and serum levels of NO, ANP, and BNP in ESRD patients.

Methods: This study included 31 end-stage renal disease patients who were enrolled. We measured WBV using a scanning capillary tube viscometer pre- and post- dialysis to quantify viscosity. Serum NO, ANP, and BNP level before hemodialysis was assayed using an ELISA method.

Results: The mean WBV variations at shear rates of 1, 5 and 300 s⁻¹ for pre-dialysis were 168.5±62.5, 76.9±30.8, and 33.3±3.8 mP, respectively. The mean values of post-dialysis WBV obtained at a shear rate of 1, 5 and 300 s⁻¹ were 240.8±48.4, 100.8±28.0, and 38.5±16.4 mP, respectively. Mean serum levels of NO, ANP, and BNP were 13.97±10.34 μg, 198.85±61.56 pg/mL, and 1323.32±280.81 pg/mL. Serum NO levels was positively correlated with WBV at a shear rate of 1, 5, and 300 s⁻¹ (p=0.015, p=0.010, and p=0.010, respectively). There was also a statistical significance at post-dialysis. Serum ANP levels were negatively correlated with WBV at a shear rate of 1, 5 and 300 s⁻¹ at only pre-dialysis (p=0.014, p=0.008, and p=0.009, respectively). However, BNP levels did not show any correlation with WBV.

Conclusions: Correlation between serum NO, ANP levels and WBV may indicate an important role of endothelial dysfunction in ESRD patients. However, whether monitoring of ANP, BNP, and NO has a relationship with WBV requires further controlled study.

Reactive Hyperemia Index and Its Clinical Correlates in Dialysis Patients

Wenjin Liu, Meijuan Yang, Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical University, Nanjing, Jiangsu, China.

Background: Reactive hyperemia index (RHI), as a reflection of endothelial function, has been suggested to be an independent predictor of adverse outcome both in the general population and patients with chronic kidney disease. However, its value in risk stratification in patients on maintenance hemodialysis remains inexplicit.

Methods: This is a cross-sectional analysis of midterm baseline data from a cohort study. Two-hundred and fifty six dialysis patients from four tertiary hospitals in East China were recruited. Reactive hyperemia index was measured by peripheral arterial tonometry (EndoPAT 2000) on a midweek nondialysis day. Blood pressure level was determined by ambulatory blood pressure monitoring. Demographic and clinical information, as well as routine laboratory results were also recorded. Stepwise linear regression analysis was used to determine independent clinical correlates with natural logarithm of RHI (LnRHI).

Results: Among the 256 patients, peripheral arterial tonometry results were available for 218 patients. Average value of LnRHI was 0.57±0.31. In univariate correlation analysis, systolic blood pressure, diastolic blood pressure and heart rate were positively correlated with LnRHI, while age and body mass index (BMI) were inversely related to LnRHI. Significant linear regression analysis results demonstrated that systolic blood pressure (β=0.004, p<0.001) and age (β=0.004, p=0.015) were independently correlated of LnRHI.

Conclusions: Our results indicate that reactive hyperemia index was affected by blood pressure and age in patients on maintenance hemodialysis. The prognostic value of RHI remains to be explored by follow up of this study population.

Funding: Government Support - Non-U.S.

Coronary Artery Calcification Score (CACS) and Cardiovascular Events in Maintenance Hemodialysis Patients

Yoshiko Nishizawa,1,2 Scott Marsh,1,2 Patrick Graham-Brown,1,2 John Walls Renal Unit, Univ Hospitals Leicester, Leicester, Leicestershire, United Kingdom; 3Department of Cardiovascular Sciences, and NHR Leicester Cardiovascular Biomedical Research Unit, Univ of Leicester, Leicester, Leicestershire, United Kingdom.

Background: This study considered left ventricular (LV) end diastolic volume (LVEDV), LV end systolic volume (LVESV), LV diastolic mass (LVM) and ejection fraction (EF) in hemodialysis (HD) patients using trans thoracic 3D echocardiography (3DE) and cardiac MRI (CMR).

Methods: 3DE and CMR (3 Tesla) scans were performed on 25 prevalent HD patients. CMR LV volumetric and mass analysis was undertaken using the software package CMR 4.3. Apical four chamber full volume 3D images (iEx33) Philips were obtained and analysed with vendor specific software. Dependent sample t-tests were performed to compare LV volumes, mass and EF by 3DE and CMR. Pearson’s correlation coefficient was used to perform correlation between variables (LVEDV, LVESV, LVM and EF) from 3DE and CMR. Statistical significance was accepted at P < 0.05 level.

Results: Eight patients were excluded from the analysis due to poor image quality from the 3DE. LVEDV (198.58 mL ± 60.88 mL versus 91.42 mL ± 25.86 mL, P<0.001) and LVESV (194.30 mL ± 59.60 mL versus 75.95 mL ± 23.95 mL, P<0.001) were significantly higher for CMR compared to 3DE. There was no significant correlation between LVEDV (r=0.470, P=0.052) for CMR and 3DE. There was a significant correlation between LVEDV (r=0.743, P<0.001) for CMR and 3DE. LVM (108.05 g ± 35.31 g versus 163.48 g ± 35.32 g, P<0.001 and EF (51.90% ± 6.72% versus 56.45% ± 8.83% P=0.011) were significantly lower for CMR compared to 3DE. Both LVM (r=0.735, P<0.001) and EF (r=0.559, P=0.020) significantly correlated between CMR and 3DE.

Conclusions: This study suggests 3DE underestimates LVEDV and LVESV compared to CMR, while LVM is overestimated by 3DE compared to CMR. EF was comparable when measured by both imaging tools.

Coronary Artery Calcification Score (CACS) and Cardiovascular Events in Maintenance Hemodialysis Patients

Yoshiko Nishizawa,1,2 Scott Marsh,1,2 Patrick Graham-Brown,1,2 John Walls Renal Unit, Univ Hospitals Leicester, Leicester, Leicestershire, United Kingdom; 3Department of Cardiovascular Sciences, and NHR Leicester Cardiovascular Biomedical Research Unit, Univ of Leicester, Leicester, Leicestershire, United Kingdom.

Background: Coronary artery calcification is known as a frequent complication in patients with chronic renal failure and contributes to their excess death with cardiovascular events. We examined the relationship between the coronary artery calcification score (CACS) and cardiovascular events in maintenance hemodialysis patients.

Methods: A retrospective study was conducted on 322 patients who received maintenance hemodialysis within 5 years between2011 and 2015. The Agatston’s CACS>400, age, sex, diabetes, alcohol, smoking, HDL cholesterol, systolic blood pressure, smoking, hemoglobin, serum creatinine, and CAC score were used as independent variable. Using multivariate logistic regression analysis using the above variables. Receiver operating characteristic (ROC) curves were used to assess the accuracy of the model. Receiver operating characteristic (ROC) curves were used to assess the accuracy of the model.

Results: Using the CACS as the outcome, we found a significant association between CACS and cardiovascular events. The area under the curve was 0.71 for CMR and 0.70 for 3DE. The 3DE CACS was significantly lower than the CMR CACS (P=0.017).

Conclusions: The CACS is a useful tool for predicting cardiovascular events in maintenance hemodialysis patients.

Funding: Government Support - Non-U.S.
The Relationship between Arterial Stiffness and Brain Small Vessel Disease in Dialysis Patients Ke Zheng,1 Xuemei Xu,2 Tan-Qi Huiqing Sun Ryoung,1

Methods: (1) Subjects 427 convenient subjects who were on chronic hemodialysis and/or peritoneal dialysis in PUMCH dialysis center were screened. (2) Arterial stiffness assessment: PWV was assessed by SphygmoCor on femoral-carotid artery. (3) Brain SVDs were evaluated by 3T-magnetic resonance imaging.

Results: (1) 202 subjects entered this study, male 47.6%, average age 56.3y, average dialysis vintage 59.9 months, HD61.4% (2)Average BP136.9/8.4mmHg, Hgb 112.0g/L, Alb38.0g/L, Calcium and phosphamid product 3.87±0.88mmol/L (3) Average PWV10.6±2.3 m/s, 47.2% participants could be diagnosed as arterial stiffness (PWV>10 m/s). (4) The difference of microbleeds was 42%, lacuna infarct was 39.5%, and abnormal white matter lesions 51.5%. (5) Compared to patients with normal PWV, patients with abnormal PWV had more lesions in all kinds of SVDs (P<0.05). (6) PWV was relative with WML scores (r=0.410), lacuna infarct (r=0.285) and weakly relative with microbleeds (r=0.164, P<0.059). Age was relative with PWV, WML and lacunar infarction. By multiple linear regression analysis, after adjusted for diabetes vintage, calcium and phosphamid product and hsCRP, PWV still was an independent risk factor of WML, but no longer risk factor of lacuna infarct. After adjusted age on above model, PWV was no longer risk factor of WML.

Conclusions: In our dialysis patients, there were a high prevalence of arterial stiffness. Patients with arterial stiffness had more severe SVDs. PWV was relative to WML and lacunar infarct. Intervention of arterial stiffness maybe can be an effective way to alleviate dialysis patients’ brain SVDs.

PUB303

The Study of Cardiac Valve Calcification in Maintenance Hemodialysis Patients and Its Related Risk Factors Ming Li,1 Huiqing Chen,2 Zengchun Ye,1 Wenbo Zhao,1 Tan-Qi Lou.1

Results: Of all the patients, male 112, female 69, the average age was 57.9±16.3 years. VC was found in 297 patients (39.8%), 60 (33.1%) with arteriole valve calcification, 30 (16.5%) with mitral valve calcification, and 18 (9.9%) with both. Compared with patients with no patients with VC were older, more obesity, had longer hemodialysis duration, higher proportion of patients with hypertension and DM, higher Plasma phosphate and serum uric acid, serum triglyceride. Multivariate Logistic regression showed that age(β=1.109, P<0.000), hemodialysis duration(β=1.390, P<0.001), BMI(β=1.187, P<0.008) were independently correlated with VC. VC also was found positive correlation to pulmonary artery hypertension(PAH)(β=0.006).

Conclusions: cardiac valve calcification (VC) is common phenomenon in MHD patients, and aortic valve calcification is more common than mitral valve calcification. The major risk factors for cardiac VC are age, hemodialysis duration and BMI. VC is positive correlation with PAH.

PUB304

Cyclophilin A and Sclerostin as Markers of Atherosclerosis in Dialysis Patients Xoo Jin Lee, Yang Wook Kim, Sihyung Park, Bongsoo Park. Internal Medicine, Haemucci Park Hospital, Busan, Republic of Korea.

Methods: Sixty patients (control n=20, hemodialysis n=20, peritoneal dialysis n=20) were enrolled in this cross sectional and single-center study. Serum CyPA, sclerostin were analyzed by ELISA. Ankle-brachial index (ABI) and carotid intima-media thickness (carotid IMT) were performed to measure atherosclerosis of peripheral and carotid arteries. Presence of atherosclerosis was defined as ABI ≤ 0.9 and carotid IMT ≥ 0.754 mm. Four patients (ABI ≤ 0.9 and carotid IMT ≥ 0.754 mm) had atherosclerosis. The level of CyPA was higher in hemodialysis group (42.8 ± 17.4 ng/mL vs. 32.21 ± 13.5 ng/mL, p < 0.01). The level of sclerostin was also higher in hemodialysis group (3.98 ± 1.51 pg/mL vs. 3.45 pg/mL, p < 0.03). In subgroup analysis without non-atherosclerosis patients, the level of CyPA was the highest in hemodialysis control (30.23 ± 11.6 ng/mL, hemodialysis: 41.7 ± 16.4 ng/mL, peritoneal dialysis: 27.0 ± 10.2, p < 0.57). Sclerostin was higher in dialysis group than control (0.91 ± 0.2 pg/mL; hemodialysis group: 5.99 ± 3.18 pg/mL, peritoneal dialysis group: 4.83 ± 2.34, p < 0.01).

Conclusions: This study showed that CyPA and sclerostin prediction of atherosclerosis in dialysis patients because of small sample size. Hemodialysis group and control group was a good biochemical parameters for assessing atherosclerosis in dialysis patients.
Recurrence of peritonitis in peritoneal dialysis in Qatar, an 8-year epidemiologic study. Mostafa F. Fadwa, 1,3 Bircan Erbas, 1 Ahmed K. Ahmad, 1 Hany Ezzat Ismail, 2 Ahmad Kaddourah, 2 Hassan Ahmed, 1 Ahlam Ali, 1 Mohamed Elsayed, 1 Fadwa S. Al Ali, 1 Nephrology, Hamad Medical Corporation, Doha, Qatar; 2 Sidra Medical and Research Center, Doha, Qatar.

Background: Acute peritonitis (AP) is a common and devastating complication in end stage renal disease patients on Peritoneal Dialysis (PD). We are reporting an epidemiologic study of recurrent AP in PD patients in Qatar over 8 years follow up.

Methods: We retrospectively reviewed the medical records of all PD patients in the biggest dialysis center in Qatar from 2007 to 2014. The analysis was conducted to report the epidemiology, outcome and associated risk factors of recurrent AP.

Results: We had a total of 318 AP episodes in 180 patients between 2007 and 2014. 99 (55%) patients had single AP while 81 (45%) had 2 episodes or more (recurrent AP).

Conclusions: This year follow up epidemiologic study; recurrent AP was prevalent (45%) among all AP cases, and its risk increases with G+ cocci infections. However, G- infections were associated with increased mortality risk. Our results signify the importance of implementing more efficient care bundles to prevent recurrent AP.

Longer haemodialysis sessions improved clinical and biochemical markers compared to conventional sessions: a non-randomised trial. Darren P. Kerr, 1 Karl B. I. Landorf, 1 Discipline of Podiatry, La Trobe Univ, Melbourne, Victoria, Australia; 2 Dept of Renal Medicine, Monash Univ, Melbourne, Victoria, Australia; 3 Dept of Public Health, La Trobe Univ, Melbourne, Victoria, Australia; 4 Dept of Nephrology, Austin Health, Melbourne, Victoria, Australia; 5 Dept of Nephrology, Monash Health, Melbourne, Victoria, Australia.

Background: Dialysis patients are at increased risk for foot ulceration, which often precedes more serious lower limb complications. Limited data exist regarding the prevalence and factors associated with foot disease in this patient group. The aim of this study was to investigate factors associated with foot ulceration and amputation in the dialysis population.

Methods: This multi-centre cross-sectional observational study recruited 450 adults on dialysis from satellite and home-therapy dialysis units in Melbourne, Australia. Data collection involved a participant interview, medical record review, a health-status questionnaire and a foot examination. Logistic regression analyses were conducted to evaluate associations between screened risk factors and the primary and secondary outcomes.

Results: Mean age was 67.5 ± 13.2 years, 64.7% were male, 94% were on haemodialysis, the median dialysis duration was 36.9 (IQR, 16.6 to 70.1) months, and 50.2% had diabetes. There was a high prevalence of previous ulceration and amputation (21.6% and 10.2%), and 10% had current ulceration. Foot examination identified 50% with neuropathy and/or peripheral arterial disease. Factors significantly associated with foot ulceration were previous amputation (OR, 10.19), peripheral arterial disease (OR, 6.16) and serum albumin (OR, 0.87). The area under the ROC curve was 0.648 (95% CI 0.57 to 0.73). The sensitivity and specificity were 36.8% and 92.9%, respectively. The logistic regression analysis showed that the pseudo R2 was 0.100. The Hosmer-Lemeshow test showed p>0.01.

Conclusions: qSOFA may not be useful in identifying sepsis in Japanese HD patients compared to that in the general population.

Recurrence of peritonitis in peritoneal dialysis in Qatar, an 8-year epidemiologic study. Mostafa F. Fadwa, 1,3 Bircan Erbas, 1 Ahmed K. Ahmad, 1 Hany Ezzat Ismail, 2 Ahmad Kaddourah, 2 Hassan Ahmed, 1 Ahlam Ali, 1 Mohamed Elsayed, 1 Fadwa S. Al Ali, 1 Nephrology, Hamad Medical Corporation, Doha, Qatar; 2 Sidra Medical and Research Center, Doha, Qatar.

Background: Acute peritonitis (AP) is a common and devastating complication in end stage renal disease patients on Peritoneal Dialysis (PD). We are reporting an epidemiologic study of recurrent AP in PD patients in Qatar over 8 years follow up.

Methods: We retrospectively reviewed the medical records of all PD patients in the biggest dialysis center in Qatar from 2007 to 2014. The analysis was conducted to report the epidemiology, outcome and associated risk factors of recurrent AP.

Results: We had a total of 318 AP episodes in 180 patients between 2007 and 2014. 99 (55%) patients had single AP while 81 (45%) had 2 episodes or more (recurrent AP).

Conclusions: This year follow up epidemiologic study; recurrent AP was prevalent (45%) among all AP cases, and its risk increases with G+ cocci infections. However, G- infections were associated with increased mortality risk. Our results signify the importance of implementing more efficient care bundles to prevent recurrent AP.
Incidence of Hepatitis C Virus Infection in a Large Cohort of Dialysis Patients in the United States

**PUB312**

**Background:** Rates of Hepatitis C Virus (HCV) chronic infection in dialysis patients are unknown. Published data are based only on HCV antibody (Ab) testing. Until the recent approval of direct acting antiviral agents (DAAs) with high efficacy and limited toxicity, no effective therapies were available for dialysis patients. Routine testing for HCV Ab and PCR is not standard of care on all dialysis facilities. Studies testing for HCV Ab and PCR are needed to determine the true incidence of chronic HCV infection in the dialysis population.

**Methods:** Observational, population-based cohort of prevalent dialysis patients, from 8 dialysis centers belonging to a large dialysis organization. All patients were tested as part of routine care between Sept 2015 and May 2016 for Hepatitis C Ab and if positive, a HCV PCR was performed.

**Results:** 687 patients were tested (626 in-center HD, 54 PD, 7 home HD), 48 were found to be HCV Ab+ (6.9% of the total). None of the HCV PCR+ patients were co-infected with either Hep B or HIV. Only 10/48 patients were aware of the HCV Ab+ diagnosis. Mean age 61 (range 30-92), Male 33 (70%), Hispanic 32 (70%), Black 5 (10%). Of the HCV PCR+ patients, by zip code analysis, mean income was $43,116, high school graduation 75.2%, and poverty rate 23.8%. At the time of this report, only 5 patients were actively being treated (14% of HCV PCR+; genotypes A1 and IB). Since this observation began, the HCV PCR+ patients, 1 died from metastatic hepatocellular carcinoma (HCC), 1 was diagnosed with HCC and 1 with renal cell carcinoma (8.8% of HCV PCR+ had malignancies detected so far).

**Conclusions:** Rates of HCV infection in dialysis patients appear significantly higher than the general population (0.7/100,000 per CDC, 1.0% per NHANES 2003-2010). All dialysis patients should be tested for HCV Ab with reflex PCR, at dialysis initiation and every 6 months thereafter. All patients without confirmed infections should be offered treatment with approved therapies. All should have abdominal imaging due to long HX of untreated infection (until now no treatment offered or possible) and overall higher rates of malignancy in dialysis patients.

**Funding:** Clinical Revenue Support

**Association of Potassium Gradient with Near-Term Clinical Outcomes in Hemodialysis Patients**

**PUB331**

**Background:** A high serum to dialysate potassium (K) gradient leads to rapid lowering of K during dialysis and may confer a greater risk of adverse events. Here, we examined the near-term association of K gradient with key clinical outcomes.

**Methods:** This retrospective (2010-2011) study considered 830,741 patient-intervals, each defined by a measurement of serum K made among adult Medicare Parts A & B enrollees who received in-center hemodialysis on a Monday/Wednesday/Friday schedule at a large US dialysis organization. K gradient was considered based on the difference in K concentration (serum - dialysate) on the date of measurement; analyses account for multiple observations per patient. Outcomes considered over the day of the gradient and the next day were: hospital admissions (all-cause and cardiovascular [CV]), emergency concentration (serum PO4), and better nutritional indices. Adjusting for patient differences, higher mean K gradient was associated with lower rates of hospitalizations and CV admissions. This association remained after adjusting for BMI and other covariates.

**Funding:** Pharmaceutical Company Support

**Associations between Sleep Quality/Depressive Symptoms and Albumin/Phosphate Level**

**PUB335**

**Background:** Patients (pts) undergoing hemodialysis (HD) often complain about poor sleep quality (SQ) and are known to be at an increased risk for experiencing depressive symptoms. As a function of a Fresenius Medical Care North America Social Worker (SW) Quality Improvement Program, we investigated whether profiles of SQ and depressive symptoms are associated with levels of albumin (Alb) and phosphate (PO4).

**Methods:** We investigated 1,244 HD pts enrolled in the 8-week SW program from 7/1/13 and 2/28/14. SQ was assessed upon enrollment to the SW program. The SQ survey included 5 items, which were reduced to 3 by factor analysis that included: difficulty sleeping, difficulty awakening, and restless legs during sleep. Each item was scored on a scale from 1-10, with 10 indicating the worst score. For depressive symptoms, the Center for Epidemiologic Studies Depression Scale-10 (CESD-10) questionnaire was utilized. Means of Alb and PO4 were calculated over 30 days before the SW program. Correlations between SQ factors/CESD and albumin/phosphate PO4 mean levels were calculated.

**Results:** Pts had a mean age of 55.3 ± 13.9 years, 52.4% were males, 68.7% were white, 57.6% had diabetes, 19.8% with coronary artery disease, and 37.5% with congestive heart failure. The mean levels of Alb and PO4 were 3.9±0.4 and 5.9±1.6, respectively. Mean scores of CESD, difficulty sleeping, difficulty awakening and restless legs during sleep were 9.7±1.6, 4.4±2.8, 2.3±2.4, 3.2±3.1, respectively. We found that Alb was negatively correlated with CESD (r=-0.06, p=0.045) as well as restless legs during sleep (r=-0.07, p=0.02); however, PO4 was positively correlated with restless legs during sleep (r=0.06, p=0.03).

**Conclusions:** This study indicates that low levels of Alb are associated with worse depressive symptoms and restless leg syndrome in HD patients, while high PO4 levels are associated with restless leg syndrome. Social work interventions that can improve SQ and depressive symptoms may have the potential to improve HD pts outcomes.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America
Background: Infection is the second leading cause of death for dialysis patients (pts). Predicting infection before occurrence of apparent clinical markers would be desirable. We examined patterns of body temperature (BT) and systolic blood pressure (SBP) in hemodialysis (HD) pts before vancomycin course for an infection.

Methods: A 3,510 HD pts from the Fresenius Medical Care Data Warehouse from Jan 2010 to Sep 2015 who were treated with vancomycin for about 2 weeks. Data for predialysis BT and SBP measurements were collected 1 month before and after the vancomycin course. We compared several combinations of time points prior to vancomycin treatment using a repeated measures analysis of variance.

Results: We observed slight, but significant increases in average BTs during the time points 6-4, 3-1, and the mean of 6-1 days before starting vancomycin, as compared to the mean or any individual time point 30-7 days prior to receiving vancomycin (all p<0.01; Figure 1A). This change coincides with a subtle decrease in SBP one week before starting vancomycin as compared to earlier period (p<0.001; Figure 1B). Albeit significant increases were observed in BT before starting vancomycin, the mean BTs rose to a maximum of clinically normal levels at 97.5°F.

Conclusions: Small but measurable increases in BT and decreases in SBP prior to vancomycin treatment in HD patients likely antedate clinical infection.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

Figure 1

Table:

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Funding: NIDDK Support

PUB318

Effects of Dialysis Modalities on Markers of Mineral and Bone Disorders in ESRD Patients

Melissa Soochoo,1 Matthew B. Rivara,1 Elani Streja,1 Scott V. Adams,2 Vanessa A. Ravel,1 Onyebuchi A. Arah,3 Kamyar Kalantar-Zadeh,1 Rajnish Mehrotra.2 UC Irvine, Irvine, CA; 1Kidney Research Inst, Seattle, WA; 2UCLA, Los Angeles, CA.

Background: Mineral and bone disorders (MBD) are highly prevalent in patients undergoing maintenance dialysis, and are associated with adverse clinical outcomes. There are limited data on the effects of implementation in clinical practice of hemodialysis with either longer treatment time or higher frequency on markers of MBD.

Methods: This cohort study used data from 132,523 incident dialysis patients treated with any of the following modalities: conventional thrice-weekly in-center hemodialysis (HD), nocturnal in-center HD (NICHD), home HD (HHD), or peritoneal dialysis (PD). We analyzed the data using marginal structural models fitted with inverse probability weights to adjust for confounding due to fixed and time-varying covariates. We estimated the effects of treatment with different dialysis modalities on time-averaging serum concentrations of four markers of MBD: calcium, phosphorus, parathyroid hormone (PTH) and alkaline phosphatase.

Results: Compared to conventional HD patients, patients treated with NICHD had lower mean PTH (21 pg/mL) and serum phosphorus (0.45 mg/dL) compared to conventional HD patients treated with NICHD (0.38 to 0.53) lower). PD (0.15 mg/dL) had higher mean phosphate concentration (0.27 to 40) lower). There were no clinically significant associations between dialysis modality and concentrations of calcium or alkaline phosphatase (Table).

Conclusions: Among incident dialysis patients, treatment with dialysis modalities with longer treatment times or higher frequency was associated with altered patterns of serum phosphorus and PTH compared to conventional HD.

Table:

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Funding: NIDDK Support

PUB319

Abstract Withdrawn

PUB320

Prognostic Significance of the Interval Change of Plasma Neutrophil Gelatinase-Associated Lipocalin Level during the First 48 Hours in Patients Starting Continuous Renal Replacement Therapy

Ha Yeon Kim, Tae Ryom Oh, Eun Hui Bae, Soo Wan Kim, Seong Kwon Ma. Dept of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea.

Background: The present study investigated the clinical significance of the interval change of plasma neutrophil gelatinase-associated lipocalin (pNGAL) during the first 48 hr in acute kidney injury (AKI) patients starting continuous renal replacement therapy (CRRT).

Methods: This retrospective observational study included 404 AKI patients treated with CRRT. The patients were divided into two groups; renal recovery (n=120, 29.7%) vs. renal non-recovery (n=284, 70.3%) or survivor (n=193, 47.8%) vs. non-survivor group (n=211, 52.2%). The cut-off value of pNGAL was 200 ng/mL, and that of serum cystatin C (SCysC) was 1.0 mg/L. The estimated glomerular filtration rate (eGFR) was calculated by CKD-EPI equation. Exclusion criteria was a patient less than 18 years old, death with 24 hr after CRRT starting or a patient with maintenance renal replacement therapy.

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

Underline represents presenting author.
Results: The volume of hourly urine output during the first 48 hr was significantly higher in the renal recovery group compared with the renal non-recovery group, and in the survivor group compared with the non-survivor group. The level of pNGAL at baseline or at 48 hr did not differ between the renal recovery group and non-recovery group, and survivor group and non-survivor group. However, the value of APNGAL was significantly higher in the renal recovery group compared with the renal non-recovery group (90.6 ± 82.9 vs. 33.8 ± 53.7, p<0.001), and in the survivor group compared with the non-survivor group (129.8 ± 182.4 vs. 98.5 ± 162.6, p<0.001). The level of sCytC at baseline, at 48 hr or ΔsCytC did not differ between the both groups. That of sCyt at baseline, at 48 hr or ΔsCyt also did not differ. The interval change of pNGAL during the first 48 hr may predict renal outcome and survival of AKI patients undergoing CRRT although the value of pNGAL per se has a limitation on the prediction of outcomes. Urine output is also a robust prognostic biomarker in these patients.

PUB321

An Effect That Parameters Using Body Composition Monitor Have on Hemodialysis Patients: A Systematic Review and Meta-Analysis of Observational Studies

Seon Doek Hwang,1 Jin Ho Lee,2 Woo Yeong Park,3 Moon-Jae Kim,3 Seoung Woo Lee,3 Inha Univ College of Medicine; Keimyung Univ Kidney Inst; Bongseng Memorial Hospital; Inha Univ College of Medicine; Inha Univ College of Medicine.

Background: It is reported that, with regard to assessment of patients' nutritional status, the interest in sarcopenia has recently risen, and an effect is produced on mortality as well, and overhydration in dialysis patient has an effect not only patient's cardiovascular mortality but also prognosis. The purpose of this study is to examine what effect is produced on dialysis patient by the measurement of tissue index and overhydration degree, using body composition monitor.

Methods: A systematic review and meta-analysis using a random-effects model was performed. We searched the Cochrane Central Register, OVID MEDLINE, EMBASE, and Pubmed until March 15, 2016. We reviewed the reference lists of relevant reviews, registered trials, and relevant conference proceedings. Definition of overhydration degree $>=15%$ and low LTI group $<10%$ compare with reference group.

Results: Six trials were included, consisting of a total of 39615 patients in the pooled analysis. In overhydration group, The pooled hazard ratio (HR) for overall survival of overhydration vs. non-overhydration was 2.01 [95% confidence interval (CI): 1.397-2.890, P (trend)=0.001]. HR for mortality in Low LTI (Group was 1.53 (95% CI), 1.407 to 1.670]; P=0.001) in a random-effects model respectively. In the sensitivity analysis, the result from the most recent study showed the most heterogeneity.

Conclusions: Being diagnosed with low lean tissue index and determining whether to be overhydrated by using BCM may become a factor in increasing mortality in dialysis patients.

PUB322

Treatment Outcomes for Calcific Uraemic Arteriolopathy: One Centre's Experience inნ

Andrew Nixon,1 Annabel Roberts, Ajay Prabhakar Bhaguide, Renal Medicine Dept, Royal Preston Hospital, Preston, Lancashire, United Kingdom.

Background: Calcific Uraemic Arteriolopathy (CUA), also known as calciphylaxis, is a rare disorder that primarily affects patients with dialysis-dependent end-stage renal disease. It is characterised histologically by medial calcification of arterioles. It is associated with severe pain, skin ulceration and a significantly increased mortality risk.

Methods: Clinical records were reviewed for all patients diagnosed with CUA between 2009 and 2015.

Results: Six patients were diagnosed. Table 1 demonstrates patient demographics and clinical characteristics.

Demographics and Clinical Characteristics

<table>
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<th>Value</th>
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<tr>
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<tr>
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<tr>
<td>Median Dialysis Vintage (range)</td>
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</tr>
<tr>
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<td>Warfarin</td>
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<tr>
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<tr>
<td>PTH Above KDOQI Targets</td>
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</tr>
<tr>
<td>Lower Limb Lesion(s)</td>
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</tbody>
</table>

Treatment included: increasing dialysis dose(6), IV sodium thiosulphate(6), dietary/pharmacological hyperphosphataemia management(6), cinacalcet if uncontrolled hyperparathyroidism(3), stopping contributory medications(3) and regular wound care(6). Wound debridement was performed for 3 patients. Amputation was required for 1 patient. Lesions resolved in 4 patients. One-year survival rate was 50% with a median survival of 8.2 months. No deaths were directly due to CUA. Figure 1 demonstrates survival analysis (months).


PUB323

Hemodialysis and Hemodiafiltration Affect VAP-1 and Endocan Levels in Regards to Type of Anticoagulant

Polanta Malyszko,1 Ewa Koc-Zorawska,1 Jacke S. Malyszko,2 2nd Dept Nephrology, Medical Univ, Bialystok, Poland; 1st Dept Nephrology, Medical Univ, Bialystok, Poland.

Background: Traditional anticoagulants used in hemodialysis-HD are heparin and low molecular weight heparins-LMWHs. Repeated and prolonged exposure to UFH and/or LMWHs may further disturb hemostasis in uremic patients. VAP-1 (vascular adhesion protein) is secreted by vascular smooth muscle cells, adipocytes, and endothelial cells with functional monoamine oxidase activity and is elevated in atherosclerosis, diabetes mellitus and obesity. Endocan is a novel soluble dermatan sulfate proteoglycan derived from endothelium. Its elevated level is connected with endothelial activation, inflammation or carcinogenesis. In this cross-sectional study we aimed to assess the effects of UFH and LMWHs on VAP-1 and endocan levels in 80 hemodialyzed patients and 17 patients treated by means of hemodiafiltration-HDF. We also assessed the effects on single HD session on VAP-1 level in endocan levels in regard to the type of anticoagulant.

Methods: Patients were selected from the group of hemodialyzed subjects who had been receiving enoxaparin (n=42), dalteparin (n=10), nadroparin (n=6) or unfractionated heparin – UFH (n=20) as an anticoagulant during their HD sessions. VAP-1 was assessed using kits from BioVendor, Modrice, Czech Republic. Endocan was assessed using commercially available kits from Lunginov, France.

Results: Diabetic patients had higher serum VAP-1 and endocan than non-diabetic. Patients on HDV had significantly lower VAP-1 and endocan when compared with HD patients. We found that VAP-1 and endocan concentration in patients dialyzed by using LMWH or UFH were similar. HD session was associated with a significant increase in endocan level (p<0.001), however, there was no effect on HD session on VAP-1 concentration.

Conclusions: HDF is associated with lower VAP-1 and endocan levels indicating less pronounced endothelial cell injury and more favorable effect of this type of treatment. Dialysis session affect endothelial function reflecting by a significant rise in endocan levels. Type of heparin seem to have no effect on VAP-1 and endocan levels in hemodialyzed patients. However, the cross-sectional but not prospective design is a limitation of this study.

Funding: Government Support - Non-U.S.

PUB324

Comprehensive Analysis of Support Interventions on Quality of Life in Patients with End Stage Renal Disease on Hemodialysis

May Christine Zeta,1 Jennie Z. Ma,2 Uta Erdrbruegger,1 Emaad M. Abdel-Rahman.1 2nd Dept Nephrology, Univ of Virginia, Charlottesville, VA; 3rd Dept Nephrology, Medical Univ, Charleston, SC; 4th Dept Nephrology, Medical Univ, Charleston, VA.

Background: Decreased health-related quality of life (HRQOL) is common in chronic hemodialysis (HD) patients and is associated with mortality, complications and reduced compliance with treatment. Interestingly, achievement of widely accepted clinical performance targets is not related to HRQOL of hemodialysis patients. The effectiveness of a multidisciplinary team approach in support interventions targeting adult patients with ERSD has not been systematically assessed. The aim of this study was to comprehensively describe these interventions and QOL measures from a pilot study with intensified HRQOL testing.

Methods: This is a pilot study of 8 adult patients on hemodialysis who consented to perform the Kidney Disease and Quality of Life questionnaire (KDQOL™) on an intensively scheduled (months 0, 3, 6, 9, and 12). Interventions normally given as standard
of care were documented for each time period (T1=0-3 months, T2=4-6, T3=7-9, T4=10-12). Four interventions were determined: education/counselling, psychosocial, medical management/treatments, and rewards/gifts.

**Results:** 40 KDQOL questionnaires completed by 8 patients during the 1-year study period were analyzed. The average KDQOL scores were: Physical=35.6, Mental=49.6, Buckle=51.6, Symptoms/Problems=80, and Effects of Kidney Disease=65. During the study the mean scores over the 1-year study period did not change markedly. The average number of interventions for each time period was 7, most of which were related to nutrition, followed by medical management. Overall no change in number of interventions were observed over time.

**Conclusions:** The HRQOL scores and number of interventions did not change markedly during the study period. Interestingly, most interventions were most related to nutrition counseling. More patients are needed to assess the effectiveness of these support interventions on patient’s quality of life and to determine the optimal frequency of its testing.

**PUB327**

The Increase of Serum Myostatin Level Was Suppressed by Intra-Dialytic Exercise in Hemodialysis Patients

**Background:** Patients with End-Stage Renal Disease on Hemodialysis included as cases and 60 patients without hemodialysis were included. The prevalence of handgrip strength and peak VO2 was significantly improved in only exercise group. Body composition, bone mineral density, and muscle mass and muscle strength (knee extension strength) have no change after exercise.

**Conclusions:** In hemodialysis patients, intra-dialytic exercise suppress the increase of serum myostatin level.

**PUB328**

Can We Use Cellulose Triacetate Membrane for Postdilution Online-Hemofiltration? Marta Albalada, Patricia Martinez-Miguel, Lourdes Borohorez, Patricia De Sequeria, Rafael Ramirez, Hanane Bouarich, Guillermina Barril, Rafael Perez-Garcia, Nephrology, Infantino Leonor Hospital, Madrid, Spain; Physiology, Alcalá de Henares Univ, Alcalá de Henares, Madrid, Spain; Nephrology, La Princesa Hospital, Madrid, Spain; Nephrology, Instituto de Investigaciones, Madrid, Spain; Nephrology, Instituto de Investigaciones, Madrid, Spain.

**Background:** Synthetic membranes have been the only used in the postdilution online-HDF. We have a new asymmetric cellulose triacetate (ACT) (Solacea®, Nipro) suitable for this technique (Kuf 76/ml/mmHg). The aim is to describe ACT performance and behaviour to identify: purifying efficiency, use in clinical practice, biocompatibility and inflammatory effect.

**Methods:** Prospective observational multicentre study. Twelve patients (9 men, 65 (41-85)years) were included. Each patient was treated with ACT for a month without changing their previous schedule. 127 full sessions were collected. Effective time (ET), Qb., ultrafiltration volume (UF), infusion volume (IV), Kt, maximum PPM and technical or coagulation problems during treatment were collected. At the first treatment, blood samples were taken before and after dialysis to determine RR of urea, creatinine, β2microglobulin, myoglobin and retinal binding protein (PRT). At 30’ one second blood was removed. Monocyte subpopulations were measured before the start of the first and the last dialysis session.

**Results:** 1) Efficiency: EET 248±9 (10.3’), effective Qb 371(28.2) ml/min, UF 2.6(0.6) l, IV 26(7.2) l, I, Kt 57.3(4.3) l, maximum PPM 35.22(6) mmHg, RRurea 81.5(2.5), Cr 74.7(4.6), mioglobin 716(8.3), β2m 76.5(4.8) and PRT 18.6(7.0) Clinical use: There were no complications or alarms or need to change dosage of heparin. 3) Biocompatibility: Leukocyte and platelet initial vs. 30’ didn’t change 4) Inflammation: After ACT of CD14+CD16++ was lower (33.8±13) vs. 26.4(13), p<0.04 (%), no differences were found in other subpopulations.

**Conclusions:** ACT achieved adequate Kt, IV and RRs without technical problems, 10m gait speed, peak VO2 and heart rate recovery has significantly improved in only exercise group. Body composition, bone mineral density, and muscle mass and muscle strength (knee extension strength) have no change after exercise.

**PUB325**

Impaction Factors for Mortality of Maintain Hemodialysis Patients

**Background:** The mortality of hemodialysis in the five-year era hemodialysis is still high, despite progression of hemodialysis technology and application of different dialysis techniques. The study of the long time survival outcome and risk factors for maintain hemodialysis (MHD) of Chinese mainland patient are currently lacking.

**Methods:** A retrospective cohort study of 91 death MHD patients wascarried out, and data was collected by the 2nd Xiangya hospital hemodialysis center from 2011 to 2015. The Kaplan-Merier test was used to analyze independent risk factors associated with 48m survival. Multivariate Cox regression was used to analyze independent risk factors of all-cause death.

**Results:** Results revealed the median survival time of 91 maintenance dialysis patient (25 female and 66 male) is 46 months. The Kaplan-Merier analysis showed the age of initiation dialysis >70y, diabetic nephropathy, cerebrovascular comorbidity, eGFR <10 ml/min/1.73m² or >10 ml/min/1.73 m² at the initiation of dialysis were risk factors of mortality. While the serum albumin<30g/L, or haemoglobin<100g/l at the initiation of dialysis, using high-flux dialyzer, AVF, HDF+HD dialysis model, Kt/V ≥1.2, dialysis frequency>2/w, dialysis initiation >70y, diabetic nephropathy, cerebrovascular comorbidity, eGFR<7 ml/min/1.73m² or ≥10 ml/min/1.73 m² were risk factors of mortality. Further, multivariate analyses showed baseline eGFR<7 ml/min/1.73m²,diabetes, cerebrovascular disease, age of initiation dialysis >70y, baseline eGFR<10 ml/min/1.73 m² were independent risk factors of higher all cause death in MHD patients; and using AVF vascular access, pre-dialysis hemoglobin<100g/L, using high-flux dialyzer, and dialysis frequency>2/w times/week were independent factors of reducing all-cause death in MHD patients.

**Conclusions:** In this study, old age, diabetes and CVD co-morbidity lead to an increased risk of death in MHD patients. Low hemoglobin and too high or low eGFR at the commencement of dialysis are associated with the poor survival time. Fortunately, dialysis frequency>2/w, fistula access and high-flux dialyzer are associated with better survival outcome.

**PUB326**

Increased Prevalence and Morbidity of Clostridium difficile Infection in Patients with End-Stage Renal Disease on Hemodialysis

**Background:** Patients with end-stage renal disease on hemodialysis (ESRD) on hemodialysis have impaired host defense mechanisms and frequently require antibiotics for various infective complications. Despite increasing efforts to prevent infection, the prevalence of hospital-associated Clostridium difficile infections (CDI) is increasing. Heightened awareness prompted this study of the prevalence and morbidity associated with CDI in ESRD patients on hemodialysis.

**Methods:** This was a single-center, retrospective case-control study. A total of 85 patients with CDI were identified based on a retrospective review of Clostridium difficile toxin assay or histology report from Seoul Red Cross Hospital from January 2011 to January 2015. CDI was diagnosed by enzyme immunoassay for toxins and, more recently, polymerase chain reaction (PCR) testing. In 85 patients with CDI, 15 patients with end-stage renal disease on hemodialysis included as cases and 60 patients without hemodialysis were used as controls. We compared the baseline characteristics and identified independent risk factors that could predict the development or prognosis of CDI. Hospital outcomes and survival were also compared between cases and controls.

**Results:** Independent risk factors for occurrence of CDI included age, duration of antibiotics and ESRD on hemodialysis. Hemodialysis patients with CDI had more baseline comorbidities and received more blood products than non-hemodialysis patients with CDI. All were treated with metronidazole or vancomycin. Patients on hemodialysis with CDI had reported poorer responses to the initial metronidazole therapy. Hemodialysis patients with CDI had more septicaemia, longer hospital stay, and lower 3-year survival than non-hemodialysis patients with CDI.

**Conclusions:** The prevalence of CDI is increasing, contributing importantly to morbidity and mortality in ESRD patients on hemodialysis.

**PUB330**

**Results:** A retrospective cohort study of 91 death MHD patients was carried out, and data was collected by the 2nd Xiangya hospital hemodialysis center from 2011 to 2015. The Kaplan-Merier test was used to analyze independent risk factors associated with 48m survival. Multivariate Cox regression was used to analyze independent risk factors of all-cause death. The average number of interventions for each time period was 7, most of which were related to nutrition, followed by medical management. Overall no change in number of interventions were observed over time.

**Conclusions:** The HRQOL scores and number of interventions did not change markedly during the study period. Interestingly, most interventions were most related to nutrition counseling. More patients are needed to assess the effectiveness of these support interventions on patient’s quality of life and to determine the optimal frequency of its testing.
PUB329
Factors Associated with Dialysis Withdrawal  Billie Axley, Michael R. O'Connell, Dugan Maddux, John W. Larkin, Marta Revirriego-Mendoza, Stephanie Johnston, Michelle L. Gilliland, Rebecca L. Wingard, Tammy C. Green, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: Little is known about the factors that may influence discussions with patients about withdrawal from hemodialysis (HD). To explore this we surveyed a group of HD staff including nephrology nurses, social workers, and dietitians.

Methods: A voluntary, electronic survey was offered to staff at 20 Fresenius Medical Care North America HD clinics during February of 2016. The survey questions identified: 1) most common reasons for a patient/family to initiate a conversation about HD withdrawal, 2) when a patient/family request(s) for HD withdrawal is most often made, and 3) describe process(s) in place to support the patient/family when a decision is made to withdraw from HD. Responses from 28 HD staff were analyzed.

Results: We found that clinic staff reported decreased quality of life and failure to thrive as the most common reasons for a patient/family member to initiate a conversation about withdrawal from HD (89% & 79%, respectively) (Figure 1A). Withdrawal requests by the patient/family were mostly made during hospitalization, followed by requests being made during HD (57% & 21%, respectively) (Figure 1B). Most common processes in place supported withdrawal from dialysis for hospice referral (68%), and home care arrangements via social workers and clinic managers (43%); 14% reported there was not a specific process in place (Figure 1C).

Conclusions: Survey results from a multidisciplinary group of dialysis clinic staff suggest that the most common reasons for patients and families to request dialysis withdrawal are decreased quality of life and failure to thrive, and these requests were commonly made while patients were hospitalized. These findings support the need for strategies that focus on the patients’ values and wishes.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB330
Provincial Initiatives to Implement a Palliative Approach to Renal Care across Ontario Sarbjit Vinita Jassal,1 2 Marnie MacKemmon,1 Sharon Gradin,2 Tea Palamarevic,2 Peter G. Blake.2 1Div of Nephrology, Faculty of Medicine, Unv Health Network, Toronto, ON, Canada; 2Div of Nephrology, Univ of Western Ontario, London, ON, Canada; 3Ontario Renal Network, Toronto, ON, Canada.

Background: The Ontario Renal Network (ORN) provides policy, financial, and governance oversight to individuals receiving renal care in the Province of Ontario. Through their planning work with patients and family members, the ORN identified palliative and end of life care as a priority. We present the provincial strategy used to develop an integrated palliative program and governance oversight to individuals receiving renal care in the Province of Ontario. Through their planning work with patients and family members, the ORN identified palliative and end of life care as a priority.

Methods: Information about current practices was collected from all renal centres across the province through a process mapping exercise. Process maps were collated and synthesized using aggregate gap analysis. Clinician understanding of palliative care was evaluated by questionnaire.

Results: The current state mapping process showed a number of clinical initiatives and plans were in place to support the patient/family when a decision is made to withdraw from HD. Responses from 28 HD staff were analyzed.

Processes were, however, often inconsistently delivered, and at risk due to poorly coordinated community engagement. Informal survey results suggest practicing clinicians are aware of the need to include a palliative care approach to renal care, but they do not feel enabled or sufficiently trained.

Conclusions: Key opportunities to effectively roll out provincial-level initiatives can be identified from the process maps. A provincial level initiative can facilitate clinician driven initiatives to improve the provision of renal services to patients.

PUB331
Development of a Medical Writing Elective for Nephrology Fellows Amir Kazov, Abhilash Koratalla, Maryam Sattari. Univ of Florida.

Background: While half of the American medical schools provide formal training in writing history and physicals, less than 15% offer any type of formal medical writing courses designed to teach the skills needed to write grant proposals and peer-reviewed journal articles. Similarly, although faculty development in the “effective writing of grants and manuscripts” continues to be a perceived need for academic physicians, there has been minimal documented progress in improving the availability of formal writing education in the recent years. To address this gap, a “medical writing elective” (MWE) was designed at the University of Florida specifically for nephrology fellows.

Methods: Based on the published literature and our own experience with development and directorship of MWE for medical students and internal medicine residents, we constructed an interactive multimodality curriculum for nephrology fellows. The goals of this renewable 2-week MWE are to (1) provide fellows with knowledge and experience about various aspects of medical writing (e.g. case reports, clinical vignettes, and poster oral presentations in scientific meetings), (2) enhance their education by advancing their medical writing skills and editing abilities, and (3) increase and enrich their scholarly output in order to improve their future career opportunities. Teaching methodology of the MWE includes (1) didactic lectures, (2) writing assignments, and (3) small group sessions with the faculty. Fellows are also assigned a writing project for the elective, for which they prepare a clinical vignette abstract and/or a case report. Examples of planned topics include introduction to writing various types of manuscripts, plagiarism/self-plagiarism, patient privacy, journal rankings, and submission/revision requirements.

Conclusions: This multimodality MWE is meant to address the need for dedicated educational resources to teach trainees the fundamental principles of medical writing. We plan to pilot-test the acceptance and effectiveness of this curriculum in a small sample of nephrology fellows using a pre- and post-test format of knowledge assessment and pre- and post-elective scholarly productivity. If successful, it can be customized for use in other disciplines and specialties.

PUB332
An Innovative Collaboration between Patients and an Industry-Supported Rare-Disease Registry Len Woodward,1 Gema Ariceta,2 Christoph Gasteyer,3 Sally A. Johnson,4 Johan Vande Walle,5 Christoph Licht.5 aHUS Alliance; 2Univ Hospital Yull d’Hebron; 3Alexion Pharma GmbH; 4Great North Children’s Hospital; 5Ghent Univ Hospital; 6The Hospital for Sick Children.

Background: Partnership between patient (pt) organizations and clinical researchers can promote innovation and support pt-focused research. Few reports on such activities exist; we describe a collaboration between a group of pt organizations and a pt registry. Methods: The global atypical Haemolytic Uraemic Syndrome (aHUS) Registry (NCT01522183) is an observational, multicentre registry of pts with aHUS which will assess long-term outcomes. The aHUS Alliance comprises 12 pt organizations worldwide that aim to work with international clinical research networks. The aHUS Registry Scientific Advisory Board (SAB) invited the aHUS Alliance to submit research ideas important to pts with aHUS. Such ideas were subsequently generated independently of the SAB by pts and the aHUS Alliance.

Results: In November 2015, 24 identified research ideas were presented to the SAB. The majority related to three topics: understanding causes of thrombotic microangiopathy, the clinical and psychological/social impact of living with aHUS, and comparing regional disease characteristics. The top five research priorities are shown (Table). The proposals have led to an ongoing analysis of data on pts with kidney transplants enrolled in the registry and a proposal to analyse annual immune cycles is in development that includes three aHUS Alliance members as investigators.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Research priorities for pts include understanding barriers to rapid
avocado consumption, which is key that the collaboration continues in the long-term. Acknowledgments: We thank the patients and the aHUS patient organisations involved.

Funding: Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.

PUB333

What Can Social Media Tell Us About Patient Experiences of Living with IgA Nephropathy? Jonathan Barre1, Karen Molloy1, Lydia Ying Yau2
1Infection, Immunity & Inflammation, Univ of Leicester, Leicester, United Kingdom; 2DataTellsLife, DataIntelligence, Co. Ltd, Hong Kong.

Background: The use of social media around the world has exploded in recent years and is changing the way medicine is practiced and healthcare is delivered. Social media is increasingly used to share experiences of living with chronic disease, the impact of treatments for these diseases and the quality of interactions with health providers. It is often the first point of contact for patients living with a disease who are searching for advice and guidance on managing their condition. IgA nephropathy is a disease that more frequently affects young adults, a population that is immersed in the social media revolution.

Methods: To understand the key issues impacting on the lives of people with IgA
and to identify areas of unmet need, particularly in terms of education about IgAN we undertook a systematic social media text mining and thematic analysis examining both twitter and Instagram feeds between 27/07/2015 and 31/05/2016.

Results: Between 27/07/2015 and 27/07/2015 there were 3575 posts including the keyword IgA nephropathy (95% twitter, 80% Instagram). 95% of users were 18 years or older, 56% were male. The most common posts were in the 18-24 age group. Of the posts, 1409 focused on medical intake and clinical management, 487 were focused on symptom management and 1345 were personal narratives and stories. A total of 504 TPE procedures were performed, with 64% of patients having chronic kidney disease (CKD). A total of 349 patients had information on their ACE/ARB prescription status, of which 54 patients were on VEL. These patients had a median eGFR of 59.8 ml/min/1.73m2, with 65% reporting statistical significance.

Conclusions: Overall the field of nephrology benefits from performing TPE. Though initially there were some start-up struggles including setting up our electronic medical records for ease of use and teaching both the faculty and nursing how to perform the procedure, ultimately we believe that TPE can be used to enhance the patient experience.

PUB336

Intensive Lifestyle Program in Chronic Kidney Disease Sahil Bawa,1 Michael J. Germain,1 Sam A. Headley,1 1Nephrology, RTANE, SPRINGFIELD, MA; 2Nephrology, Baystate Medical Center, Springfield, MA; 3Exercise Science, Springfield College, Springfield, MA.

Background: Cardiorespiratory fitness(CRF) level and Physical Activity(PA) levels are low in Chronic Kidney Disease(CKD) which contribute to increased mortality in these patients(Pts). There is relatively little research to determine the impact of the lifestyle intervention on the quality of life in CKD Pts.

Methods: Twenty-Five,Springfield, MA, GRT, 59-151ml/min/1.73m2, CKD Pts’ between the ages of 18-75 not currently enrolled in a regular exercise training program(3 days/week for 6 months) and who do not suffer from severe bowel obstruction,impaction or Pts’ without postoperative motility disorders will be enrolled. Pts’ will be randomly assigned to intervention or control group, and will be allowed to participate only if their nephrologist gives them the permission to do so following which they will be asked to complete a 3 day diet log and Exercise Benefits/Barrier Scale at the start of the study and also be asked to wear a 7 day activity monitor. An assessment will be done at the start of study which will include the evaluation of blood pressure, medications and state of the blood vessels. Other indices of physical function(Movement Function Screen, hand grip strength, 6 minute walk, sit to stand test, short physical performance battery, leg strength and power) will be done. Pts’ will be re-evaluated with blood work and physical examination at months 1,3 and 6 months. It is expected that all Pts’ will be on ACE/ARB if they are not then also they can participate. Serum Potassium levels will be monitored regularly and if it goes >5.2mEq/L (VelasSs VEL) will be prescribed to the intervention group.

Results: To determine the effect of a 6 month comprehensive,integrated and individualised lifestyle intervention(CILI) program on SBPBP and other indices of physical function,Pts’ with ACE/ARB prescribed VEL compared to those not on VEL and CRF levels in patients with stage 3-4 CD.

Conclusions: We hypothesize that a CILI program will lead to enhanced physical function primarily assessed by SBPBP and patients prescribed VEL will better tolerate the ACE/ARB prescription that not on VEL and better CRF levels in the intervention group.

PUB337

Electronic Cigarettes Induce Renal Fibrosis: A Novel MIR-29b-3p Mediated Mechanism Christopher A. Drummond,1 Laura E. Crotty Alexander,2,3 Tian.1 1Medicine, Univ of Toledo, Toledo, OH; 2Pulmonary Critical Care Section, Veterans Affairs San Diego Healthcare System, San Diego, CA; 3Div of Pulmonary, Critical Care and Sleep Medicine, Univ of California San Diego Health Sciences, San Diego, CA.

Background: Clinical studies indicate that combustible cigarette smoke increases renal and cardiac tissue injury progression and functional decline in the setting of chronic kidney disease (CKD). Novel nicotine delivery devices like electronic (e)-cigarettes are used by over 10% of the population and produce vapor which may also induce renal injury. We undertook these studies to estimate the effects of e-cigarettes and to investigate mechanisms by which renal tissue injury occurs.

Methods: Our current study induced 8 week-old female CD-1 mice to inhale e-cigarette vapor containing 24mg/mL nicotine suspended in a solution of 50% propylene glycol and 50% vegetable glycerin for 1-6 months.

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

Underline represents presenting author.
Results: Following e-cigarette exposure, assessment of renal fibrosis and expression of the profibrotic microRNA miR-29b-3p were evaluated. Mice exposed to e-cigarette vapor suffered a 31% decline in renal tissue expression of miR-29b-3p vs air-exposed controls (p<0.05). Additionally, mRNA targets of miR-29b-3p that regulate fibrosis formation or are part of fibrosis were also significantly increased in the kidneys of e-cigarette exposed mice versus air controls, i.e., Collagen 1A1 (increased 98%; p<0.05); Collagen 3A1 (129% increase; p<0.05); Collagen 4A1 (72% increase; p<0.05); Integrin beta 1 (58% increase; p<0.05); and Fibronectin 1 (100% increase; p<0.05). Lastly, we observed a significant increase in renal fibrosis as assessed by Trichrome staining in these animals.

Conclusions: These data are the first to indicate that e-cigarettes induce renal fibrosis. More importantly, these data provide a novel miR-29b-3p mediated mechanism linking e-cigarette vapor exposure and renal injury.

Funding: NIDDK Support, Other NIH Support - NHLBI, VA Support, Private Foundation Support

PUB338
Protection Mechanisms of Ferulaic Acid for Podocyte in Adriamycin-Induce Nephropathy Rats
Minggang Wei,1, Edward Stern,2, Hongli Gu,1, Min Zhang,1, Jinhao Sun,3, Xiangchen Wang,3, Xifeng Gu,4, Toru Tanaka,5, Hitoshi Sugiyama,6, Toshio Wada,7, Eiji Onishi,8, Hitoshi Sugiyama,9, Toshio Wada,10, Keiko Tamaka,11, Toshio Sugiyama,12, Masashi Kitagawa,13, Tatsuyuki Inoue,14, Jun Wada.15
1Dept of Nephrology, Yueyang Hospital of Traditional Chinese and Western Medicine, affiliated to Shanghai Univ of T.C.M. Shanghai, China; 2Division of Nephrology, Endocrinology and Metabolism, Okayama Univ Graduate School, Okayama, Japan.

Background: Chronic renal failure (CKD) is one of the important public health problem. Renal fibrosis is the main reason for the progressing of CKD. Ferulaic acid is one of the main active material which extracted from some chinese herbs such as Radix Angelicae Sinensis et al. The podocyte is the main component of glomerular filtration membrane, and it’s damage or apoptosis directly related to renal fibrosis. In this study, we verified that ferulaic acid could delay renal fibrosis through protecting the intact structure of podocyte and regulating the level of cell factors such as TGF-β, and Smads et al.

Methods: In this study, we established the adriamycin-induce nephropathy rat model characterized by podocyte damage and renal fibrosis. We can find that the expression of TGF-β, Smads2/3, and extracellular matrix (ECM) such as collagen and fibronectin were significantly increase in renal tissue. Meanwhile, the expression of podocyte markers protein of nephrin significantly decrease in renal tissue. Using ferulaic acid obviously attenuate the level of collagenI, collagenIV, and fibronectin of TGF-β, and Smads2/3. In the vitro, ferulaic acid up-regulate the level of nephrin and podocine for TGF-β, and Smads2/3. Furthermore, the expression of collagenI, collagenIV, fibronectin, Smads2/3 and ILK decrease significantly after add ferulaic acid in the well. If up-regulating the respond of Smads2/3, we can see the cell factors and ECM have the same manifestation as the adriamycin-induce nephropathy rat model. If inhibiting the respond of Smads2/3, we can see the opposite phenomenon.

Results: whether the podocyte is integrity or not has intimate relation with renal fibrosis. Ferulaic acid can relieve the damage of podocyte and the level of ECM both in rat modle. If inhibiting the respond of samd2/3, we can see the opposite phenomenon.

Conclusions: Ferulaic acid maybe one of the utility traditional medicine which can delay renal fibrosis.

Funding: Government Support - Non-U.S.

PUB339
Urinary Cell Adhesion Molecules as Markers of Renal Involvement in Systemic Sclerosis
Edward Stern,1, Aine Burns,2, Robert J. Unwin,3, Christopher Paul Denton.2
1Centre for Rheumatology and Connective Tissue Diseases, UCL, London, United Kingdom; 2Centre for Nephrology, UCL, London, United Kingdom.

Background: Renal involvement in systemic sclerosis (SSc) includes scleroderma renal crisis as well as progressive organ fibrosis. Detection and management of these disease complications is challenging and there is a clinical need for biomarkers that reflect renal involvement. The immunoglobulin superfamily adhesion molecules ICAM-1 and VCAM-1 are upregulated in affected tissues in SSc and other connective tissue diseases. Serum levels of ICAM-1 and VCAM-1 have been evaluated in previous studies, but this may reflect the multi-organ burden of disease and organ-specific analysis may be more robust.

Methods: We collected urine and serum from 80 SSc patients, with or without renal disease, and compared them with patients with CKD of other causes (n=10) and healthy controls (n=12). We used bead-based multiplex analysis to measure cell adhesion molecule concentrations. Results were compared among groups by Kruskal-Wallis test.

Results: 40 SSc patients had CKD defined by eGFR. Risk factors for renal involvement (SSc-CKD) included diffuse skin involvement and anti-RNA polymerase III antibodies. Serum concentrations of ICAM-1 or VCAM-1 did not differ significantly between SSc-CKD and the three control groups. Urine VCAM-1 concentrations were increased in SSc patients with renal involvement (mean VCAM-1:creatinine ratio 922, SD 953 versus 654, SD 708 for those with and without involvement) but this did not reach statistical significance. Urine ICAM-1 was significantly upregulated in SSc-CKD (mean ICAM-1:creatinine ratio 1601, SD 1394 versus 806, SD 701 for SSc without renal involvement and 1307, SD 1211 for CKD of other causes, p<0.001).

Conclusions: This is the first study to examine urinary cell adhesion molecule concentrations in SSc. Our results confirm the potential utility of urine sCAM-1 as a marker of renal involvement in SSc.

Funding: Government Support - Non-U.S.

PUB340
Urinary and Serum Trefoil Factor 3 Is Significantly Associated with Renal Tissue Fibrosis in Patients with Tubulointerstitial Nephritis

Background: TFF3 is a small peptide involved in mucosal protection. TFF3 is widely expressed in multiple tissues including kidney. Previous studies have suggested that serum and urinary TFF3 significantly increase in patients with chronic kidney disease and that urinary TFF3 decreases in rats with acute kidney injury. However, it is unclear whether serum or urinary TFF3 is associated with human renal tissue injury. The aim of this study is to elucidate the relationship between the serum and urinary levels of TFF3 and the degree of renal tubulointerstitial injury.

Methods: The total study population included 112 patients (tubulointerstitial nephritis [TIN], n=34; IgA nephropathy [IgAN], n=57; and patients with minor glomerular abnormalities and thin basement membrane disease as controls, n=21) who underwent renal biopsy. The serum and urinary TFF3 concentrations were determined by a specific ELISA. The degrees of tubulointerstitial cell infiltration and fibrosis in biopsy specimens were semiquantitatively graded and defined by the inflammation score and the fibrosis score, respectively.

Results: The median serum and urinary levels of TFF3, and the mean fibrosis score and inflammation scores of the TIN group were significantly higher than those of the other groups (p<0.0005). A statistically significant positive correlation was observed between both the urinary and serum levels of TFF3 and the renal fibrosis score in the TIN group. A similar but non-significant tendency was observed in the IgAN group. There was no correlation between either the serum or urinary level of TFF3 and the renal inflammation score in the control and TIN groups.

Conclusions: The data indicate that the serum and urinary levels of TFF3 are significantly increased and they could reflect renal tissue fibrosis in patients, especially those with tubulointerstitial nephritis. Further studies are required to elucidate the precise distribution of renal TFF3 protein and mRNA, and the mechanism underlying the contribution of TFF3 to renal fibrosis.

PUB341
Icarin Plays a Protective Role in Angiotensin II-Induced Renal Fibrosis Independent of Estrogen Receptor Signaling Pathway
Yi Wang, Hongli Zhang, Min Chen, Xiangchen Gu. Dept of Nephrology, Yueyang Hospital of Traditional Chinese and Western Medicine, affiliated to Shanghai Univ of T.C.M.

Background: Ang II plays a crucial role in the development and progression of renal fibrosis. Previous studies have demonstrated that estradiol could attenuate AngII induced renal fibrosis. Icarin, an active ingredient extracted from the Chinese herb Epimedium, has been proved to have the same effect as estradiol on many animal disease models. In this study, we tried to ascertain the effect of icarin on the Ang II-induced renal fibrosis rodent model.

Methods: Ovariectomized SD rats were randomized into 4 groups, treated with icarin after implantation of Ang II osmotic mini pumps at the rate of 1000mg/kg/min. The rats were sacrificed after 4 weeks of treatment. The serum estrogen level, pro-fibrotic factors, renal function, renal morphology and ER (estrogen receptor) α and β expression levels
were assessed. NRK-49F cell lines with ER knockdown and empty vector were generated using a lentiviral vector. The cells were stimulated with Ang II after pretreatment of Icariin. The profibrotic markers were measured as well.

Results: In contrast to AngII model group, rats treated with Icariin exhibited a significant decrease in the mRNA levels of TGF-β1, CTGF, Cola1, ColIV and Fibronectin by qPCR method. Masson trichrome staining also demonstrated loss Collagen depositions in this group. Renal functions of the treatment group were improved as well, compared to that of AngII model group. However, ER α and β expressions remained the same in all groups. In vitro study demonstrated that pretreatment of Icariin significantly decreased the expressions of profibrotic factors induced by AngII in NRK-49F cell lines with both ER knockdown and empty vector.

Conclusions: Icariin can attenuate AngII induced renal fibrosis. But it might not be related to the estrogen receptors signaling pathway.

**Conclusions:**

**Role of Smad3 Linker Region Phosphorylation in Nocantharidin Inhibiting Renal Interstitial Fibrosis**

Ying Li, Nannan Yu, Yingjin Liao, Jun Li, Fuyou Liu, Hong Liu, Lin Sun. Dept of Nephrology, Second Xiangya Hospital, Central South Univ, Changsha, Hunan, China.

Background: Our previous study showed that Nocantharidin(NCTD) could inhibit renal interstitial fibrosis and also promote Smad3 linker region phosphorylation. Based on the above results, this study will investigate: 1) effect of Smad3 linker region phosphorylation on renal interstitial fibrosis; 2) role of Smad3 linker region phosphorylation in NCTD inhibiting renal interstitial fibrosis.

Methods: 1.Human proximal tubular cell line (HK-2) cells separately transfected with Smad3 linker region phosphorylation site mutant viruses (TGF-β1-S3-LM group) or wild type viruses (TGF-β1-S3-WT group) were stimulated by 5 ng/ml TGF-β1 for 24h. The expressions of fibronectin (FN) and collagen I(Col)-mRNA and protein in each group were detected by real-time PCR and western blot. 2. HK-2 cells separately transfected with Smad3 linker region phosphorylation site mutant viruses (NCTD+TGF-β1-S3-LM group) or wild type viruses (NCTD+TGF-β1-S3-WT group) were simultaneously treated with 5ng/ml TGF-β1 and 2.5μg/ml NCTD for 24h. The expressions of FN and Col-I mRNA and protein in each group were detected by real-time PCR and western blot.

Results: 1. Compared to blank control group, the expressions of FN and Col-I mRNA and protein were increased in TGF-β1-group. And their expressions were higher in TGF-β1-S3-LM group than in TGF-β1-group and TGF-β1-S3-WT group(P<0.05). 2. Expressions of FN and Col-I mRNA and protein were decreased in NCTD+TGF-β1-S3-LM group compared to TGF-β1+S3-WT group and TGF-β1+S3-LM group(P<0.05). 3. NCTD+TGF-β1+S3-LM group were also lower in NCTD+TGF-β1-S3-WT group than in TGF-β1-S3-WT group(P<0.05). But expressions of FN and Col-I were higher in NCTD+TGF-β1+S3-LM group compared to TGF-β1+S3-LM group(P<0.05).

Conclusions: 1. Smad3 linker region phosphorylation could block TGF-β1 signaling pathway in HK-2 cells and thus inhibit renal interstitial fibrosis; 2)NCTD’s anti-renal interstitial fibrotic effect was not fully dependent on its promotion of Smad3 linker region phosphorylation.

**Funding:**

*Government Support - Non-U.S.*

**Conclusions:**

**A Monoclonal Antibody Neutralizing Transforming Growth Factor Beta Delays the Progressive Decline of Glomerular Filtration Rate in Hyperoxaluria-Related CKD**

Stefanie Steiger,1 Quyue Ma,1 Julia Felicites Grill,1 Shrirant R. Mulay,1 Patrick Finn,1 Hans J. Anders,1 Nephrologisches Zentrum, Klinikum der Univ München, Munich, Germany; Sanoﬁ- Genzyme, Framingham.

Background: Hyperoxaluria can lead to progressive chronic kidney disease (CKD), e.g. in primary hyperoxaluria, a process that is associated with massive intraternal crystal deposition, nephron loss and tubulointerstitial fibrosis. There is little evidence that fibrosis is a cause rather than a consequence of nephron loss, hence, we hypothesized that blocking fibrogenesis would not affect CKD progression.

Methods: We used a model of progressive oxalate nephropathy by feeding mice a sodium oxalate-rich, calcium-free diet for 14 days. Mice were randomized to injections with either a neutralizing TGFβ1 or control Ig antibody until the end of the study.

Results: As expected antibody treatment decreased interstitial fibrosis, which was associated with less tubular atrophy and RNA expression levels of kidney injury and fibrosis, and decreased the number of profibrotic macrophages. Most importantly, this antifibrotic effect significantly improved renal excretory function as demonstrated by a significant increase in the glomerular filtration rate from 20μl/min to 100μl/min (P<0.01), and reduced serum creatinine (1.7mg/dl to 1.0mg/dl, P<0.01) and BUN (78.9mg/dl to 38.2mg/dl, P<0.05) levels.

Conclusions: These results support the concept that TGFβ1-mediated renal fibrosis contributes to nephron loss. A monoclonal antibody against TGFβ1 may retard CKD progression in primary hyperoxaluria and potentially other forms of CKD.

**Conclusions:**

**The Expression of WNT1-Inducible Signaling Pathway Protein-1 Correlates with Renal Fibrosis**

Xiang Zhong, Guisen Li, Li Wang. Renal Div and Inst of Nephrology, Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: WNT1-inducible signaling pathway protein-1 (WISP-1) plays a pathological role in pulmonary fibrosis, but the role of WISP-1 in renal fibrosis is unknown. In this study, we explored the expression of WISP-1 in renal fibrosis in patients and in TGF-β-treated tubular epithelial cells (TECs) and in the obstructive nephropathy mouse model.

Methods: The serum and kidney tissues from renal biopsy-proved renal fibrosis patients including idiopathic nephropathy (IDN, N=39) and primary focal segmental glomerular sclerosis (FSGS) (N=22) were collected to examine the levels of WISP-1 by ELISA and Immunohistochemistry staining, respectively, and the minimal change disease (MCD) and the healthy as controls. The expression of WISP-1 was also examined in TGF-β-induced renal fibrosis in tubular epithelial cells (TECs) and in the fibrotic kidneys of obstructive nephropathy model by Realtime PCR and Western blotting.

Results: Immunohistochemical analysis showed that WISP-1 was highly expressed in tubulointerstitial area in renal fibrosis patients of IGAN, DN and FSGS, but not in the expression of WISP-1 in MCD and healthy. The expression of WISP-1 in TGF-β-induced renal fibrosis in tubular epithelial cells (TECs) that is biologically- and bioactivity- proved renal fibrosis patients by ELISA was significantly increased compared with
the control groups (P=0.05). More importantly, the WISP-1 expression was positively correlated with renal fibrosis (r=−0.228, P=0.037) and serum creatinine (Scr) (r=−0.046, P=0.023), while negatively with estimated glomerular filtration rate (eGFR) (r=−0.051, P=0.017). In accordance with these results, when the fibrotic indexes including Col I, a-SMA, fibronectin were increased both in TGF-b-induced renal fibrosis in TECs and in UUO mouse model, the expression of WISP-1 was also significantly elevated (P=0.05).

Conclusions: We explored the WISP-1 was highly expressed not only in biopsy-proved renal fibrosis patients, but also in TGF-b-induced renal fibrosis in TECs and in the fibrotic kidneys of obstructive nephropathy model. And the WISP-1 expression level in serum correlated with the fibrosis in renal tissue, and also correlated with the renal function.

**PUB347**

A Challenging Case of Poorly Controlled Hypertension in a Patient with a Solitary Kidney

David Levey, Sai Subbodhini Reddy. Div of Nephrology, Univ of Rochester Medical Center, Rochester, NY.

**Introduction:** Patients with a solitary kidney secondary to unilateral renal atrophy often have poorly controlled hypertension (HTN). Elevated renin levels and subsequent activation of the renin angiotensin aldosterone system (RAAS) are expected due to reduced renal perfusion to the atrophic kidney. Since the pathophysiology of HTN in patients with an atrophic kidney is similar to patients with renal artery stenosis, treatment with RAAS blockade seems appropriate.

**Case Description:** JD is a 36 year old male who was referred to nephrology for evaluation of his poorly controlled HTN and CKD. Prior to his initial visit a renal ultrasound showed an atrophic right kidney (Figure 1). He was treated with losartan and metoprolol. However his HTN remained poorly controlled, and he had worsening azotemia (Table 1). Since he had progressive renal dysfunction and uncontrolled HTN, there were ongoing discussions with the patient of stenting his right renal artery. While he was considering this intervention, amiodipine was added. Subsequently, he had significant improvement in his blood pressures and proteinuria.

<table>
<thead>
<tr>
<th>Date</th>
<th>Blood Pressure Reading</th>
<th>Medications and Dose</th>
<th>Spot urine TPV Cr (g/day)</th>
<th>Serum Cr (mg/dl)</th>
<th>eGFR/ml/min/1.73m²</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/03/2015</td>
<td>197/110</td>
<td>Losartan 50mg daily, Metoprolol XL 50mg daily</td>
<td>3.16</td>
<td>1.84</td>
<td>46</td>
<td>Losartan increased</td>
</tr>
<tr>
<td>12/07/2015</td>
<td>197/123</td>
<td>Losartan 75mg daily, Labetalol 400mg BID Not Checked</td>
<td>1.87</td>
<td>45</td>
<td>Losartan increased</td>
<td></td>
</tr>
<tr>
<td>1/21/2016</td>
<td>180/105</td>
<td>Losartan 100mg daily, Labetalol 400mg BID</td>
<td>1.76</td>
<td>2.06</td>
<td>40</td>
<td>Amiodipine started</td>
</tr>
<tr>
<td>3/17/2016</td>
<td>142/82</td>
<td>Losartan 100mg daily, Amiodipine 10mg daily, Labetalol 400mg BID</td>
<td>0.89</td>
<td>1.87</td>
<td>45</td>
<td>None</td>
</tr>
</tbody>
</table>

**Discussion:** Combination therapy with RAAS blockade and amiodipine may reduce the potential need for renal artery stenting in patients with poorly controlled HTN and progressive renal disease in the setting of a solitary kidney.

**PUB348**

Breast Nodules: An Unusual Metabolic Complication in a Dialysis Patient

Abhilash Koratala, Dara N. Wakefield, Negin Pourafshar, Rajesh Mohandas. Univ of Florida.

**Introduction:** Calcific uremic arteriolosclerosis (CUA) or Calciphylaxis affects 1-4% of the population with End Stage Renal Disease (ESRD) and associated with high mortality. About 90% lesions occur on the lower extremities followed by lower abdomen. We report a case of CUA of the breast, which is an uncommon location.

**Case Description:** A 54 year old Caucasian woman on hemodialysis secondary to diabetic nephropathy for a year was admitted for management of breast lesions. Other past medical history includes hypertension, atrial fibrillation on Warfarin and morbid obesity. She noted a tender nodule under the skin on the lower right breast 3 months ago which progressed to open wound with surrounding redness and intense pain. Also developed similar nodule in the left breast a month ago.

**Discussion:** CP is usually considered to be a safe antibiotic and is widely prescribed with few adverse reactions reported. We did the literature search which revealed only a few reports of CP induced AIN and the drug was discontinued on day 2 of hospital admission. CP level 48 hours after the last dose was 94 mcg/ml (elevated) and Cr stayed high. So, we suspected CP induced AIN and the drug was discontinued on day 2 of hospital admission.

**PUB349**

Cefepime Induced Eenchephalopathy and Acute Interstitial Nephritis


**Introduction:** Cefepime (CP) is an extended-spectrum, 4th generation cephalosporin that has been implicated in encephalopathy especially in patients with renal impairment. Rarely, it can also lead to acute interstitial nephritis (AIN). We report the case of a patient who presented with both these entities.

**Case Description:** 58 year old Caucasian male with history of Chronic kidney disease stage 3a, Hypertension, Diabetes mellitus was admitted for altered mental status (MS). He was discharged 10 days prior to presentation on IV CP for the treatment of Thoraco-lumbar osteodiscitis, started 2 weeks ago at 2g every 12 hours. CT head was negative. He was completely disoriented and exhibited myoclonic jerks. EEG revealed frequent generalized rhythmic delta activity with triphasic morphology without overt seizure suggestive of possible CP induced encephalopathy. He also had Acute Kidney injury at presentation with serum creatinine (Cr) of 4.84 mg/dl (baseline 1.9). He also had anion gap metabolic acidosis with serum bicarbonate of 16 mmol/L and normal lactate, osmolar gap and toxicology. Urinalysis showed 47 white blood cells per hpf with positive urine eosinophils. No significant proteinuria or evidence of proliferative glomerulonephritis. No skin rash. We considered CP induced AIN and the drug was discontinued on day 2 of hospital admission. CP level 48 hours after the last dose was 94 mcg/ml (elevated) and Cr stayed high. So, we chose to treat him with oral steroid therapy for AIN (Prednisone approx. 0.8mg/kg/day) and creatinine showed downward trend with improvement in MS.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
one published case of CP induced AIN (Mac et al. 2015). Clinicians should be aware of its potential nephrotic and neurotoxic effects and promptly discontinue the drug with consideration of Steroids if AIN is suspected.

**PUB350**

Aloe Vera Juice Induced, Biopsy Proven, Acute Tubular Necrosis

Joshua L. Rein, Sri Lokha Tummala palli, Steven G. Coca, Christina M. Wyatt, Tonia K. Kim. Div of Nephrology, Dept of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

**Introduction:** Aloe vera juice is sold over-the-counter as a natural remedy for constipation and arthritis. Numerous compounds contained in the Aloe vera plant have been shown to inhibit cytochrome-p450-2 (COX-2). We present a case of Aloe vera juice-induced, biopsy proven, acute tubular necrosis (ATN).

**Case Description:** 50 year old woman with a past medical history of CKD3, diabetes mellitus, and hypertension presented with increasing dyspnea on exertion, orthopnea, and bilateral leg edema over the past 2 weeks. She denied taking any nephrotoxins. One month prior, she started drinking Aloe vera juice daily for joint pain. Physical exam was remarkable for bibasilar crackles on lung auscultation and 4+ bilateral leg edema. Labs revealed K 5.5 mEq/L, HCO₃ 19 mEq/L, BUN 88 mg/dL, Cr 7.14 mg/dL, albumin 2.0 g/dL. Ten months prior to presentation, serum Cr was 1.3 mg/dL. UA showed>1000 protein, 11-25 RBC, 5-10 WBC, FENa 3.7%, and urinary protein excretion was 11.67 g/24hr. Further testing revealed normal C3/C4, ACE 11.3%, negative for HIV, HBV, HCV, anti-GBM ab, normal ANA titer, ASO titer, SPEP and UPEP. Renal US showed normal sized diffusely echogenic kidneys without hydronephrosis or calculi. She remained hypervolemic despite high dose diuretics and hemodialysis was initiated. Renal biopsy revealed ATN with nodular diabetic glomerulosclerosis, moderate arterial sclerosis, and mild parenchymal scarring.

**Discussion:** Aloe vera contains compounds including aloesin, aloeordenin, and isosorba diocrom, which have demonstrated in vitro and in vivo activity against COX-2, NO synthase, and prostaglandin E2 production. Additionally, Aloe vera extract can induce ATN in rats. Frequent ingestion of these biologically active substances could theoretically induce afferent vasoconstriction in patients who are prostaglandin-dependent to anti-inflammatory drugs or corticosteroids. The combination of AIN and nephrotic syndrome can be challenging in terms of diagnosis and management, especially in the absence of an identifiable cause. While the pathophysiology of Aloe vera-induced ATN remains unclear, this case highlights the need for further research into the potential nephrotoxicity of this commonly used supplement.

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Underline represents presenting author.

**PUB351**

An Unusual Case of Atypical Hemolytic Uremic Syndrome

Kevin H. Beers, Kevin Zarrabi, Yezina T. Nagiwal, Wilfred Lieberthal. Stony Brook Univ Hospital.

**Introduction:** Hemolytic uremic syndrome (HUS) is characterized by a microangiopathic hemolytic anemia (MHA) and acute kidney injury (AKI). The most common cause of HUS is the classic form associated with a Shiga toxin-producing strain of E. coli. The combination of MHA and AKI can also be caused by atypical HUS (aHUS), which involves deficiency of complement factors regulating the alternative complement pathway. The incidence of aHUS is far lower than that of classic HUS.

**Case Description:** A 19 year old female presented with abdominal pain, bloody diarrhea and oliguria. On admission she was alert and oriented. Vital signs, examination of the heart, lungs and abdomen were normal. Laboratory data: WBC 22 k/uL, Hgb 6.1 g/dL, platelets 290 k/uL, blood urea nitrogen 77 mg/dL, creatinine 7.23 mg/dL, serum LDH 1042 U/L, haptenoglobin undetectable. Coombs’ test was negative. Blood smears revealed many schistocytes. A diagnosis of aHUS was made after excluding classic HUS (negative Shiga toxin test) and TTP (ADAMTS13 activity 77%). Blood tests were sent to look for abnormalities in complement factors known to be associated with aHUS. The patient was started on prednisone and plasma exchange. Renal function slowly improved and creatinine peak was found to be 1.5 mg/dL. However, the MHA persisted and plasma exchange was continued. The patient then developed nephrotic range proteinuria. A renal biopsy was done which showed features of vascular microangiopathy consistent with aHUS. Complement profiles demonstrated the presence of autoantibodies to complement factor H (CFH) as well as a heterozygous deletion of genes encoding CFHR1 and CFHR3. The patient was started on once weekly doses of eculizumab, after which the MHA resolved completely. Plasma exchange and prednisone were discontinued.

**Discussion:** Atypical HUS can be caused by a genetic defect (caused a combined abnormality remains to be elucidated.

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**PUB352**

Methotrexate Nephrotoxicity Treated with Glucarpidase


**Introduction:** Methotrexate (MTX) is an antimetabolite used in the treatment of malignancies and rheumatologic conditions. High-dose MTX (HDMTX), defined as doses > 500 mg/m², is implicated in renal toxicity. We report a case of MTX nephrotoxicity successfully treated with Glucarpidase (GP), a recombinant enzyme that inactivates MTX.

**Case Description:** 67 year old Caucasian male with history of Heart transplant (on Cyclosporine), Hypertension, Chronic Kidney Disease stage 5a likely secondary to calcineurin (CNI) toxicity was admitted for new-onset seizure. He was diagnosed with Post-transplant lymphoproliferative disorder and started on high-dose MTX (8200 mg/day) and rituximab 2 days prior to Nephrology consult for Acute Kidney Injury (AKI). His baseline serum creatinine (Cr) was ~1.5 mg/dL. No IV contrast exposure, diarrhea, vomiting, or urinary symptoms. IV sodium bicarbonate & Leucovorin were given with MTX. When we were consulted, Cr was 3.27 mg/dL & urine Pb was 6. The next day, Cr increased to 3.6 & 24-hour MTX level was 26 mcg/mL (markedly elevated). MTX was held and IV hydration was given. Cr continued to rise to 4.0 mg/dL (day 3). Decision was made to administer GP on day 4 due to worsening renal function. MTX level on day 5 was 0.69 mcg/mL. His Cr plateaued and trended down to 2 mg/dL at discharge and was 1.47 at 1 month follow up. No renal replacement therapy was needed. Cr trend shown below.

She was treated with ACEI and at 3-month follow-up she was asymptomatic, without edema and urine protein-creatinine ratio (UPCR) had decreased to 7g/g. She was lost to follow-up for 5 years until this recent admission. In the interim, she apparently had a second successful pregnancy but no data was available. Placental biopsy after the current pregnancy

**Discussion:** HDMTX causes AKI by tubular crystal precipitation, exacerbated by acidosis & volume depletion. It can also cause transient decline in GFR which may be prolonged in the presence of concomitant nephrotoxins (our patient was on CNI). Even with fluids & urine alkalization, the risk of HDMTX nephrotoxicity is ~2%. Awareness of the utility of GP (FDA-approved) may mitigate the need for dialysis in selected cases of HDMTX renal injury. The drawback of GP is its cost and availability.

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**PUB353**

Course of Membranous Nephropathy during Multiple Gestations: A Case Report

Abhilash Koratala, Kathwer Farouk Aklanda, Dara N. Wakefield, A. Ahsan Ejaz. Nephrology, Hypertension and Renal Transplantation, Univ of Florida; Pathology, Immunology and Laboratory Medicine, Univ of Florida.

**Introduction:** Physiological adaptations in Pregnancy (PG) can unmask underlying occult proteinuric renal disease. However, the effect of multiple pregnancies on the course of the disease is unknown. We report the clinical course of a case of idiopathic membranous nephropathy (MN) through multiple pregnancies.

**Case Description:** 25 year-old Hispanic female was referred for 21gm of proteinuria at 35 weeks gestation during her 3rd pregnancy. She was previously seen at our institution five years ago during her 1st pregnancy when 13gm of proteinuria was recorded at 25 weeks of gestation. At that time, she was treated with oral steroids and delivery was induced at 35 weeks due to intra-uterine growth restriction. Placental biopsy revealed focal, tightly adherent blood clot, consistent with possible abruption. Renal biopsy performed in the postpartum period was consistent with MN.

**Discussion:** Atypical HUS can be caused by a genetic defect (caused a combined abnormality remains to be elucidated.

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

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showed the placenta was critically small for gestational age and had focal intervillosus fibrin deposition. At one month post-partum, UPCR was 1.8 g/dL, without any treatment. Patient unfortunately was again lost to follow-up.

Discussion: We conclude that spontaneous remission of MN can occur despite physiological changes associated with pregnancy and the natural course of MN probably establishes the long term safety of this medication, though results are not necessarily generalizable to all patients.

PUB354
Not a Malignant or a Granulomatous Process, It’s a Lurking Infection: Hypercalcemia with Pneumocystis jirovecii Pneumonia
Blavnish Bucktowarsing,1 James M. Raja,2 Aarthi Rajkumar.1 1Internal Medicine, Canton Medical Education Foundation/NEOMED, Canton, OH; 2Nephrology, Kidney and Hypertension, Canton, OH.

Introduction: 1-25 dihydroxy vitamin D mediated hypercalcemia is observed in granulomatous diseases and many immunocompromised patients are affected. Pneumocystis jirovecii pneumonia (PCP) in HIV patients is rarely implicated as a cause of hypercalcemia through this mechanism.

Case Description: A 74-year-old male presented to us with generalized weakness. He had a calcium level of 13.4 mg/dL, with appropriately suppressed parathyroid hormone (PTH) level (18) and normal PTH-related peptide. Elevation of 1-25 Dihydroxy Vitamin D (155) with a decrease in 25-OH vitamin D (24) was detected. Serum and urine electrophoresis were normal. A bone scan revealed a lesion on the right 7th rib. This was biopsied and found to be negative for malignant cells as well as mycobacterial, fungal, granulomatous and lymphoproliferative disease. His respiratory status declined and he developed acute hypoxic respiratory failure. CT scan thorax revealed bilateral 'ground-glass' opacities and pulmonary nodules. Subsequent bronchoscopy showed organizing pneumonitis with 'cotton-candy' intra-alveolar exudates. Silver stain was positive for PCP. HIV was positive by western blot assay, viral load was 123388 and his CD4 count was 12. No evidence of cytomegalovirus was seen on biopsied specimens. The patient was started on Trimethoprim/ sulfamethoxazole and steroids and his Calcium level gradually normalized.

Discussion: Hypercalcemia in HIV patients occurs in the setting of extra renal production of 1-25 dihydroxy vitamin D from granulomatous infection mediated release of cytokines and activation of macrophages. A case report described PCP infection causing hypercalcemia from SS that remained stable on Mycophenolate mofetil (MMF) for the past 14 years.

Case Description: In 2002, a 25 year old Caucasian woman presented to our clinic for elevated serum creatinine (Scr) for few months and a renal biopsy demonstrating TIN that did not respond to 1 month course of prednisone 60mg/day. In 2000, she was diagnosed with Sjogren’s syndrome (SS) characterized by dry eyes, dry mouth, and Raynaud’s phenomenon. In 2003, she was started on MMF 500mg bid along with alkali therapy for RTA. Her Scr remained stable for 2 years & MMF tapered off in early 2004. In late 2004, she was started back on MMF 500mg bid as her Scr increased to 2 mg/dL and her MMF was eventually increased to 1000mg bid in early 2005. She unilaterally stopped MMF and her Scr increased to 2.7 mg/dL. A repeat renal biopsy showed significant TIN, mesangial expansion without glomerular deposits.

Discussion: When our patient was started on MMF in 2002, there was not much experience with it in SS induced TIN and the data favored steroid monotherapy. We chose MMF as a steroid-alternative agent with a better side-effect profile. Though she required prolonged therapy, she did well with stable renal function. Our case supports the use of MMF for SS induced TIN in line with currently emerging evidence. 14 year follow-up establishes the long term safety of this medication, though results are not necessarily generalizable to all patients.

PUB356
The Use of Calcineurin Inhibitors for Lupus Flare in Pregnancy
Le Dang Ha,1 Youou Kyose,2 Shubha Shastri.1 1Internal Medicine - Residency Program, Rochester General Hospital, Rochester, NY; 2Dept of Nephrology, Rochester General Hospital, Rochester, NY.

Introduction: When lupus nephritis flares during pregnancy, it becomes challenging to preserve renal function, save the life of the fetus, and avoid teratogenicity. The following case describes a strategy that resolved this dilemma.

Case Description: A 24-year-old woman with biopsy-proven lupus nephritis (class IV) was admitted during her last trimester after deteriorating renal function was discovered on routine blood test. Lupus nephritis was diagnosed in ‘14 when she presented with skin rash and hematuria. She was treated with Prednisone and Mycophenolate. Renal function improved, but in Mar’15, Mycophenolate was replaced with Azathioprine 200mg BiD because she was not using contraception reliably. In Aug’15, kidney function was stable and Azathioprine was reduced to 150mg BiD with Prednisone 2.5mg daily. Later that month, she became pregnant. For the first 2 trimesters, her creatinine was 0.6mg/dL, but, in early Jan’16, creatinine increased to 1.2mg/dL and she was admitted for 3 days of intravenous ceftriaxone. Azathioprine was increased to 200mg BiD and Hydroxychloroquine 400mg daily was added with 60mg Prednisone daily. Her creatinine increased to 1.7mg/dL and urine protein/creatinine ratio decreased from 1198 to 370mg/g. Tacrolimus was chosen for greater immunosuppression with a better safety profile than Mycophenolate or Cyclophosphamide. Within 1 week of starting Tacrolimus, creatinine stabilized at 1.0mg/dL and urine protein/creatinine ratio decreased to 102mg/g. Her pregnancy went to full-term and a healthy boy was delivered.
Case 9-9 [MAC] level was elevated while factor H, factor B and C3 nephritic factor were all within normal limits. He was managed with Lisinopril while currently undergoing screening tests to initiate eculizumab.

Discussion: C3 glomerulonephritis, [previously mis diagnosed as Post Infectious GN due to the GBM deposits] is related to dysregulation of alternative pathway of complement. The cause remains relatively unknown.

PUB358

Introduction: Cocaine, especially if adulterated with Levamisole, has been associated with several forms of vasculitis. Even though, pauci-immune crescentic glomerulonephritis in association with antineutrophil cytoplasmic antibodies has been the only nephritis described, other forms may soon emerge.

Case Description: A 48 year old Caucasian man with chronic sinusitis was noted to have acute kidney injury (AKI) (creatinine of 2.7mg/dL from baseline of 1.2mg/dL) after having routine lab work. At that time, he was admitted for intravenous hydration. Renal function improved with the intervention, but creatinine did not return to baseline. Work up in the hospital revealed leukopenia WBC 2.9 x 10^9/L, anemia Hb 11.8 g/dL, 2+ protein and 3+ blood on urinalysis, positive ANA of 1:160, positive MPO- and PR3-ANCA, and low C3 88 mg/dL and C4 14 mg/dL levels. Anti-dsDNA and anti Sm antibodies were negative. On follow up, he only complained of nonspecific arthralgia. Vital signs and physical exam were normal. Urine microscopy showed many RBCs/hpf but no casts. On further questioning, he admitted to chronic cocaine use leading to severe intranasal inflammatory erosion and septal perforation. He then underwent a kidney biopsy, which revealed immune complex mediated membranous glomerulonephritis with focal proliferation. No necrosis, crescents, or thrombi. Immunofluorescence studies showed diffuse membranous and mesangial staining for IgG, IgM, C3, C4, Kappa, and Lambda consistent with lupus nephritis. Further serological work up was negative except for positive anti-chromatin and anticardiolipin IgM antibodies. HIV and hepatitis were negative.

Discussion: In this peculiar case, it is difficult to distinguish with certainty between idiopathic vs drug induced lupus nephritis. Even though cocaine/Levamisole induced lupus nephritis has not been described, there has been case reports that it can lead to cytopenias, low complements, and positive ANA - Anti-dsDNA antibody. This patient’s presentation of AKI, non-specific arthralgia, cocaine induced septal perforation/severe intranasal inflammatory erosion together with Caucasian ethnicity, no family history of autoimmune disease, and mixed serology makes us wonder if this is more than just idiopathic lupus nephritis.

PUB359
The Saga of Mis-Folded Proteins Ahmed H. Alainj, Saeed Farrada, Alain Casper, Saeed Shaffi. Nephrology, UNM, Albuquerque, NM.

Introduction: Amyloid light chain (AL) amyloidosis is a disorder that is characterized by a clone of plasma cells that produce an abnormal protein which deposit on organs. We describe a case of AL amyloidosis with renal involvement, but no bone marrow abnormality.

Case Description: A 74-year-old previously healthy female presented to the hospital with malaise, and swelling of the lower extremities. Physical examination was significant for pallor, normal vitals, a 2/6 ejection systolic murmur and 2+ lower limb edema. Pertinent laboratory data are shown in Figure 1.

Kidney biopsy showed extensive renal glomerular involvement with amyloidosis. Immunofluorescence and liquid chromatography tandem mass spectrometry showed peptid profile consistent with AL amyloidosis. Bone marrow biopsy was non-colluric without plasma cell abnormalities. Fat pad biopsy was negative. Echocardiography was normal. She was started on bortezomib and dexamethasone chemotherapy and is being followed in the nephrology clinic for her progression of kidney disease.

Discussion: Light chain amyloidosis is caused by a small clone of plasma cells which secrete a protein that has a propensity to mis-fold and deposit on organs as beta pleated sheets which stain Congo red on light microscopy. The bone marrow biopsy might be normal because of the paucity of the abnormal cells. This is different from immunoglobulin deposition disease where a large clone of abnormal plasma cells secretes light and/or heavy chains that deposit on renal parenchyma, but do not mis-fold and form beta pleated sheets; thus don’t stain with Congo red. Bone marrow biopsy shows abnormal plasma cells. Plasma cells can also secrete freely filtered light chains that bind to Tamm-Horsfall protein and form proteinaceous casts resulting in cast nephropathy. It is imperative to elucidate signs of end organ damage when plasma cell dyscrasias are suspected as the bone marrow biopsy might not reveal plasma cell abnormality.

PUB360

Introduction: Infectious complications of the vascular access are an important cause of morbidity and mortality among HD patients. Type of vascular access and cannulation techniques are risk factors for these complications. Herein, we report an unusual case of subcapsular abscess associated with buttonhole cannulation technique (BHCT) of AVF for HD access.

Case Description: 51 y.o. Caucasian male with ESRD secondary to diabetes, on HD using BHCT of RUE AVF for 6 months, presented with a 2 day history of right shoulder pain. Contrast CT demonstrated a complex abscess beneath right scapula without scapular osteomyelitis. Blood cultures were positive for MRSA and appropriate antibiotics were administered. Subsequently, a CT-guided pigtail catheter was inserted to drain the abscess. Culture of the abscess aspirate was also positive for MRSA. TEE was negative for valvular vegetations and US of AVF negative for localized infection. Eventually, symptoms subsided and cultures turned negative.

Discussion: In the absence of other etiologies, we suspect that BHCT was the likely source of blood stream infection (BSI) that culminated in subcapsular abscess.

Discussion: AVF is the most preferred long term HD access due to lower associated complications. BHCT is gaining popularity due to less pain, aneurysm formation and complications. However, it may pose an additional risk factor for development of infectious complications. In fact, recent evidence suggests a higher rate of local infection and bacteremia associated with BHCT, which is an important concern for immunocompromised dialysis patients. Nephrologists should be aware of these potential risks while recommending BHCT to their patients and have a high index of suspicion for BSI-related complications while evaluating HD patients presenting with unusual symptoms.

PUB361
Acute Kidney Injury with Acute Interstitial Nephritis Nonreversible, Requiring Hemodialysis, Unmasking Primary Amyloidosis Himabindu Valluru, Rahul Valluru, Muner Mohamed, Moro O. Salifu, Mary C. Mallappalil. Nephrology, SUNY Down State, Brooklyn, NY.

Introduction: Primary systemic amyloidosis is a monoclonal plasma cell characterized by deposition of extracellular immunoglobulin light chain fibril in various organs. It is a rare disease with broad range of manifestations. Signs and symptoms may not be experienced until the condition is advanced. We report a case of acute interstitial nephritis to an antibiotic which did not resolve despite steroid treatment that unmasked primary amyloidosis on kidney biopsy.

Case Description: A 64 year-old man with hypertension, presented with confusion, progressive bilateral lower extremity edema and was found to have acute ischemic stroke on CT head. In addition he was also noted to have new onset of systolic heart failure (CHF). Both CVA and sCHF symptoms were improving but he had a fever with suspected peripheral intravenous line infection for which he was started on prophylactic vancomycin and zosyn. Subsequently, he was noted to have an acute rise in serum BUN and creatinine levels. Acute interstitial nephritis was suspected, antibiotics were discontinued with no improvement in renal function despite being started on prednisone. Hemodialysis was started and a kidney biopsy was obtained which revealed acute interstitial nephritis with interstitial fibrosis/inflammation, tubular atrophy and AL type Lambda light chain restricted amyloidosis. Bone marrow biopsy consistent with lambda restricted plasma cell neoplasm.

Case description revealed cardiac amyloidosis. He progressed to become dialysis dependent while chemotheraphy was planned.
**Discussion:** Upon review of literature, patients with AL amyloidosis presented with symptoms of specific organ involvement at the onset. This is a rare case of a patient who presented with normal renal function and developed acute kidney injury due to acute interstitial nephritis which unmasked an underlying primary systemic amyloidosis with renal and cardiac involvement.

**PUB362**

**Pazopanib Induced Hypertension and Proteinuria: A Case Report**


**Introduction:** Pazopanib (PZ), an oral anti-angiogenic Tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF) receptor is one of the first line treatment options for advanced renal cell carcinoma (RCM), Proteinuria (PTN) and uncontrolled hypertension (HTN) from Bevacizumab (a VEGF inhibitor) is well established but there is paucity of such data with the use of PZ. We report a case of PZ induced nephrotic-range PTN and HTN.

**Case Description:** 68 year old Caucasian male with history of HTN, Coronary artery disease and hypothyroidism presented to our institution with HTN emergency, with a BP of 220/120 and troponinemia from demand ischemia. 5 months prior to presentation, he was diagnosed with metastatic right RCC for which he underwent radical right nephrectomy and started on PZ therapy. His baseline creatinine (Cr) was 1.1 mg/dL, which stabilized at ~1.3 mg/dL after nephrectomy. At presentation, his Cr was 2.3 mg/dL, with Urine protein-creatinine (Upc) ratio of ~5.5 g/g. His HTN was well controlled before starting PZ. He was given IV Labetalol without much response and so transitioned to Nitroglycerin drip after which BP improved. His 24-hour urine protein was 4.9 g and serum albumin 3.4 g. His BP improved over the next few days and Cr trended down to 1.7 mg/dL. We diagnosed the case to be complications of PZ therapy and discontinued the drug. We chose to monitor him expectantly without renal biopsy. At 1 month follow up, his Cr was 1.6 mg/dL and Upc was ~2.5 g/g.

**Discussion:** There has been conflicting evidence on whether HTN can be used as a biomarker for efficacy of VEGF inhibitor therapy. However, there is no evidence to say that treatment of HTN in these patients would compromise outcome. Clinicians must monitor all patients treated with VEGF inhibitors for the development of HTN and PTN. Choice of anti-hypertensives depends on patients' co-morbidities. However, it's reasonable to treat with vasodilatory drugs such as ACEIs, Calcium channel blockers & nitrates based on the mechanism of VEGF inhibitors causing decrease in production of Nitric oxide and Prostacyclin in Vascular endothelial cells leading to vasoconstriction. PTN caused by these agents is usually non-nephrotic (unlike our patient) and rarely warrants discontinuation of therapy.

**PUB363**

**Unusual Presentation of an Uncommon Disorder: Type I Distal Renal Tubular Acidosis**

Joseph H. Zeidan, Gaurav K. Sharma, Luis A. Lopez. Internal Medicine, Mercy Hospital and Medical Center, Chicago, IL.

**Introduction:** Renal Tubular Acidosis (RTA) is an uncommon disorder that rarely occur in adults. Each type of RTA has a different etiology along with a different mode of presentation. As this case will show, following a step-wise approach to acidosis will ultimately lead to a diagnosis.

**Case Description:** A 33-year old woman presented with abdominal pain and diarrhea for 3 days. On exam, she had tenderness in the RLQ without guarding or rigidity. Labs showed a serum bicarbonate of 14 mmol/L, a normal anion gap of 16, blood pressure 110/80 mmHg, urine pH of 6.0. Arterial blood gas was obtained to evaluate the acidosis with a pH 7.32, HCO3 10 and pCO2 19.5. The acidosis worsened to a level of 10 to which the patient was given IV Labetalol without much response and so transitioned to Nitroglycerin drip after which BP improved. Hermsen et al showed an increase in his urine osmolality to 685 mOsm/kg while his SNa+ stayed constant at 130 mEq/L. His SNa+ remained between 129-132 mEq/L for the rest of the hospitalization and on follow-up (See Figure).

**Discussion:** A reset osmostat was diagnosed by demonstrating normal urinary dilution at a SNa+ of 110-127 mEq/L but with urinary concentration at a SNa+ of 130 mEq/L. We hypothesize that this patient’s reset osmostat may have developed secondary to prolonged exposure to exogenous desmopressin.

**PUB365**

**Urinary Excretion of α1 Microglobulin Is Not an Accurate Marker of Tubulointerstitial Nephritis**

Anneke Bech,1 Michiel W.P. Bleeker,1 Meyeke Hermens,2 Bart Smeets,2 Jack F. Wetzels.3 Nephrology, Radboud Univ Medical Center; 3Pathology, Radboud Univ Medical Center; Nephrology, Bernhoven Hospital.

**Introduction:** Tubulointerstitial nephritis (TIN) is a frequent cause of kidney injury. Kidney biopsy is considered the gold standard for diagnosis, however cannot be used for guiding treatment and diagnosing relapse. Serum creatinine is being used but is neither sensitive nor specific. Urinary excretion of α1microglobulin (a1m) reflects tubular inflammation and may be a promising tool. Median urinary a1m excretion in 13 patients with suspected TIN indeed was elevated (147 mg/100 ml creatinine, IQR 98-201). The following case however questions its use in patients with TIN.

A 66 year old lady was evaluated for a rise in serum creatinine. She did not have complaints and did not use any drugs. Her medical history revealed Sjogren’s syndrome with two episodes of TIN. The first episode of biopsy proven TIN was in May 2010 for which she was successfully treated with oral prednisone for 18 months. In October 2012 she developed a relapse with a rise in serum creatinine up to 141 µmol/l. She received oral prednisone and mycophenolate mofetil until June 2015. Since then serum creatinine started to rise from 105 µmol/l to 155 µmol/l. A TIN relapse was considered less likely in view of an a1m excretion of only 47 mg/10 ml creatinine. A kidney biopsy was performed, which showed an active TIN with multiple infiltrating lymphocytes in proximal tubules. The proximal tubules had normal brush borders and revealed normal staining for megalin (not shown). Figure legend: Kidney biopsy with staining for CD3 (lymphocytes) and lectin (brush border) showing active inflammation in the cortex.

**Discussion:** A reset osmostat was diagnosed by demonstrating normal urinary dilution at a SNa+ of 110-127 mEq/L but with urinary concentration at a SNa+ of 130 mEq/L. We hypothesize that this patient’s reset osmostat may have developed secondary to prolonged exposure to exogenous desmopressin.

**PUB367**

**Oral prednisone and mycophenolate mofetil were restarted resulting in rapid decrease of serum creatinine.**

**Discussion:** This case shows that a (near) normal urinary excretion of a1m does not rule out active TIN.

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

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988A
PUB366
An Unusual and Fatal Case of Cryptococcal Infection in a Renal Transplant Recipient
Yong Al Azzi, Ibadele Sulejmani, Geoffrey K. Dube. Medicine, Columbia Univ, New York, NY.

Introduction: Disseminated cryptococcal infections are a known complication of immunosuppression. However, the presentation can be atypical and can lead in some cases to fatal outcomes. We present here a case of a renal transplant patient who initially presented for non-specific abdominal pain, was suspected to have malignant TB but succumbed to splenic rupture in the setting of disseminated cryptococcal infection with lung, liver and renal allograft involvement.

Case Description: 58yo M ESRD 2/2 to type 2 DM, s/p LRT from his daughter in 2016 (Canavan induction, maintained on tacrolimus and mycophenolic acid). Seven months post transplant, he experienced epigastric pain with occasional dry heaves for 1 wk, and noted that this pain was persistent and more intense than his usual reflux. On presentation, CT of the abdomen was unremarkable except for malignant lesions at the lung base suspicious for TB. His review of systems was positive for night sweats. He worked at a prison and had never had a positive PPD. CT chest and abdomen showed miliary nodules throughout the lungs, two cavitary lesions on the peripheral lung and splenomegaly with nonspecific patchy hyperdense foci likely due to blood products. Sputum cultures were negative for AFB. He was started empirically on anti-TB therapy. One day later, he developed hypotension associated with an acute drop in his hemoglobin from 11 to 8.5. He had a PEA arrest and expired. The next day, his serum cryptococcal antigen was reported to be positive with a titer of >1:1024. His blood and sputum cultures remained negative for AFB. Autopsy showed diffuse splenomegaly with ischemic infarcts and splenic rupture, necrotizing cryptococcal pneumonia with pulmonary lesions throughout the parenchyma and pleura, necrotizing cryptococcal hepatitis, cryptococcal myocarditis, and infiltration of the renal allograft with Cryptococcus, consistent with disseminated Cryptococcal infection.

Discussion: To our knowledge, this is the first case of disseminated cryptococcal infection in a renal transplant recipient causing death by splenic rupture. This case highlights the need to be aware of atypical presentations of cryptococcal infection in immunosuppressed patients, especially renal transplant recipients.

PUB367
Is It All in the Head? - An Interesting Presentation of Hyponatremia
John Sy, Mitchell R. Lunn. Div of Nephrology, Dept of Medicine, UCSF, San Francisco, CA.

Introduction: Inpatient-onset hyponatremia can present an interesting diagnostic and management challenge. We present a case of rapid-onset hyponatremia caused by trimethoprim and review reports of this uncommon occurrence.

Case Description: A 32F was admitted for altered mental status and diagnosed with anti-NMDA receptor encephalitis. A culprit teratoma was excised on hospital day 15. On day 19, she was transferred to our hospital due to limited response to treatment with immunoglobulin and high-dose steroids. On day 23, she was started on a steroid taper, lansoprazole, trimethoprim/sulfamethoxazole, fluconazole, calcium/vitamin D, and tenofovir (to prevent latent hepatitis B reactivation). On day 27, her serum sodium fell to 117 from the day prior, she seized, and nephrology was consulted. Vitals were notable for a BP 113/69, HR 82, temperature 36.8°C, and SpO2 100% on ambient air. She denied melanotic stool or other signs of bleeding, two sets of FOBt were negative and the LDH and lactate were normal and Coombs negative. Reticulocyte count showed a normal bone marrow response and physical exam was benign. She was discharged on day 33 without need for salt supplementation or fluid restriction to a nursing facility.

Discussion: Although this presentation was suggestive of SIADH and she was managed accordingly, her hypotension suggested a salt-wasting disorder. Resolution of her hyponatremia after stopping of medications suggested an iatrogenic etiology, and literature review identified trimethoprim as the likely culprit. This case highlights that SIADH remains a diagnosis of exclusion; alternative etiologies should be sought if clinical findings are inconsistent with the presumed diagnosis.

PUB368
Pauci-Immune Glomerulonephritis in the Very Elderly: To Treat or Not to Treat?

Introduction: Anti-Neutrophil cytoplasmic antibody (ANCA) positive renal vasculitides constitutes ~ 20% of biopsied acute kidney injury (AKI) cases in the very elderly. Treatment strategies in this population are not well defined. Herein, we report a case of disseminated Nocardial brain abscess as a complication of immunosuppression (IS).

Case Description: An 80 year old Caucasian man with CKD stage 3b due to hypertension & biopsy proven cANCA associated glomerulonephritis (GN), presented with new-onset seizures, altered mental status, AKI & non-nephritic range proteinuria. Four months prior to presentation, he was diagnosed with ANCA-GN & received 2 monthly doses of IV Cyclophosphamide (~1g/dose). Additional doses were held due to poor tolerance. Prednisone 40mg/day was continued & SCR improved from 3 mg/dL at initial presentation to ~2 mg/dL. CT/MRI of the brain revealed multiple intracranial axial lesions suggestive of abscesses with extension of the temporal lobe lesion into the ventricular system causing secondary pyocephalus.

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989A
The Utility of Skin Biopsy in Dialysis Patients with Necrotic Skin Lesions

Medicine - Div of Nephrology, Univ of Rochester Medical Center; Rochester, NY.

Introduction: Calciphylaxis is a rare but devastating condition that mainly affects patients with end stage renal disease (ESRD). Clinically, diagnosing calciphylaxis can be challenging as it may present similarly to peripheral vascular disease, also common in dialysis patients.

Case Description: A 39 year old male with a history of ESRD due to type 1 diabetes on thrice weekly hemodialysis (Kt/V of 0.7 in the setting of many missed sessions), hypertension and severe peripheral vascular disease complicated by a left lower extremity amputation, presented with necrotizing penile lesions, which ultimately required partial penis amputation. Pathology was consistent with ischemia. He was also noted to have a pericardial rub which was managed by daily dialisys to partial effect. Several months later, he presented once again with painful, necrotic thigh lesions. He was noted to have bilateral thigh lesions (see figure) in the setting of inadequate dialysis (Kt/V of 1.1 and many missed sessions), and a recurrent pericardial rub. Due to concern for calciphylaxis a skin biopsy was performed. The biopsy showed pandermal necrosis and intravascular thrombi; findings consistent with calciphylaxis rather than ischemia. His PTH was noted to be 181pg/ml, serum calcium of 7.6mg/dl and phosphate was 7mg/dl which improved to 4.8 after increasing his dose of Sevelamer. He was started on sodium thiosulfate and a pain regimen.

The biopsy showed pandermal necrosis and intravascular thrombi; findings consistent with calciphylaxis rather than ischemia. His PTH was noted to be 181pg/ml, serum calcium of 7.6mg/dl and phosphate was 7mg/dl which improved to 4.8 after increasing his dose of Sevelamer. He was started on sodium thiosulfate and a pain regimen.

Discussion: Our case demonstrates the potential benefits of obtaining a skin biopsy of dialysis patients presenting with necrotic skin lesions. Since most patients with ESRD have complex medical histories including vascular disease, it can be challenging to clinically differentiate between calciphylaxis and ischemic disease.

A Case of Epstein-Barr Virus Associated Post-Transplant Lymphoproliferative Disorder Appearing in Cervix
Hafiz Ali Sroya, Rawan T. Al-Odat, Eduardo A. Alas, Antonia Harford, Pooja Singh. UNM School of Medicine.

Introduction: PTLD is the most common malignancy complicating solid organ transplantation (excluding non melanomatous skin cancer and in situ cervical cancer). Recent reports suggest that PTLD is increasing in frequency. Manifestations include involvement of the GI tract, lungs, skin, liver, CNS and the aloigraft itself. PTLD involving the cervix in a renal transplant recipient has not been reported previously, to our knowledge.

Case Description: A 48 YO female with ESRD due to IgA nephropathy underwent DDKT 13 years ago with thymo induction and subsequent maintenance immunosuppression with Tacrolimus & MMF and had excellent graft functions. Two years post-transplant, she developed a 1.5 cm right lower lobe mass with CVVH. No penicillamine given. Patient was transferred to an outside hospital for liver transplantation (excluding non melanomatous skin cancer and in situ cervical cancer). Renal involvement in Wilson's disease frequently causes damage to the proximal tubule, acidification defects, and decreases in filtration rate in only a few case reports worldwide. Renal involvement in Wilson's disease has been reported but is very rare. Case Description: We present a case of a 47-year-old man who presented to the hospital with chronic progressive abdominal pain for the past 4 months. Patient had a liver biopsy 1 month prior suggestive of Wilson’s disease. The patient endorsed 3 weeks of progressive lower extremity swelling. Patient had associated lightheadedness, fatigue, and decreased appetite. Vital signs on admission were BP 100/60mmHg HR 77 97 79 98%/RA. Physical exam notable for jaundice, ascites, 2+ edema. No Kayser-Fleischer rings noted. Within 48 hours, the patient developed respiratory failure requiring intubation and hypotension requiring vasopressor support. CXR revealed pulmonary edema. CT abdomen revealed a stable renal cyst, no hydronephrosis. Blood, urine, sputum, ascites fluid cultures were all negative. Serum ceruloplasmin level was 29.9 mg/dl, serum copper 0.96 mcg/mL, 24 hour urine copper excretion 561 mcg/spec. Serum calcium 10.3mg/dl, anion gap 11, BUN 51 mg/dl and creatinine 1.1 mg/dl, Ca++ of 14.8 mg/dl, Mg++ of 0.7 mg/dl and Phos 1.2 mg/dl. PTH was 7 pg/ml. Urine pH was 5.5. Urine electrolytes panel was UN 77 mg/dl, UCI 85 mg/dl, UK 17 mg/dl, yielding a UAG of +9. 24-hr urine calcium was 208 mg. Her calcium normalized to 8.2 mg/dl and bicarbonate normalized to 23 mg/dl concomitantly with 4-day intravenous hydration. Potassium, phosphorus, and magnesium were replaced. Her OTC multivitamins and calcium carbonate were discontinued, but her repeat BMP remained hypercalcemic in the post-hospital clinic visit. Finally, a sestamibi parathyroid scan revealed a small parathyroid adenoma.

Discussion: PTLD was low normal which limited its use for differentiating causes of hypercalcemia. At a glance, patient’s history suggested Milk-Alkali syndrome, which was described as excessive calcium and alkali intake and impaired calcium excretion by alkalinosis, as the cause of the hypercalcemia. However, patient’s paracalcitonin and metabolic acidosis went against Milk-Alkali syndrome. PTLD can inhibit Na-H exchange in distal tubule causing increased bicarbonate wasting, hypercalcemia and type 1 RTA. Hypercalcemic metabolic acidosis led to an investigation of PTLD-dependent mechanism and the discovery of a subtle parathyroid adenoma.

A Case of Wilson’s Disease Presenting with Acute Renal Failure Requiring Continuous Veno Venous Hemofiltration
Nick D. Yousuff, Dept of Nephrology, Darimouth Hitchcock, Lebanon, NH.

Introduction: Wilson’s disease is a genetic abnormality inherited in an autosomal recessive manner that disrupts cellular copper transport. Impaired biliary copper excretion leads to accumulation of copper in several organs most commonly the liver, brain, and cornea. Renal failure associated with Wilson’s disease has been reported but is very rare.

Case Description: We present a case of a 47-year-old man who presented to the hospital with chronic progressive abdominal pain for the past 4 months. Patient had a liver biopsy 1 month prior suggestive of Wilson’s disease. The patient endorsed 3 weeks of progressive lower extremity swelling. Patient had associated lightheadedness, fatigue, and decreased appetite. Vital signs on admission were BP 100/60mmHg HR 77 97 79 98%/RA. Physical exam notable for jaundice, ascites, 2+ edema. No Kayser-Fleischer rings noted. Within 48 hours, the patient developed respiratory failure requiring intubation and hypotension requiring vasopressor support. CXR revealed pulmonary edema. CT abdomen revealed a stable renal cyst, no hydronephrosis. Blood, urine, sputum, ascites fluid cultures were all negative. Serum ceruloplasmin level was 29.9 mg/dl, serum copper 0.96 mcg/mL, 24 hour urine copper excretion 561 mcg/spec. Serum calcium 10.3mg/dl, anion gap 11, BUN 51 mg/dl and creatinine 1.1 mg/dl, Ca++ of 14.8 mg/dl, Mg++ of 0.7 mg/dl and Phos 1.2 mg/dl. PTH was 7 pg/ml. Urine pH was 5.5. Urine electrolytes panel was UN 77 mg/dl, UCI 85 mg/dl, UK 17 mg/dl, yielding a UAG of +9. 24-hr urine calcium was 208 mg. Her calcium normalized to 8.2 mg/dl and bicarbonate normalized to 23 mg/dl concomitantly with 4-day intravenous hydration. Potassium, phosphorus, and magnesium were replaced. Her OTC multivitamins and calcium carbonate were discontinued, but her repeat BMP remained hypercalcemic in the post-hospital clinic visit. Finally, a sestamibi parathyroid scan revealed a small parathyroid adenoma.

Discussion: PTLD was low normal which limited its use for differentiating causes of hypercalcemia. At a glance, patient’s history suggested Milk-Alkali syndrome, which was described as excessive calcium and alkali intake and impaired calcium excretion by alkalinosis, as the cause of the hypercalcemia. However, patient’s paracalcitonin and metabolic acidosis went against Milk-Alkali syndrome. PTLD can inhibit Na-H exchange in distal tubule causing increased bicarbonate wasting, hypercalcemia and type 1 RTA. Hypercalcemic metabolic acidosis led to an investigation of PTLD-dependent mechanism and the discovery of a subtle parathyroid adenoma.

Acidotic Hypercapnia: A Case Series of Acidosis Driven Respiratory Muscle Dysfunction
Catherine King, Rahul Mukherjee. Respiratory Medicine, Birmingham Heartlands Hospital, Birmingham, West Midlands, United Kingdom.

Introduction: It is commonly assumed that respiratory acidosis follows the development of acute hypercapnia. This case series describes 4 patients with hypercapnia secondary to metabolic acidosis demonstrated through serial arterial blood gases (ABG) treated with Non-invasive Ventilation (NIV).

Case Description: Case 1: A 64 year-old with diabetes on metformin and chronic obstructive pulmonary disease (COPD) with pneumonia and non ST-elevation myocardial infarction. Initial ABG - metabolic acidosis which deteriorated despite standardised treatment, with onset of hypercapnia and NIV requirement. Case 2: A 75 year-old with COPD admitted with breathlessness with an oxygen saturation of 84% treated with NIV for 24hrs, and NIV to treat acidotic hypercapnia. Applying the Henderson-Hasselbach equation to his ABG, predicts bicarbonate 29mmol/L not 17.9, confirming metabolic acidosis. Case 3: A 78 Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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990A
year-old with severe COPD and shortness of breath/cough, treated for acute exacerbation COPD. Initial ABG - metabolic acidosis but later developed progressive hypercapnia requiring NIV. Case 4: A 60 year-old obese lady with drowsiness/ agitation, treated for sepsis. ABG - mixed respiratory/metabolic acidosis due to combination of obstructive sleep apnoea and non-steroidal anti-inflammatory drug-induced acute on chronic renal failure. NIV was later commenced for worsening hypercapnia.

**Discussion:** Acidotic hypercapnia is an under-recognised subtype of respiratory failure; in all 4 cases this acidosis reversed completely with NIV and optimal medical management. Acidosis is a known cause of muscular dysfunction and may contribute to respiratory muscle fatigue. We postulate a similar causation of respiratory failure described previously due to circulatory shock (Type 4 respiratory failure) which resolves when shock is corrected. Further trials are required to decide the best management of acidotic hypercapnia.

**PUB375**

**Steroid May Be an Effective Treatment for Warfarin Related Nephropathy**

Nataong Thamcharoen,1 Ridhmi P. Rajakankar,1 Raquel M. Rosen,1 Vivette D. D’Agati,2 Medicine, Bassett Medical Center, Cooperstown, NY; 1Pathology and Cell Biology, Columbia Univ College of Physicians and Surgeons, New York, NY.

**Introduction:** Warfarin-related nephropathy (WRN) manifests as acute kidney injury (AKI) from over-anticoagulation, mostly INR > 3, causing glomerular hemorrhage and tubular obstruction by red blood cell (RBC) casts and oxidative stress damage to tubules. We report a case of a patient with biopsy-proven WRN and therapeutic INR.

**Case Description:** An 83-year-old man with CKD stage 3A, coronary artery disease, atrial fibrillation, admitted for AKI with creatinine (Cr) of 3 mg/dL, tea-colored urine. He had several hospitalizations over the past 6 months and was exposed to multiple antibiotics. Last antibiotic use was a month ago. He had gastric bleeding (GIB) 4 months ago from INR of 6 resulting in hypotension and AKI with renal recovery to baseline (1.2 mg/dL). Lab showed rapidly rising Cr over several weeks.

**Clinical course of renal disease**

![Graph showing clinical course of renal disease](image)

INR was within therapeutic range after the GIB. Urinalysis showed RBC presented since 4 months ago. Urine protein creatinine ratio was 1.8 g/g. Urine sediment showed dysmorphic RBC and RBC casts. Serologic tests and complement levels were all normal. He received steroids for presumed vasculitis related nephropathy. Renal biopsy later showed diffuse acute tubular injury and numerous RBC casts, suggestive of WRN without evidence of glomerulonephritis or allergic interstitial nephritis. Cr improved with steroid therapy which was gradually tapered. Later, warfarin was switched to aspirin.

**Discussion:** When other causes have been excluded, WRN should be considered as a cause of AKI despite therapeutic INR. The standard treatment includes reversal of coagulopathy and supportive care. Interestingly, prednisone was proven to be effective in our patient, however its role should be further evaluated.

**PUB376**

**Hypernatremia after Bariatric Surgery: A Case of NDI with Unknown Etiology**

Jiandong Zhang,1 Itunu O. Owoyemi,1 Reginald Ifeanyi Obi,2 Hsiao Ling Lai.2 1General Internal Medicine, Vidant Medical Center, Brody School of Medicine, East Carolina Univ; Greenville, NC; 2Div of Nephrology and Hypertension, Vidant Medical Center, Brody School of Medicine, East Carolina Univ; Greenville, NC.

**Introduction:** Hypernatremia is a common electrolyte disorder with incidence of about 0.3-5.5% in hospitalized patient, bearing 30-80% mortality in ICU. Thus, appropriate recognition of underlying etiology is vital to the appropriate treatment of this disorder.

**Case Description:** Here we report 56 y/o CM with Hx of T2DM, morbid obesity, who was referred to nephrology consult for hypernatremia (day 45 of admission). He was initially present for gastric bypass operation, and complicated for EJ tube leakage which require multiple OR visits for drainage manipulation. His lab revealed a serum sodium in the range of 140-150 prior to this episode of 160-165. Serum osmolality as 320-330 mOsm, Uosm 100-200 mOsm on multiple occasions, UA revealed a UNa+ of 20s mmol/L, UCr 18.18 mg/dL. Negative for protein or glycosuria. His free water deficit was calculated as 11L, D5W was initiated to replace free water. Shortly after, patient then developed massive volume of urinary output > 4L per day. DDAVP was administered without improvement in UOP or osmolality, suggesting that nephrogenic diabetes insipidus is likely to attribute to this case. Thereafter, HCTZ and amlopidine was started and polyuria-polydipsia was gradually tailed in a period of about 3 weeks course. Pt was educated to have good management of osmotic load and water intake, and discharged with HCTZ 12.5mg bid.

**Discussion:** DI is a rare cause of hypernatremia, but inherits with unique interventions. In adult settings, most of DIis are acquired form secondary to medications or electrolyte abnormalities. Here, we ruled out lithium use, hypokalemia or hypercalcemia. Genetic test for possible mutations in patient and his family was discussed. Nephrogenic diabetes insipidus (NDI) is a rare kidney disorder that may be inherited or acquired, caused by impaired ability of kidney collecting duct tubules to concentrate urine. Management for NDI paradoxically involves diuretics beyond correction of modifiable secondary contributing components.

**PUB377**

**A Case of Tenofovir-Induced Acute Kidney Injury (AKI) with Fancioni Syndrome**

Michael J. Rosland,1 Allison Bigeih,2 Elise J. Barney,3 Medicine, Banner Univ Medical Center, Phoenix, AZ; 1Clinical Medicine, AT Still Univ, Kirkville, MO; 2Nephrology, Phoenix VA Healthcare System, Phoenix, AZ.

**Introduction:** Tenofovir disoproxil fumarate (TDF) is a nucleotide-reverse transcriptase inhibitor used in HAART therapy for HIV. TDF is filtered by the glomerulus and secreted by proximal tubular epithelial cells. Nephrotoxicity, although rare, is well described, specifically causing proximal renal tubular acidosis or rarely Fancioni Syndrome (FS). The suppressed DCT sodium reabsorption via AQP2 and ammonia channel. Here we report a case of TDF-induced AKI in an HIV+ patient with acute renal failure.

**Case Description:** A 65-year-old non-diabetic male with history of hypertension and HIV on HAART therapy presented with acute hiccunnications, 2 months of oliguria and admitted with AKI. Labs showed BUN 66, creatinine 6.79, total CO2 16, anion gap 15, and normal potassium, phosphorous, and lactate. Urinalysis showed glycosuria and proteinuria; urine protein/creatinine ratio was 829 mg/g. Serologies and workup, including urine microscopy were negative. HgA1c was normal. HIV RNA was 55 copies/mL. Renal ultrasound was unremarkable. TDF was held; however the patient became anuric and required hemodialysis. Two months later, he is non-oliguric but remains dialysis-dependent. Recent urinalysis showed persistent glycosuria and 24-hour urine confirmed proteinuria of 815 mg. Renal biopsy showed acute tubular injury with diffuse early fibrosis. Chart review revealed 7 years of glycosuria, subnephrotic proteinuria with chronic renal dysfunction over the last 2 years (creatinine 1.24-1.39), and recent hypophosphatemia. The consistent factor was TDF therapy for many years.

**Discussion:** There are limited data regarding TDF-induced FS and its course, although it is thought to be reversible with cessation. Chronic kidney disease due to TDF has been debated. As TDF is a cornerstone of HAART, early recognition of FS is crucial. This case highlights the importance of monitoring kidney function closely, as proximal tubule dysfunction may present indolently and could be permanent if diagnosis is delayed.

**PUB378**

**Echocardiographic Evidence of Dialysis-Related Amyloidosis Presenting as New-Onset Ascites and Liver Failure**

Carsten R. Hamann,1 Nicole Syed,2 Nicole Kristine Shah-Ghassemzadeh,1 Seyed-Ali Sadjadi.1 1Dept of Internal Medicine, Loma Linda Univ Medical Center, Loma Linda, CA; 2Dept of Family Medicine, Univ of California: Riverside: Moreno Valley, CA.

**Introduction:** Dialysis-associated amyloidosis(DRA) is a common but infrequently reported complication of long term hemodialysis(HD) and peritoneal dialysis, caused by deposition of beta-2-microglobulin(B2M) amyloid fibrils in articular and visceral tissue. B2M is a ~12,000 dalton glycosylated polypeptide, inefficiently filtered through traditional HD filters, notably low-flux filters. DRA most commonly presents with articular involvement, notably carpal tunnel syndrome and scapulohumeral periarthritis. Visceral involvement of DRA is rarely reported.

**Case Description:** We present the case of a 33 year old female with end stage renal disease(ESRD) secondary to hemolytic uremic syndrome on HD, hypertension(HTN), pulmonary HTN, and recently diagnosed diastolic heart dysfunction. B2M was elevated to 64.8 mg/dl. Echocardiogram showed hyperdynamic left ventricular function, an ejection fraction of 70%, right ventricular systolic pressure ~45 mmHg, severe dilation of all four chambers, and a speckled appearance of left ventricular walls suggestive of amyloidosis. Serum B2M was elevated to 64.8 mg/dL.

**Discussion:** We believe this case exemplifies a rare presentation of visceral DRA with cardiac involvement. Clinicians taking care of patients with ESRD who have been on long term hemodialysis or peritoneal dialysis must be cognizant of the myriad ways DRA can present. Visceral DRA, in particular DRA with cardiac involvement, is rare but should be on the differential for any patient with ESRD who presents with signs of infiltrative heart disease, including congestive liver failure, ciritis and ascites.
Renaissance failure due to direct infiltration of chronic lymphocytic leukemia

Bartłomiej Posnisk, Nina Undeivia Yedavalli.

Internal Medicine, West Suburban Medical Center, Oak Park, IL.

Introduction: Chronic lymphocytic leukemia (CLL) is a cancer due to uncontrolled growth and accumulation of mature B lymphocytes. Asymptomatic kidney involvement of is fairly common with up to 90% of patients having interstitial infiltration on autopsy. Less than twenty cases of acute renal failure due to direct CLL infiltration have been reported in the literature.

Case Description: An 86-year-old African American female was diagnosed with stage IV CLL when she presented with extensive lymphadenopathy. Treatment with bendamustine and chlorambucil was discontinued due to poor compliance, creatinine of 1.95 mg/dL, and disease progression. Creatinine was later found to be 4.2 mg/dL with renal ultrasound consistent with medical renal disease. Protein electrophoresis with immunofixation of urine and serum was normal. Creatinine reached a maximum value of 5.7 mg/dL. Renal biopsy demonstrated dense infiltration of small lymphoid cells consistent with low grade B cell lymphoma as well as some focal segmental glomerulosclerosis.

Discussion: Renal insufficiency is not uncommon in CLL patients as it can be seen in 75% of patients at the time of initial diagnosis and another 16.2% at some later time. The mechanism of renal failure in patients with direct CLL infiltration is thought to be due to compression of the renal tubules and microvasculature leading to obstruction and ischemia. The most common pattern seen on kidney biopsy is dense interstitial infiltration in the cortex with some degree of glomerular fibrosis/sclerosis. Most important is the absence of immune complexes. There is no agreed upon standard of care for treatment, it should be individualized. Regardless of the treatment modality, there seems to be a high recurrence rate. Recognition of this rare phenomenon is crucial as prompt recognition and intervention may reverse renal damage and recover function.

Acute Oxalate Nephropathy - The Answer Is in the Urine

Mahrrukh Rizvi, Rebecca D. Monk.

Nephrology, Univ of Rochester School of Medicine, Rochester, NY.

Introduction: Prompt recognition and rapid institution of therapy is crucial to preserve renal function in AKI. An easy but underutilized test is urine microscopy. We highlight the importance of urine microscopy in this case of suspected ethylene glycol (EG) ingestion. Ultimately a renal biopsy confirmed the diagnosis.

Case Description: A 59 y/o male presented with ~ 10 hrs of odd behavior. He was disoriented, dilated, and hypertensive (225/120) with labs notable for pH 7.2, HCO3 7.8, PCO2, 8.4, anion gap (AG) 26, albumin 4.1, lactate 8.4, BUN 19, Cr 1.9 (0.7 one year ago).

A drug screen and toxic alcohols were negative. On transfer to our hospital, ~ 30 hrs after initial symptomatology, an OG was obtained and negative. Urine microscopy revealed sheets of needle shaped calcium oxalate monohydrate crystals. EG ingestion was suspected and he was started on a Na-Bicarb drip to prevent tissue deposition of EG metabolites, however, patient refusal, lack of OG and EG level continued to lead away from a final diagnosis of EG toxicity and early dialysis. His renal function quickly deteriorated over the next 48 hrs ultimately necessitating dialysis. A renal biopsy was obtained which revealed diffuse lymphocytic tubulointerstitial inflammation, acute tubular injury and numerous calcium oxalate crystals.

Discussion: EG is metabolized in the liver with a half life of 2.5-8.4 hrs. A lack of OG, presence of AG and Calcium Oxalate crystals suggest a late presentation when a negative OG and EG level is not unusual. This case highlights the utility of early urine microscopy and the importance of understanding the toxicokinetics of EG and other toxic alcohols to allow prompt diagnosis of ingestion despite significant laboratory gaps and lack of exposure history particularly in high risk patients with severe depression. Our patient ultimately allowed to EG ingestion and currently remains on dialysis.

AA Amyloidosis in an IV Drug User – A Cautionary Tale

Mahrrukh Rizvi, Rebecca D. Monk.

Nephrology, Univ of Rochester Medical Center, Rochester, NY.

Introduction: Most common reports of renal disease in IV drug users are related to HIV, HBV, and HCV infections. This has led to harm reduction initiatives nationwide aiming to decrease disease transmission via needles. A relatively rare but catastrophic form of renal disease in IV drug users is systemic amyloidosis, first reported in the 70’s. Given grave outcomes, it deserves the spotlight, especially to encourage early wound care into harm reduction initiatives in this population.

Case Description: A 38 year old Hispanic female with IV heroin and cocaine abuse with chronic lower extremity (LE) ulcers at injection sites presented with pain. Her exam was notable for a BP of 176/105, HR 75, Temp 97.3. Skin exam revealed superficial erosions on bilateral forearms, large wound bed in the left LE and ulceration with tender areas of eschar in the right LE. Admission labs revealed a creatinine of 2.4 mg/dL, albumin of 1.4 g/dL, CRP 70 mg/L, antibodies to Hepatitis C, 18 g of protein in the urine, oral fat bodies in the urine sediment with no red blood cells. A renal biopsy revealed AA amyloidosis with severe tubular atrophy and loss and interstitial fibrosis.

Discussion: In a case series, ~90% of patients with AA amyloidosis from IV drug use required dialysis within one month. Median survival is reported to be 25 months, which compares unfavorably with median survival of 52 months for all patients with AA amyloidosis on dialysis. Providing dialysis is challenging in these patients due to difficulties obtaining permanent vascular access, tunnelled lines being used for drug injection, poor hygiene, and infectious complications. This case underscores a grave, albeit rare complication of IV drug use resulting from chronic soft tissue infection. Whether street contaminants contribute to development of AA amyloidosis remains unknown. We bring this case to the spotlight to encourage early attention to skin complications in IV drug users. Isolated programs for easily accessible, cost-effective medical and wound care for IV drug users with soft tissue infections have been established. This has resulted in significant reductions in ED visits, hospital admissions, and costs in those areas. Perhaps, similar efforts should be initiated nationally.
Case Description: An 85 year old female with history of breast cancer treated with lumpectomy and radiation therapy, diet controlled diabetes mellitus and hypertension was diagnosed with lambda light chain restricted B-cell lymphoproliferative disorder by bone marrow biopsy (immunophenotypically consistent with Marginal zone lymphoma) five years prior to presentation and managed conservatively. She recently presented with lower extremity edema, dyspnea and 10 lb weight gain and diagnosed with nephrotic range proteinuria with urine protein/creatinine ratio 5.5 g/g and acute kidney injury with serum creatinine of 1.3 mg/dl from baseline 0.6 mg/dl. Serologies for hepatitis B & C, HIV, ANA, anti-ds DNA and complement levels (C3 and C4) were negative. SPEP showed low kappa and lambda light chain with normal ratio of 0.9 with negative urine immune-fixation for para-proteins. Age-appropriate cancer screening was negative but no prior colonoscopy reported. CT scan abdomen and pelvis showed stable splenomegaly, and scattered retroperitoneal and right common iliac lymph nodes, the largest measuring 1.1 cm. Kidney biopsy was performed with findings of AL amyloid nephropathy (light chain type lambda-restricted), without deposition in the glomeruli and arterioles, mild interstitial fibrosis and tubular atrophy, and moderate arteriosclerosis. As her AL amyloid nephropathy was likely secondary to BCLPD, the plan was to initiate chemotherapy. Due to poor performance status and limited cognitive function, chemotherapy was withheld. Her condition declined and sadly she passed away.

Discussion: AL amyloidosis is a rare manifestation of BCLPD with limited cases reported. This condition is more common in elderly female patients with multi-systemic involvement upon presentation. Aggressive therapy with high-dose melphalan and stem cell transplantation may improve patient survival. AL amyloidosis should be in the differential diagnosis of proteinuria in patients with BCLPD.

PUB384

Denosumab for Treatment of Immobilization-Related Hypercalcemia in a Patient with End-Stage Renal Disease

A 58 year old male with a history of abdominal aortic aneurysm repair presented with fatigue and nausea. Laboratory studies showed a creatinine of 14.8 mg/dL, bicarbonate of 11 mEq/L, glycosuria and proteinuria. Urine sediment was notable for muddy brown casts. TDF was withheld and a renal biopsy was performed. The biopsy showed regenerative changes with simplified, attenuated epithelium in the proximal tubules on H&E staining (A) and by EM (B). Megamitochondria with markedly diminished cristae, typical of TDF toxicity, were seen (C). Lastly, nitrotyrosine immunostaining highlighted areas of oxidative and nitrosative stress in the proximal tubules (D). The patient required hemodialysis, but subsequently, his renal function improved sufficiently to discontinue hemodialysis and his creatinine decreased over several months.

Discussion: Immobilization-related hypercalcemia in patients undergoing maintenance dialysis is not rare. The report on the effectiveness and safety of denosumab for immobilization-related hypercalcemia in patients with ESRD has been scarce. Our case indicated that denosumab can be a vial for intractable immobilization-related hypercalcemia in patients with ESRD.

PUB385

A Dying Kidney's Last Stand: Removal of Renin-Secreting Atrophic Kidney Improves Blood Pressure Control

A 79-year-old man with diabetic nephropathy was diagnosed with gastric cancer and gastric resection was recommended five months prior to admission. However, he developed acute kidney injury due to contrast-induced nephropathy. He admitted and initiated hemodialysis, but he experienced acute myocardial infarction and acute heart failure, for which he became bedridden, and operation was cancelled. Afterwards, his serum calcium gradually elevated from 8.8 to 12.9 mg/dL, and general fatigue developed. Immobilization-related hypercalcemia was diagnosed after excluding other possibilities. Alendronate was given for two weeks, without any improvement. He was then administered 60 mg of denosumab subcutaneously with calcium supplement and alfalcaldiol and his serum calcium decreased to 9.3 mg/dL one week later, and was controlled within the 9.0-10.0 mg/dL range.

Discussion: Immobilization-related hypercalcemia in patients undergoing maintenance dialysis is not rare. The report on the effectiveness and safety of denosumab for immobilization-related hypercalcemia in patients with ESRD has been scarce. Our case indicated that denosumab can be a vial for intractable immobilization-related hypercalcemia in patients with ESRD.
Case Description: A 67-year-old male with history of diabetes and multiple comorbidities, presented with a right hand cellulitis. He was found to have MSSA sepsis, aortic valve vegetation, L3-L4 discitis, epidural abscess, and osteomyelitis. Patient was admitted to ICU for septic shock with persistent hypotension and right upper quadrant pain. He was found to have raised inflammatory markers and blood cultures positive for MSSA. CT scan of chest showed right lower lobe consolidation and right pleural effusion. CT scan of abdomen showed free fluid in right upper quadrant. A serum titer for ASO was negative. Renal biopsy showed acute glomerulonephritis with mesangial IgA deposition, negative ANA, negative anti-DS DNA, negative ANCA, negative GBM antibody, and high anti-dsDNA titer. The patient was started on IV Cefazolin. His recovery was complicated by worsening renal function. A renal ultrasound showed chronic renal failure with bilateral atrophic kidneys. The patient was diagnosed with IgA-dominant Staphylococcus infection-associated glomerulonephritis. Along with RAS blockade agents, patient was treated with 12 months of antibiotics. Follow up blood work showed Cr and UPC improved to 1.21 mg/dL and 3.8, respectively.

Discussion: Although patients with IgA-dominant Staphylococcus infection-associated glomerulonephritis usually present with a urinary tract infection or sepsis, our patient presented with a right hand cellulitis. Our case illustrates that longer duration of antibiotics may be employed for worsening renal failure. Further studies will be needed to focus on the length of an antibiotic course in IgA-dominant Staphylococcus infection-associated glomerulonephritis.
occurred given the irreversible ESRD. She had systemic manifestations of her disease for 2 years, which had led her to recurrance in a non-transplant group. Patients who present with advanced renal disease due to glomerulonephritis and malignant hypertension with MAHA should be evaluated for aHUS as treatment can manage systemic manifestations and prevent recurrence in allografts.

PUB392

Antithrombotic Cyclosporine Antibody Negative Granulomatosis with Polyangiitis Associated with Crescentic IgA Nephropathy - A Clinical Conundrum

Shriram Sharma, Eric J. Bloom, Rassib Raja. Nephrology, Einstein Medical Center, Philadelphia, PA.

Introduction: GPA could present as ANCA negative in 40% of patients. Chen et al reported 32.9% patients who were ANCA negative had fewer extramural symptoms than patients who tested positive. Interestingly, there have been several case reports of ANCA vasculitis associated with crescentic IgAN. Since the majority of the patients were ANCA negative, not much is known about the treatment of ANCA negative GPA with Crescentic IgAN.

Case Description: We present the case of a 52 year old gentleman who presented with palpable purpura, epistaxis, polyarthritis, hematuria, proteinuria and chronic sinusitis. A left thigh punch biopsy showed intense perivascular and interstitial infiltrate and leukocytoclasia. He tested negative for hepatitis, ANA, MPO and PR3. He was started on Mtx and PredniRone 60 mg daily. CT chest was negative for granulomas. Subsequently, the patient developed right foot drop secondary to mononeuritis multiplex and digital ischemia of bilateral fourth toes, bearing loss and blurry vision. Given the progression of his symptoms he was switched to Rituximab 850 mg every 4 weeks. A kidney biopsy was done given the hematuria and proteinuria which was consistent with IgA nephropathy (MEST score 0). His S.Cr remained normal for 1 year and the U Pr/Cr improved. However the patient stopped Mtx on his own. His S.Cr increased to 1.32 and proteinuria worsened. A repeat kidney biopsy showed advanced IgA nephropathy with crescents (M2E1S0T1). Repeat ANCA testing was negative. He was started on pulse steroids and IV Cyclophosphamide and now his S.Cr is 1.37 mg/dl with persistent proteinuria.

Discussion: Due to lack of prospective clinical trials for ANCA negative vasculitis, the treatment is tailored to the patients clinical response and the side effect profile. Rituximab appears to be effective for ANCA negative GPA, but steroids and cyclophosphamide have been shown to be more beneficial for Crescentic IgAN. 5yr renal survival 28%. The association between ANCA negative GPA and Crescentic IgAN is rare and the interest in an adequate treatment strategy remains high.

PUB393

ANCA Associated Crescentic Glomerulonephritis in a HIV Positive Patient with Disseminated Kaposi Sarcoma

Tamara Duggal, 1 Manoj Das, Nilang G. Patel, 1 Pradeep Arora. 1 Medicine, VCU, Richmond, VA; 2 Medicine, VAMC, Richmond, VA.

Introduction: A 53 year old male was admitted with serum creatinine of 5.6 mg/dl. He had HIV infection since 1997 accepting HAART therapy sporadically, hypertension, drug abuse and hepatitis C. Physical examination revealed T 101 F, BP 130/80 mmHg, and right side external erythema. Laboratory data included: Hgb 12.4 mg/dl, WBC 10.2 K/cu mm, RBCs and 30 WBCs; 24 hour urine protein excretion of 6.4 g; HIV PCR viral load of 7400; and 1+ lower extremity edema. Laboratory data included: UA with 30 mg/dl protein, 20 haem, ANCA +.

Case Description:

A 53 year old caucasian male was presented to our institution for weakness, failure to thrive and hypokalemia. She has history of HIV for ~8 years, well controlled on tenofovir containing HAART, 4 months prior to presentation, she suffered a sudden cardiac arrest after a diarreheal episode and required ICU stay at outside facility where she was told that her serum potassium at admission was ‘close to zero’. Cardiac catheterization did not reveal any ischemic etiology. She was discharged with oral potassium supplementation 40mgEq twice a day. However, she was feeling sick with weakness, nausia, intermittent vomiting & weight loss and thus came to us. At presentation, her serum potassium was 2.5 2.2 mg/dl, sodium 132.1 130.5 mg/dl, phosphate 1.6 mg/dl and bicarbonate 13.3 mmol/L with anion gap of 14. Her renal function was preserved and had mild proteinuria of ~0.5 g/dl. Initial work up was negative for malignancy. We noted that she had glycosuria with normal serum glucose and had a potassium-creatinine ratio of 1.4. She also had a fractional excretion of sodium of ~65%.

Case Discussion:These patients should be frequently monitored with urinalysis and renal function panel while on therapy. Raising the awareness among clinicians with regard to this potential side effect is vital for early intervention and prevention of life-threatening complications.

PUB394

TMA in the Setting of CMV Reactivation

Jordan Gabriela Nestor, Hilda E. Fernandez. Dept of Medicine, Div of Nephrology, Columbia Univ Medical Center, New York, NY.

Introduction: Renal disease due to abnormalities in the complement alternative pathway (AP) includes C3 glomerulopathies and atypical HUS. PA disorders result from loss of surface or fluid-phase complement control caused by acquired or genetic defects. AP diseases are often clinically indistinguishable in the setting of allograft.

Case Description:

30yo A F w/ 3/5 strength all extremities. Admitted w/ initial labs notable for Cr 1.0 mg/dL, CPK 22000 IU/L, LDH 2500 IU/L, SMA Ab, and muscle biopsy c/w necrotizing myopathy. Treated with 7 day steroid pulse w/o improvement. On HD#38, biopsy witnessed C3 on HD17. CT head w/ hypodensities c/o infarcts. MRI with multiple FLAIR hyperintensities. MRA/MRV unremarkable. ICU transfer on HD19. CBC showed platelet count 49k/mL with repeat 6k/mL. Also had low haptoglobin, normal coagulation factors/fibrinogen, elevated bilirubin, transaminis, and schistocytes on peripheral smear. One month in setting insetting of HD, by 1st dose of eculizumab on HD#36 patient had stable LDH, improved though MRA/MRV panel negative for STEC. LP bland. Concern for Macrogluoplasia Activating Vasculitis, started anakinra for elevated ferritin CRP. BM bx w/o evidence of malignancy. Developed amuric AKI, initiated CRRT. New CMV viremia HD23 detected (6k copies/mL). MRI with multiple FLAIR hyperintensities. MRA/MRV unremarkable. ICU transfer on HD19. CBC showed platelet count 49k/mL with repeat 6k/mL. Also had low haptoglobin, normal coagulation factors/fibrinogen, elevated bilirubin, transaminis, and schistocytes on peripheral smear. One month in setting insetting of HD, by 1st dose of eculizumab on HD#36 patient had stable LDH, improved though MRA/MRV panel negative for STEC. LP bland. Concern for Macrogluoplasia Activating Vasculitis, started anakinra for elevated ferritin CRP. BM bx w/o evidence of malignancy. Developed amuric AKI, initiated CRRT. New CMV viremia HD23 detected (6k copies/mL). MRI with multiple FLAIR hyperintensities. MRA/MRV unremarkable. ICU transfer on HD19. CBC showed platelet count 49k/mL with repeat 6k/mL. Also had low haptoglobin, normal coagulation factors/fibrinogen, elevated bilirubin, transaminis, and schistocytes on peripheral smear. One month in setting insetting of HD, by 1st dose of eculizumab on HD#36 patient had stable LDH, improved though MRA/MRV panel negative for STEC. LP bland. Concern for Macrogluoplasia Activating Vasculitis, started anakinra for elevated ferritin CRP. BM bx w/o evidence of malignancy. Developed amuric AKI, initiated CRRT. New CMV viremia HD23 detected (6k copies/mL). MRI with multiple FLAIR hyperintensities. MRA/MRV unremarkable. ICU transfer on HD19. CBC showed platelet count 49k/mL with repeat 6k/mL. Also had low haptoglobin, normal coagulation factors/fibrinogen, elevated bilirubin, transaminis, and schistocytes on peripheral smear. One month in setting insetting of HD, by 1st dose of eculizumab on HD#36 patient had stable LDH, improved though MRA/MRV panel negative for STEC. LP bland. Concern for Macrogluoplasia Activating Vasculitis, started anakinra for elevated ferritin CRP. BM bx w/o evidence of malignancy. Developed amuric AKI, initiated CRRT. New CMV viremia HD23 detected (6k copies/mL). MRI with multiple FLAIR hyperintensities. MRA/MRV unremarkable. ICU transfer on HD19. CBC showed platelet count 49k/mL with repeat 6k/mL. Also had low haptoglobin, normal coagulation factors/fibrinogen, elevated bilirubin, transaminis, and schistocytes on peripheral smear. One month in setting insetting of HD, by 1st dose of eculizumab on HD#36 patient had stable LDH, improved though MRA/MRV panel negative for STEC. LP bland.
tamponade. Pericardiocentesis was done with drainage of ~6L serous fluid and analysis was negative for infection or malignancy. His KiV was optimal and he was dialyzed him daily for a week but he had recurrent PEF. CT showed thrombosis with total occlusion in left brachiocephalic vein, distal right brachiocephalic vein and proximal SVC with extension into distal part of bilateral internal thoracic veins. Collaterals were noted in abdominal and chest wall as shown in the CT angiogram.

He ultimately required pericardiectomy for management of recurrent PEF.

Discussion: Serious complications of SVC stenosis associated with CVC use is an under-recognized problem and should be considered HD patients with persistent or recurrent unexplained shortness of breath.

PUB397

A Case of Hyponatremia Associated with SGLT-2 Inhibitor Empagliflozin

Lauren Paster,1 Kurram Mehtabdin,1 Kenar D. Jhaeveri,1 Alyson Myers,2 Richard L. Barnett,1 ‘Div of Kidney Disease and Hypertension, Northwell Health, Great Neck, NY; 2 Div of Endocrinology, Northwell Health, Great Neck, NY.

Introduction: Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are increasingly used to treat type 2 diabetes mellitus (T2DM). Volume depletion alone or with diuretics has been noted but hyponatremia has not been reported with these agents. We describe the first case of symptomatic hypovolemic hyponatremia in a patient treated with empagliflozin and hydrochlorothiazide (HCTZ).

Case Description: A 69 year old Caucasian female with history of T2DM and hypertension presented with dizziness. She had been initiated on empagliflozin 9 days prior, in addition to 6 month continuous use of HCTZ-isopirnol, diltiazem, atenolol, and atorvastatin. At that time she was counseled to augment water intake to reduce risk of urinary tract infections. Labs from one month prior to empagliflozin initiation included Cr 1.3 mg/dl and Na 134 mmol/L. Physical exam was notable for orthostatic changes but negative for edema, confusion or seizure-like activity. Admission bloodwork included Na 112 mmol/L, Cr 1.7 mg/dl and glucose 207 mg/dl. Urine studies included: Na 27, Cl <1%, U FeCl <1%, U Cr <15, U Na <250 and persistent glycosuria were noted, consistent with prolonged empagliflozin +/- HCTZ effect.

Discussion: A literature search revealed no associations between SGLT-2 inhibitors and hyponatremia. Adding empagliflozin to a patient on HCTZ who was advised to increase free water intake promoted her symptomatic hypovolemic hyponatremia. Given the increasing utility of SGLT-2 inhibitors in patients with T2DM and hypertension, caution should be used when combining these agents with thiazide diuretics.

PUB398

Renal Response to Acute Hyponatremia during Alcohol Withdrawal

Vikrampal Ahsan1, Abhilash Barnett,1 A. Ahsan Ejaz,2,3 Al quadan,1,4 Ahsan Zb,2,3,4 1 Div of Endocrinology, Northwell Health, Great Neck, NY; 2 Div of Nephrology, Hypertension and Renal Transplantation, Univ of Florida.

Introduction: We present this case of hyponatremia to illustrate the renal physiology of sodium and water balance. Clinical presentation and laboratory data are depicted in the form of a graph.

Case Description: A 56 year old female with history of alcohol abuse and binge drinking 1) presented with agitation, tremors, mouth dryness and signs of alcohol withdrawal after abstinence for several days. No nausea, vomiting or pain. On exam, BP was 230/140mmHg with heart rate 120bpm, respiratory rate 22pm, chest clear to auscultation, abdomen non-tender, no organomegaly, no lower extremity edema, non-local neurologic exam. Routine chemistries including alcohol level and drug screen ordered. 2) Given intra venous Lorazepam and agitation improved. 3) 1 hour later, there was a precipitous drop in BUN from 22mg/dL to 7mg/dL admission was 11mg/dL. Baseline serum sodium was 140mmol/L documented at clinic visit 2 weeks prior to ER visit. 4) 1 liter Normal saline bolus administration, additional Half liter Normal saline. 5) Brisk urine output noted. 6) Serial serum sodium with upward trend. Patient more coherent, intact neurological exam. Urine osmolar changes shown. 7) Urine volume decreased with improved serum sodium. Oral rehydration allowed. Patient discharged to rehabilitation facility after 72 hours with normal neurological, medical and laboratory status.

Discussion: Hyponatremia is a commonly encountered problem and treatment varies with the nature of onset - acute or chronic, severity and symptoms. In the above case of hypovolemic hyponatremia, intravascular volume repletion reduced ADH secretion (decreased UOsm) and the kidneys responded by producing dilute urine (brisk diuresis), excreting free water and subsequent correction of hyponatremia.

PUB399

Dialysis Disequilibrium Syndrome with Mild Azotemia due to Septic Encephalopathy

Sushanta K. Goswami, Joe Ghaita, Satish Kumar. Medicine/NeUrology, Univ of Oklahoma Health Sciences Center and VA Medical Center, Oklahoma City, OK.

Introduction: Dialysis Disequilibrium Syndrome (DDS) was initially described as a constellation of neurological symptoms of cerebral edema, occurring early during the first dialysis in patients with high BUN. We present a patient who continues to have DDS at low levels of BUN, two years after an episode of severe sepsis.

Case Description: A 24 year old woman presented in septic shock from Group A streptococci, two days after a vaginal delivery. She had DIC with distal gangrene in all four extremities. She also had AKI and has remained dialysis-dependent two years later. Since discharge, she has had persistent memory deficits, and periodic headache and vomiting. These symptoms worsen after 2 hours on dialysis. Pre and post-dialysis CT scans showed cerebral edema on the post-dialysis scan only. MRI of brain showed diffuse cerebral edema with bifrontal predominance. Lab tests done pre and post-dialysis showed changes in osmolality 291 to 289, BUN 17 to 9, CO2 29 to 31 and ADH 2 to 13. There were no signs of volume overload or orthostasis. Symptoms improved with reduction of dialysis time to 2 hrs on a small dialyzer without ultrafiltration, using 145 Na and 35 HCO3 concentration in the dialysate.

Discussion: DDS was first described in 1962, occurring early during first dialysis in patients with high BUN. Animal studies demonstrated that the major mechanism of DDS was the rapid lowering of blood urea by dialysis. Slower diffusion of urea from brain to blood created an osmotic gradient that induced movement of water from the blood to the brain. Classic DDS has now become uncommon, perhaps due to the wide-spread recognition of DDS and the earlier start of dialysis. Recent reports describe DDS occurring without high levels of BUN suggesting that additional mechanisms may be involved. In our patient, a severe episode of systemic sepsis has left her with a propensity for recurrent cerebral edema late in dialysis. We speculate that septic encephalopathy has caused persistent changes in the blood-brain/brain-CSF barriers or in neuronal transporters that make her more susceptible to DDS even with small osmotic shifts at low level azotemia. Disclaimer: None

Funding: VA Support, Clinical Revenue Support
PUB400
Late-Onset Warfarin-Induced Skin Necrosis Suspected to Be Calciphyaxis in a Patient with End-Stage Renal Disease on Hemodialysis
Emily Lu,1 Joanna Harp,2 Jeffrey I. Silberzweig.1 1Nephrology & Hypertension, Weill Cornell Medicine/New York Presbyterian Hospital (WC/YNYPH), New York, NY; 2Dermatology, WC/YNYPH.

Introduction: Warfarin-Induced Skin Necrosis (WISN) is a rare complication almost always occurring <10 days after warfarin initiation; “late-onset WISN” develops beyond this time. It is characterized by cutaneous purpuric, necrotic lesions requiring prompt diagnosis and treatment due to high morbidity/mortality. We present a case of cutaneous purpuric and necrosis in end-stage renal disease (ESRD) initially attributed to calciphyaxis.

Case Description: A 58-year-old woman with ESRD on hemodialysis (HD), peripheral vascular disease and deep vein thromboses on chronic warfarin presented with extensive lower extremity cutaneous purpuric, necrotic lesions. She had calcium 8.9mg/dL, albumin 1.8g/dL, phosphorous 3.4mg/mL (8.5 in the past year); intact parathyroid hormone 99 pg/mL (1000 in the past year). Her INR was 4.0 but labile. Leg X-ray showed marked vascular calcification. Hyperacuglobulin vasculopathy (this admission and one year ago) was unrevealing. Proteins C and S (from warfarin use) and Factor X activity were decreased; but Factor V Leiden, Prothrombin gene mutation, Antithrombin III mutation, Cardiolipin IgG/IgA/IgM antibodies, Homocysteine, complement levels C3 and C4, cryoglobulins, SPEP and HBT antibody were negative/normal. A full APS workup could not be performed due to warfarin use. Platelet count was normal. Infectious studies were negative. Based on these findings, her skin lesions were initially attributed to calciaphaxis. Two subsequent skin biopsies demonstrated pauci-inflammatory thrombogenic vasculopathy with no vascular calcium deposition (negative Von Kossa stain), suggesting a thrombotic or procoagulant etiology and effectively ruling out calciaphaxis. Given the dramatic presentation of skin lesions, labile INR, and exclusion of other compatible etiologies, we diagnosed late-onset WISN. The skin biopsy findings were pivotal in directing our treatment and led to improvement of skin lesions.

Discussion: This case highlights the diagnostic challenges and importance of skin biopsy in establishing the diagnosis of WISN, particularly in ESRD patients when calciaphaxis is suspected.

PUB401
Idiopathic Tubulointerstitial Nephritis and Uveitis

Introduction: NIA is an uncommon cause of acute kidney injury, mostly related to infections, drugs or systemic diseases.

Case Description: We report the case of a 18-year-old caucasian female who presented with vomiting, nausea, fever, weight loss and impaired renal function. She had neither urinary symptoms nor rash, arthralgias or recent infection. She took no regular medication and there was no prior use of antibiotics or non-steroidal agents. Physical examination was normal. Laboratory revealed hemoglobin 9.6g/dl, creatininemia 2.9mg/dL and urea 66mg/dL. Liver function tests and inorganic phosphorus were normal. Urine examination revealed 24h-proteinuria 400mg and no eosinophiluria. Urine culture was sterile. Renal ultrasound was normal. Immunologic study was negative for antinuclear antibodies, anti-citrullinated protein antibody, anti-neutrophil cytoplasmic antibody, myeloperoxidase and proteinase 3, anti-cardiolipin antibody, lupic anticoagulant antibody and anti-beta-2 glycoprotein. TASSO, rheumatoid factor and IGRA were negative. Serologic study was negative for HIV, HBV, HCV, Adenovirus, Parvovirus, Coxsackie, EBV, CMV, Herpes virus, Salmonella, brucella, borrelia burgdoferi, leptospira interrogans, Togavirus, coxiella burnetii, Legionella, Mycoplasma pneumoniae, Chlamydia pneumonieae and trachomatis. ACE levels and body CT scan were normal. A kidney biopsy was performed and revealed acute interstitial nephritis, with edema and inflammatory cell infiltration with multiple eosinophils. One-week later she was diagnosed with anterior uveitis. The diagnosis of idiopathic tubulointerstitial nephritis and uveitis (TINU syndrome) was then made and she started prednisolone 1mg/kg/day, tapered over 14 weeks, with complete renal function and ocular manifestations recovery.

Discussion: TINU diagnosis can be especially difficult in some cases because manifestations may not occur at the same time as illustrated in this case. Still, TINU syndrome should be considered in the differential diagnosis of renal-ocular syndrome. The renal prognosis is excellent and nephritis is often self-limited. Symptoms respond well to corticosteroids, but uveitis often relapses even after a long term follow-up.

PUB402
MPO-C-ANCA-Associated Necrotizing and Crescentic Glomerulonephritis

Introduction: MPO and PR-3 are the major autoantigens in ANCA-associated vasculitis (AAV). 90% of patients with AAV have either MPO- (P-ANCA) or PR-3 (C-ANCA). Generally, antibodies causing cytoplasmic (C) ANCA pattern are directed against PR-3 while those causing perinuclear (P) ANCA are directed against MPO. We present a case of necrotizing and crescentic glomerulonephritis where antibodies against MPO produced a cytoplasmic pattern.

Case Description: A 73 y.o. white male, former smoker was admitted with progressive flu-like symptoms and SOB attributed to multifocal pneumonia and pulmonary fibrosis. He was started on antibiotics. Later, he developed ARDS needing mechanical ventilation with FiO2 55-60%. Bronchoscopy showed diffuse alveolar hemorrhage. C-ANCA and MPO positive, but PR-3 negative. Clinical course was complicated by hypotension and SCr worsened from 0.8mg/dL to 2.35mg/dL. However urine output remained at 2-2.7L/day. Renal US revealed 13.5cm right and 12.7cm left kidney. UA: 288 RBC/hpf, 2 WBC/hpf, 1 coarse granular cast and 1 RBC cast. Renal biopsy showed necrotizing and crescentic glomerulonephritis with 50% glomerular involvement with necrosis and/or crescents and arterial and arteriolar nephroclerosis. IF was nonspecific. Treated with IV methylprednisolone, Cyclophosphamide and Plasmap exchange. SCr improved to 1.58mg/dL and he was discharged. He did not require dialysis during hospital stay.

Discussion: False positive MPO-C-ANCA can occur in autoimmune entities whereby antibodies to epitopes on MPO can produce cytoplasmic pattern. Regardless of the staining pattern, it may be the induction of MPO (e.g., propylthiouracil) or anti-MPO antibodies that result in the necrotizing glomerulonephritis as illustrated above. Underlying lung disease, suspected recent flu and other environmental factors are also contributing stimuli for the development of MPO-antibodies. Our case supports the pathogenic role of MPO in AAV.

PUB403
An Obscure Cause of Recurrent Hyperphosphatemia
Shameen Ahmad Beigh, David Levy, Sai Subhodhini Reddy. Nephrology Div, Univ of Rochester Medical Center, Rochester, NY.

Introduction: Dialysis patients often struggle with multiple dietary constraints imposed on them due to renal failure. Phosphate restriction is commonly stressed due to the known increased risk of mortality of patients with higher serum phosphate levels. The combination of a limited phosphate diet, prescription medication and residual renal function often limit the prevalence of significant hyperphosphatemia among peritoneal dialysis patients. We will present a case of a patient with recurrent hyperphosphatemia secondary to drinking water which was refractory to medical therapy.

Case Description: HS is a 51 year old male with ADPKD complicated by ESRD and started on peritoneal dialysis (CPD), dwell volume of 2L, 4 exchanges with 1.5% glucose solution and manual day exchange with 2.5 L of 2.5% glucose) in November 2014. Since September 2014 he was noted to have high levels of serum phosphate which was initially treated with Sevelamer 2400 mg three times daily with meals. In spite of this his serum phosphorous remained high (6.6-7.8 mg/dL) and Sevelamer 800mg with snacks was added. In January 2016 his serum phosphate was noted to be 7.5mg/dl and his Kt/V was 2.33. Velphoro 1000mg with meals was started. In March 2016 he switched from tap water to bottled water and his serum phosphate improved to 4.9 mg/dL. Further investigation was done due to the patient and it was determined that phosphate was being added to the water supply to prevent pipe corrosion.

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<th>Serum calcium (mg/dL)</th>
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<td>N/A</td>
<td>Velphoro 1000mg</td>
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</thead>
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<td>Sevelamer</td>
<td>800 mg with snacks added</td>
<td>800 mg with snacks added</td>
<td>Velphoro 1000mg</td>
<td>Changed to bottled water from tap water</td>
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</tbody>
</table>

Discussion: Our case demonstrates the importance of investigating all potential sources (including drinking water) of exogenous phosphate intake.
A Case Report Describing Therapy for Acute Urate Nephropathy in Spontaneous Tumor Lysis Syndrome from Chronic Myelomonocytic Leukemia

Introduction: Tumor lysis syndrome (TLS) with release of intracellular potassium, phosphate and nucleic acids, occurs in certain cancers after chemotherapy, but may occur spontaneously in cancers with a high proliferative rate or large tumor burden. One type of kidney injury from TLS is caused by uric acid crystal precipitation within renal tubules.

Case Description: An 84-year-old man with chronic myelomonocytic leukemia was seen in the emergency room for abdominal pain. Serum creatinine (Cr) was 2.56 mg/dL (baseline 1.13 mg/dL). A non-contrast CT abdomen/pelvis revealed moderate right hydropnephrosis and hydrourereter from a 7 mm stone at the ureterovesicular junction and other non-obstructing calculi. He was discharged home with urology follow up, but was admitted to the hospital two weeks later after repeat labs showed a serum creatinine (Cr) of 4.9 mg/dL. On return to the hospital, physical exam revealed normal vital signs and dry mucous membranes. Other findings included hypokalemia (3.1 mmol/L), hypophosphatemia (5.2 mg/dL), hyperuricemia (22.3 mg/dL), and leukocytosis (100.1 K/mm³). Urinalysis (UA) detected small blood, pH 5.1, and uric acid crystals which were confirmed with microscopy. The patient was administered rasburicase, IV fluids (3 amps of sodium bicarbonate per liter of D5 0.45% normal saline at 150 cc/hour), and IV furosemide. Urine output was 3-4 L/day. Repeat UA on hospital day #3 was notable for absence of uric acid crystals and pH 7. Cr was 2.18 mg/dL at discharge on hospital day #6. Repeat CT abdomen/pelvis showed resolution of hydropnephrosis and disappearance of uric acid stones.

Discussion: Acute urate nephropathy therapy includes IV fluids and loop diuretics as well as medications aimed at reducing the uric acid burden. Urinary alkalization is generally not recommended due to concern for calcium phosphate crystal precipitation. Our case suggests that treatment with IV sodium bicarbonate and loop diuretics in selected cases may be effective in the treatment of acute urate nephropathy without the untoward consequences of alkali therapy.

Unsuspected Protein S Deficiency Caused Vascular Thrombosis and Loss of Pancreas and Kidney Grafts Despite Initial Excellent Function and No Rejection

Case Description: An 84 year old man with chronic myelomonocytic leukemia was admitted for abdominal pain, nausea and vomiting. Physical exam was positive for abdominal tenderness. Vital signs were stable except blood pressure of 190/100 mmHg. Her home medications include sevelamer 2400 mg TID with meals, ciprofloxacin 500 mg qd, lisinopril 20 mg qd, nifedipine 60 mg qd, oxycodone 10 mg 3 times daily and 50,000 IU vitamin D. During the previous admission 8 days ago she was treated with cefepime and PD catheter was removed on the third day of treatment due to persistent, leukocytosis and effluent culture positive for pseudomonas aeruginosa. She was discharged on oral ciprofloxacin to complete antibiotic treatment for duration of 2 weeks after improvement based on sensitivity report. On repeat admission, patient was treated intravenous cefepime and also discharged on intravenous antibiotics because of large cultures were now resistant to florquinolones.

Discussion: Sevelamer is a phosphate-binding cationic polymer that is devoid of calcium which leads to decrease in relative oral bioavailability of ciprofloxacin when administered together. Concomitant administration of these drugs may decrease clinical efficacy of the drug and promote bacterial resistance to ciprofloxacin. It is very important to instruct CKD patients on sevelamer to take ciprofloxacin 2 hrs before or 6 hrs after sevelamer ingestion to avoid decreased bioavailability and to prevent the emergence of bacterial resistance.

Unsuspected Protein S Deficiency Caused Vascular Thrombosis and Loss of Pancreas and Kidney Grafts Despite Initial Excellent Function and No Rejection

Case Description: 1.To our knowledge, she is the first reported case of diffuse vascular occlusion causing strokes & MI. It rarely induces thrombosis of allograft without rejection, as well as medications aimed at reducing the uric acid burden. Urinary alkalization is generally not recommended due to concern for calcium phosphate crystal precipitation. Our case suggests that treatment with IV sodium bicarbonate and loop diuretics in selected cases may be effective in the treatment of acute urate nephropathy without the untoward consequences of alkali therapy.

Case Description: We reviewed clinical & lab data for hypercoagulable risk factors to define the role of protein S. Both kidney & pancreas functioned well from d 1 to 7. Nadir phosphate and nucleic acids, occurs in certain cancers after chemotherapy, but may occur spontaneously in cancers with a high proliferative rate or large tumor burden. One type of kidney injury from TLS is caused by uric acid crystal precipitation within renal tubules.

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PUB411

An Atypical Presentation of Atypical Hemolytic Uremic Syndrome

Marilyn (Linli) M. Phung, Christoph Licht, Jocelyn S. Garland.

Introduction: Atypical hemolytic uremic syndrome (AHUS) is a systemic thrombotic microangiopathy (TMA) caused by dysregulation of the complement system that cause significant morbidity and mortality, most notably with renal involvement.

Case Description: A 21-year-old previously healthy male presented to the emergency room with a 2-week history of epigastric pain and non-bloody diarrhea. She had been seen twice before with these symptoms but had been sent home after supportive care, with no preserved renal function. On her third visit, she had developed vomiting, fever, severe colicky flank pain and anuria. Her creatinine was found to be elevated and continued to worsen despite aggressive fluid resuscitation. Post-renal causes were excluded. Urine microscopy was non-contributory. Hemolytic work up showed worsening anemia and thrombocytopenia, elevated lactate dehydrogenase and bilirubin. Stishocytes were absent in blood smear and direct Coombs was negative. On history, she reported recent exposure to contaminated water from camping. Plasmapharesis was started, and an urgent renal biopsy was performed which later confirmed TMA. ADAMTS13 activity returned as sufficient and Stool Shiga toxin was negative, suggesting against TTP or STEC-HUS. With complement low, the patient was diagnosed with AHUS. Unfortunately, LDH and creatinine remained high despite plasmapharesis, thus requiring dialysis; she was started on eculizumab after blood counts failed to improve. Her medical condition stabilized and she was discharged home to continue maintenance eculizumab infusions and hemodialysis as an outpatient.

Discussion: This case highlights the importance of early recognition and treatment of TMA to mitigate the rapid development of end-organ damage. Evidence of a TMA process does not always require the presence of fragments on blood smear, or low haptoglobin levels. Subsequently, it is always important to distinguish between the etiologies of TMA as their management is notably different.

Funding: Government Support - Non-U.S.

PUB412

Acute Generalized Exanthematous Pustulosis Leading to Acute Kidney Injury through Glomerular Damage

Larissa Kruger Gomes, Poorva Bindal, Ryan D. Stephenson.

Introduction: Acute generalized exanthematous pustulosis (AGEP) is a rare drug-mediated reaction leading to sterile pustule formation and systemic inflammation. The most common end-organ involvement in AGEP is acute kidney injury (AKI), happening in up to 10% of cases. Nonetheless, the pattern of renal injury varies. We show a case of AKI mediated by AGEP in the setting of glomerular damage.

Case Description: 51-year-old female with past medical history of chronic obstructive pulmonary disease and morbid obesity presenting with a whole body pustular rash. Two weeks prior to admission the patient had an episode of cellulitis of the left foot for which she was being treated with vancomycin and ceftazidime. On day nine of treatment she developed a generalized exanthematous pustular rash, which got progressively worse and became associated with altered mental status. Furthermore, on admission she presented with a white blood cell count of 20,000 cells/mL and a creatinine (Cr) of 2.4 mg/dL, from her baseline of 0.8mg/dL. The urinalysis (UA) showed dysmorphic red blood cells, 0.8 Protein/Cr ratio and a fena of 1.1%. Urine was negative for eosinophils or casts. After removing the antibiotics the patient’s Cr returned to baseline after one week. No corticosteroids were used. A biopsy of the skin was obtained to confirm a pattern of involvement compatible with AGEP. No kidney biopsy was obtained.

Discussion: Normally, drug-mediated renal injury involves an acute interstitial nephritis or tubular injury. We present a rare case of crystalline Light chain proximal tubulopathy as a late form of injury to confirm a pattern of involvement compatible with AGEP.

Funding: Government Support - Non-U.S.

PUB413

Crystalline Light Chain Proximal Tubulopathy with Monoclonal Plasma Cell Infiltrate

Abhilash Koratalla, William L. Clapp, Dara N. Wakefield, A. Ahsan Ejaz.

Introduction: We present a rare case of crystalline Light chain proximal tubulopathy (LCPT) in a patient with Multiple myeloma.

Case Description: 69-year-old white male presented to the ER with fatigue and atypical chest pain. MI was ruled out but noted to have elevated sCr of 12.5mg/dL (14 months ago, sCr was 1.7mg/dL). On exam, vitals were stable, he was mildly lethargic and no pedal edema. Labs: Na 140nmol/L, K 3.8nmol/L, Cl 98nmol/L, HC03 19nmol/L, BUN 112mg/dL, Ca 9.5mg/dL, Phos 10mg/dL, Hgb 6.2g/dL. UA: pH 6.0, protein 100mg/dL, RBC 1-2/hpf, WBC 2/hpf, no casts. Renal US: R. 15.5cm, L. 15cm, no hydronephrosis. He did not respond to iv fluids and developed pulmonary congestion and became more lethargic which prompted urgent initiation of hemodialysis. Renal biopsy showed a prominent interstitial injury associated with accumulation of PAS negative luminal casts which have eosinophilic, hard,
Bone marrow biopsy confirmed multiple myeloma. Treated with Cyclophosphamide, Bortezomib and dexamethasone. Patient remains dialysis-dependent.

Discussion: Our case of LCPT is characterized by occurrence in an older patient, cytoplasmic inclusion of kappa-restricted monoclonal LC, crystals not detected by LM or IF but by EM and was associated with heavy-burden myeloma. IF-Frozen and IF-Peroxidase have low sensitivity for detection of LCPT, and pronase digestion for formalin-fixed sections may be required to detect crystalline LCPT. Alternately, immuno-gold staining may be required.

Case 6: A 59-year-old man with a history of hypertension and antiphospholipid syndrome (APS) on chronic anticoagulation presented with severe pleuritic chest pain and back pain and nausea. CT angiogram and transesophageal echocardiogram performed for a peak serum troponin level of 12 ng/ml excluded epicardial coronary thrombosis and aortic dissection. MRI of the heart revealed transmural enhancement of the lateral wall and apical segment of myocardium typical for infarction. The patient was treated for presumed lupus myopericarditis with methylprednisolone, colchicine, and mycophenolate mofetil without any clinical improvement. Her course was further complicated by worsening thrombocytopenia and new upper extremity DVT. The patient’s serum creatinine also increased to 1.3 mg/dL from a baseline value of 1.1 mg/dL with 1.14 g/d of proteinuria and back pain prompting hospitalization. The patient was then worked up for nephrotic syndrome & CKD stage 3. Workup revealed Factor 10 deficiency, so heparin, pulse steroids, plasmapheresis, and rituximab therapy were initiated.

Discussion: Catastrophic antiphospholipid syndrome (CAPS) is a rare but important cause of thrombotic microangiopathy.

Case Description: A 27-year-old woman with history of lupus, epilepsy, and deep venous thrombosis (DVT) on chronic anticoagulation presented with severe pleuritic chest pain and back pain and nausea. CT angiogram and transesophageal echocardiogram performed for a peak serum troponin level of 12 ng/ml excluded epicardial coronary thrombosis and aortic dissection. MRI of the heart revealed transmural enhancement of the lateral wall and apical segment of myocardium typical for infarction. The patient was treated for presumed lupus myopericarditis with methylprednisolone, colchicine, and mycophenolate mofetil without any clinical improvement. Her course was further complicated by worsening thrombocytopenia and new upper extremity DVT. The patient’s serum creatinine also increased to 1.3 mg/dL from a baseline value of 1.1 mg/dL with 1.14 g/d of proteinuria and back pain prompting hospitalization. The patient was then worked up for nephrotic syndrome & CKD stage 3. Workup revealed Factor 10 deficiency, so heparin, pulse steroids, plasmapheresis, and rituximab therapy were initiated.

Discussion: Catastrophic antiphospholipid syndrome (CAPS) is a rare but important cause of thrombotic microangiopathy.
The Efficacy of Eculizumab in Patients with Atypical Hemolytic Uremic Syndrome (aHUS) varies by cases. We present three cases of aHUS who recovered from kidney damage, which initially required hemodialysis.

Case Description: Case 1: A 67 year-old male was admitted to our hospital with a diagnosis of aHUS. Despite receiving plasma exchange treatment, he required hemodialysis. After 2 weeks of hemodialysis, administration of eculizumab was started. The patient recovered kidney function and hemodialysis was stopped. Kidney biopsy revealed TMA, no evidence of glomerulosclerosis and tubulointerstitial change. Case 2: A 43 year-old male was found to have TMA by blood test. He was diagnosed with aHUS. Serum creatinine level was high (15.78 mg/dL) therefore he urgently required hemodialysis. Kidney biopsy revealed TMA, glomerulosclerosis and moderate tubulointerstitial change. Although eculizumab treatment was commenced 4 weeks after starting hemodialysis, his kidney function deteriorated and hemodialysis had to be maintained. Genetic examination showed an abnormality in C3. Case 3: A 35 year-old patient presented with bPHT syndrome and AKI associated with renal phosphate wasting from genetic tubular defects causing hypophosphatemia.

Introduction: We conclude that immediate administration of eculizumab may avoid progression to kidney dysfunction in aHUS. Furthermore, the efficacy of eculizumab correlates with the degree of glomerulosclerosis and the extent of tubulointerstitial lesions.

Severe Hypercalcemia in a Young Man Who Loves Milk and Takes Vitamin Supplements

Paul El Azouy,
Alan Segal.
Nephrology, Univ of Vermont, Burlington, VT.

Introduction: The most common causes of hypercalcemia are primary hyperparathyroidism, paracancerotic syndromes, and variants of the so-called “milk-alkali” syndrome. Hypercalcemia is common in patients with cancer, mechanisms include PTHrP, osteolytic lesions and 1,25 (OH)2D3 production. Milk Alkali syndrome consists of ingestion of multiple vitamin supplements including vitamin A and vitamin D (10,000 IU/mL). Milk Alkali syndrome demands the triad of hypercalcemia, metabolic alkalosis, and AKI. Due to the high calcium intake, patients are predisposed to develop renal injury as a result of hypercalcemia. Hypercalcemia is also associated with renal tubular acidosis, aminoaciduria and renal glycosuria which inhibit the specific transporters of these solutes.

Case 1: The patient was a 48-year-old female hospitalized for general fatigue. Blood tests revealed hypercalcemia, anemia, kidney dysfunction, and reduced cell fragments in peripheral blood. She was diagnosed with aHUS. She underwent plasma exchange for one week without improvement in her thrombocytopenia and kidney function. She was thus started on eculizumab. The patient recovered her kidney function, and hemolytic anemia and thrombocytopenia resolved. Kidney biopsy revealed thrombotic microangiopathy (TMA), no evidence of glomerulosclerosis and tubulointerstitial change. Genetic examination showed an abnormality in C3. Case 2: A 67-year-old male was referred to our hospital with a diagnosis of aHUS. Despite receiving plasma exchange treatment, he required hemodialysis. After 2 weeks of hemodialysis, administration of eculizumab was started. The patient recovered kidney function and hemodialysis was stopped. Kidney biopsy revealed TMA, no evidence of glomerulosclerosis and tubulointerstitial change. Case 3: A 43-year-old man was found to have TMA by blood test. He was diagnosed with aHUS. Serum creatinine level was high (15.78 mg/dL) therefore he urgently required hemodialysis. Kidney biopsy revealed TMA, glomerulosclerosis and moderate tubulointerstitial change. Although eculizumab treatment was commenced 4 weeks after starting hemodialysis, his kidney function deteriorated and hemodialysis had to be maintained. Genetic examination showed an abnormality in C3.

Discussion: We report that immediate administration of eculizumab may avoid progression to kidney dysfunction in aHUS. Furthermore, the efficacy of eculizumab correlates with the degree of glomerulosclerosis and the extent of tubulointerstitial lesions.
Introduction: Pregnancy causes physiologic changes in one’s body. Cardiovascular, hormonal, renal, and respiratory changes occur. These are normal adaptations to accommodate the fetus and are imperative in an event of complications. We are presenting a case of a pregnant lady with respiratory alkalosis and severe hypokalemia.

Case Description: A 32 y old lady with pmdh of hypokalemia exacerbated during pregnancy was seen in renal clinic for hypokalemia. She was 23 weeks with her 2nd pregnancy on her 1st renal visit. Her serum potassium levels were between 2.4 meq/L to 3.8 meq/L. It has been on the higher side after her potassium supplement was increased to 120 meq per day. Symptoms include nausea and vomiting. Prior to the raising of her supplements, she was complaining of fatigue and leg cramps. No other subjective complaints. Laboratory studies showed glucose 85 meq/L, sodium 134 meq/L, potassium 3.3 meq/L, chloride 103 meq/L, bicarb 21 meq/L, BUN 0.52 mg/dl and creatinine 0.52 mg/dl. Urine pH 7.0 and sg 1.014. Urine: UNa 67, UK 76, UCr 44.2 Thyroid function tests were within normal limits. Renin activity was 47 ng/ml/hr and Aldosterone 94 ng/dl. Cortisol level at 12:49 pm was 9.0 mcg/dl. ABG showed pH 7.46, PCO2 30, PO2 105, Bicarbonate 21.3.

Discussion: In pregnancy, there is an increase in total body K but a slight decrease in serum K. Serum renin activity and aldosterone level increase due to decreased systemic vascular resistance. The kaliuretic effect of aldosterone is countered by the potassium retention induced by elevated progesterone. Due to the physiologic changes in the lungs and increased progesterone, respiratory alkalosis is common. In normal pregnancy, serum potassium level is usually normal and serum bicarbonate level can be low. This is a unique case of a pregnant patient with severe hypokalemia and respiratory alkalosis. With an elevated TKG of 12, her hypokalemia is most likely from renal loss and less likely by intracellular shift caused by alkalosis. In her case, she may have an underlying condition causing hypokalemia that is exacerbated by pregnancy. The plan is to work her up for other causes of hypokalemia after her pregnancy.

Gordon’s Syndrome: A Rare Cause of Hypertension and Hyperkalemia

Chinonye Chika Ogbonna-Odog, Internal Medicine, Rutgers NJMS, Newark, NJ.

Introduction: Gordon syndrome is a rare disorder characterized by hypertension, hyperkalemia, metabolic acidosis in the presence of normal GFR. It has been reported to be caused by genetic mutation that happen specifically in the population, but can also be inherited in an autosomal pattern.

Case Description: A 23-year-old man with no reported past medical history, presented for evaluation, after referral from his primary provider, for lab abnormalities. The patient reported taking Theratul for cold symptoms, two days prior to presentation. He denied any complaints except poor vision and headaches both chronic from childhood. He was afibrile, BP 146/78 mmHg, pulse 60 bpm, respiratory rate 16 breaths per minute, and oxygen saturation of 99% on room air. He was blind in the left eye but exam was otherwise benign. Pertinent laboratory studies were; potassium 7.2 meq/L, carbon dioxide 18 meq/L, creatinine 1.0 mg/dl and GFR >60 ml/min. Urinalysis: specific gravity 1.021, pH 5, negative for protein, glucose, ketones, blood, nitrite, and leukocyte esterase. RBC 3, and WBC 1. ECG showed sinus rhythm at 60 BPM with peaked T waves in most leads. He was treated with calcium, insulin and sodium polystyrene, twice within the next twelve hours, each time with improvement in hyperkalemia. His blood pressure was noted to be persistently elevated during hospitalization. Further studies to analyze etiology of hyperkalemia were done. Aldosterone level was slightly elevated but others including, renin level, cortisol stimulation test, TKG, HIV,ANA, were normal. His blood pressure and hyperkalemia responded with 25 mg of hydrochlorothiazide. Given constellation of findings, patient history and blood pressure response to hydrochlorothiazide, the diagnosis of sporadic Gordon syndrome was made. At one month follow up he had self-discontinued hydrochlorothiazide, and metabolic acidosis and hyperkalemia recurring. Lifelong adherence to medication was stressed.

Discussion: Gordon syndrome is an important and easily treatable cause of hypertension and hyperkalemia that might be a frequently missed diagnosis due to its rarity. Recognition of this entity is important to ensure proper therapy.

PUB426

Aspergillus niger Peritonitis Saad Mohammed Shariff, Eric L. Wallace. Univ of Alabama, Birmingham, AL.

Introduction: Fungal Peritonitis is a serious complication of peritoneal dialysis (PD) accounting for 3-10% of PD related peritonitis. Molds peritonitis, such as Aspergillus niger is a rare cause of peritonitis with a high mortality rate.

Case Description: A 70-year-old African American male with end stage kidney disease on PD presented with abdominal pain, chills, generalized weakness, diarrhea, nausea and vomiting for 5 days. Two weeks prior to admission patient noticed cloudy PD fluid and was treated for suspected bacterial peritonitis with Vancomycin and Cefazidine. Upon presentation, the patient was in septic shock. PD fluid analysis showed 1,879 WBC’s, 82% neutrophils, 13% Macrophages, 3% Mesothelial cells, 2% Eosinophils and cultures were sent. Patient was continued on his original therapy with Vancomycin and Cefazidine. Despite appropriate empiric antibiotics, repeat PD fluid analysis showed worsening of cell counts at 6994 WBC’s with 78% neutrophil. Gram stain was negative. Linezolid and Micalufing were started and PD catheter was removed. Preliminary PD fluid cultures at three days showed mold and on day 7 this was identified as Aspergillus Nigter. He was transitioned to Voriconazole. Repeat cultures done 2 weeks showed no more fungal growth. A home visit by the PD nurse found out that there was mold growing under the PD machine.

Discussion: Aspergillus niger is a rare cause of fungal peritonitis in an immunocompetent patient on PD. Early antifungal therapy with removal of PD catheter is important. Based on our case report it is important for a home visit, especially after multiple episodes of peritonitis to identify and prevent fungal peritonitis; as in this case there was mold growing under the patient’s catheter.

PUB427

Siroliimus Induced Pneumonitis Jin Han Lim, Won Kim, Kyung Pyo Kang, Sung Kwang Park, Sik Lee. Internal Medicine, Chonbuk National Univ Med School and Research Inst of Clinical Medicine, Jeonju, Korea.

Introduction: Siroliimus is a potent immunosuppressive drug that has been successfully used with or without cyclosporine as an alternative to calcineurin inhibitors in patients who have undergone kidney transplantation. The major side effects of sirolimus are anemia, hyperglycemia, hyperlipidemia, and hyperkalemia. Clinical adverse effects have also been reported with the increasing use of sirolimus. Of these, pulmonary toxicity is a rare but potentially serious complication. Herein, we report a case of sirolimus-induced pneumonitis in a renal transplant recipient 6 month after initiation of sirolimus treatment that was promptly resolved after the discontinuation of the drug.

Case Description: A 34-year-old male visited the emergency room for hemoptysis with dyspnea. He underwent renal transplantation 10 years ago and had switched the immunosuppressive drugs to sirolimus with tacrolimus 6 months ago. His basal serum creatinine level was 1.1 mg/dL. Physical examination revealed coarse crackling breath. Laboratory findings revealed a white blood cell count of 12600/mm³, hemoglobin level of 13.1 g/dL, and platelet count of 306,000/mm³. Arterial blood gas analysis showed arterial PO2 of 55 mmHg. A chest CT scan showed extensive ground-glass opacity and consolidation in both lung fields. However, any definite signs of bacterial or fungal infection were not observed. We considered it as sirolimus-induced pneumonitis and promptly stopped sirolimus use. Treatment was continued with antibiotics and high- flow oxygen therapy. After discontinuation of sirolimus, radiological findings and clinical prognosis of the patient improved.

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

1002A
Discussion: SIRL-increased pneumonitis is a potentially fatal side effect. In patients with hemoptysis and being treated with sirolimus, this complication must be considered because early recognition along with drug discontinuation is essential to reverse the adverse effects.

PUB428


Introduction: Patients receiving glucocorticoids and immunosuppressants are at high risk for severe infections, which can be a major cause of death during the disease course. Here we report two rare cases of disseminated varicella zoster virus (VZV) infection with lupus nephritis (LN) during remission induction therapy.

Case Description: Case 1. A 46-year-old woman was admitted because of leukocytopenia, proteinuria, hypocomplementemia, and positivity for anti-nuclear antibody. By kidney biopsy, she was diagnosed as LN class III (A/C), and started on remission induction therapy with 45 mg of prednisolone and 3 mg of tacrolimus daily. Because of the kidney dysfunction, the tacrolimus was changed to mycophenolate mofetil (MMF) and the plasma exchange was started because of disseminated VZV infection, and laboratory examinations demonstrated liver dysfunction and disseminated intravascular coagulation (DIC). Despite immediate administration of acyclovir and glucocorticoid pulse therapy, she died of hemorrhagic shock 7 days after the onset of abdominal pain. Case 2. A 26-year-old man was admitted because of weight loss and fever, with a creatinine of 1.9 mg/dl (baseline 1.4-1.5 mg/dl) and urine protein-to-creatinine ratio (UPCR) of 9 g/g. Initially, he was put on plasmapheresis. He was also given Rituximab using the RA VE protocol and was started on pulse prednisolone because of his renal failure included negative p:ANCA, c-ANCA of 1:40, normal C3 and C4 levels, and negative MPO, PR3, ANA, dsDNA, HIV, anti-GBM, and hepatitis B and C. A renal biopsy showed numerous glomeruli with fibrocellular crescents but with negative immunofluorescence. Electron microscope showed no deposits. He was started on pulse dexamethasone and was put on plasmapheresis. He was also given rituximab using the RAVE protocol and was eventually started on hemodialysis. He remains on hemodialysis up to the present time.

Discussion: ANCA-negative pauci-immune glomerulonephritis is a relatively underappreciated disease. The mechanism for this disease is unclear but neutrophils and possibly other antigens are thought to be involved. This syndrome may be undiagnosed as ANCA serologies or other serum markers usually influence the decision to perform renal biopsies. This case illustrates the importance of maintaining high clinical suspicion for pauci-immune crescentic glomerulonephritis, particularly in patients with rapid deterioration in renal function, in spite of negative anti MPO or PR3 antigens.

PUB431

A Case of Recurrent Membranous Nephropathy in Transplant Patient With Deep Vein Thrombosis. Del Ra Penafiel, 1 Dylan Nelson, 1 Divya Raghavan, 1 Monica Patricia Revelo Penafiel, 1 Josephine Abraham, 1 Faris A. Ahmed.1 1Dept of Nephrology, Univ of Utah, Salt Lake City, UT; 2Dept of Pathology, Univ of Utah, Salt Lake City, UT; 3Dept of Pathology, Intermountain Central Lab, Murray, UT.

Introduction: Thromboembolism is a known complication of the nephrotic syndrome. We report a case of recurrent membranous nephropathy (MN) in the transplant kidney presenting with extensive deep vein thrombosis (DVT).

Case Description: A 58 year old man presented to clinic with bilateral leg pain (greater on the right). His history was significant for ESRD from MN status post living donor renal transplant a year ago. He was on mycophenolate sodium, prednisone and tacrolimus. Physical exam revealed mild tenderness below the allograft site and swelling of the right lower extremity from thigh to mid-calf. Labs showed a creatinine of 1.69 mg/dl (baseline 1.4-1.5 mg/dl) and urine protein-to-creatinine ratio (UPCR) of 10 g/g. Duplex ultrasound (US) showed DVT involving right common femoral vein and extending into right external iliac vein, along with DVT of left femoral, popliteal and posterior tibial veins. US of the transplant kidney showed a non-occlusive thrombus of the renal vein. He was admitted to the hospital and started on a heparin drip. He underwent catheter-directed thrombolysis of the right common femoral and right external iliac veins and was started on lisinopril for proteinuria and warfarin for anticoagulation. Biopsy was deferred because of anticoagulation. Donor specific antibody testing was negative. Chest, abdomen and pelvis to evaluate for secondary causes of MN was unremarkable. He was treated with rituximab 1 g for presumed recent MN and the dose was repeated in 2 weeks. His creatinine improved to 1.37 mg/dl and UPCR to 2.2 g/g about 2 months post-discharge. One year post proteinuria in transplant patients negative with a history of MN should not trigger prompt evaluation. MN can recur in the transplant kidney with a reported incidence between 10-40% in different studies. Patients with recurrence are at risk of graft loss and complications from the nephrotic syndrome. There is some data suggesting the efficacy of rituximab in these cases.
Adey,1, Dr. Silvi Shah, Dr. Casey T. Weaver,1 Gaurav Agarwal. 1. Nephrology, Univ of Alabama at Birmingham, Birmingham, AL. 2. Pathology, Univ of Alabama at Birmingham, Birmingham, AL.

Introduction: Aminoglycosides nephrotoxicity is a well-known clinical entity. Nebulized aminoglycosides are used to reduce nephrotoxicity. We describe the clinical case of a 57-year-old woman who developed acute kidney injury after using inhaled tobramycin for the treatment of pulmonary infections.

Case Description: A 57-year-old white woman with history of end stage renal disease due to unknown etiology and living unrelated kidney transplant seven years ago presented to the clinic for evaluation of acute kidney injury. She received induction immunosuppression with alemtuzumab and was maintained on tacrolimus and mycophenolate mofetil. She had history of bronchiectasis and recurrent pulmonary infections with multidrug resistant Pseudomonas; and was on preventive therapy with tobramycin inhalation for the last 6 months. Physical examination was unremarkable except for bilateral wheezes on lung auscultation. Her baseline serum creatinine was 1.9 mg/dL. Blood work showed elevated serum creatinine of 2.5 mg/dL corresponding to estimated glomerular filtration rate of 24 mL/min/1.73 m². Urine microscopy did not show proteinuria or hematuria. Donor specific antibody and renal transplant ultrasound were unremarkable. Serum BK virus was not detectable. Tacrolimus trough level was therapeutic. Renal biopsy was performed for the evaluation of acute kidney injury. Light microscopy revealed acute tubular injury and acute tubular necrosis superimposed on chronic glomerulonephritis and mild interstitial fibrosis/ tubular atrophy. Electron microscopy showed presence of cytosomegysomes and myeloid bodies in proximal tubular epithelial cells consistent with aminoglycoside toxicity. Inhaled tobramycin was discontinued and patient’s renal function improved.

Discussion: There is minimal systemic absorption with inhaled aminoglycosides and renal toxicity has not been reported in randomized clinical trials. Acute kidney injury occurred in our patient due to use of inhaled tobramycin. Clinicians should be aware of this rare complication and patients on inhaled aminoglycosides should be monitored closely for worsening renal function.

Cryoglobulin Mediated Renal Failure in the Setting of B Cell Lymphoma

Sudipta Chaudhry,1 Shuchil I. Vyas. 1. Dept of Medicine, Univ of Californa, Riverside, CA; 2. Nephrology Dept, Kaiser Permanente, Riverside, CA.

Introduction: Cryoglobulinemia involves the deposition of specific insoluble immune complexes in the microvasculature. While most adults remain asymptomatic, there are a wide variety of potential clinical manifestations - renal failure, MPGN, proteinuria, hematuria, cutaneous lesions, arthralgia, neuropathy, etc. About 80% of cryoglobulinemia is associated with hepatitis C infection. While the concurrence of cryoglobulinemia and MPGN is well documented in the literature [1]. However, many other less common etiologies and associations exist.

Case Description: An 84 year old male with history of essential hypertension presented with one year of hematuria and pruritic rash over his chest and lower extremities. He was found to a creatinine of 5.4 (GFR 9) in ER. The patient was admitted for work up and management of acute kidney injury. He developed worsening renal failure so was started on hemodialysis. A broad infectious, autoimmune, and myeloma work up revealed pANCA 1/1280 and qualitative serum cryoglobulin, prompting renal biopsy for suspicion of vasculitic glomerulonephritis. The biopsy revealed immune complex mediated glomerulonephritis with cryoglobulin deposition and 10% crescents. Given lymphadenopathy noted on CT, a left groin lymph node biopsy was pursued at the same time and revealed atypical lymphoid proliferation nondiagnostic for malignancy. Plasmapheresis was initiated for cryoglobulinemia. The patient was also treated with corticosteroids. The results of the lymph node biopsy prompted a second left inguinal lymph node biopsy. This biopsy revealed low grade B-cell lymphoma. Oncology was consulted, but chemotherapy was deferred due to the patient’s unstable clinical status. Hospital course was complicated by encephalopathy requiring endotracheal intubation for airway security and urobacteremic sepsis requiring ICU care. Hospitalization was over 5 months, trace protein and moderate blood on UA with urine spot protein 53 mg/dL. Immunofixation confirmed Bence-Jone protein (lambda type). Urine free light chains were elevated to a ratio of 5.3. With high degree of clinical suspicion for nephrotic syndrome secondary to systemic disease, renal biopsy was recognized as an important diagnostic component that could hasten treatment while other biochemical studies were pending results. Renal biopsy confirmed AL Amyloidosis.

In conclusion, the diagnosis of AL Amyloidosis associated with Monoclonal Gammapathies was established by renal biopsy prompting initiation of treatment that may have otherwise been delayed.

Case Description: Gender Differences in the Associations of Obstructive Sleep Apnea and Cardiovascular Outcomes in Patients with End Stage Renal Disease: A Systematic Review and Meta-Analysis

Pulkit Gandhi,1 Manoj Das,2 Shweta Sharma. 1. Internal Medicine, Wright Ctr for Graduate Med Ed, Scranton, PA; 2. Nephrology, Virginia Commonwealth Univ, Scranton, PA; 3. Internal Medicine, Wright Ctr for Graduate Med Ed, Scranton, PA.

Introduction: Obstructive sleep apnea (OSA) increases risk for cardiovascular events, especially stroke in the general population and in patients with ESRD. However, gender differences in these associations are unclear, as studies that assessed these differences reported conflicting results. We sought to systematically review and pool all available evidence that has assessed the gender differences in the associations of OSA and cardiovascular outcomes in ESRD patients.

Case Description: Medical, Embasse, Cochran central library, and electronic databases were searched for relevant studies in English language and full text restriction.

From a total of 2793 retrieved citations, 7 observational studies, representing 732 men and 550 women with ESRD and a diagnosis of OSA, were included in the review. In the pooled analysis, men were at lower odds for stroke (OR: 0.64, 95% CI: 0.44 – 0.92, P = 0.02, I²: 78%, 6 included studies), but odds of CAD (OR: 0.86, 95% CI: 0.54 – 1.37, P = 0.51, I²: 74%, 5 included studies) and cardiovascular mortality (OR: 0.95, 95% CI: 0.71 – 1.27, P = 0.71, I²: 0%, 5 included studies) was similar in both men and women. We found no evidence of interaction between gender and OSA on the risk of stroke. When restricted to data from sleep clinic based studies the lower odds of stroke in men persisted (OR: 0.60, 95% CI: 0.37 – 0.98, P = 0.04, I²: 81%, 6 included studies) but disappeared in population based studies (OR: 0.65, 95% CI: 0.29 – 1.46, P = 0.3, I²: 84%, 3 included studies). Factors responsible for the high heterogeneity could not be assessed due to lack of availability of gender specific data.

Lower odds of stroke among men with OSA may likely be due to selection bias as this was true only in the sleep clinic based studies and not in population based studies. More population based studies with gender specific details of OSA determinants like atrial fibrillation are needed to clearly elucidate this association in ESRD patients.

Case Description: Morton Lite Salt Induced Hyperkalemia

Ryan A. Kunjal,1 Adey Hasan,2 Abdalagani Ahmed Abakar Baher,1 Ciel Harris,1 Andrea Poenaru. 2. Dept of Internal Medicine, Univ of Florida College of Medicine, Jacksonville, FL; 2. Dept of Nephrology, Univ of Florida College of Medicine, Jacksonville, FL.

Introduction: We present a case of Morton Lite salt - induced hyperkalemia in a patient with stage 2 chronic kidney disease (CKD). There is increasing use of lower sodium content salt and salt substitutes as healthy alternatives for the control of hypertension. These typically contain high quantities of potassium chloride which can predispose patients with CKD to hyperkalemia.

Case Description: A 61-year-old male with Hypertension, Type 2 Diabetes, CKD and Schizophrenia disorder presented with potassium of 9.2mmol/L found on routine laboratory investigations. His medications included Aspirin, Lisinopril, Metoprolol and Quetiapine. He was asymptomatic on arrival with unremarkable vital signs and physical examination. The EKG demonstrated normal sinus rhythm with diffusely peaked T waves. Repeat serum potassium was consistent with the previous level in the absence of hemolysis. His creatinine was 3.06 mg/dl and eGFR was 27.56 ml/min. Serum sodium and aldosterone were normal and spot urine potassium was mildly elevated at 154mmol/l. The renal sonogram was essentially normal. Calcium gluconate, insulin and oral sodium polystyrene sulfonate were successful in normalizing his potassium. The peaked T waves on EKG also resolved. Metoprolol was held due to possible contribution to hyperkalemia. Nevertheless, the underlying cause remained elusive. Later, the patient admitted to daily use of 2 tsp. of Morton Lite Salt for bowel regularity over the past month. This was equivalent to 70mEq of K+/day which likely caused such severe hyperkalemia. He made a full recovery.

Discussion: Large potassium intake is a rare cause of severe hyperkalemia especially in the setting of normal or mildly impaired kidney function as in our patient and makes this case unique. However the patients to whom these products are targeted tend to also be those at highest risk for hyperkalemia due to concomitant renal impairment or use of medications such as ACE inhibitors. Greater awareness is needed of the potential dangers of these products and it is imperative that their labeling reflect such risks.
ANCA-Positive Pauci-Immune Crescentic Glomerulonephritis and Bronchial Carcinoid: Accomplice or Innocent Bystander? Jason Christopher George, Alicia Meadows, Jamie Alton Green. Nephrology, Geisinger Medical Center, Danville, PA; Rheumatology, Geisinger Medical Center, Danville, PA.

Introduction: Paenoeplastic glomerulonephritis (GN) is a well-known but rare phenomenon that can occur with various malignancies. Diagnosis is important to avoid potentially harmful therapy. We present a case of a patient who was concurrently diagnosed with anti-neutrophil cytoplasmatic antibody (ANCA), pauci-immune crescentic glomerulonephritis and bronchial carcinoid.

Case Description: A 62-year-old woman with known history of hypertension presented with 7 months of fatigue, shortness of breath and persistent cough. She also had bilateral leg swelling and worsening hypertension. She denied joint pain or rash. Labs showed progressive renal dysfunction (creatinine 3.0 mg/dL from 2.2 mg/dL four months prior), serum albumin 3.5 mg/dL, microscopic hematuria (50+HFP) and nephrotic-range proteinuria (protein/creatinine ratio 5.53). Serologies showed positive p-ANCA with confirmatory anti-myeloperoxidase antibody. CT scan showed a 2.3 cm lung mass and biopsy confirmed well-differentiated bronchial carcinoid. Renal biopsy showed pauci-immune crescentic glomerulonephritis with mild interstitial fibrosis and tubular atrophy. It was unclear if the GN was idiopathic or related to malignancy. Her primary tumor was resected and she was started on high-dose prednisone and rituximab for treatment of her GN with improvement in proteinuria.

Discussion: Paenoeplastic GN involves renal manifestations of malignancy not directly related to tumor burden. It is most commonly described with membranous nephropathy and minimal change disease. Malignancy-associated ANCA-positive glomerulonephritis has been described with renal cell carcinoma, adenocarcinoma of the lung, and gastric carcinoma. However, association with bronchial neuroendocrine malignancy has not been frequently reported. The pathophysiology is not completely understood but thought to be related to dysregulated T-cell and cytokine response. Treatment with immunosuppression frequently reported. The pathophysiology is not completely understood but thought to be related to dysregulated T-cell and cytokine response. Treatment with immunosuppression frequently reported. The pathophysiology is not completely understood but thought to be related to dysregulated T-cell and cytokine response. Treatment with immunosuppression frequently reported. The pathophysiology is not completely understood but thought to be related to dysregulated T-cell and cytokine response. Treatment with immunosuppression frequently reported. The pathophysiology is not completely understood but thought to be related to dysregulated T-cell and cytokine response. Treatment with immunosuppression frequently reported. The pathophysiology is not completely understood but thought to be related to dysregulated T-cell and cytokine response. Treatment with immunosuppression frequently reported. The pathophysiology is not completely understood but thought to be related to dysregulated T-cell and cytokine response. Treatment with immunosuppression frequently reported. The pathophysiology is not completely understood but thought to be related to dysregulated T-cell and cytokine response. Treatment with immunosuppression frequently reported.
deficiency, and thus he was incapable of producing any more cortisol. We gave him a trial of methylprednisolone increased from 500 mg to 119 by the next morning. A second dose of methylprednisolone 500 mg was given and sodium improved further to 127 the next day. Patient was then placed on scheduled fludrocortisone and sodium eventually normalized. We had hoped to more fully evaluate his pituitary-adrenal axis and establish a diagnosis of hyponatremia, by reducing aldosterone secretion. We advocate for consideration of aldosterone deficiency, in the appropriate clinical scenario regardless of a normal morning cortisol.

PUB442
Anti-Glomerular Basement Membrane Negative Goodpasture Disease with Positive Serum Myeloperoxidase

Introduction: In patients who present with rapidly-progressive glomerulonephritis, serologic testing is heavily relied upon in making a diagnosis. Presented here is a case of biopsy-proven anti-GBM disease (Goodpasture Disease) with negative anti-GBM IgG serology, but positive MPO serology.

Case Description: The patient is a 52-year-old woman with a history of Graves disease over 30 years prior, hypothyroidism, and eczema, who presented with 1 month of anorexia and hematuria. She denied hemoptysis, arthralgia, rash, fever, chills, NSAIDs, or herbal agents. Physical exam revealed a well-appearing, thin, white, middle-aged woman with an intact peripheral edema. The rest of her exam was normal. Baseline serum creatinine (sCr) was 0.6 mg/dL. 4 weeks prior to presentation, sCr was 1.9 mg/dL, then steadily rose to a peak of 4.6 mg/dL upon presentation. Serum electrolytes and bicarbonate were normal. C3 and C4 were normal, ANA was negative, and MPO was 164 AU/mL (High). Anti-GBM IgG by indirect fluorescent antibody (IFA) and by multiplex bead assay were both negative. She then had a renal biopsy. Light microscopy showed necrosis and cellular to early-fibrillarular crescents involving greater than 50% of sampled glomeruli. Global glomerulosclerosis and segmental scarring/fibrous crescents were noted in 25% of glomeruli. She had mild early tubulointerstitial fibrosis. Immunofluorescence microscopy showed linear staining of glomerular basement membranes (GBM) for IgG, consistent with Goodpasture Disease. She was treated with methylprednisolone 750 mg IV for 3 days, then switched to prednisone and cyclophosphamide. Anti-GBM IgG testing by both IFA and multiplex bead assay were repeated and again, were negative. She received 7 sessions of plasmapheresis. After 3 months of steroids and cyclophosphamide, she was switched to maintenance azathioprine and low-dose prednisone. Her sCr at 3 months had improved to 1.3 mg/dL.

Discussion: This case underscores the importance of renal biopsy for definitive diagnosis of rapidly-progressive glomerulonephritis, as the serologic workup can be misleading. Renal biopsy in this case helped identify the true pathology and helped with therapeutic plan and prognosis.

PUB443
Renal Graft versus Host Disease with Focal Segmental Glomerulosclerosis

Introduction: Graft Versus Host Disease (GVHD) is a feared, yet common complication of stem cell transplant (SCT). Kidney involvement remains unusual contrary to the typical liver, skin and gastrointestinal manifestations. Main renal presentations pertain to nephrotic syndrome from either a membranous nephropathy in the majority of cases or minimal change disease. Rare cases related to focal segmental glomerulosclerosis (FSGS) have been described. We present a case of renal GVHD post SHT with nephrotic syndrome from FSGS.

Case Description: 56 y/o man with ALL whom underwent chemotherapy prior to a matched unrelated donor allogenic stem cell transplant. He was preconditioned with whole body irradiation and pentostatin, engrafted on day 13 and was maintained on sirolimus and tacrolimus. His course was notable for a biopsy proven skin GVHD, severe sepsis complicated by idiopathic thrombotic purpura requiring pulse steroids, intra venous immunoglobulins and acute kidney injury secondary to acute tubular necrosis from which he recovered fairly rapidly. Sirolimus was stopped for concerns of lung toxicity. He was continued on tacrolimus and prednisone. During the same hospitalization, the former was discontinued for unclear reasons. No recurrent acute kidney injury or other side effects of tacrolimus were documented. Several weeks later, he represented to the hospital with nephritic syndrome with up to 10g of proteinuria. He underwent a kidney biopsy which showed resolving TMA, enlarged glomeruli with collapsing capillary loops on light microscopy, complete foot process effacement on electron microscopy. Our renal pathologist concluded that these lesions were consistent with FSGS. He was restarted on tacrolimus for those findings along with persistent proteinuria. The proteinuria has since resolved.

Discussion: Case reports have associated cessation of immunosuppression with onset of renal GVHD, which was the case for our patient. What renders this case interesting is the high pathological findings of FSGS. A review by Troxel et al, mentioned that about 6% of published biopsy proven glomerulopathy in renal GVHD has similar findings. We also conclude that in this setting, those lesions respond well to immunosuppressive therapy.

PUB444
A Case of Undifferentiated Connective Tissue Disease with Membranous Glomerulonephritis in a Child

Introduction: The diagnosis of undifferentiated connective tissue disease (UDCTD) is used to those with features of autoimmune disease but not fulfilling the criteria of specific disorder. Membranous nephropathy (MN) is considered as a primary glomerular disease, also referred as idiopathic (Children have a higher frequency of secondary MN than adults). We described unusual case of coexistence of MN resulting in nephrotic syndrome (NS) with UDCTD in child.

Case Description: A 12 years old male presented to us with NS, proteinuria was 3 g/day, creatinine normal. C3 was normal. He started steroid full dose for one month with remission. He relapsed after 2 months, there was edema, polyomysitis, bilateral symmetrical gluteal and thigh induration with no tenderness, fingers swellings and scales. Dermatological consultation found localized scleroderma (morphea) like lesion, anti-Scl 70, ANA, anti-double strand DNA and PANCAs were negative. Skin biopsy was not done as the parents refused. EMG, nerve conduction velocity for gluteal and muscles of thigh and Doppler on renal arteries were normal. Patient was back on full dose corticosteroid for six weeks without remission. Renal biopsy showed diffuse MN with early secondary segmental sclerosis. We excluded secondary causes of MN. The patient started cyclophosphamide orally on 2 mg/kg/day, with full dose oral steroids EOD. After 2 weeks of therapy, the patient was completely improved. The gluteal, thigh induration and proteinuria were disappeared. Cyclophosphamide completed for 3 months with steroid withdrawal the patient is stable and in complete remission till now.

Discussion: Missing anti RNP excluded MCTD, presence of polyomysitis and scleroderma with missing anti Sel 70 excluded the diagnosis of Overlap Syndrome; thus we proposed our case with UDCTD. MN with one of the mixed connective tissue diseases was reported previously in three cases one was 60 years old, one with renal cell carcinoma and one female child with MN for 5 years followed by developing scleroderma. We started cyclophosphamide with steroid as this combination was reported to be safer than using chlorambucil with steroid. Our case is considered one of few cases with this presentation of MN and UDCTD in children.

Funding: Private Foundation Support

PUB445
Bile Cast Nephropathy Associated with Acute Hepatitis A

Introduction: Acute kidney injury is well developed in advanced liver diseases, such as liver cirrhosis and acute hepatic failure. This acute renal dysfunction usually results from decrease of renal perfusion caused by hypovolemic condition. Severe jaundice may also contribute to the acute kidney injury caused by bile acid or bilirubin. Now, we present a interesting case, bile cast nephropathy complicated by acute hepatitis A.

Case Description: A 35-year-old male visited our emergency department with symptoms of nausea, abdominal discomfort, and oliguria. These symptoms and signs were developed abruptly recent several days ago, so he took a digestive medicine, however, these symptoms were aggravated although fluid therapy. His general condition was poor. His urine output was less than 300 mL/day, with peak of 4.6 mg/dL upon presentation. Serum electrolytes and bicarbonate were normal. C3 was normal. he started steroid full dose for one month without remission. Renal biopsy showed diffuse MN with early secondary segmental sclerosis. We excluded secondary causes of MN. The patient started cyclophosphamide orally on 2 mg/kg/day, with full dose oral steroids EOD. After 2 weeks of therapy, the patient was completely improved. The gluteal, thigh induration and proteinuria were disappeared. Cyclophosphamide completed for 3 months with steroid withdrawal the patient is stable and in complete remission till now.

Discussion: In conclusion, bile cast can result in the acute kidney injury of patients with severe jaundice and hepatic failure. A direct bilirubin toxicity for renal tubules may contribute to this renal injury. We may carefully suggest that recovery of acute tubular necrosis can be delayed by the presence the tubular bile cast through this case.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Intratireal VEGF Inhibitors Causing Allergic Interstitial Nephritis

Debbie Valsan, 1 Saifullah Kazi, 2 Zia M. Umruddin, 2 Lankenau Medical Center; 1Potstown Memorial Hospital.

Introduction: This case highlights the effect of intratireal VEGF inhibitors in causing AIN.

Case Description: A 51 y/o male with a history of DM and HTN presents to his primary care office for nausea and vomiting in December 2010. His creatinine was 1.2 mg/dl in July 2010 and 1.9 mg/dl in October 2010 with repeat creatinine of 11mg/dl with a BUN of 106mg/dl. His medications include metformin, glyburide and Bevacizumab monthly intratireal injections that he began on February 2010. Physical exam was unremarkable. Urine microscopy showed granular casts and eosinophils were negative. Ultrasound revealed normal sized kidneys with normal echotexture and no hydronephrosis. He was placed on pulse dose steroids given his rapid onset of renal failure with no clear etiology and pending serologic workup. Hemodialysis was initiated for uremic symptoms. Complete serologic panel was negative and complement levels were normal. Biopsy results showed AIN with ATN and early diabetic glomerulosclerosis. Bevacizumab was discontinued. He was placed on dialysis temporarily with oral steroids with improvement of creatinine to baseline. His creatinine was noted to slowly trend up at 1.72mg/dl in October 2015 and then at 2.4mg/dl a month later. Our patient was started on Ranibizumab intra ocular injections since August 2015 by a different ophthalmologist. Given his previous history, recommendations were made to stop the current therapy with Ranibizumab as no other etiology for this acute kidney injury was evident and his creatinine declined to 1.6 mg/dl.

Discussion: Histologic findings in patients who have been on VEGF inhibitors have included TMA, collapsing glomerulopathy, and isolated reports of cryoglobulinemic and immune complex GN. We report the first case of AIN in the setting of intratireal Bevacizumab used for DME. Discontinuation of the potential causative agent is a mainstay of therapy. Drug-induced AIN is not dose dependent, and recurrence or exacerbation can occur with a second exposure to the same or a related drug. This was seen in our case with initiation of Ranibizumab. Regular monitoring of the renal function in these patients will help identify this problem and avoid significant morbidity associated with these new biologic agents.

“Extraperitoneal Dialysis” in Severe Obesity


Introduction: We report a case where a patient with misplaced Tencoff catheter in extra-abdominal cavity underwent 5 months of “peritoneal dialysis”.

Case Description: A 46 year old male started PD for ESRD secondary to hypertensive nephroclerosis. He was extremely obese, weighing 158kg with BMI of 51.0kg/m2. Four exchange of 2.5L dialysate per day was successfully delivered without any infusion/drainage trouble. He was well despite of relatively low dialysis dose; a weekly Kt/V of 0.99 (peritoneal 0.84, renal 0.14), a total CC of 46.0L/week (peritoneal 30.0, renal 15.9), ultrafiltration volume of 1500ml per day. Peritoneal equilibration test showed “low” category. Five months after initiation of PD, he was admitted to our hospital for PD peritonitis. A CT scan, taken with dialysate in the patient’s abdomen, revealed a fluid collection approximately the size of 11cm x 19cm x 17cm in the abdominal wall, just between the rectus abdominis and peritoneum membrane. The tip of the catheter was detected outside of peritoneal cavity. Subsequently, he had his catheter surgically removed and switched to HD.

Discussion: Catheter misplacement can be easily detected because it would immediately result in difficulty in infusion and drainage; however, in this case, misplacement was not detected and “peritoneal dialysis” could be continued for a considerable amount of time. This is probably due to the patient’s thick abdominal wall, which obscured the symptoms. This case shows that fluid and solute can be transported even when peritoneal dialysate is dwelled outside the abdominal cavity, between abdominal muscle and peritoneum. For obese patients, confirming the catheter position with additional measures such as lateral abdominal radiography is recommended, even without outflow failure at the time of catheter placement.
An Unexpected Diagnosis when Expecting: Scleroderma in a Patient with Class III Lupus Nephritis

Xi,1 Yuhei2

Introduction: We present an interesting case of a 39-year-old woman who was previously diagnosed with cutaneous lupus with pANCA with low C4, which initially responded to topical treatments. She continued with topical treatments until her third pregnancy. However, at the beginning of her pregnancy, she was diagnosed with systemic sclerosis when her fetus was unable to be visualized on abdominal ultrasound due to severe skin thickening that rapidly progressed during the pregnancy. She delivered successfully, and continued with steroid-sparing therapy for her cutaneous lupus until her scleroderma symptoms worsened in the setting of lupus nephritis.

Case Description: Her systemic sclerosis became complicated with diffuse skin thickening with calcinosis, chronic skin infections, Raynaud’s phenomenon, pulmonary hypertension, and esophageal dysmotility. Her creatinine began to rise from a normal range of 1.0 mg/dL to 3.4 mg/dL over 3 years of diagnosis because disease complications, specifically hypertension and renal function that can complicate pregnancy.

Discussion: This case highlights the importance of screening patients who have been previously diagnosed with a single autoimmune disease entity for other autoimmune disorders as these syndromes often cluster and exacerbate renal dysfunction. The initial physical finding of thickened abdominal skin during a first trimester ultrasound that led to moftei was slowly uptitrated as a steroid sparing therapy aligning with the Imperial Lupus Trial. Her urine protein levels stabilized and the patient is stable currently.

Slowly Progressive Light Chain Cast Nephropathy with Proximal Tubulopathy

Yuka Kawasaki, Yuhei Kirita, Itaru Kirita, Yayoi Shiotzu, Tetsuro Kusaba, Keiichi Tamagaki.

Introduction: Monoclonal gammopathy manifests as various forms of renal diseases. Light chain cast nephropathy (LCCN) is a common cause of acute kidney injury with multiple myeloma. Light chain proximal tubulopathy (LCTP) is an increasingly recognized, yet uncommon renal complication of monoclonal gammopathy. LCTP, particularly with crystals, usually presents as a myeloma syndrome. We report a case of slowly progressive renal insufficiency due to LCCN with LCTP.

Case Description: A 55-year-old man with a medium build presented with a gradual increase in the serum creatinine (Cr) level from 1.2 to 1.6 mg/dL in a year. His estimated GFR-creatinine (eGFRcr) and -cystatin C (eGFRCys) were 35.4 and 59.2 mL/min/1.73 m², respectively, with a difference between the values. Laboratory data showed mild proteinuria of 0.21 g/gCr, with no evidence of glycosuria, water-electrolyte imbalance, acidemia, or hypoalbuminemia. Urinary immunofixation showed the presence of free kappa light chains in the serum free light chains as 1,020 mg/dL and 13.3 mg/dL, respectively. However, bone marrow-biopsy specimen revealed less than 10% of plasma cells. Renal biopsy showed crystalline variants of LCCN and LCTP. We diagnosed monoclonal gammapathy of renal significance and started chemotherapy along the guidelines for multiple myeloma.

Discussion: This case highlights the fact that LCCN can present an indolent course and LCTP with crystals does not always occur with Fanconi syndrome; thus, a diagnosis of slowly progressive renal insufficiency without any symptoms or abnormalities in laboratory evaluations should be made carefully. This case showed a difference between eGFRcr and eGFRCys, which may be useful for detecting LCTP. Cystatin C is freely filtered by the glomerulus, whereas Cr is not only filtered by the glomerulus but also secreted by the proximal tubule to some extent. Tubular injury induced by LCTP may elevate serum Cr than serum cystatin C, and make a difference between the eGFRcr and eGFRCys.

Mycobacterium Genavense in a Kidney Transplant Patient

Felix Nadrowitz,² Philip Kirschner,³ Jan Menne,³ 1Dept of Nephrology and Hypertension, Hannover Medical School, Germany; 2Inst for Medical Microbiology and Hospital Epidemiology, Hannover Medical School, Germany.

Introduction: Transplant recipients are highly susceptible for atypical infections as a consequence of their immunocompromised state. We report an exceptional case of a disseminated Mycobacterium genavense infection in a kidney transplant patient.

Case Description: The 26 years old Caucasian women received a kidney transplant from her father in 2010. In January 2016 she was admitted to our hospital with fever and diarrhea. Her immunosuppressive therapy consisted of tacrolimus, sirolimus and prednisolone. On admission inflammation markers were increased (CRP 23mg/L). Elevated serum creatinine (max. 198 μmol/L) indicated acute kidney injury. Differential blood count revealed pancytopenia and in particular distinct lymphocytopenia with 300/μL. Her urine cultures and stool samples were repetitively negative. An InferFeron-y release assay was negative, as well. A kidney biopsy proved polyomavirus nephropathy, which is rare six years after transplantation. Thus, immunosuppression was reduced. Moreover, a colonoscopy and supplemental biopsies showed CMV-Colitis. Treatment with intravenous ganciclovir terminated diarrhea. However, fever persisted and inflammation parameters further increased, despite of additive broad-spectrum antibiotics. A chest CT scan detected bilateral ground glass infiltrates, in particular in the upper right lobe. Bronchoscopy was inconspicuous. 16S rRNA gene sequencing identified Mycobacterium genavense in blood cultures and the bronchoalveolar lavage after six weeks, proving a disseminated infection. Antiinmycobacterial therapy was started with Clarithromycin, Rifampicin, Moxifloxacin and Ethambutol, adjusted to the impaired kidney function. However, patient’s inflammatory parameters and fever episodes did not resolve after 12 weeks of therapy.

Discussion: This exceptional case illustrates rare infectious complications in a patient six years after kidney transplantation. The identification of Mycobacterium genavense is challenging due to the unspecific symptoms and its slow growth.

Clinical Manifestations of Nephrotic Syndrome Complicated by Renal Artery Thrombosis: A Case Report

Liuba Wang,¹ Xi Qiao,¹ 1Nephrology, Second Hospital of Shanshi Medical Univ, Taiyuan, China; 2Shansi Kidney Disease Inst, Taiyuan, China.

Introduction: Although thrombotic complications in the venous system are common in patients with nephrotic syndrome, arterial thromboses associated with nephrotic syndrome are much less common. The main renal artery thromboses are extremely rarely observed. We report a case of nephrotic syndrome complicated by main renal artery thrombosis.

Case Description: The clinical data of a patient, who suffered from nephrotic syndrome complicated by right main renal artery thrombosis, were analyzed. The patient was a 38-year-old man, who presented with features of main renal artery thrombosis, when the nephrotic syndrome relapses after 1 year complete remission. The clinical manifestations were the appearance of severe lumbago suddenly, fever, percussion pain of ipsilateral kidney area, increase of the total number of white blood cells, white nucleus left, massive proteinuria, and aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBDH) was increased obviously, hyperuricemia did not occur. Renal artery thrombosis was diagnosed by echo Doppler and confirmed by computed tomography angiography (CTA).

Intravenous thrombolyis therapy was effective. CTA showed complete lysis of renal thrombus; clinically there was a regression of flank pain.

Discussion: Nephrotic syndrome with main renal artery thrombosis is rare, and the clinical manifestations are acute renal infarction. Renal Doppler and CTA should be carried out in these patients. When the disease is diagnosed at an early stage, an intravenous thrombolysis can be attempted. Timely diagnosis and proper treatment are important for improving the prognosis of patients.

C-ANCA+ RPGN following Anti-TNF Use in Autoimmunity

Anne S. Yu, Susan E. Quaggan, Jennifer A. Tuazon. Nephrology, Northwestern Univ, Chicago, IL.

Introduction: Rapidly progressive glomerulonephritis (RPGN) is characterized by rapid loss of renal function and glomerular crescent formation. In patients with rheumatoid arthritis (RA), there have been 3 case reports of acute renal failure due to pauci-immune necrotizing crescentic GN in the setting of anti-tumor necrosis factor-alpha (anti-TNFs) use. We present a case of a patient with RA who developed RPGN following treatment with etanercept.

Case Description: A 43-year-old woman with history of long standing RA (treated with steroids intermittently for 9 years and etanercept for 5 months), hypothyroidism, and recent pulmonary embolism, presented with headache, nausea, epigastric pain, and malaise. On admission, she was found to have acute renal failure (Cr 5.8 mg/dl from baseline 0.8 six weeks prior) with hematuria (>100 RBCs and RBC casts on urinalysis), sub-nephrotic range proteinuria (1.2 g/g Cr), and anemia (Hb 7.8). On exam, she was not hypertensive, with clear lungs, no leg edema, and no rashes. A renal biopsy was performed which revealed severe pauci-immune necrotizing crescentic GN with significant tubulointerstitial inflammation and minimal scarring. She had a positive C-ANCA (titer 1:1280) and anti-PR3 (158). She received pulse steroids and cyclophosphamide, with downtrend in Cr from peak of 6.5 to 4.6 by day of discharge and never required renal replacement therapy. Renal function continued to improve with Cr down to 1.2 after extended steroid taper and maintenance of cyclophosphamide over 3 months, with plan for a 6 month total treatment course.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Discussion: Treatment of RA with anti-TNFα agents has been associated with development of vasculitis and rarely pauci-immune GN. While anti-TNFα agents may stimulate formation of autoantibodies, mechanisms are unclear. The temporal relation of anti-TNFα use and new-onset renal disease suggests a pathogenic role of TNFα antagonists in development of GN. RPGN should be considered in patients with underlying autoimmune and exposure to anti-TNFα who develop renal failure, as early diagnosis and initiation of therapy are essential to prevent irreversible loss of renal function.

PUB455
Crescentic IgA Nephropathy in a Patient with Active Pulmonary Tuberculosis
Asafere Hafifaradaran, Golriz Jafari, Ruchika Bhasin, Phuong-Thu T. Pham, Phuong-Chi T. Pham. 1. Olive View-UCLA Med Ctr, 2. UCLA.

Introduction: The presence of crescents in IgA nephropathy (IgAN) may be associated with a 1.5-fold increased risk of kidney failure. Concurrent diffuse mesangial proliferation may lead to a 50% risk of reaching end stage renal failure within 5 years. Given its worse prognosis compared with non-crescentic IgAN, the addition of cyclophosphamide to glucocorticoids has been suggested.

Case Description: 79-year old male with chronic obstructive pulmonary disease and alcoholism presented with anorexia and generalized weakness. Full evaluation revealed active pulmonary tuberculosis (TB). Patient received rifampin, isoniazid, pyridoxine, and ethambutol (RIPE) therapy when he began to develop new onset rapid kidney injury (creatinine [Cr] increase from 0.9 to 6.5 mg/dL within 2 weeks), proteinuria (none to protein/creatinine ratio 2.0 g/g), hematuria, and red blood cell casts. Kidney biopsy revealed active glomerular crescents approximated at 20%, with necrotizing lesions and acute tubular necrosis. Given the concurrent active pulmonary TB, patient was only given minimal glucocorticoids (solumedrol 300 mg IV daily for 3 days followed by a rapid prednisone taper to off within 2 1/2 months). Both kidney injury and proteinuria resolved minimal glucocorticoids (solumedrol 300 mg IV daily for 3 days followed by a rapid prednisone taper to off within 2 1/2 months). Both kidney injury and proteinuria resolved.

Discussion: Active TB has been reported to be associated with IgAN, mesangial proliferative, crescentic, membranous glomerulonephropathies, among others. Of interest, rifampin has also linked to crescentic GN. In the current case, patient received continuing full dose RIPE and a short course of glucocorticoids with complete resolution of proteinuria, hematuria, and marked improvement of Cr within 3 months. Given the acute onset of kidney injury following the diagnosis of active TB and the rapid resolution of kidney injury with RIPE, we suspect that the crescentic IgAN was associated with active pulmonary TB and less likely, rifampin or others. The association is important to recognize because unlike other underlying etiologies of crescentic IgAN where aggressive immunosuppressive may be indicated, it is contraindicated and unnecessary in patients with active pulmonary TB.

PUB456
Hyponatremia in an Unexpected Case of Extrapulmonary Tuberculosis
Savema Saijadi, Reginald Icanyi Obi. Nephrology and Hypertension, East Carolina Univ, Greenville, NC.

Introduction: Accurate diagnosis of hyponatremia is pivotal to optimum management. Discovery of the cause of hyponatremia is not always straightforward and requires thorough investigation and attention to detail. We describe a case of subacute hypoosmolar hyponatremia in a patient with multiple risk factors for various etiologies of hyponatremia.

Case Description: 51 year old male with history of HIV and subdural hematoma was admitted with concern for septic shock secondary to pneumonia. His exam was pertinent for BP 84/50 mmHg and Pulse 108. He was cachectic, tachycardic, with clear lungs, and irritable. Labs were pertinent for sodium 124 mEq/L, potassium 5.9 mEq/L, serum osmolality 260 mOsm/kg, urine osmolality 681 mOsm/kg, urine sodium 84 mEq/L, and morning cortisol 5.6 ug/dL. His PPD and Quantiferon Gold test were positive. He was started on broad-spectrum antibiotics as well as Haldol for agitation. Pulmonary TB was ruled out. A differential of SIADH and Cerebral Salt Wasting (CSW) was considered. CSW was ruled out after hydration led to further drop in sodium. A suspicion for adrenal insufficiency was entertained because of hyperkalemia in the setting of low normal cortisol. Evaluation with a cosyntropin stimulation test was performed and confirmed primary adrenal insufficiency likely due to infection of the adrenal glands with TB. The patient received appropriate therapy leading to resolution of hyponatremia.

Discussion: In the setting of various potential etiologies for hyponatremia, thorough work-up is critical. Based on this patient’s history of pneumonia, HIV, antipsychotic medication use, drop in sodium after receiving isotonic fluids, and urine and plasma sodium studies, SIADH may be suspected. However, detailed diagnostics review revealed primary adrenal insufficiency likely secondary to extrapulmonary TB and led to initiation of appropriate therapies. SIADH is the most common electrolyte abnormality in extrapulmonary TB. Infectious adrenalitis secondary to TB can lead to hypocortisolism and relative hypersecretion of antidiuretic hormone, which leads to hyponatremia. Understanding the primary cause and mechanism of hyponatremia in this case led to appropriate therapy and resolution of hyponatremia.

PUB487
A Case of Atypical PostInfectious Glomerulonephritis in an Elderly Male Patient with Liver Cirrhosis
Markia Manolopoulos,1  Markus Lusco,2 Leslie S. Gewin.3 1. Div of Nephrology and Hypertension, Vanderbilt Univ Medical Center; 2. Dept of Pathology, Microbiology and Immunology, Vanderbilt Univ Medical Center; 3. Div of Nephrology and Hypertension, Veterans Affairs Medical Center, Nashville, TN.

Introduction: Postinfectious Glomerulonephritis (PIGN) is usually a childhood disease that occurs after an upper respiratory tract infection or impetigo and follows a benign course. We present a case of an elderly male patient with liver cirrhosis with clinical evidence of RPGN and pathologic features of PIGN on biopsy.

Case Description: A 60 year old male patient with CKD 3, DM2, HCV cirrhosis (viral load undetectable on Harvoni therapy) presented with shortness of breath, edema, elevated proteinuria, and elevated creatinine (1.4 g/L). Hematuria and serum creatinine at 1.3 mg/dL. Hospital course was complicated by oliguria and peak serum creatinine of 5.3. Aside from low complements, he had negative workups both for causes of glomerular disease as well as active infections. Renal biopsy was performed and showed focal proliferative glomerulonephritis, mild diabetic nephropathy with a dominant C3 granular and chunky mesangial and segmental capillary loop staining in a “starry sky” pattern by IF. A late phase or resolving postinfectious etiology was suggested without evidence of subepithelial hump-type deposits. He was treated with a course of steroids, and on hospital day 10 his urine output and subsequently his renal function improved.

Discussion: PIGN follows a more aggressive course in elderly patients with multiple comorbidities. Even though there is no strong evidence that steroids help PIGN, our patient perhaps improved after steroid administration. Given pathologic evidence of PIGN with characteristic staining, this case illustrates the possibility that PIGN and C3 glomerulopathy might be diseases of the same disease spectrum.

PUB458
Bilateral Obstructing Ureter Calculi, the Cause of Stage 3 Acute Kidney Injury
Sai Prasad Godula,1 Siwadon Pinkuewtrakul,2 Sree V. Pillai.1 Internal Medicine, St. Francis Hospital, Evanston, IL; 2. Internal Medicine, St. Francis Hospital, Evanston, IL.

Introduction: Non-contrast CT abdomen and pelvis should be the imaging modality of choice in a patient with rapidly worsening kidney function.

Case Description: A 69-year-old man with altered mental status. His medical history included alcoholic liver cirrhosis, schizoaffective disorder. His medications included the trazodone. He was admitted for elevated ammonia level and urinary tract infection suspicion. Patient was afebrile, his HR was 85/mm and BP 109/52 mm Hg, RR 20/min, and oxygen saturation 94 % on 4 liters nasal cannula. The neurological examination was unremarkable but he did not make urine overnight. On hospital day 4 he made 300 ml of urine. Urine analysis revealed cloudy urine, Specific Gravity 1.002, pH 6, moderate blood, large leukocytes, rbc’s 21-50/ hpf. Urine sodium revealed 48 mmol/L, FENA 3.6%. The wbc was 21000/ccmm, with 17000 absolute neutrophils. The sodium was 130 mmol/L, K 4.5 mmol/L, cl level 103 mmol/L, HC03 level 21 mmol/L, BUN level 43 mmol/L, creatinine level 5.0 mg/dL, GFR MDRD 12 ml/min/1.73 m, and blood ammonia level 85 UMOL/L. Renal ultra-soundogram revealed no evidence of hydronephrosis. On hospital day 5 he had myoclonic jerks on examination. He underwent emergent hemodialysis. On hospital day 6 he had non-contrast CT abdomen and pelvis which revealed bilateral obstructing calculi within the mid distal ureters measuring approximately 8 mm in diameter. Patient subsequently underwent bilateral anti-grade pyelogram and bilateral nephrostomy tube placement under ultrasonic guidance.

Discussion: Renal ultrasound is the initial imaging of choice in renal failure; but lacks sensitivity to identify the cause of obstruction when obstruction is in the lower part of ureter. This case report give special importance to non-contrast CT abdomen and pelvis in management of rapidly worsening kidney function.

PUB489
A Case of Membranoproliferative Glomerulonephritis in Hyaline Variant Multicentric Castleman’s Disease
Sindhuca Bobba, Davis Massey,1 Qiang Wang, Wei Fan,1,2 Drew H. Kidd. Department of Internal Medicine, Div of Nephrology, Virginia Commonwealth Univ Health System.

Introduction: Membranoproliferative glomerulonephritis (MPGN) is a pattern of histology characterized by endocapillary proliferation, mesangial hypercellularity, and capillary wall remodeling. MPGN is frequently immune complex mediated or due to complement dysregulation. Less commonly, MPGN can be seen without immunoglobulin or complement deposition. We present an uncommon case of the MPGN pattern of injury related to Castleman’s disease.

Case Description: A 23 year old Caucasian man presented for evaluation of acute renal failure with progressive anaemia and mediasinal mass. At presentation, his serum creatinine was 1.8 mg/dL. Urinalysis was significant for monoclonal hematuria and proteinuria. A spot urine protein to creatinine ratio was 0.9 mg/mg. Hemoglobin was 9.3 g/ dl. Contrasted tomography scan of his chest, abdomen and pelvis showed bilateral pleural effusions, anterior mediasinal mass and mediasinal lymphadenopathy. A serologic work up was unremarkable including negative EBV IgM, CMV, HIV. Biopsy of the mediastinal mass was negative for malignancy. A biopsy of a lung nodule was unremarkable. Renal biopsy was performed. Light microscopy was significant for a...
membranoproliferative pattern of injury. Immunofluorescence was unremarkable. No immune complexes were present on electron microscopy. He underwent anterior lymph node biopsy that showed multicentric Castelman’s disease of hyaline vascular variant. He received 4 doses of etoposide and one dose of rituximab. Most recent serum creatinine was 0.72 mg/dl and he has lost 27 kg.

**Discussion:** A membranoproliferative pattern of injury is present in our patient without any immune complexes, complement deposition or evidence of TMA. Increased production of IL6 and vascular endothelial growth factor (VEGF) have been implicated in the pathogenesis of CD. In mouse models, increased IL6 has been shown to induce podocyte apoptosis and podocyte specific overexpression of VEGF resulting in collapsing glomerulopathy. It is unclear if either play a role in CD related renal manifestations. More study into the pathogenesis of renal disease in CD is needed. 1 Bartlett, amnurev-physiol 2016.

**PUB460**

Calcific Atrial Mass in End-Stage Renal Disease  
**Mohamad Altriki,** Prabir Roy-Chaudhury, Bijin Thajudeen.  
*Nephrology, Banner Univ of Arizona Medical Center, Tucson, AZ.*

**Introduction:** Metastatic cardiac calcification (MCC) has been widely reported in patients with ESRD promoted by elevated serum calcium-phosphate product, increased PTH, and reduction in blood fluid inhibitors of calcification. Dystrophic cardiac calcification (DCC) is often associated with damaged tissue or systemic inflammation and when present, is usually0, often encompassing multiple cardiac chambers and valves. We present an unusual case of DCC as well as MCC involving left atrium (LA) in the setting of ESRD.

**Case Description:** A 55-year-old Caucasian male with h/o HTN, ESRD on HD, failure of previous renal transplant presented with symptoms of fever and chills. He was diagnosed with sepsis due to methicillin-resistant *Staphylococcus aureus* infection. A transesophageal echocardiogram done as part of the workup for MRSA bacteremia showed a large 2.2 cm x 1.2 cm calcified, highly mobile echo density attached to the Cournaud ridge within LA representing an old, calcified vegetation or a calcified thrombus.

Cardiac MRI confirmed the mobile calcified mass. Laboratory tests showed PTH of 670 pg/ml, corrected calcium of 8.9 mg/dl and phosphorus 6.2 mg/dl.

**Discussion:** In our patient, the calcification in the LA is a product of DCC promoted by MCC resulting from abnormal bone mineral metabolism disorder. Calcium deposition often involves the mitral valve, left ventricular free wall and septum as well as the LA appendage. It can lead to complicated valvular stenosis, cardiac arrhythmias, cardiac block and abnormal cardiac hemodynamics by effecting systolic and diastolic cardiac function. Over time LA pressure can increase due to decreased compliance of the LA wall and can be transmitted through pulmonary veins resulting in derangements in right heart hemodynamics. Awareness, early detection and treatment of the underlying cause, and resulting complications is the key to the patient outcome.

**PUB462**

Nivolumab Induced Renal Failure with Collapsing Focal Segmental Glomerulosclerosis (FSGS) - A Case Report  
**Abhishek Sinha Ray,** Sreepar Ghosh,  
*Nephrology and Hypertension, Kansas Univ Medical Center, Kansas City, KS; Internal Medicine, Interfaith Medical Center, Brooklyn, NY; Pulmonary, SIU-SOM, Springfield, IL.*

**Introduction:** Nivolumab, a monoclonal antibody against PD-1 (Programmed cell death protein 1) receptor, suppresses PD-1 pathway-mediated inhibition of anti-tumor immune response. This agent has been approved for metastatic melanoma, non-small cell lung cancer, advanced renal cancer, relapsing Hodgkin’s lymphoma. Immune-mediated nephritits of varying severity is reported in early literature and most had complete recovery with high dose steroid. However clinical experience is limited. We report a case of severe renal insufficiency with Nivolumab requiring long term renal replacement therapy.

**Case Description:** 42-year-old male with stage IV adenocarcinoma of lung with disease progression despite chemo and radiation therapy received one dose of Nivolumab. Baseline creatinine (Cr) was 1.3 mg/dl; urine analysis was negative for proteinuria. His 2nd dose of Nivolumab, scheduled after 2 weeks, was held due to elevated Cr (3.13 mg/dl) and he was subsequently admitted. He developed progressive acute kidney injury without any response to conservative management with intravascular volume expansion. He had 30.8 g/day proteinuria and was started on high dose intravenous steroid for suspected immune-mediated nephritis. His renal function and urine output worsened and renal biopsy was performed. Pathology showed collapsing focal segmental glomerulosclerosis (FSGS) involving 20 out of 46 glomeruli without any significant immune deposit. He continued to have heavy proteinuria, oliguria with Cr 8.2 mg/dl on 12th day of hospitalization. He had to be started on dialysis for significant volume overload and severe azotemia. Steroid was slowly tapered off. Nivolumab therapy was never restarted, but even after 8 months of the index event, he continued to be dialysis dependent.

**Discussion:** Nivolumab is reported to cause steroid-responsive immune-mediated nephritits but our patient, who otherwise had mild non-proteinuric chronic kidney disease, developed end stage renal disease due to non-immune mediated collapsing FSGS after a single dose of Nivolumab.

**PUB463**

A Case of Subclavian Steal Syndrome Accompanied by Back-Flow of Vertebral Artery Detected after Arteriovenous Fistula Creation  
**Matsuo, Ichiro,** Okhido, Keitaro Yokoyama, Takashi Yokoo.  
*Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.*

**Introduction:** Subclavian steal syndrome (SSS) has a feature of a negative pressure gradient between the vertebral-subclavian artery junctions, resulting in altered vascular hemodynamics. SSS is relatively rare, but diabetes and atherosclerosis are strong risk factors. Especially, SSS becomes a major problem at the time of arteriovenous fistula (AVF) creation because of the diminished cerebral blood flow as a result of increased forearm blood flow. A 71-year-old man was admitted for the initiation of hemodialysis (HD). He was already diagnosed as end-stage renal disease (ESRD) due to diabetic nephropathy, and got an operation of left forearm AVF creation just a month ago. He had no neurological symptoms including syncope and vertigo. There was no bilateral difference in blood pressure, and he did not complain numbness nor weakness in arm. Because carotid Doppler examination revealed back-flow of left vertebral artery, we considered the presence of SSS. Angiography revealed severe stenosis at the origin of left subclavian artery, and we performed percutaneous transcatheter angioplasty (PTA).
After PTA, stenosis of left subclavian artery disappear, the blood flow of left vertebral artery became normal, and he initiated HD using AVF in safety.

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

**Underline represents presenting author.**

1011A
Severe Acute Tubular Necrosis Associated with Tenofovir Alafenamide

Introduction: Tenofovir disoproxil fumarate (TDF) is a prodrug that is metabolized to tenofovir, which is subsequently converted intracellularly via phosphorylation to tenofovir-diphosphate, the active form of the drug responsible for antiviral properties. Elevations of tenofovir have been associated with nephrotoxicity. However, tenofovir alafenamide (TAF), a new prodrug of tenofovir, limits plasma exposure of tenofovir to <5% less than TDF; and hence, TAF has been associated with less nephrotoxicity. We describe a case in which TAF was associated with biopsy proven severe acute tubular necrosis (ATN).

Case Description: A 70 year old male with a medical history significant for HIV and chronic kidney disease [baseline creatinine (Cr) 2 mg/dL and Cr clearance > 40 mL/min] presented to the department with complaints of shortness of breath for the past 2 weeks. He was recently switched from a single drug regimen consisting of efavirenz, etravirine, emtricitabine, and TDF to a combination of efaviravin, cobicistat, emtricitabine, and TAF 2.5 weeks prior to presentation. Physical exam was remarkable for moderate respiratory distress with use of accessory muscles, diffuse wheezing and rales in bilateral lung fields, and bilateral lower extremity edema. Laboratory values depicted severe anion gap acidosis (pH of 7.07) with serum bicarbonate level of 5 mmol/L, PCO2 of 16, blood urea nitrogen of 125 mg/dL, and Cr of 10.5 mg/dL. Urine microscopy showed many red blood cells and white blood cells but no casts. Patient had 2.2 g/24 hrs of proteinuria. Urine output was <500 mL/day. Renal ultrasound was unremarkable. Subsequently, patient underwent hemodialysis for volume overload and severe metabolic acidosis. Renal biopsy showed diffuse and severe proximal tubular degenerative changes and mild foot process effacement consistent with acute tubular necrosis.

Discussion: Although TAF is approved for use in patients with mild to moderate kidney disease (Cr clearance of >30 mL/min), our case depicts a patient who had ATN after being switched to a single tablet antiviral therapy which included TAF. Therefore, clinicians need to be cautious in using this new agent.

PUB468
Streptozocin Induced Acute Tubulo-Interstitial Nephritis

Introduction: Drug induced acute tubulo-interstitial nephritis is an important cause of acute renal failure. Streptozocin has been used as an anti-cancer agent, its nephrotoxicity has been reported as reversible proteinuria, proximal tubular dysfunction; but tubulo-interstitial nephritis has been rarely reported.

Case Description: 65 year old female with adrenal carcinoma, initially on cisplatin based chemotherapy which was changed to streptozocin, presented with acute kidney injury. Her creatinine was <1 mg/dL and urinalysis was benign before streptozocin therapy. She developed fatigue, malaise, nausea/vomiting and decreased appetite within days after starting streptozocin and had a creatinine of 6.2 mg/dL three weeks after streptozocin administration. Urine microscopy showed many muddy brown casts and few non-dysmorphic RBCs. Hemoglobin was 7.5 and platelet count was as low as 11 with normal LDH, lactoglobulin and total bilirubin and no schistocytes on peripheral smear. She had peripheral eosinophilia and also had urinary eosinophils. Ultrason showed normal sized kidneys. She was started on prednisone for presumed interstitial nephritis as biopsy was deferred due to thrombocytopenia. Creatinine improved to 4 mg/dL and was discharged on a 3 week prednisone taper. She was in the outpatient setting and her symptoms recurred after stopping the prednisone. She was re-admitted for worsening renal failure, with creatinine of 10 mg/dL (5 weeks after administration). Renal sonogram and urinalysis were unchanged. Urine eosinophils were negative and peripheral eosinophils were improved. Kidney biopsy was performed which showed severe ATN with interstitial lymphocytic infiltrate and the diagnosis was severe acute tubulo-interstitial nephritis. She was discharged with a creatinine of 9 mg/dL and most recent labs revealed a slight decrease to 8.5 mg/dL (9 weeks after administration). She was given another 4 weeks of prednisone after the biopsy results.

Discussion: Monitoring of renal function after starting streptozocin and early diagnosis of tubulo-interstitial nephritis is important as it is potentially reversible by removing the suspected agent and may respond to short course of steroids.

PUB470
Relapsing Calciphylaxis after Kidney Transplantation

Introduction: Calciphylaxis is a debilitating condition with calcification and thrombosis of cutaneous arterioles leading to ischemic necrosis. Risk factors include end stage kidney disease (ESRD), female sex, obesity, malignancy, chronic inflammation, hypercoagulable state, elevated calcium and phosphorus product and parathyroid hyperactivity. Available treatment modalities of calcification include hyperbaric oxygen, pulse dexamethasone, surgical resection and good wound care. Kidney transplantation may improve this condition through a reduction in systemic inflammation and restoration of normal calcium-phosphorus metabolism. We describe a kidney transplant patient with relapsing calciphylaxis.

Case Description: A 58 year old woman with ESRD due to IGA nephropathy complicated by antiphospholipid syndrome on hemodialysis for 15 years. The patient had calciphylaxis treated with intravenous sodium thiosulfate and parathyroidectomy 5 years pre-transplant. Lupus was quiescent and patient was on fondaparinux. The patient received a kidney transplant and had a mild calciphylaxis at 1 year after transplant. She was transitioned to everolimus in addition to tacrolimus, mycophenolate mofetil and prednisone. 4 months post-transplant the patient developed painful purpuric necrotic and indurated lesions on both thighs and forearms. Skin biopsy showed calcification of subcutaneous vessels with necrosis of dermis and epidermis consistent with calciphylaxis. Workup showed normal levels of aluminum, protein C and S and a negative antiphospholipid antibody test. Creatinine 0.9mg/dl, iPTH 38.2 pg/mL, Ca 9.5 mg/dL, Phosphorus 3.5 mg/dL, Alb 3.8 mg/dL. Tacrolimus levels 5-7 ng/dL. Patient received intravenous sodium thiosulfate, hyperbaric oxygen and specialized wound care. A percutaneous enteric feeding tube provoked further calciphylaxis lesions with extensive areas of skin and soft tissue necrosis. The patient developed sepsis and expired in spite of preserved kidney function.

Discussion: Kidney transplantation may not prevent recurrence of calciphylaxis. Calciphylaxis in transplant recipients decreases osteoprotegerin and increase receptor activator of nuclear factor-ƙ B ligand (RANK-L) leading to increased extracellular mineralization and vascular calcification and may have contributed to the patient’s disease.

PUB471
Mucin-1 Kidney Disease: A Family History

Introduction: Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) refers to a group of diseases characterized by autosomal dominant inheritance, bland urinary sediment, absent-to-mild proteinuria, no severe hypertension, normal or small-sized kidneys on ultrasonography, pathologic changes of tubular and interstitial fibrosis, and slowly progressive chronic kidney disease (CKD), resulting in the need for dialysis in the fourth through seventh decades of life. It is caused by mutations in the genes encoding uromodulin (UMOD), hepatocyte nuclear factor-1B (HNF1B), renin (REN), and mucin-1 (MUC1). We describe a case of a 30 year-old caucasian female who was admitted to our department due to uremic syndrome. She had a chronic kidney disease of unknown etiology, with a previous creatinine of 2.7mg/dl when she was 27 years-old and had had no follow-up since then. She had a chronic hypoalementin and metabolic acidosis, a bland urinary sediment and normal sized kidneys on ultrasonogram. Immunologic, serologic and renal biopsy testing were negative. She had a family history of chronic kidney disease without deafness or visual loss. Her grandmother died after 30 years of chronic kidney disease; her father had a history of gout and received a renal transplant at 37 years old; a cousin with chronic kidney disease in dialysis since he was 57 years old, with multiple cutaneous cysts, a kidney biopsy with tubulointerstitial nephritis, and negative study of the uromodulin gene; and also an uncle in dialysis since he was 60 years old. Genetic testing of the MUC1 gene was positive. She started peritoneal dialysis one month after being discharged and remains in this technique at a 2 year follow-up.

Case Description: Mucin-1 kidney disease is a familial disease known as medullary cystic kidney disease type 1 is a familial progressive tubulointerstitial nephropathy belonging to the recently defined group of ADTKD. MUC1 gene encodes mucin-1, a protein expressed in many tissues, however no extrarenal manifestations have been described. Onset of end-stage renal disease is very variable between and within families as illustrated in our case.

PUB472
Everolimus Associated Acute Tubular Injury with Proteinaceous Casts

Introduction: Mammalian target of rapamycin (mTOR) inhibitors are associated with marked proteinuria in patients with renal impairment and can lead to a unique form of cast nephropathy. Cast nephropathy with mTOR inhibitors has been associated with simultaneous use of calcineurin inhibitors. Many patients are placed on mTOR inhibitors for immunosuppressive therapy, but caution should be taken in the setting of tubular injury because of the risk associated with proteinuria and increased tubular damage.

Case Description: A 40 year old female with a history of type 1 DM received a simultaneous pancreas and kidney transplant. She had multiple admission to the hospital due to diarrhea and volume depletion associated with mycophenolate use. She was transitioned to everolimus in addition to tacrolimus due to the significant side effects related to diarrhea and volume depletion. She had an everolimus level of 9.2 ng/mL. Renal biopsy was performed and showed marked acute tubular injury and proteinaceous casts.
Everolimus was determined to be the cause of her proteinuria and contributed to her tubular injury. Proteinuria decreased to 3 grams upon cessation of everolimus. The patient had significant renal fibrosis upon recovery as evidenced by repeat renal biopsy 2 months after the insult.

**Discussion:** Our patient developed cast nephropathy with nephrotic range proteinuria as a result of everolimus use. Proteinuria improved significantly upon cessation of everolimus. Therapy with the use of mTOR inhibitors increases proteinuria and can lead to cast nephropathy. These medications can also delay recovery in the presence of tubular injury with simultaneous use of calcineurin inhibitors.

**PUB474**

Acute Renal Infarction as an Unusual Cause of Acute Abdomen and a Rare Complication of Cardiac Angiography

**Case Description:** A 59 yo WM S/P kidney transplant for ESRD sec to DM2, simulect induction, on prednisone, everolimus & tacrolimus presented with AKI serum Cr 5 (baseline Cr 1), had DSA of 4300. Transplant biopsy showed Banff borderline cellular rejection, started on Steroids and IVIG. He presented with AKI Cr 9.2, no bleed, thrombocytopenia, transaminitis, 2+ blood in urine and was started on dialysis, steroids, thymoglobulin, changed immunosuppression to MMF/tacrolimus. Repeat biopsy showed borderline cellular rejection, TMA, C4d 2+. He was started on Plasmapheresis+IVIG. PBS showed no schistocytes, Cr dropped to 1.6 with DSA down to 2800.

**Discussion:** Our cases illustrate HUS secondary to everolimus/tacrolimus and TMA secondary to acute AMR. Post-transplant TMA should be identified early, differentials include AMR, TTP/HUS, and drugs (CNI/mTOR), with appropriate treatments can reverse AKI resulting in good renal outcome.

**PUB475**

Acute Renal Infarction as an Unusual Cause of Acute Abdomen and a Rare Complication of Cardiac Angiography

**Case Description:** A 43 -year-old man presented with sudden onset of left flank pain and left lower back pain for four hours. Three days ago, he was admitted in the hospital for chest pain, underwent coronary angiography. He was discharged on aspirin and dipyridamole after an abnormal stress test with angina. He presented with intermittent nocturnal hematuria, and congestive heart failure. Admission vitals and clinical examination were normal. He denied any systemic symptoms. Initial investigations revealed acute kidney injury with serum creatinine of 4.5, hyperkalemia of 6.1 and elevated ESR and CRP with microscopic hematuria. Autoimmune work up was significant for elevated myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA) titers. Kidney histopathology showed pauciimmune vasculitis with crescentic Glomerulonephritis. He had received flu vaccine 3 weeks prior to onset of symptoms. During hospitalization he was treated with steroids, cyclophosphamide and plasmapheresis that resulted in improvement in renal function.

**Discussion:** ACVAs-proteinuria is speculated to be caused by auto-immunity. The mechanisms proposed for the induction of vasculitis by infectious agents include direct microbial invasion into endothelial cells, immune complex mediated vessel wall damage, and the activation of auto-reactive B and T cells through molecular mimicry and superantigens. The latency period between vaccination and autoimmunity has been reported to be around 12 to 21 days and it is a diagnosis of exclusion. Similar vasculitic manifestations have also been reported with other vaccines like BCG and HPV. On review of literature, treatment modalities of influenza vaccine associated ANCA vasculitis includes steroids, cyclophosphamide, rituximab and plasmapheresis with some success. In our case, he received 7 sessions of plasmapheresis, oral cyclophosphamide and steroids with improvement in kidney function. It is important to recognize possible association between flu vaccine and ANCA vasculitis. Nephrologist should be vigilant for the possibility of developing renal vasculitis post flu vaccination.

**PUB476**

Non Hodgkin Lymphoma Presenting with Rapidly Progressive Glomerulonephritis due to Membranoproliferative Glomerulonephritis with Concurrent Thrombotic Microangiopathy: Long Term Remission with Rituximab

**Case Description:** A 73 yr old male with hypertension and diabetes mellitus with normal renal function, presented with an episode of gross hematuria with subsequent microscopic hematuria. Imaging studies of the abdomen and cystoscopy were negative. He developed anorexia and vomiting and acute renal failure: creatinine 7.2 mg/dL. Urinalysis was 4+ positive for blood and 24 hr urine protein excretion was 0.7 gm. Renal function initially improved with intravenous fluids, creatinine 3.1 mg/dL; however, proteinuria and microscopic hematuria persisted. He subsequently developed worsening anemia, dyspnea, and lower extremity edema. There was no hepatosplenomegaly or lymphadenopathy. Laboratory: hemoglobin 7.5 g/dL and platelets 156 K/uL. Studies for hepatitis B, C, HIV, antinuclear antibody, ASO titer, ANCA panel, ADAMTS13, and urine and blood cultures were normal or negative. C3 was low 75 (90-180 mg/dL) and C4 10 (10-40 mg/dL). Serum and urine electrophoresis did not identify any monoclonal proteins; however, serum free kappa /lambda ratio was elevated, 14.1. Cryoglobulins were trace positive with elevated rheumatoid factor. Kidney biopsy showed membranoproliferative GN with subendothelial immune complex deposition, basement membrane duplication, and evidence of alternative complement pathway activation and intraluminal TMA. Concurrent thrombotic microangiopathy is a rare complication of B cell Non Hodgkin lymphoma. Therapy with rituximab resulted in remission of both hematologic and renal manifestations.

**PUB477**

Acute Alcoholic Pancreatitis Induced aHUS: Role for Eculizumab

**Case Series of Everolimus with Tacrolimus Causing Hemolytic Uremic Syndrome (HUS) within 3 Months Post Kidney Transplantation**

**Case Description:** A 67 year old man presented to emergency room with complaints of fever and myalgia for 3 weeks. His medical history includes diabetes, hypertension and congestive heart failure. Admission vitals and clinical examination were normal. He denied any systemic symptoms. Initial investigations revealed acute kidney injury with serum creatinine of 4.5, hyperkalemia of 6.1 and elevated ESR and CRP with microscopic hematuria. Autoimmune work up was significant for elevated myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA) titers. Kidney histopathology showed pauciimmune vasculitis with crescentic Glomerulonephritis. He had received flu vaccine 3 weeks prior to onset of symptoms. During hospitalization he was treated with steroids, cyclophosphamide and plasmapheresis that resulted in improvement in renal function.

**Discussion:** ACVAs-proteinuria is speculated to be caused by auto-immunity. The mechanisms proposed for the induction of vasculitis by infectious agents include direct microbial invasion into endothelial cells, immune complex mediated vessel wall damage, and the activation of auto-reactive B and T cells through molecular mimicry and superantigens. The latency period between vaccination and autoimmunity has been reported to be around 12 to 21 days and it is a diagnosis of exclusion. Similar vasculitic manifestations have also been reported with other vaccines like BCG and HPV. On review of literature, treatment modalities of influenza vaccine associated ANCA vasculitis includes steroids, cyclophosphamide, rituximab and plasmapheresis with some success. In our case, he received 7 sessions of plasmapheresis, oral cyclophosphamide and steroids with improvement in kidney function. It is important to recognize possible association between flu vaccine and ANCA vasculitis. Nephrologist should be vigilant for the possibility of developing renal vasculitis post flu vaccination.

**Case Description:** A 59 yo WM S/P kidney transplant for ESRD sec to DM2, simulect induction, on prednisone, everolimus & tacrolimus presented with AKI serum Cr 5 (baseline Cr 1), had DSA of 4300. Transplant biopsy showed Banff borderline cellular rejection, started on Steroids and IVIG. He presented with AKI Cr 9.2, no bleed, thrombocytopenia, transaminitis, 2+ blood in urine and was started on dialysis, steroids, thymoglobulin, changed immunosuppression to MMF/tacrolimus. Repeat biopsy showed borderline cellular rejection, TMA, C4d 2+. He was started on Plasmapheresis+IVIG. PBS showed no schistocytes, Cr dropped to 1.6 with DSA down to 2800.

**Discussion:** Our cases illustrate HUS secondary to everolimus/tacrolimus and TMA secondary to acute AMR. Post-transplant TMA should be identified early, differentials include AMR, TTP/HUS, and drugs (CNI/mTOR), with appropriate treatments can reverse AKI resulting in good renal outcome.

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

Underline represents presenting author.

1013A
Anti-GBM was positive at 31 units/ml (reference range 0-20 units/ml). Renal biopsy revealed a thick basement membrane with normal underlying cortex and medulla, but was notable for the absence of a diffuse crescentic picture, which is typically seen in anti-GBM glomerulonephritis. The biopsy also showed nodular glomerulosclerosis which is a very rare finding. After treatment with steroids, cyclophosphamide and plasmapheresis, hemoptysis resolved and serum creatinine improved to 1.8 mg/dL.

Discussion: In contrast to the classical presentation of anti-GBM disease, the patient presented with less severe renal failure in addition to having kidney biopsy findings which lacked an overt crescentic picture. Similar cases have recently been reported which importantly display poor renal survival when treated with conventional therapy despite a mild elevation in serum creatinine. Although this patient improved with standard treatment for anti-GBM disease, the subset of patients with atypical anti-GBM disease require special attention during diagnosis and treatment in order to achieve good outcomes.

PUB480
Complete Normalization of Serum Creatinine from Very High Levels due to Obstructive Uropathy

Amar V. Patel, Muner Mohamed, Moro O. Salifu, Mary C. Mallappalli
Div. of Nephrology, SUNY Downstate Medical Center, Brooklyn, NY.

Introduction: Acute renal failure is one of the commonest reasons for inpatient Nephrology consultation. Of these, 5-10% of cases are classified as being obstructive. The time to recovering renal function after the resolution of the obstruction determines the need for emergency dialysis. We report a case of a patient presenting with a serum creatinine of 35.9mg/dL and fully recovering renal function with relief of obstruction and without dialysis.

Case Description: A 66-year-old man with a past medical history of hypertension, presented to the emergency room (ER) with bilateral leg edema, distended abdomen, difficulty urinating and decreased appetite for 3 weeks duration. He was previously seen in the ER when he had a urinaria infection and was treated with ciprofloxacin and hydrochlorothiazide. Significant finding on physical examination were BP 190/120mmHg, 1+ lower extremity edema, and a distended bladder. Initial laboratory data revealed Na 131mEq/L, K of 7.9mEq/L (non-hemolyzed), BUN 184mg/dL, and Cr 35.92mg/dL. Renal consultation requested for urgent dialysis. Foley catheter was placed with approximately 4L of blood tinged urine. Later in the day there was an additional 5L or urine. Over the next 30 hours patient laboratory data improved dramatically.

<table>
<thead>
<tr>
<th>Na</th>
<th>K</th>
<th>HCO3</th>
<th>BUN</th>
<th>Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>131</td>
<td>7.9</td>
<td>148</td>
<td>35.92</td>
<td></td>
</tr>
</tbody>
</table>

Patient was ultimately found to have obstructive uropathy secondary to prostatic cancer with a prostate specific antigen noted to be 61. His baseline creatinine 2 months later was 1mg/dL. He never had any hemodialysis.

Discussion: Obstructive nephropathy requires advanced clinical decisions due to the multitude of factors potentially requiring a patient to undergo urgent dialysis. Our case exemplifies these points and the patient ultimately did not require hemodialysis with rapid recovery of renal function. The key factor was immediate urinary output after release of obstruction. This is the highest serum creatinine (35.9mg/dL) reported in the literature with complete recovery of renal function (serum creatinine 1mg/dL) after resolution of obstruction.

PUB481
Glomerular Basement Membranes under Stress - When a Big Organ Lands in a Small Body

Francois Gougeon,1 Alexei V. Mikhailov,2 Keisha L. Gibson,2 Harsharan Kaur Singh,1 Volker Nicklelet,1 Nephrology, UNC-Chapel Hill, Chapel Hill, NC; 2Nephrology, UNC-Chapel Hill, Chapel Hill, NC.

Introduction: Donor/recipient body weight mismatch in kidney transplantation can be associated with decreased graft survival and increased proteinuria. These findings are reported in patients receiving kidneys too small for their body size. Glomerulomegaly, focal and segmental glomerulosclerosis, and rarely a peculiar form of glomerulopathy with basement membrane (GBM) remodeling have been observed. Glomerular alterations are attributed to non-immunological factors such as hyperfiltration and GBM ‘shear stress’.

Case Description: We present a case of a 9 year old child with dwarfism (below 3rd percentile for age) who received an adult-sized kidney (11 cm in length) at age 5. She developed persistent nephrotic range proteinuria (urine protein to creatinine ratio of 8.1) within a year of transplantation. Serum creatinine levels were stable at 0.2-0.3 mg/dL. Hematuria and donor specific antibodies (DSA) were absent. Two biopsies performed to evaluate the cause of proteinuria (3 and 4 years post-grafting) revealed markedly remodelled GBM with splitting mimicking hereditary nephropathy (changes not seen in a remote native renal biopsy nor in the donor organ at time of transplant). There was no evidence of rejection, no interstitial fibrosis and C4d was not identified along peri-tubular capillaries. Diffuse C4d staining was however noted along the GBM. Graft function and proteinuria remained unchanged until end of follow-up 50 months post grafting.
Emergent kidney biopsy showed severe crescentic glomerulonephritis with no evidence of TMA. Additionally, she had leukocytosis as high as 38.5 K/UL and single lung lesion imaging suspicious for lung abscess. She was treated with plasmapheresis (3 sessions), pulse dexamethasone and IV Cefotaxim along with broad-spectrum antibiotics and started on hemodialysis. She responded dramatically with pitting edema and fever resolving, and serological markers normalizing within a few weeks of treatment and eventually came off dialysis.

Discussion: While low C3 has been described previously, low C4 along with low C3 has rarely been described in AAV. In a case series of 46 patients with AAV where complement levels were analyzed, only one patient had both low C3 and C4. Here, we report another such a case.

**Table 1: Lab Results**

<table>
<thead>
<tr>
<th>Lab (reference range)</th>
<th>Day 1</th>
<th>Day 20</th>
<th>Day 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (136-144mEq/L)</td>
<td>129</td>
<td>138</td>
<td>133</td>
</tr>
<tr>
<td>Potassium (3.5-5.1mmol/L)</td>
<td>5.8</td>
<td>4.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>6.07</td>
<td>6.44 (on HD)</td>
<td>3.85 (off HD)</td>
</tr>
<tr>
<td>WBC (3.5-10.5 K/UL)</td>
<td>24.5</td>
<td>25.5</td>
<td>11.2</td>
</tr>
<tr>
<td>ANCA</td>
<td>POSITIVE</td>
<td>POSITIVE</td>
<td>Negative</td>
</tr>
<tr>
<td>ANA</td>
<td>&lt;1:1280</td>
<td>1.640</td>
<td>1.640</td>
</tr>
<tr>
<td>Complement 3 (69-152 mg/dL)</td>
<td>67</td>
<td>88</td>
<td>106</td>
</tr>
<tr>
<td>Complement 4 (16-38 mg/dL)</td>
<td>9</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Proteinase 3AR (&lt;10.0 AU)</td>
<td>113.5</td>
<td>23.9</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Discussion:** In our case, absence of preclampsia or significant transaminases made HELLP unlikely. The ADAMTS13 level with failure of plasmapheresis made TTP unlikely. Diagnosis of aHUS was substantiated by microangiopathy on biopsy, negative shiga toxin, and improvement in thrombocytopenia and renal function with eculizumab. aHUS accounts for 8–18% of all TMA cases during pregnancy, most occurring postpartum. With complement gene abnormalities the likelihood of recurrence in future pregnancies is high. aHUS mimics preeclampsia, HELLP and TTP. First episode had 25% mortality with 50% requiring dialysis. Thus, consideration of early treatment for aHUS is imperative on clinical suspicion alone.

**PUB484**
Atypical Presentation of Vascular Calcification in a Chronic Haemodialysis Patient Vishvas Raghunath, Kenneth Yong. Kidney Care Centre, Prince of Wales Hospital, Sydney, New South Wales, Australia.

**Introduction:** Calciphylaxis (calcific uraemic arteriopathy) is a well described entity in patients with end stage kidney disease (ESKD). Though it presents primarily with skin lesions, atypical presentations have been reported. We report a case of calciphylaxis masquerading as giant cell arteritis, causing progressive visual loss in a haemodialysis patient.

**Case Description:** A 72-year gentleman with ESKD on hemodialysis presented with headache and progressive visual loss in his single right eye. He was on oral anticoagulation for a prosthetic aortic valve and had recently undergone coronary artery bypass surgery, complicated by chronic ulcer at saphenous chronic graft sites. Clinical examination revealed reduced visual acuity. Right eye fundoscopy revealed mild optic disc oedema and cotton wool spots. Investigations revealed an elevated ESR (89mm/hr) and normal calcium phosphate balance. The clinical presentation was suspicious for temporal giant cell arteritis. He received empiric treatment with pulse methyl prednisolone and underwent a temporal artery biopsy which revealed medial arterial calcification with no signs of vasculitis, suggestive of calciphylaxis. His visual loss did not improve and he was given a trial of hyperbaric oxygen therapy to improve retinal blood flow. Further imaging included a CT-angiogram of the brain and neck, which indicated significant calcified bilateral carotid stenosis; an MRI brain showing no acute ischaemia; and a cerebral perfusion scan showing diffuse perfusion abnormality. After a multi-disciplinary meeting, it was determined that his visual loss was irreversible and the benefits of carotid recanalisation were unclear. His dialysis program and medications were optimised to maintain a favourable haemodynamic and biochemical profile, and to retard progressive vascular calcification.

**Discussion:** This case report illustrates the challenges of managing the atypical presentation of an abruse condition. There are few cases of calciphylaxis masquerading as giant cell arteritis described in literature. A high degree of suspicion is necessary for early diagnosis of calciphylaxis in a chronic haemodialysis patient on warfarin and assist in appropriate management.

**PUB485**
Successful PD Catheter Placement in a New ESRD Patient with Combined Antiphospholipid Syndrome and Factor XI Deficiency Antony Joseph Ferrey, Roy Fujitani, Min-Ha Tran, Yongen Chang, Wei Ling Lau. Univ of California, Irvine, Orange, CA.

**Introduction:** Coagulopathies and bleeding disorders impact surgical morbidity and potential dialysis modalities for new ESRD patients. Our patient is a 68 year old female with a history of autoimmune hepatitis, antiphospholipid syndrome (APL), and factor XI deficiency. She is the first reported successful PD catheter placement in a patient with such combined bleeding and clotting disorders.

**Case Description:** She was diagnosed with APL after a workup for recurrent TIAs and a lacunar CVA, noted to have positive lupus anticoagulant, anticardiolipin, B2-glycoprotein, and antithrombin antibodies. She has a history of recurrent bleeding, for which a detailed evaluation uncovered a factor XI deficiency. Over the last 7 years she has had a gradual decline in eGFR, was referred to Nephrology and found to have nephrotic range proteinuria. A renal biopsy was considered but not done since the risk outweighed potential benefits; in the setting of APL the prolonged PT TTT could not be corrected despite multiple FFP infusions. The patient met criteria for initiation of PD as she was unable to tolerate dialysis. She was started on PD with heparin and nadropragulin, with multiple risks associated with HD in the setting of her complex hematologic disorders, including bleeding with repetitive needle sticks vs. thrombosis of the AV fistula. Coagulation and platelets were administered prior to placement of a temporary HD catheter. Hemodialysis was done before surgery to decrease uraemic platelet dysfunction. The following day, additional FFP and platelets were infused followed by successful laparoscopic placement of a peritoneal dialysis catheter. DDAVP was not used due to its (rare) thrombosis side effect, as the patient has history of TIAs/CVA. After a session of hemodialysis was done before the catheter was removed. Low volume recurrent exchanges were started one week later and her PD prescription has gradually been increased. For two months she has been doing well on PD.

**Discussion:** To our knowledge, this is the first report of a successful PD catheter placement and initiation of PD in a patient with combined antiphospholipid syndrome and factor XI deficiency. Careful peri-operative planning can avoid adverse thrombotic or bleeding events.
Rhabdomyolysis and Acute Uricle Nephropathy from Synthetic Bath Salt: (e)Uphoria to Uricle Nephropathy
Ali Hassan,1 Paras Dedhia,1 Charuhas V. Thakar,1,2
1Dept of Nephrology and Hypertension, Univ of Cincinnati, Cincinnati, OH; 2Renal Section, Cincinnati VA, Cincinnati, OH.

Introduction: Bath salts are synthetic cathinone derivatives of plant Catha edulis. “Flakka” is the street name for chemical compound α-Pyrrolidinopentiophenone (α-PVP). It is a stimulant of the monoamine catecholamine class.

Case Description: A 37-year-old Caucasian male with no significant past history admitted to medical ICU after found down and unresponsive for unknown duration. He was intubated for airway protection. EMS noted that he was very combative and violent at the time of arrival. Physical examination was remarkable only for sinus tachycardia. Lab data was significant for anion gap metabolic acidosis (AG=15) with venous lactate of 30 mmol/L. Over next 24 hours, lactate decreased to 2.2 mmol/L with IV fluids. Hospital course was complicated by oliguric AKI with rapid worsening of creatinine from 1.1 mg/dl to peak creatinine of 9.9 mg/dl on hospital day 7. Urine toxicology screen was negative. Urimnsialy showed small blood with 3 RBC. AKI work up was also significant for rise in uric acid to 16.7 mg/dl and urine sediment showed rhomboid shaped uric acid crystals. His fractional excretion of uric acid was 148 %. Due to hyperkalemia and oliguric AKI, he was started on dialysis and required six sessions of dialysis prior to recovery of renal functions. Follow up serum Cr at one month was 0.9 mg/dl. He confirmed injecting “Flakka” prior to hospital admission.

Discussion: Case studies have reported bath salts induced AKI from hemodynamic mediated ATN and rhabdomyolysis. This case highlights possibility of uric acid nephropathy as an additional mechanism. It also underscores importance of examining urinary sediment especially in cases where AKI pathogenesis is not well known.

Binge Correction
Guilherme Piovezani Ramos,1 Larissa Kruger Gomes,2 Kianoush Banaci-Kashani,3
1Internal Medicine, Mayo Clinic, Rochester, MN; 2Internal Medicine, Univ of Connecticut, Farmington, CT; 3Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Introduction: Severe hyponatremia (HNa) is associated with high morbidity and mortality, which can be worsened by rapid corrections. Ethanol abuse can lead to HNa through different mechanisms. Identifying the primary process is crucial to correct sodium (Na) appropriately and prevent complications.

Case Description: A 40-year-old male presented with a week history of confusion and weakness with pulse 90 bpm, blood pressure (BP) 130/73 mmHg, and a pulse oximetry of 98% on room air. On examination he had non-specific unsteady gait. A CT scan discovered a 3.7 cm right renal mass, and after total nephrectomy histology revealed papillary RCC type 2. Non-neoplastic kidney tissue did not have signs of glomerular or tubular disease, nor amyloid deposition. Workup for metastatic disease was negative. The decision was made to proceed with biopsy of left renal mass to rule out metastatic disease. Total of 6 glomeruli were sampled, one was globally sclerotic, 4 of 6 glomeruli were necrotizing with crescenting features. One focus of inflammation was admixed with smooth muscle cells raising the possibility of large vessel vasculitis. High dose steroids and cyclophosphamide was not successful in halting the decline in renal function, and hemodialysis was started.

Discussion: There is increasing evidence that RCC and ANCA associated PGN demonstrate a common underlying immunologic mechanisms of glomerular injury which are regulated by the podocytes Von Hippel Lindau gene. Our patient had severe systemic symptoms that did not improve after nephrectomy, suggesting that another process was at play. However review of the surgical specimen confirmed no evidence of PGN at that time. Early ANCA screening could be beneficial in newly diagnosed RCC and further investigation of the role of chemokine specific therapy is warranted.

Recurrence of ANCA Negative Pauci-Immune Crescentic Glomerulonephritis
Pradeep Varilta,1 Alton Brad Farriss,2
1Transplant Nephrology, Emory Univ; 2Renal Pathology, Emory Univ.

Introduction: Pauci-immune crescentic glomerulonephritis is a relatively common cause of rapidly progressive renal failure. Frequency of ANCA negative pauci-immune glomerulonephritis is reported to be 20-30%. Recurrence of pauci immune glomerulonephritis is reported to be seen in 10-15% post kidney transplantation. However the recurrence of ANCA negative pauci immune glomerulonephritis post kidney transplantation is rarely reported. Very few case reports are available in the published literature.

Case Description: 49 year old caucasian female with no known medical problems presented with acute kidney failure in 2014. She was diagnosed with severe crescentic glomerulonephritis secondary to ANCA negative pauci-immune glomerulonephritis. She was treated with total plasma exchange and Rituximab but progressed to end stage renal failure. She received a living related renal transplantation in July 2015. Immunosuppression protocol: Basiliximab induction followed by maintenance with belatacept, tacrolimus, mycophenolate mofetil and prednisone. Per our institution protocol, tacrolimus was tapered off at 9 months post transplantation. After the taper of tacrolimus, she developed acute kidney injury with non nephrotic range proteinuria and microscopic hematuria. Kidney biopsy revealed crescentic glomerulonephritis. Immunofluorescence and electron microscopy revealed no immune complex deposits or basement membrane thickening. Serology was negative for anti nuclear cytoplasmic antibody and anti glomerular basement antibody. She was started on high dose steroids and intravenous cyclophosphamide, response to treatment needs to be followed. Since no detectable circulating antibody was present, total plasma exchange was thought to be not helpful in this scenario.

Discussion: Recurrence of ANCA negative pauci-immune glomerulonephritis is rare. Reported data suggests, ANCA negative pauci-immune glomerulonephritis in native kidneys have poor renal prognosis and patients have less extra renal manifestations. It is important to consider recurrence as a possible etiology as the course of the disease is often rapid.

Simultaneous Serious Infection of Trichosporon asahii and Multi Drug Resistant Pseudomonas aeruginosa in Kidney Transplant Patient

Introduction: Trichosporon species are increasingly recognized as a cause of systemic illness in immunocompromised patients. However such infection in kidney transplant patient is rare. We report a life-threatening case of simultaneous infection of Trichosporon asahii and multi drug resistant pseudomonas aeruginosa (MDRP) in kidney transplant recipient.

Case presentation: A 59 year old male patient was admitted with marked anemia and multi organ dysfunction. He was transferred from another hospital due to uncontrolled hypertension. He had received cadaveric kidney transplant six years ago, was admitted for a few days history of fever and right knee pain. His vital signs were a max body temperature of 40°C, heart rate (HR) 90 bpm, blood pressure(BP) 130/73 mmHg, and a pulse oximetry of 98% on room air. On physical exam he had his right knee pain along with distal weakness of both active and passive ranges of motion. Blood and sputumoid fluid was sent for culture, and piperacillin/tazobactam was started empirically. Blood culture grew trichosporon asahii,
and synovial fluid grew multi drug resistant pseudomonas aeruginosa (MDRP). Therefore, antibiotics was switched to meropenem and aztreonam, and voriconazole was added. Oral involvement was not detected. Since he had simultaneous serious infection of *Trichosporon asahii* and MDRV, immunosuppressants, cyclosporine and mycophenolate mofetil were discontinued, and left prednisone alone. His medical course was complicated with C.difficile infection, but 6-week of antibiotic therapies were completed and he was fully recovered.

**Discussion:** *Trichosporon asahii* infection is increasingly recognized as a cause of systemic illness in immunocompromised patients. Most cases are observed among hematologic malignancies while few cases are reported among transplant recipients. This case was successfully treated with triple antibiotics and discontinuation of immunosuppressants.

**PUB491**

**HIV Associated Immune Complex Disease of the Kidney**Rawan T Al-Odah, Saeed Kamaran Shafi.

**Nephrology, Univ of New Mexico, Albuquerque, NM.**

**Introduction:** HIV associated nephropathy (HIVAN) with histological features of focal segmental glomerulosclerosis (FSGS) has been well described in literature. However, in the era of highly effective anti-retroviral therapy (HAART), HIV immune complex disease of the kidney (HIVICK) is increasingly being recognized.

**Case Description:** A 43 years old male presented with malaise, fever, chills, night sweats and progressive swelling of the extremities. Physical examination was remarkable for a blood pressure of 170/100 mmHg, puffiness of face and trace edema of the upper and lower extremities. Pertinent diagnostic data are shown in Figure 1. Kidney biopsy showed collapsing FSGS as well as immune complex-mediated glomeronephritis with a focal proliferative pattern of glomerular injury. He was started on HAART and losartan with improvement in kidney function.

**Discussion:** HIV can affect the kidneys in various ways. HIVAN – a condition which was identified in the pre-HAART era – is caused by direct viral infection of the podocytes resulting in collapsing FSGS. In HARRT naive patients, immune complex mediated proliferative pattern of injury is increasingly being recognized with membranous, membranoproliferative and IgA nephropathy phenotypes seen on kidney biopsy. HIVICK lesions are caused by an immune response to HIV antigens and thus require presence of HIV viremia. HIVICK is less likely to progress to end stage renal disease (ESRD) than HIVAN. HAART therapy dramatically improves outcomes of HIV associated renal disease irrespective of histological features.

**PUB492**

**Alport Syndrome with Right-Hand Preaxial Polydactyly in Two Siblings**Yoko Fujii,1,2 Akira Ashida,1 Hideki Matsumura,2 Akihiko Shirasu,2 Satoshi Yamazaki,2 Hyogo Nakakura,1 Kandai Nozu,1 Kazumoto Iijima,3 Motoshi Hattori,1 Hiroshi Tama,1 1Pediatrics, Osaka Medical College, Osaka, Japan; 2Internal Medicine, Kansai Municipal General Hospital, Hyogo, Japan; 3Pediatrics, Kobe Univ Graduate School of Medicine, Hyogo, Japan; 4Pediatric Nephrology, Tokyo Women’s Medical University, Tokyo, Japan.

**Introduction:** Alport syndrome is one of the familial hereditary hemorrhagic nephritides leading to end-stage kidney disease. The genes responsible are COL4A3, COL4A4 and COL4A5, which encode the α3, α4, α5 chains of collagen type IV, involved with the glomerular basement membrane. Polydactyly is characterized by supernumerary fingers or toes. Its etiology is not so apparent, but has been explained in terms of heredity, environmental factors, and other influences. Here we present the first report of two siblings with Alport syndrome and polydactyly.

**Case Description:** The patients were two siblings (a boy and a girl) with Alport syndrome. Their mother had hematuria, but had not developed any vision or hearing problems. Genetic analysis of the patients and their mother revealed a missense mutation (c.2822G>A) that is not part of an anomaly syndrome, and no mental retardation was evident. The patients also had congenital preaxial polydactyly of the right hand. The polydactyly was not part of an anomaly syndrome, and no mental retardation was evident.

**Discussion:** To our knowledge there has been no previous report of patients with polydactyly in Alport syndrome. The present cases of polydactyly cannot be simply explained in terms of mutations on the basis of the phenotypes. Some previous reports have indicated that preaxial polydactyly follows an autosomal dominant model, but this did not seem to be so in the present cases. Therefore, we intend to perform whole-genome sequencing to analyze the gene mutations in these patients. We believe that these two present cases will be useful for clarifying the pathogenesis of polydactyly associated with Alport syndrome.

**PUB493**

**Childlike Spots in an Older Man: A Case of Malignancy-Associated Adult Henoch-Schonlein Purpura with Severe Multi-Organ Involvement**Ana Claudia Onuchic,1,2 Vivek Alagh,1,2 Catherine A. Zanoria,1,2 Tanya L. Belle,1,2 Sankar Narayan Niranjan,3 Prashant Grover,4 1Univ of Connecticut, Farmington, CT; 2St. Francis Hospital, Hartford, CT.

**Introduction:** Henoch-Schönlein purpura (HSP) is a systemic small-vascular vasculitis associated with deposition of IgA immune complexes, typically manifested in childhood. Rare cases are described in adults, often more severe and disseminated, with malignancy as a predisposing factor.

**Case Description:** A 68 y/o male recently diagnosed with bladder cancer presented with a two-day history of abdominal pain, vomiting and back pain, associated with a persistent dark red rash of lower extremities and torso a few weeks prior. Outpatient skin biopsy had shown leukocytoclastic vasculitis but the rash recurred despite prednisone course. Initial outpatient workup showed acute kidney injury with serum creatinine (S Cr) of 2.3mg/dL and urinalysis with leukocyturia, hematuria, 3+ protein and hyaline and white blood cell casts. Abdominal CT consistent with inflammation in the terminal ileum prompted exploratory laparotomy, revealing terminal ileum erythema/inflammation suggestive of vasculitis. Respiratory and renal deterioration, to S Cr of 8.6mg/dL, required intubation and hemodialysis. Methyprednisolone 20mg IV q12hrs was started for presumed HSP. Skin biopsy was repeated to avoid the risk of renal biopsy, confirming leukocytoclastic vasculitis and IgA deposition by immunofluorescence. Serum IgA was high at 485mg/dL. New on set atrial flutter with episodes of wide complex tachycardia required prophylactic antiarrhythmia, complicated by intestinal bleed. Abdominal CTA showed contrast extravasation in the ileum, requiring embolization. Pulse-dose methyprednisolone and intravenous immunoglobulin were given; bleeding improved, but renal failure persisted. Despite herpes zoster and anti-arrhythmic agents, atherhytmia proved intractable and he expired.

**Discussion:** We present a case of adult HSP with renal, gastrointestinal, skin and likely cardiac involvement. This is one of few descriptions of HSP associated with bladder cancer in adults. HSP is a rare but important cause of rapid progressive glomerulonephritis and should be considered, especially in the setting of malignancy.

**PUB494**

**Cutaneous Marginal Zone B-Cell Lymphoma in a Renal Transplant Recipient**Yan Song, Jiahua Chen. Kidney Disease Center, The First Affiliated Hospital, Zhejiang Univ, Hangzhou, Zhejiang, China.

**Introduction:** A 57-year-old Chinese female was presented with multiple cutaneous nodules and ulcers on the trunk and extremities for 1 month. The lesions first appeared as nodules and subsequently progressed to ulcer. The patient had no fever and fatigue. She had received a kidney from a living donor 11-year prior because of renal failure secondary to hypertension. The patient was maintained on oral prednisone (2.5 mg daily), mycophenolate mofetil (1000mg daily), and calcineurin inhibitors. She had no history of previous opportunistic infections, including Epstein-Barr virus infection. On physical examination, her vital signs were normal. Cutaneous nodules and ulcerations were found on the legs and back.

**Laboratory test results revealed a white blood cell count of 4.3* 10^9/L. Her serum creatinine was 387μmol/L. A skin sample obtained from a nodule on the leg showed atypical lymphocytes infiltration. Immunohistochemistry revealed the atypical lymphoid cells were diffuse positive for CD20, CD79a, Bcl-2, and EBER. CD10, Bcl-2 and T cell markers were negative.** No evidence of systemic involvement was found for the patient. A diagnosis of cutaneous marginal zone B-cell lymphoma was made. Her anti-rejection drug cyclosporine was changed to everolimus. After four months, the cutaneous nodules disappeared. Post-transplant lymphoproliferative disorders are a group of heterogeneous lymphoid complications, which range from indolent polyclonal proliferations to aggressive lymphomas. Generally, it is considered to be a consequence of intensive immunosuppressive drugs administered following solid organ or hematopoietic transplantation. The overall incidence of post-transplant lymphoproliferative disorders in adult kidney transplantation recipients is 3% worldwide. Treatment of 10mg/kg daily) anti-rejection. He had no history of previous opportunistic infections, including Epstein-Barr virus infection. On physical examination, her vital signs were normal. Cutaneous nodules and ulcerations were found on the legs and back.

**Funding:** Government Support - Non-U.S.
Kidney Transplantations with Both Recipients of Kidneys from the Same Deceased Donor with Diabetic Nephropathy 

**Na ir.**

A 76-year-old female with history of hypertension, gastrointestinal stromal tumor (GIST) was initiated on imatinib after surgical resection for adjuvant therapy. Although risk of nephrotoxicity is small with imatinib treatment, physicians must closely monitor during imatinib therapy due to lack of availability of alternate chemotherapy with close monitoring of renal function. 3 months out, the Scr stabilized at 1.6mg/dl and the patient is disease free.

**Case Description:** A 76-year-old female with history of hypertension, gastrointestinal stromal tumor (GIST) was initiated on imatinib after surgical resection for adjuvant therapy. Acute kidney injury (AKI) was noted on admission and she was on hemodialysis. We report a case of a patient with chronic renal failure due to diabetic nephropathy who was treated with imatinib. A 76-year-old female with history of hypertension, gastrointestinal stromal tumor (GIST) was admitted to the hospital for surgical resection of a 5 cm mass in the greater curvature of the stomach. The mass was resected and a biopsy was performed.

**Discussion:** Although Nephrotic Syndrome (NS) is known to cause hypercoagulability, thrombotic complications are uncommon, with serious limb-threatening peripheral arterial thrombosis being extremely rare. We report a case of a child with leg cramps, progressing to cold pulseless right leg and amputation of the toes in his first relapse of nephrotic syndrome. Although Nephrotic Syndrome (NS) is known to cause hypercoagulability, thrombotic complications are uncommon, with serious limb-threatening peripheral arterial thrombosis being extremely rare. We report a case of a child with leg cramps, progressing to cold pulseless right leg and amputation of the toes in his first relapse of nephrotic syndrome.

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- We report a case of a patient with chronic renal failure due to diabetic nephropathy who was treated with imatinib.

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**Case Description:** An 8-year-old African American boy with a new diagnosis of Nephrotic Syndrome developed a relapse during the steroid wean. Over the next week, he presented twice to the ED with intermittent right leg cramps. Evaluation was unrevealing and he was discharged home after both visits. Subsequently, he developed intense right leg pain and limb swelling. Physical examination revealed a cold, pale right lower leg with absent popliteal and dorsalis pedis pulses. US Doppler of the leg revealed a complete occlusion of the peroneal, anterior and posterior tibial arteries. Emergent surgical thrombectomy was performed.
unsuccessful, thus catheter directed thrombolysis, systemic heparinization and antithrombin III (ATIII) infusion were initiated. Interval thrombectomy was then performed together with a fasciotomy for compartment syndrome. The distal perfusion improved, despite this, all 5 digits of the right foot became gangrenous necessitating amputation. Investigation into the etiology of his thrombosis revealed low ATIII levels but normal levels of factors II, VII, IX, X and XII. Genetic analysis for Prothrombin gene mutation, Plasmaomen Activator Inhibitor Type 1 and Factor V Leiden mutation were negative. Complement levels were normal. Anti-DNA, ANCA and antiphospholipid antibodies were negative. Diagnosis of Focal Segmental Glomerulosclerosis (FSGS) was made by renal biopsy. After 7 weeks of hospitalization, the patient was able to ambulate with assistance and was discharged home.

Discussion: Severe arterial thrombosis in our patient occurred during the relapse of NS (FSGS), without evidence of thrombophilia due to other primary or secondary cause. This case demonstrates a need for a high index of suspicion for arterial thromboembolic complications in Childhood Nephrotic syndrome.

PUB501
Pressor-Induced Hyponatremia
Prdeep Chaganti, George C. Bonifant, Kari En Hackem, Steven D. Smith, Germaine Z. Chan, Anip Bansal.
Nephrology, Mount sinai St. Luke’s and Mount Sinai West Hospital, New York, NY.

Introduction: Vaspressin has vasoconstrictive effects through smooth muscle V1 receptors and also has antidiuretic activity via renal V2 receptors. Although rare, exogenous vasopressin administration in doses used for management of shock can be responsible for significant hyponatremia.

Case Description: A 39-year-old man with past medical history of Crohn’s disease, ankylosing spondylitis, lung fibrosis and spondyloarthritides was admitted for cavitary pneumonia with sputum positive for tuberculosis. Over the next few days he developed acute respiratory failure with septic shock requiring mechanical ventilation septice and renal failure. A diagnosis of pressor-induced hyponatremia was made. He had normal cortisol and TSH levels. On switching vasopressin to another pressor, the serum sodium increased prior to this event for empiric Pneumocystis pneumonia treatment. He had normal cortisol and TSH levels. On switching vasopressin to another pressor, the serum sodium increased rapidly from 122 mEq/L to 135 mEq/L along with a relative increase in urine output and decrease in urine osmolality. Dextrose infusion was started to prevent overly rapid correction.

Discussion: Vasopressin does not usually result in hyponatremia when used in the management of shock. Possible explanations include lack of renal responsiveness secondary to renal hypoperfusion in setting of acute kidney injury, or lack of intake of hypertonic fluids. This side effect can happen due to concurrent factors like vasopressin support for shock, endotoxin induced vasopressin release in early septic shock, or relative cortisol deficiency in the setting of hypotonic solution administration.

PUB502
Post-Infectious Atypical Hemolytic Uremic Syndrome in an Adult Presenting without Schistocytes on Peripheral Blood Smear
Dianne Victoria Vieja. 
Internal Medicine, Section of Nephrology, Philippine General Hospital, Manila, Philippines.

Introduction: Hemolytic Uremic Syndrome refers to the triad of hemolytic anemia, uremia and acute renal failure. Its hallmark feature is microangiopathic hemolytic anemia. However, there are patients who present with hemolysis and uremia that do not fit the typical criteria of HUS. These patients may be overlooked and hence important disease-modifying therapeutic intervention missed.

Case Description: A 38 year old man with presented with a 2 day history of watery diarrhea. On workup, he was had leukocytosis, hypokalemia, azotemia, hyperbilirubinemia, metabolic acidosis and high LDH. Proteinturia and hematuria were also noted. Stool, urine and blood cultures were negative. Antibiotics and electrolyte correction were started. Over the next days, patient remained oliguric and subsequent exam revealed anemia, thrombocytopenia and worsening azotemia. Further testing showed elevated reticulocyte count, negative Coombs’s test but no schistocytes on peripheral blood smear. Renal replacement therapy was done and patient eventually discharged improved.

Discussion: HUS is a Thrombotic Microangiopathies resulting from an infection affecting children and elderly. It is due to Shigella or E.Coli with incidence rate of 90%. However, some cases are due to infections by viruses. Diagnosis rests on evidence of mechanical, non-immune hemolytic anemia (schistocytes), high LDH and renal injury. Clinical presentation may be mild and some may not present typically. Serres and Isenring in 2009 performed a retrospective study which showed that up to 44% of patients with biopsy-proven Thrombotic Microangiopathy HUS had normal platelet counts and no schistocytes. This is due to low level of hemolysis at the time of examination, as seen by the only mild thrombocytopenia in the patient. This case report emphasizes that HUS may be considered in the absence of the usual bacterial growth and also in the absence of schistocytes, both of which are textbook definitions of HUS.

PUB503
A Rare Case of Sweet Syndrome in Azathioprine Treated ANCA Vasculitis
Mohamed Elsaidy,1,2 Ahmed Alghali,1,2 Alaa M. Ali,1,2 Arunkumar Aruna Udakumar,1,2 Muhammad Umar Sharif,1,2 Dustin G. Stock.1,2
Nephrology Dept, Univ Hospital Limerick; 2Graduate Entry Medical School, Univ of Limerick; 3Health Research Inst, Univ of Limerick, Ireland.

Introduction: ANCA associated vasculitis is frequently encountered in renal practice with immunosuppression being the main stay of management. Azathioprine (AZA) is commonly used and relatively safe for maintaining remission. AZA induced Sweet syndrome is a rare complication that was first reported in 2003.

Case Description: We describe a case of a 53-year-old male with MPO-ANCA vasculitis treated initially with pulse steroid therapy and rituximab achieving clinical remission although his MPO titre remained elevated. Azathioprine was commenced for maintenance therapy. Two weeks later, he presented with an acute onset of a generalized painful rash over the trunk and limbs. This was associated with fever and non-specific constitutional symptoms. Examination revealed conjunctivitis & painful erythematous papules/plaques.

Discussion: Immunosuppressive therapy requires good surveillance for side effects and complications. Although rare, it is prudent to consider AZA induced Sweet syndrome in patients presenting with fever and rash within weeks of initiating therapy after excluding infections, malignancy and acute vasculitis flare.

Laboratory results showed 12.8x10^10/l leukocytosis with 87% neutrophilia , CRP of 237 mg/l , ESR of 60mm/hr and stable renal function with benign sediment. Infectious work up was negative. A skin biopsy showed acute neutrophilic dermatosis with no evidence of vasculitis confirming a diagnosis of Sweet syndrome. Work-up for occult malignancy was negative. A diagnosis of azathioprine-induced sweet syndrome was made based on temporarity. Almost complete resolution was achieved with AZA discontinuation and a short pulse of oral steroids and colchicine therapy.

Discussion: Immunosuppressive therapy requires good surveillance for side effects and complications. Although rare, it is prudent to consider AZA induced Sweet syndrome in patients presenting with fever and rash within weeks of initiating therapy after excluding infections, malignancy and acute vasculitis flare.

PUB504
Pheochromocytoma(Paraganglioma) of the Urinary Bladder Causing Secondary Uncontrolled Hypertension
Eyesaalem Engida Bayssa.1,2 Amina Khan.1,2 Nephrology, Kansas Univ Medical Center; Kansas City, KS; 2Nephrology, Kansas City FA, Kansas City, KS.

Introduction: Secondary hypertension due to a catecholamine secreting paraganglioma is extremely rare.

Case Description: A 56 year-old AAM presented with urinary urgency, frequency, dribbling and lower abdominal discomfort. Blood pressure was 162/110 mmHg on lisinopril 40mg, hydrochlorothiazide 25 mg daily and carvedilol 25 mg twice daily. Abdominal CT showed 9.4 x 6.9 cm right posterior bladder wall mass and enlarged bilateral pelvic lymph nodes. Urinalysis was significant for 11-15 RBC’s/hpf. Pathology revealed paraganglioma. Free plasma metanephrine levels were elevated, 14690 pg/ml (normal <= 205). PET scan showed possible extension to the prostate and right lateral pelvic wall and left deep inguinal nodal enlargement. Radical cystoprostatectomy, bilateral lymph node dissection and urinary diversion by ileal conduit was done. Post op BP controlled with Propranolol 20mg every 6 hours, phenoxybenzamine 30mg TID, lisinopril 40mg, amiodpine 5mg

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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and hydrochlorothiazide 25mg daily. Intraoperative findings showed a bulky tumor that was unrespectable and large grossly positive lymph node. Oncology recommend therapy in 3-4 weeks.

Discussion: Phaeochromocytoma is a rare tumor occurs in less than 0.2% of patients. Diagnosis can pose a challenge, as in our patient, when associated with changes were in the frontal and parietal regions. Patient had recurrent seizures, which is below. The most common abnormalities on MRI are punctuate or confluent areas of

PUB505
Acute Kidney Injury, Seizures and Thrombocytopenia in a Young Patient with Lupus Nephritis

Hector Alvarez Verdugo,1 Anjali Acharya.2 1Medicine, Jacobi Medical Center, Bronx, NY; 2Nephrology, Jacobi Medical Center, Bronx, NY.

Introduction: Posterior reversible encephalopathy syndrome (PRES) is a complex clinico-radiologic syndrome of varied etiologies, with neurological findings mainly suggestive of the posterior white matter involvement that frequently is reversible. Prompt recognition and treatment of underlying etiology is crucial.

Case Description: A 22 year-old patient with Systemic Lupus Erythematous (SLE) complicated with chronic kidney disease secondary to lupus nephritis class IV, presented with recurrent seizures and uncontrolled hypertension. She had acute kidney injury and thrombocytopenia. Repeat biopsy showed diffuse endocapillary and extracapillary proliferative with crescent (Figure 1) and membranous lupus nephritis (ISN-RPS class IV+G+V), new changes with endocapillary swelling secondary to severe hypertension; but no thrombotic microangiopathy. Brain imaging showed left frontal and parietal infarct with improvement of lesions and symptoms after controlling blood pressure (BP), making PRES the diagnosis. She had recurrent episodes of seizures with brain edema on imaging.

Discussion: PRES is thought to be associated with disordered cerebral auto-regulation and endothelial dysfunction. Most cases present with systolic BP over 200 mm Hg or at least a 35% increase from baseline. Our case presents several unusual scenarios as described below. The most common abnormalities on MRI are punctate or confluent areas of increased signal on T2-weighted images in the posterior fossa but in this patient, the MRI changes were in the frontal and parietal regions. Patient had recurrent seizures, which is unusual in PRES. Diagnosis can pose a challenge, as in our patient, when associated with SLE, as it can be confused with lupus vasculitis. In addition, treatment with cytotoxic agents if required can be an additional problem as these agents can contribute to PRES.

PUB506
Recurrent C3 Glomerulonephritis Treated with Eculizumab: A Case Report

Trevor R. Smith, Mazdak A. Khalighi, Monica Patricia Revelo Penafiel, Josephine Abraham, Kalani L. Raphael. Univ of Utah.

Introduction: C3 glomerulonephritis (C3GN) is a rare cause of kidney disease that has a high recurrence rate (>50%) in the renal allograft. We present a case of recurrent C3GN in a renal allograft that was treated with and rapidly responded to eculizumab.

Case Description: A 70 year old male with membranoproliferative glomerulonephritis (MPGN) type I diagnosed in 2005 received a deceased donor renal transplant in 2013. Eighteen months later, he developed dysmorphic hematuria, sterile pyuria, and acute creatinine rise from 1.0 to 1.4 mg/dL; urine protein/creatinine was 200 mg/g. His immunosuppressive regimen included prednisone, mycophenolic acid, and etanercept. Renal biopsy demonstrated a focal exudative glomerulonephritis, C3-dominant immunofluorescence (IF), and mesangial, subendothelial, and intramembranous deposits by electron microscopy, consistent with C3GN. His original biopsy was re-evaluated, which was also consistent with C3GN. C3 and Factor B levels were markedly elevated. Complement C3a (959 ng/mL) and C5 (0.04 mg/mL) were elevated. C3 nephritic factor was negative, and no genetic variants were identified. The patient was monitored for 6 months, however, his creatinine increased to 1.7 mg/dL as did proteinuria. Eculizumab was initiated at 900 mg intravenously weekly for 4 weeks followed by 1200 mg every two weeks. After 1 month of therapy, the protein/creatinine ratio decreased from 1500 to 128 mg/g and hematuria and pyuria resolved. The most recent creatinine was 1.2 mg/dL, two months after starting eculizumab.

Discussion: There are few case reports regarding the use of eculizumab in C3GN and even fewer in kidney transplant patients, and the response to this therapy has been variable. This patient had a rapid response to eculizumab with resolution of proteinuria, hematuria, and pyuria and a near normalization of serum creatinine within two months. The sustainability of this response as well as the duration of treatment is uncertain. This case also highlights how the IF-based classification of MPGN, which is based on pathogenetic mechanisms, has impacted the diagnosis, evaluation, and treatment of MPGN.

PUB507
Multifactorial Hypertension - A Challenge to the Clinician


Introduction: Incidentally discovered adrenal masses are common. About 15% of adrenal adenomas occur bilaterally and present challenges both in diagnosis and management. We describe a case of bilateral adrenal adenomas causing resistant hypertension (HTN).

Case Description: A 50 year old male with uncontrolled HTN for 25 years, chronic kidney disease stage III (baseline creatinine 1.6), and schizoaffective disorder was admitted to the hospital for hypertensive urgency with a blood pressure of 190/130. Patient’s anti hypertensive regimen consisted of valsartan, amiloride, metoprolol and doxazosin. He was taking potassium citrate supplements for hypokalemia and metabolic acidosis, which was attributed to topiramate. Other medications included monthly testosterone injections and over-the-counter caffeine supplements. Workup for secondary HTN was notable for elevated plasma aldosterone level (38.3 ng/dl), suppressed renin (<2.1 pg/dl), and normal metanephrines. Renal artery duplex showed no evidence of significant renal artery stenosis.

Discussion: The most common abnormalities on MRI are punctate or confluent areas of increased signal on T2-weighted images in the posterior fossa but in this patient, the MRI changes were in the frontal and parietal regions. Patient had recurrent seizures, which is unusual in PRES. Diagnosis can pose a challenge, as in our patient, when associated with SLE, as it can be confused with lupus vasculitis. In addition, treatment with cytotoxic agents if required can be an additional problem as these agents can contribute to PRES.

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1020A
Sulfamethoxazole Crystal-Induced Nephropathy - A Rare Cause of Acute Kidney Injury in an HIV Patient

Introduction: Drug-induced crystalluria can be a cause of acute kidney injury (AKI). Sulfonamides are known to cause crystallization in the urine. We report a case of AKI due to sulfamethoxazole crystal induced nephropathy in a patient with HIV who was treated with intravenous (IV) Trimethoprim-Sulfamethoxazole (TMP-SMX). Case Description: 56-year old male with normal baseline serum creatinine (SCr) of 0.7 presented with respiratory failure. He was empirically being treated for community acquired pneumonia. He was diagnosed with HIV with CD4 count of 18. Bronchoalveolar lavage was performed and patient was diagnosed with Pneumocystis jirovecii Pneumonia (PJP). He was started on IV TMP-SMX. Within one day of the treatment initiation, his SCr started to trend up to 1, then to 1.3 and then 2. He also had refractory hyperkalemia (PJP). He was started on IV TMP-SMX. Within one day of the treatment initiation, his SCr started to trend up to 1, then to 1.3 and then 2. He also had refractory hyperkalemia (PJP). He was started on IV TMP-SMX. Within one day of the treatment initiation, his SCr started to trend up to 1, then to 1.3 and then 2. He also had refractory hyperkalemia. Patient's renal function recovered and he did not require additional dialysis treatments. Repeat urine microscopy revealed disappearance of the crystals.

Discussion: SMX induced crystal nephropathy is an uncommon cause of AKI. While it is usually considered as a well-known entity, literature describing the appearance SMX crystals is actually scarce. This case provides images of SMX crystals and highlights the importance of urine microscopy in the diagnosis of AKI.

It’s More Than HIV and HAART in HIV with AKI

Introduction: Immune reconstitution syndrome (IRS) is a multiorgan inflammatory condition in human immunodeficiency virus (HIV) patients following initiation of antiretroviral (HAART) therapy. Rarely does IRS cause acute kidney injury (AKI). This case presents a patient who developed AKI thought to be due to IRS.

Case Description: A 35-ye-old man was hospitalized for uremia (BUN = 146 mg/dL, Cr = 16 mg/dL) and hemodialysis (HD) initiation. He had recently been started on triple therapy for pulmonary MAI (ethambutol, chloramphenicol, and rifabutin), and recently had his HAART modulated to elvitegravir/cobicistat/tenofovir/emtricitabine/tenofovir. He also previously developed IRS several months earlier from initiation of HAART. An ultrasound demonstrated normal sized echodense kidneys with with multiple punctate calcific lesions noted in both kidneys and his liver. A kidney biopsy revealed acute tubular necrosis (ATN), mononuclear interstitial infiltrates, and myoglobin cast nephropathy. In addition, one core sample revealed granulomatous material which contained acid-fast bacteria, later identified as MAI. No mitochondrial or glomerular damage was noted. Given the mononuclear interstitial infiltration of the glomeruli, the AKI was suspected to be caused from IRS. Prednisone was started on IRS treatment, mycophenolic replaced ethambutol for MAI treatment, and his HAART was restarted after a brief hiatus. With these changes, the patient recovered renal function, with a new baseline creatinine of 1.73 mg/dL, and no longer required HD.

Discussion: This case demonstrates that IRS can cause AKI, and is treatable with steroids, as well as continuation of HAART. Although considerably rare, this phenomenon has been reported in the literature over the past 15 years; most are associated with concomitant mycobacterial infection. When appreciated, a mononuclear interstitial infiltrate is demonstrated on the kidney biopsy, with sparing of the glomeruli. Furthermore, this case demonstrates the utilization of kidney biopsy in an HIV patient to accurately define the pathology for proper therapeutic intervention.

IgA Vasculitis versus IgA Dominant Post-Infectious Glomerulonephritis? A Case of Severe Oxacillin Resistant S. aureus (ORS) Cellulitis

Introduction: IgA dominant post-infectious proliferative glomerulonephritis has been described in association with ORSA. These cases may be difficult to differentiate from primary IgA nephropathy or IgA vasculitis with superimposed infection. We present a case illustrating this differential diagnosis.

Case Description: 59 yo female with a history of Hepatitis C and venous stasis presented with lower extremity ulcerated wounds and acute kidney injury. A large ulcer with heaped borders and purulent base extended from the left knee to the ankle. A smaller ulcer affected the right mid-thigh. Purulent exudate was draining a subcutaneous abscess on the left thigh, forearm and hands. Wound cultures grew ORSA which was treated with vancomycin. Serum Creatinine (Cr) was 1.92 mg/dl (from <1 a month earlier). Her urine was tea colored, the sediment revealing numerous dysmorphic red blood cells. Urine protein:creatinine ratio = 16 g g. Serum C3, C4, rheumatoid factor, ANA, ANCA and Hepatitis B surface Ag were normal. Hepatitis C viral load was 794775 [IU]/ml with normal AST and ALT: ESR: 44mm/hr and CRP: 2.7mg/dL. A renal biopsy demonstrated moderate mesangial matrix expansion and hypercellularity, focal and segmental endocapillary proliferation and cellular crescents in the affected glomeruli. There was 3+ IgA and C3 granular deposition within the mesangial space and along peripheral glomerular capillary walls. Intratubular red blood cell casts were noted. No large subepithelial deposits were found by electron microscopy. A skin biopsy from the arm showed granular depositions of IgA and fibrinogen in the papillary dermal vessels, thus confirming a diagnosis of IgA vasculitis. Corticosteroids were initiated because of progressive decline in GFR.

Discussion: This case illustrates an acute nephritic exacerbation of IgA vasculitis, precipitated by the ORSA infection. This is supported by the normal serum complements, the absence of large subepithelial immune complex type deposits, and the skin biopsy findings. Differentiating between this and IgA dominant post infectious glomerulonephritis is crucial to direct therapy.
An Unusual Case of Pulmonary Hemorrhage with Acute Renal Failure due to Systemic Lupus Erythematosus and Polycystic Kidney Disease

Muhammad Nazmul Anustup Datta, Marius C. Florescu.
Nephrology, Univ of Nebraska Medical Center, Omaha, NE.

Introduction: Pulmonary hemorrhage with proliferative glomerulonephritis is a characteristic manifestation of anti-glomerular basement disease or pauci immune vasculitis but unusual in Systemic Lupus Erythematosus (SLE).

Case Description: A 69-year old male patient presented to ER with hemoptysis, dyspnea and decreased urine output for 1 week. Physical examination revealed bilateral basal lung consolidation.2x ankle edema but no rash, organomegaly or lymphadenopathy. Laboratory tests significant for severe renal failure with hyperkalemia. Chest X ray showed bilateral consolidation. She was intubated and anuric. Emergent hemodialysis and plasmapheresis initiated. Labs included positive anti-nuclear, anti-double stranded DNA, anti-nuclear cytoplasmic antibodies with perinuclear pattern of distribution, low C3 and C4, negative lupus anticoagulant, anti-GBM, anti-proteinase 3 and anti-myerscopexidase antibodies. Blood culture showed Escherichia coli and Enterobacteriaceae. Urine microscopy revealed RBC’s and WBC clumps. Renal biopsy showed diffuse proliferative glomerulonephritis with cellular crescents and fibrinoid necrosis, “full house staining” on immunofluorescence consistent with Type IV lupus nephritis. Following plasmapheresis, she received 6 months of oral cyclophosphamide, prednisone and hydroxychloroquine. After 6 weeks hemodialysis her renal function improved and hemodialysis stopped.

Discussion: Pulmonary renal syndrome is a rare life threatening complication of SLE. Presence of p-ANCA may indicate an associated acute vasculitis with biopsy showing fibrinoid necrosis. Antecedent infection could trigger widespread vasculitis reaction with underlying medical illness of lupus. Clinical presentation was concerning of vasculitis but further work up confirmed active lupus. This case highlights that different disease processes can be responsible for the occurrence of pulmonary renal syndrome. Association between small vessels vasculitis and SLE signifies the fact that small group of patient with SLE may also have an underlying polycystis where biopsy findings provide valuable guidance for appropriate early intervention which is paramount due to the severity of their illness.

PUBS13

Incercated Inguinal Hernia as a Presenting Complication of Polycystic Kidney Disease Ahmed Daoud,1 Mostafa Alshifawy;2 Nephrology, UAMS, Little Rock, AR;2 General Medicine, Queens’ Hospital, New York, NY.

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is a multisystemic disorder with renal and extrarenal complications. End stage renal disease is the most feared complication affecting almost 50% of ADPKD patients by 60 years. We are presenting a case of ADPKD that was diagnosed when the patient presented with incarcerated inguinal hernia. The incarcerated hernia is probably a result of increased intra-abdominal pressure due to polycystic kidneys.

Case Description: Herein we present a 56 year old Male with ADPKD who presented to the emergency room with abdominal and groin pain. He was admitted for possible small bowel obstruction and CT scan performed and showed incarcerated inguinal hernia and bilateral huge cystic kidneys, cystic liver and pancreas. Patient was managed conservatively then he was discharged and scheduled for outpatient bilateral inguinal hernia repair with mesh.

Discussion: ADPKD affects approximately one in 1000 people. The most common presentation is a palpable mass, hypertension (after their third decade of life), abdominal pain, and hematuria. Abdominal wall hernias are up to five times more common in ADPKD patients with prevalence estimated to be 45%. The increased prevalence is thought to be due to a combination of increased intra-abdominal pressure from enlarged kidneys and weak abdominal musculature due to the connective tissue pathology. Our patient was discovered to have Polycystic Kidneys after presenting with incarcerated hernia. Up to our knowledge, this is the second case of ADPKD presenting with incarcerated hernia. Our point is that incarcerated hernia may be a rare presentation of ADPKD.

PUBS14

A Case of Plasmapheresis in Treatment of Myeloma Kidney Shehrayr H. Asifah, Niralee Patel, Ruchir D. Trivedi. UCONN Health Center, Farmington, CT.

Introduction: Myeloma kidney, also called light chain cast nephropathy, is caused by monoclonal immunoglobulin infiltration and light chain deposition many times requiring renal replacement treatment. Treatment includes chemotherapy, but the use of plasmapheresis has been used for removal of light chains in acute disease.

Case Description: We present a 69-year-old male patient diagnosed with multiple myeloma with associated acute kidney failure requiring hemodialysis. Due to significantly elevated lambda SFLC and renal disease, plasmapheresis was initiated. He received plasmapheresis for three days, subsequently, began chemotherapy. SFLC levels were obtained daily, prior to any interventions of the day. Lambda SFLC decreased by 19% from two sessions of plasmapheresis prior to starting chemotherapy and a tremendous 60% after 11 days (figure 1).

Discussion: Chemotherapy decreases SFLC production, thus affecting the underlying myeloma kidney disease. However, after initial diagnosis, plasmapheresis can be utilized to physically remove the SFLC and directly decrease the damage to the kidney. Based on a study by Zucchelli et al., there was an observed increased survival with the use of plasmapheresis in addition to chemotherapy. However, Clark et al. reached no statistically significant difference with plasmapheresis with chemotherapy. Hutchinson et al. found that decreasing SFLC by 60% in 21 days resulted with renal recovery. Our patient was treated successfully by reducing SFLC by 60%. We hope for renal recovery in the future, by becoming independent of dialysis.

PUBS15

BRAF Inhibitors- Induced Renal Injury and Electrolyte Disturbances Ahmed Daoud, Gerren Hobby, Umbar Ghaffar.
Nephrology, UAMS, Little Rock, AR.

Introduction: Agents that inhibit the BRAF kinase pathway showed promise in treating malignant melanoma. Two specific agents, vemurafenib and dabrafenib, and the MEK inhibitor, trametinib, have been licensed since 2011 for treatment of patients with unresectable or metastatic melanoma with BRAF mutation. While these drugs have greatly improved the prognosis of this disease, they have been associated with nephrotoxicy & electrolyte disturbances.

Case Description: 74 year old male with recently diagnosed metastatic malignant melanoma, was admitted to our facility with confusion and found to have AKI & hypercalcemia. AKI was initially thought to be due to hypercalcemia but did not improve with volume repletion. Based on urine sediment findings, diagnosis of acute interstitial nephritis was made and patient started on steroids. During admission, patient was continued on BRAF inhibitor therapy with Dabrafenib and trametinib. Renal function continued to deteriorate & patient required hemodialysis for few weeks followed by recovery of renal function. He was readmitted a month later following a syncopal episode with another episode of AKI. At this time his urine showed presence of persistent white blood cells and protein indicating likely chronic interstitial nephritis related to his chemotherapy agents which were stopped. Renal function slowly recovered. He also had persistent hypokalemia with a normal anion gap acidosis that has been described with BRAF inhibitors.

Discussion: BRAF inhibitors vemurafenib and dabrafenib have significantly improved survival in patients with BRAF V600-mutant metastatic melanoma, when compared with standard therapy. However, both of these drugs appear to be associated with an increased risk for acute kidney injury. Data from the US Food and Drug AdministrationAdverse Event Reporting System (FAERS) revealed that from July 2011 through June 2014, 132 cases of acute kidney injury were reported in patients receiving vemurafenib therapy. In addition, 13 cases of renal injury were reported in those receiving dabrafenib. BRAF inhibitors cause tubulointerstitial damage and electrolyte disturbances. Careful monitoring of renal function and electrolytes is strongly recommended for patients on BRAF inhibitors.

PUBS17

Successful Outcome Using Belatacept in a Recipient with Systemic Thrombotic Microangiopathy after Receiving a Donor Kidney with Fibrin Thrombi Amit K. Rajput, Beatrice P. Concepcion, Paisit Pauksakon, Derek E. Moore, Manish Anand. Vanderbilt Univ Medical Center.

Introduction: Deceased donor kidneys with diffuse fibrin thrombi due to disseminated intravascular coagulation in the donor have a high rate of delayed graft function or primary non-function. Traditionally, this has been in the setting of cancer treatment inhibitor (CTI) maintenance immunosuppression. In this case, we describe a patient who received a kidney with known fibrin thrombi resulting in subsequent slow graft function, severe thrombocytopenia, and microangiopathic hemolytic anemia immediately post-transplant. Tacrolimus was switched to belatacept with immediate clinical improvement.

Case Description: A 71-year-old female with end stage renal disease secondary to polycystic kidney disease received a deceased donor kidney transplant from a 22-year-old donor who died of a gunshot wound to the head. The donor’s terminal creatinine was 0.9 mg/dL and donor procurement was complicated by diffuse renal fibrin thrombi. The recipient had a panel reactive antibody of 98%, was induced with alemtuzumab/tacrolimus and started on mycophenolate mofetil on post-operative day (POD) 1. The post-operative course was complicated by worsening thrombocytopenia (POD 3: Platelets 28,900/mcL) and hemolytic anemia (Hct 19%, LDH 924 units/L, Haptoglobin<8mg/dL and shistocytes on peripheral smear). A biopsy was performed, which showed diffuse thrombotic microangiopathy (TMA) and extensive acute tubular injury, but no evidence of acute rejection. Tacrolimus was discontinued and belatacept was initiated. The patient had immediate improvement in both thrombocytopenia and serum creatinine (0.8mg/dL three months post-transplant).

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

1022A
Discussion: Belatacept should be considered as an alternative to CNIs for maintenance immunosuppression in patients who receive deceased donor kidneys with fibrin thrombi and subsequently have slow/delayed graft function, or in those who develop systemic signs of TMA. CNIs are known to cause drug-induced TMA via endothelial injury and in this setting, may augment ongoing injury in the donor kidney. Avoidance of CNIs may lead to a more rapid resolution of the TMA and improvement in allograft function.

**PUB518**

Hypokalemic Tetraparesis as the First Manifestation of Autoimmune Disorder: A Case Report

Nicola Lepori,1 Matteo Floris,1 Andrea Angiolii,1 Riccardo Cao,1 Maura Conti,1 Anna Maria Asunis,1 Alice Atzeni,1 Valentina Loi,1 Patrizia Mealli,1 Stefania Aresu,1 Giulia Dessi,1 Dolorosa Piras,1 Antonello Panu,1 Nephrology, G. Brotzu Hospital, Cagliari, Italy; 2Pathology, G. Brotzu Hospital, Cagliari, Italy.

Introduction: We report an unusual case of life-threatening potassium wasting due to selective damage of the distal tubule, hypothesized as being related to circulating ENA-SSA Ab.

Case Description: A 50 y/o woman was admitted to our hospital because of severe hypokalemic tetraparesis (K+ 1.6 mEq/L) with no obvious underlying causes. Further laboratory tests showed normal renal function, hyperchloremic metabolic acidosis, urinalysis potassium wasting (88 mmol/24h) and alkaline urine, suggesting type 1 renal tubular acidosis (RTA). Supporting therapy with i.v. NaHCO3 and KCl led to temporary recovery. Meanwhile, SPEP showed an IgG monoclonal spike, ANA (1:640), elevated ENA-SSA (689 U/ml), while anti-dsDNA were normal. We recommended a renal biopsy, but the patient refused. Two months later she was admitted to our Division complaining of blood hypertension and ankle swelling. At that time, renal function was normal, K+ 2.7 mEq/L, CRP 0.7 mg/dl. Urinalysis revealed microhematuria and 24h proteinuria of 3.6 g. IgG monoclonal spike was confirmed by immunofixation. Serology revealed low C3 and C4, ANA (1:320), elevated ENA-SSA (314 U/ml) and rheumatoid factor (258 U/ml); viral serology was negative. A renal biopsy was then performed, revealing MPAGN with focal pseudotubulins (with IgG and C3 deposits) and severe tubulointerstitial nephritis (TIN) with preponderant lympho-plasmacytic infiltrate. Finally, mixed cryoglobulinemia was confirmed by serology. Sjogren syndrome was suspected, but exocrine glands were unremarkable.

Discussion: Occasionally, type 1 RTA is part of puzzling autoimmune disorders. This case highlights life-threatening hypokalemic tetraparesis as the first manifestation of a systemic autoimmune process, albeit with no evident extra-renal involvement. Hopefully, follow-up and response to treatment will reveal more about it.

**PUB519**

Fatal Disseminated Adenovirus Infection in Renal Transplant Recipient

Darpan Gandhi,1 Olorunkemi O. Oluwole,1 Alisa Caudell,2 Maria N. Salazar,1 Prince Mohan.1 Div of Nephrology, Medical Univ of South Carolina, Charleston, SC; 2Dept of Pathology, Medical Univ of South Carolina.

Introduction: Adenoviruses are increasingly recognized as contributors to morbidity and mortality among solid-organ transplant recipients. Mortality from disseminated adenovirus disease is as high as 75% in immunocompromised host.

Case Report: 61 year old female with ADPKD received cadaveric renal transplant from 8 year old female who died in motor vehicle accident. She received of basiliximab (induction) with maintenance immunosuppression of tacrolimus, prednisone, and MMF. 49 days post-transplant she presented with cough and diarrhea. She had neutrophilia (ANC 0.77K/CUMM); acute kidney injury, serum creatinine (sCr) of 1.4 mg/dl (baseline sCr 0.9 mg/dl), elevated AST 549 U/L, and ALT 228 U/L. Chest CT showed diffuse bronchiectasis. MMF and tacrolimus were stopped. Colonoscopy showed active colitis with biopsy negative for CMV. Serum adenovirus PCR was 1.3 billion copies, and was also detected in stool and respiratory panel. AST and ALT peaked to 3515 U/L and 555 U/L respectively. She was treated with antibiotics, IVIG and cidofovir. She required hemodialysis, developed respiratory failure and after 7 days, she expired from septic shock despite aggressive resuscitation with vasopressors. Autopsy showed isometric vacuolization of tubular epithelium of transplant kidney without viral inclusions and extensive necrosis of liver.

Discussion: Adenovirus should be included in differential diagnosis of post kidney transplant hepatic, hepatic failure and colitis. Infection occurred within first two months of transplant and donor kidney did not show viral inclusion suggesting novel infection or reactivation of latent infection in recipient. Diagnosis is poor and therapy remains challenging despite reducing immunosuppression, use of IVIG, and cidofovir.

**PUB520**

No Smoke but Raging Fire- Urinalysis Is an Imperfect Clue

Melissa L. Swee,1 Lana A. Noureddine.2 Div of Nephrology, Univ of Iowa, Iowa City, IA.

Introduction: The urine dipstick has long been considered a “liquid biopsy of the kidneys,” providing valuable diagnostic information. However, the absence of proteinuria does not rule out pathology. We present a case illustrating this cautionary principle.

Case Description: A 59 year old female presented with a two-month history of nightly fevers (up to 101.3°F), decreased appetite and 20-pound weight loss. She denied urinary symptoms, hematuria, edema, dysuria, cough, or rash. Vital signs were notable for fever (100.6°F), tachycardia (109bpm), and hypertension (147/70mmHg); the rest were within normal limits. Cardiopulmonary, dermatologic and musculoskeletal examinations were unremarkable. There was no pedal edema or costovertebral angle tenderness. Comprehensive metabolic panel revealed increased serum creatinine (2.8mg/dl); but blood urea nitrogen (21mg/dl), which, 3 months ago, were 1.1mg/dl and 1mg/dl, respectively. C-reactive protein and erythrocyte sedimentation rate were also elevated (17.3mg/dl and 120mm/hr). Urine dipstick repeated thrice did not reveal any proteinuria, hematuria, leukocyte esterase, or nitrite. ANA, complement levels, and ASO were negative but ANCA titers were elevated at 1:320. MPO was also high (>8 AI) but not PR3. This was confirmed on renal biopsy, which demonstrated pauci-immune, necrotizing glomerulonephritis, with crescents as seen on immunofluorescence staining for fibrin.

**PUB521**

Case Report: A Case of Anti-Neutrophil Cytoplasmic Antibody Glomerulonephritis, Drug Induced Lupus and Sweet Syndrome

Ahmed Daoud,1 Gerren Hobby,1 Neriman Godden,2 John M. Arthur,1 Manisha Singh.1 Nephrology, UAMS, Little Rock, AR; 2Pathology, UAMS, Little Rock, AR.

Introduction: We report a case of ANCA vasculitis with co-existing Sweet syndrome & drug induced lupus. Sweet syndrome is a hypersensitivity reaction that occurs in response to systemic factors, such as hematologic disease, infection, or drug exposure. All three disease processes ANCA GN, drug induced lupus & Sweet syndrome in this patient appear to be secondary to use of Hydralazine.

Case Description: A 73 year old Caucasian man, hypertensive on Hydralazine was referred to Haematology-Oncology for suspected Waldenstrom's Macroglobulinemia (WM). He developed A-fib for which he was admitted. WM was ruled out with bone marrow biopsy. He developed a maculopapular rash after admission on the face, scalp, and upper torso. Dermatology diagnosed the rash to be Sweet syndrome after skin biopsy. Following this he developed acute kidney injury (AKI). Creatinine during hospitalization was initially 2.5 - 2.7mg/dl, but rose to 3.1mg/dl. Urine sediment showed dysmorphic RBCs. ANCA and anti-histone titers, as well as lupus panel. Serology showed low complements, with C3 1.7mg/dL, C4 0.1mg/dL, C3 100mm/hr, and 120mm/hr. Serum creatinine peaked at 4.6mg/dL. He developed a maculopapular rash after admission on the face, scalp, and upper torso. Dermatology diagnosed the rash to be Sweet syndrome after skin biopsy. Following this he developed acute kidney injury (AKI). Creatinine during hospitalization was initially 2.5 - 2.7mg/dl, but rose to 3.1mg/dl. Urine sediment showed dysmorphic RBCs. ANCA and anti-histone titers, as well as lupus panel. Serology showed low complements, with C3 1.7mg/dL, C4 0.1mg/dL, C3 100mm/hr, and 120mm/hr. Urine dipstick repeated thrice did not reveal any proteinuria, hematuria, leukocyte esterase, or nitrite. ANA, complement levels, and ASO were negative but ANCA titers were elevated at 1:320. MPO was also high (>8 AI) but not PR3. This was confirmed on renal biopsy, which demonstrated pauci-immune, necrotizing glomerulonephritis, with crescents as seen on immunofluorescence staining for fibrin.

Discussion: ANCA-associated vasculitis is a set of systemic vasculitides that frequently leads to pauci-immune crescentic glomerulonephritis. As such, proteinuria and hematuria are the most common renal manifestations of the disease, but this is not strictly required. This case emphasizes that nephrologists should have a high index of clinical suspicion for ANCA-associated vasculitis in patients with deterioration of kidney function even in the absence of proteinuria or hematuria.

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1023A
A Case of Granulomatous Interstitial Nephritis in a Patient with History of Crohn Disease without Evidence of Active Flare or Current Use of Saliycylates

Dominick Riffat, Maria Joana Tavares, Ron Zanger,

Introduction: Granulomatous interstitial nephritis (GIN) is a condition associated with Crohn disease and characterized by interstitial inflammation and granuloma formation in the renal parenchyma, most cases of which are reported with an active flare or use of 5-aminosalicylate (5-ASA) derivatives. We present a case of GIN in the absence of a clinical flare of Crohn disease or recent 5-ASA exposure, and while taking a TNF-alfa inhibitor, which is not usually associated with treatment of inflammatory disorders.

Case Description: A 43 year old lady was admitted with an elevated creatinine. Her history included Crohn disease for 4 years, treated with mesalazine and budesonide for only a few months. Twenty months before admission, she developed jejunal perforation and underwent partial small bowel resection. She was started on infliximab for her CD, leading to GIN. Alternatively, TNF-alfa inhibitors are reported to have evidence of decline in renal function, making 5-ASA an implausible cause of her GIN. Her CD was clinically quiet, thus eliminating the two most common causes of GIN with CD. Her serum infliximab level was in the low end of the target range and may have failed to treat subclinical CD, leading to GIN. Alternately, TNF-alfa inhibitors are reported to have a paradoxical effect and may have precipitated the granulomatous nephritis in our patient.

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A Different Kind of Renal Crisis

Albarn Said, Darwish Naji, Cybele Ghosssein.

Introduction: Systemic sclerosis (SSc) is an autoimmune disorder characterized by skin thickening with variable systemic organ involvement. Renal involvement often takes the form of sclerodermata renal crisis (SRC) and is typically characterized by abrupt onset of severe hypertension and acute kidney injury. Additional findings on presentation include congestive heart failure and coagulopathy. SRC is also known as rapidly progressive glomerulonephritis (RPGN). SRC is sometimes difficult to distinguish from other forms of TMA as the presentations may be similar. We present a patient with an established diagnosis of scleroderma who presented with symptoms consistent with SRC but biopsy revealed TMA not related to SRC.

Case Description: A 47 year old female with known SSc with positive anti-RNA polymerase III autoantibodies presented to the hospital with shortness of breath and lower extremity edema. She had undergone hematopoietic cell transplantation (HCT) for SSc 15 days prior to admission for which she had received large doses of glucocorticoids. On admission she was found to have an elevated creatinine and a systolic blood pressure of 80mmHg above her baseline. ACE inhibitor therapy was initiated for presumed SRC. Kidney function continued to deteriorate. A renal biopsy was performed and showed changes consistent with TMA confined to the glomerular compartment, and none of the classic vascular changes seen in SRC. Her respiratory status worsened necessitating ICU admission where she was found to have H1N1 pulmonary infection. As her infection was treated, her renal function stabilized and her TMA resolved.

Discussion: Due to its significant mortality, SRC should always be empirically treated when patients with SSc present with acute hypertension and AKI. While SRC is typically a clinical diagnosis, renal biopsy can help confirm diagnosis. Our patient’s biopsy confirmed the presence of TMA however she had no pathologic features of SSc. Our patient’s diagnosis of H1N1 introduces the possibility that her TMA could have been related to H1N1. A literature search revealed two cases of patients with H1N1 associated TMA, however to our knowledge this is the first case in a patient with SSc.

Acute Kidney Injury in End Stage Renal Disease Patients on Hemodialysis and Renal Function Recovery

Paul Zamudio, Rifatt Jafri, Kamran Karimi, Hesuick Stuh, Kendal K. Wadhw.

Introduction: Chronic kidney disease (CKD) patients are at risk for developing acute kidney injury (AKI) and once labeled as ESRD, emphasis on renal function recovery becomes a lower priority. We report two chronic hemodialysis (HD) patients (AKI-D) managed with coordinated care among various health care providers and were successfully taken off HD with return of renal function.

Case Description: Case 1: A 77 year old woman with CKD stage 4 who underwent cardiac and renal artery catheterization for recurrent flush pulmonary edema and hypertension which showed 99% stenosis of the left renal artery with successful stent placement and 80% stenosis of the right renal artery with no stent. Afterward, she became anuric with a serum creatinine 9.63 mg/dL. HD was initiated with left radiocephalic AV fistula. Her intradialytic weight gain and blood pressure control were monitored with improvement in urine output. Her HD frequency decreased twice to once a week. She received by phone function (CvVHD) and was successfully taken off HD one year later. She remained off HD for 9 months so far. Case 2: A 70 year old woman with CKD stage 4 and left atrioipathic who underwent catheterization due to ST elevation myocardial infarction. She developed AKI with uricemic symptoms and creatinine 5.25 mg/dL. She was started on HD with left brachial-axillary Acusa AV graft. Three months post HD initiation; she was decreased to twice a week HD then once a week 6 months later. Ten months later, she was taken off HD with current S Cr of 2.14 mg/dL. She has been off HD for 4 months so far.

Conclusion: CKD patients who develop AKI needs individualized care, focused on renal function recovery. This type of directed care is important as AKI patients in future can receive HD at ERSD facilities as of Jan 1, 2017. Creation of an arteriovenous access can slow decline in GFR. Both were successfully taken off HD through careful management of their dry weights, blood pressures, medications leading to progressive tapering of their HD schedules.

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Non-Uremic Calciphylaxis Treated with Intralesional Sodium Thiosulfate
Venkat Ram Rakesh Mondra, Eric L. Wallace, James C. Harms, and Christopher D. Adams. 1st University of Alabama, Birmingham, AL; 2nd East Alabama Medical Center, AL.

Introduction: Calciphylaxis is characterized by systemic medial calcification of the arteries that leads to ischemia and subcutaneous necrosis. It is rarely reported in ESRD patients but even more rarely seen in non-ESRD patients. Treatment strategies are also less defined in non-uремic calciphylaxis with only three cases reporting the use of IV sodium thiosulfate (STS) and no cases reporting treatment with intralesional STS.

Case Description: Case: A 61-year-old female with a history of rheumatoid arthritis, chronic corticosteroids, TNF inhibitors, Tolulzumab, Abatacept, Tofacitinib, Anakinra and recently started on denosumab developed a left lower extremity lesion that started as papular erythema and progressed to have a necrotic center. Laboratory examination revealed GFR ranging 55 to 77 mL/min and normal serum calcium and phosphorus. Vitamin D was elevated at 111 ng/mL. PTH was elevated at 320 ng/mL. Fibroblast Growth Factor 23 level was only mildly elevated. Anticardiolipin antibody was normal. Other negative work up included, negative PR3 and MPO. Biopsy was consistent with calciphylaxis. The leg wounds continued to worsen until intralesional STS was instituted. Her initial lesion improved significantly, however, further lesions developed on her opposite leg and as such plans to institute IV STS are underway.

Discussion: Intralesional sodium thiosulfate may be a useful strategy for treatment of non-uремic calciphylaxis but based on the appearance of new lesions may not be adequate in all cases if systemic calciphylaxis is present.

PUB528
Aggressive IgA Nephritis Presenting with Microangiopathic Hemolytic Anemia Andrea L. Oliverio. Internal Medicine - Nephrology, Univ of Michigan, Ann Arbor, MI.

Introduction: Microangiopathic anemia (MAHA) is not a classical feature in IgA vasculitis; though, recent case reports have suggested aberrations in the alternative complement cascade may contribute to this phenotype. Here, we describe an aggressive case of IgA vasculitis presenting with acute on chronic nephritis and MAHA without any detectable abnormalities in the alternative complement cascade.

Case Description: A previously healthy 19 year old Caucasian female presented with a six month history of headache, nausea, and abdominal pain. Three weeks after the initial onset of symptoms, she developed arthralgias and decreased urination without hematuria. At presentation, she complained of edema. On exam, she appeared pale with 1+ lower extremity edema but had no rash. Her initial laboratory tests revealed BUN 65 mg/dL, creatinine 14 mg/dL, hemoglobin 7.8 mg/dL, and platelets 70 k/UL. Haptoglobin was undetectable and peripheral smear had rare schistocytes. Serologic testing including ASO, ANA, dsDNA, complements, ANCA, anti-GBM, ADAMTS-13 as well as stool studies were negative. She was started on renal replacement therapy and plasmapheresis. She had a renal biopsy which showed acute on chronic necrotizing and necrotizing glomerulonephritis as well as a thrombotic and necrotizing arteritis with IgA deposits in the vascular wall in addition to the glomeruli. She had extensive interstitial fibrosis and tubular atrophy. Though her renal function was not thought to be salvageable, the severe vasculitis and MAHA were treated with high dose Solumedrol and Rituximab. Her hemoglobin stabilized, her thrombocytopenia resolved, and haptoglobin remained low but was now detectable. Genetic analysis for complement abnormalities detected no known mutations and complement activation panel was normal, making atypical hemolytic uremic syndrome less likely.

Discussion: This case was confounded by the aggressive IgA vasculitis leading to MAHA. Recent studies have suggested that adding immunosuppressive therapy to intensive supportive care in IgA vasculitis and advanced nephropathy yields no significant outcome benefit. In this unique case, despite the poor renal prognosis, the severe vasculitis prompted use of immunosuppression to curb ongoing MAHA.

PUB529
Isolated Hyperphosphatemia with Suppressed Urinary Phosphate Excretion in a Patient with Undifferentiated Leukemia
Putthapiban, Prapaipan, James Oliverio, L. -Nephrology, Bone and Mineral Metabolism, Univ of Kentucky, Lexington, KY.

Introduction: Calciphylaxis is characterized by systemic medial calcification of the arteries that leads to ischemia and subcutaneous necrosis. It is rarely reported in ESRD patients but even more rarely seen in non-ESRD patients. Treatment strategies are also less defined in non-uремic calciphylaxis with only three cases reporting the use of IV sodium thiosulfate (STS) and no cases reporting treatment with intralesional STS.

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Discussion: Intralesional sodium thiosulfate may be a useful strategy for treatment of non-u ремic calciphylaxis but based on the appearance of new lesions may not be adequate in all cases if systemic calciphylaxis is present.

PUB530
Idiopathic Granulomatous Intestinal Nephritis: A Diagnosis Dilemma Adeleve Annick Edoju, Sadig Ahmed. B. Peter Sawaya. Nephrology, Bone and Mineral Metabolism, Univ of Kentucky, Lexington, KY.

Introduction: Granulomatous intestinal nephritis (GIN) is a rare histologic diagnosis found in 0.5% to 0.9% of native renal biopsies. The causes of GIN include medications, sarcoidosis, tubulointerstitial nephritis and uveitis, paraproteinemia and fungal infections. Herein we describe a case of idiopathic GIN and review the workup necessary to exclude secondary causes.

Case Description: A 45 year-old man with a history of positive hepatitis C antibody presents with a serum creatinine (SCr) level of 4.93mg/dL. It was 3.69mg/dL 2 weeks prior, 2.7mg/dl 6 months prior and 0.8mg/dl 2 years earlier. His BP was 138/84; he denied: dysuria, skin rashes, arthralgia, and taking any medications. The urinalysis showed 20mg/dL protein, 9WBCs, 2RBCs, no cellular casts. Spot urine protein/creatinine ratio was 0.4mg/mg. The following labs were either normal or negative: C3/C4, hepatitis C viral load, Hepatitis B antibodies, anti MPO, anti PR3, ANCA, ANA, ACE level, quantiferon TB gold, cryoglobulins, antiphospholipid antibodies, anti-thrombosis, anticoagulants and anti-cyclic collagens antibodies. A kidney biopsy revealed GIN. Staining for bacteria, mycobacteria, IgG4 was negative. B showed T lymphocytes without monoclonality.

Discussion: We suspect the patient may have renal resistance to FGF-23, perhaps mediated by Klotho and associated either with her malignancy or cytarabine.

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1025A
Case Description: A 68-year-old man with IgAN presented with sudden onset of dyspnea 6 months after he was diagnosed with IgAN. He was treated with antibiotics for pneumonia without improvement. Further work-up revealed an acute right popliteal deep venous thrombosis (DVT) and VQ scan showed high probability for pulmonary embolism. Serum creatinine (SCr) was at baseline of 2.2 mg/dL and urinary total protein to creatinine ratio (UPCR) was 1 g/g of Cr. Serum albumin was 3.1 g/dL. All hypercoagulable work-up were negative. He was treated with heparin and prolonged warfarin given unprovoked TEP. He presented with purpuric rashes with central necrosis on both shins 1 year later. He also had recurrent acute DVT at the same area. Since warfarin-induced skin necrosis was a side effect, he was referred to a dermatology clinic. He also developed RENAL type picture with an elevated SCr up to 3.19 mg/dL and UPCR was up to 3.3 g/g of Cr. Renal biopsy was performed and showed IgAN without crescent. He was treated with high dose steroids without improvement of renal function. Nine months later, SCr trended up to 4.16 mg/dL and UPCR was in nephrotic range of 4.4 g/g of Cr (Figure 1). He was referred for pre-kidney transplant evaluation. All routine age-appropriate cancer screening was negative.

Discussion: Our patient presented with an early onset of TEP and slightly hypoalbuminemia; however, he had nephrotic range proteinuria with normal serum albumin at the second episode of DVT. Although IgAN complicated by TEP IS not as common as membranous glomerulonephritis, TEP could occur even without a known risk factor such as hypoalbuminemia.

Bevacizumab Induced Nephrotic Range Proteinuria Managed with Dual RAAS Blockade
Haritha Karuppari, Jason Prosek. Nephrology, Ohio State Univ, Columbus, OH.

Introduction: Nephrotic range proteinuria (NRP) caused by vascular endothelial growth factor (VEGF) inhibitors like bevacizumab is a known entity. Patients who develop NRP are at risk for renal and cardiovascular adverse events. While guidelines recommend discontinuing bevacizumab (BZ) in NRP, there is no evidence-based protocol for management of proteinuria. We report a case of a BZ induced NRP managed with dual renin-angiotensin-aldosterone system (RAAS) blockade.

Case Description: 35-year-old Caucasian man underwent resection of glublastoma followed by chemoradiotherapy. He began BZ (100mg/kg) every 2 weeks with temozolomide for progression of disease. After 6 cycles, he developed hypertension (HTN) and was started on amlopidine. After 9 cycles BZ was developed. Originally, HTN was thought to be related to the amlopidine. He was later referred to Nephrology. Amlopidine was replaced by Lisinopril. After 4 weeks, proteinuria decreased to 0.3 g/day. BZ was then added at 21 day cycles. Since BP remained elevated, losartan was added. After 8 weeks of maximal RAAS blockade, proteinuria declined to 1 g/day. BZ was then resumed at 14 day cycles. Given dry cough, Lisinopril was replaced with eplerenone. After 14 cycles of BZ, proteinuria remains 0.5-1.0 g/day. No adverse effects were noted, with normal renal function and potassium.

Discussion: Renal adverse outcomes from VEGF-inhibitors are NRP and HTN. Etiology of VEGF-inhibitor induced NRP include loss of endothelial fenestration podocyte dysfunction and in rare instances thrombotic microangiopathy. Implications of asymptomatic proteinuria are unknown. However, overt proteinuria is a known risk factor for chronic kidney disease and cardiovascular adverse events. Our case is unique for several reasons. First, it demonstrates the beneficial effects of dual RAAS blockade for NRP. While dual RAAS blockade is not tolerated in patients with vascular disease it may be a viable option in young patients when monitored closely. Second, when BZ was resumed, NRP did not recur while on dual RAAS blockade. This suggests that RAAS inhibitors may provide a direct protective effect on podocytes and endothelial cells. In the appropriate population, dual RAAS blockade is an effective longterm strategy to enable extended use of anti-VEGF targeted therapies.

A Case of Azysgos Vein Embolism Associated with Transient Antiphospholipid Syndrome in Urinary Tract Infection with Escherichia coli
Sang Jo Han, Hong Joo Lee. Dept of Nephrology, Seoul Red Cross Hospital, Seoul, Korea.

Introduction: The classical antiphospholipid syndrome (APS) is characterized by the presence of antiphospholipid antibodies (aPL)-that is, lupus anticoagulant or anticardiolipin antibodies-which bind target phospholipid molecules and are associated with recurrent fetal loss, thrombosis, and thrombocytopenia. In more recent years, other infections may be accompanied by these antibodies, aPL and, in some, these increases may be accompanied by clinical manifestations of APS.

Case Description: A 73-year-old woman with diabetes admitted for treatment of an intertrochanter fracture of the femur and a urinary tract infection (UTI) with Escherichia coli developed thrombosis in her right azysgos vein, which was thought to be associated with antiphospholipid and IgM antcardiolipin antibodies. After antibiotier therapy, antiphospholipid antibody was undetectable, and a repeat chest computed tomography revealed complete resolution of the azysgos vein thrombosis.

Calciphylaxis in Myeloma Multiple and Chronic Kidney Disease
Fernanda Paula Feres Rios Da Costa, AliciaImada, Luis Fernando Cristiani, Maria Izabel Neves de Holanda. Nephrology, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil.

Introduction: Calciphylaxis is a rare and serious complication observed mainly in secondary hyperparathyroidism to chronic kidney Disease(CKD). Others diseases also can complicate with it: HIV, primary hyperparathyroidism and hematologic diseases such as multiple myeloma(MM). It is characterized by cutaneous ischemia, acute and progressive installation, secondary calcification of blood vessels of small or medium size. Diagnosis is done throughhistopathological analysis of the injuries. The pathogenesis is unclear. The treatment is prevention, maintenance of adequate levels of calcium and phosphorus.

Case Description: We report a case of a patient presented CKD and Myeloma multiple(MM) that evolved with Calciphylaxis secondary lesions one year after diagnoses. G.C.S, 70 y.o, female, diagnosed in June 2015 MM after headache, dizziness, back pain and diaphoresis. She denied comorbidities and medications use. The exams showededema, renal dysfunction, hyperkalemia, hypercalemia, lytic lesions in skull and reduced sizes of kidneys. She started hemodialysis and the MM treatment using urteconium and dexamethasone. During this period, she was admitted several times for infectious episodes and presenting refractory hypercalemia. She didn’t present a good response for the MM. In 02/2016 she was readmitted with pneumonia and evolved ulcerations in the lower limbs. The lesions started as erythematous areas, progressing to ulcerations of necrotic center and intense pain refractory to common analgesia. The venous/arterial doppler excluded thrombosis and skin biopsyshowed calciphylaxis. We started alendronate, low calcium in hemodialysis, phosphate binders(renagel) and dexamethasone as therapy for the underlying disease. Patient died few days after with sepsis and worse in less. There are few reports in the literature relating MM and calciphylaxis.

Discussion: This case demonstrated an aggressive calciphylaxis manifestations in end stage of Chronic kidney disease. The lack of response of the underlying disease influenced the severity. Calciphylaxis a rare complication and has high morbidity and mortality, our knowledge is important to prevent its appearance.

Leaky Pipes: A Case Report of Pseudo-Azotemia Secondary to Intraperitoneal Extravasation of Urine following a Urological Procedure
Payam Pourhassani, Christopher Richard Kern, Sandeep Aggarwal. Internal Medicine, Drexel Univ College of Medicine, Philadelphia, PA.

Introduction: Azotemia is a marker of net nitrogen balance that depends on both production and excretion. Consequently, BUN and creatinine may rise in the absence of renal disease. Causes of azotemia not related to renal injury or reduction of GFR if either process is impaired, leading to “pseudo- azotemia.” We report a case of a post-operative increase in serum creatinine secondary to a urinoma (pararenal pseudocyst), initially labeled as acute kidney injury.

Case Description: A 50-year-old man with history of prostate cancer underwent robot-assisted laparoscopic prostatectomy with bilateral pelvic lymph node resection. On post-operative day 1, he became oligoanuric and had a sudden rise in serum creatinine which peaked at 8.74 mg/dL. However, he was without uremic signs/symptoms, dyselectricity, or severe acidosis. He subsequently had a retrograde urogram with Cystografin that showed extravasation at the ureterovesical interface. He had an IR drain placed, followed by surgical placement of bilateral ureteral stents with complex foley placement, to ensure that the ureteral orifices were not draining outside of the ureterovesical anastomosis. On the following day his creatinine decreased from 8.74 to 3.31 mg/dL, his discharge creatinine was 2.72 mg/dL.

Discussion: The elevation of serum biomarkers of renal failure (i.e. BUN and creatinine) following bladder rupture is well elucidated and occurs from diffusion of solutes from the extravasated urine through the peritoneal membrane. Patients can develop uremic symptoms requiring hemodialysis if the diagnosis is delayed. Where available, kidney injury biomarkers like NGAL/KIM1 may be helpful in determining true renal tissue injury.

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**Case Description:** A 27-year-old man was admitted with jaundice and dark-colored urine. Laboratory tests showed progressive obstructive jaundice including high bilirubin levels and anuric renal failure requiring prolonged hemodialysis. Computed tomography of the hepatoportal system revealed normal intrahepatic and extrahepatic duct size with normal common bile duct without any sign of hepatoportal duct obstruction. Liver biopsy showed primary sclerosing cholangitis. A kidney biopsy, performed a few days after the initiation of dialysis, demonstrated the presence of bile casts along with acute tubular injury. The patient is continuing to be hemodialysis and waiting for liver transplantation.

**Discussion:** We present here an unusual case of kidney injury secondary to BCN occurring in a context of PSC.

**PUB536**

**Rare Case of Histiocytoma Glomerulopathy with Spontaneous Resolution of Nephrotic Syndrome**

**Tarek Rashid, 1 Kamaldeep Singh, 2 Belinda Jim, 1 Glen S. Markowitz, 1 Kira Anis.**
1 Dept of Medicine, Jacobi Medical Center, Bronx, NY; 2 Dept of Medicine, North Central Bronx Hospital, Bronx, NY; 3 Dept of Pathology & Cell Biology, Columbia Univ Medical Center, New York, NY.

**Introduction:** Histiocytoma glomerulopathy (HGP), a recently described glomerular pathology, is characterized by prominent glomerular histiocytic infiltrates. Clinically, it can present with the onset of acute kidney injury (AKI) and nephrotic syndrome and has also been reported in association with hemophagocytic syndrome (HPS). CASE PRESENTATION: A 33-year-old Female, from Bangladesh, with a past medical history of hypothyroidism, migraines, and occasional NSAID use, presented with a non-specific febrile illness associated with low grade fever, myalgia, arthralgia and dysuria, suspected to be urinary tract infection and treated with NSAIDS and nitrofurantoin.She returned a week later with nausea, vomiting, AKI (creatinine 1.6 mg/dl), and new onset of nephrotic syndrome. Patient was normotensive and physical exam was remarkable for 3+ edema. Urinalysis showed small blood with 0-6 RBC, 300/mg protein. Urine protein to creatinine ratio was 14 g/g with a bland urine sediment on microscopy. She had hypoproteinemia, mildly elevated AST/ALT, LDH, triglycerides and ferritin, positive ANA, and depressed C3 and C4 levels. All Other serologies were normal. She had a decrease in her Hgb and platelets during the course of illness. Renal ultrasound was unremarkable. Kidney biopsy showed glomeruli with prominent infiltrating monocytes/histiocytes, endothelial swelling, and foot process effacement, most consistent with histiocytic glomerulopathy. Over the course of 2 weeks, in the absence of immunosuppressive therapy, we witnessed spontaneous resolution of her symptoms and nephrotic syndrome. DISCUSSION: HGP is typically associated with HPS and can occur in the setting of acute viral infection, autoimmune disease, or malignancy. Our patient did not meet the current diagnostic criteria for HPS on presentation. This is the first reported case of HGP with nephrotic syndrome, occurring without definitive evidence of HPS, with an extremely short self-limiting clinical course.

**PUB537**

**An Interesting Case and Treatment Dilemma Involving a Progressive Immune Complex Mediated Membranoproliferative Glomerulonephritis**

**Abdul Hameed Zaidi, Robert D. Zenenberger.**
Internal Medicine, Saint Barnabas Medical Center, Livingston, NJ.

**Introduction:** Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury with segmental and endocapillary proliferation, and glomerular basement membrane thickening. Recently, greater understanding of the pathophysiology of MPGN has led to subsequent reclassification based on immunofluorescence. Immunoglobulin staining with complement suggests an immune complex mechanism from certain infections, autoimmune diseases or a monoclonal gammapathy. Isolated complement staining suggests disorders of alternate complement pathway. We present an interesting case and treatment dilemma of an immune complex mediated MPGN.

**Case Description:** A 61 year old Chinese man presented with progressive renal insufficiency and proteinuria. He had chronic Hepatitis B (HBV) leading to end-stage liver disease undergoing an orthotopic liver transplant 4 years earlier, and was on Mycophenolate and Entecavir®. History included a CNS lymphoma and subsequent systemic lymphoma, second malignancy, without definitive evidence of HPS, with an extremely short self-limiting clinical course.

**Discussion:** This patient presented with a polyclonal immune complex mediated MPGN and had a history of both HBV and lymphoproliferative disease. Steroids should generally be avoided in a histologic MPGN, but this patient had persistently undetectable viral loads. The possibility of recurrent lymphoproliferative disease or an infectious process causing the Type III cryoglobulinemia was certainly possible, but was not evident. Considering the progressive nature of the glomerular disease, more aggressive immunosuppression to target the cryoglobulins was warranted. A second graft biopsy revealed only recurrent FSGS. ACTH 40 units subcutaneous twice a week was a started and then increased to 80 units subcutaneous twice a week. Four weeks after initiating a repeat serum creatinine was 2.25 mg/dl and UPCR decreased to 4.2 mg/g. Three months later serum creatinine increased again to 3.5 mg/dl and UPCR increased to 6.2 mg/mg. A third graft biopsy revealed more advanced recurrent FSGS so every other day plasma exchange was started and Achtar gel was continued along with mycophenolate mofetil and prograf. Kidney function continued to decline slowly with progressive rise of serum creatinine to 4.5 mg/dl and UPCR persisted around 6 g/mg.

**Conclusion:** This case report describes our experience using ACTH in treating recurrent FSGS in a live donor kidney transplant.

**PUB540**

**Diet and the Domino Effect in Oxalate Nephropathy**

**Rungwasee Ratanavich, Laura J. Maursetter, Tripit Singh, Gauri Bhutani.**
Nephrology, Univ of Wisconsin, Madison.

**Introduction:** Oxalate nephropathy (ON) is an under-recognized entity, important to consider in individuals at risk for fat malabsorption since timely intervention may preserve renal function.

**Case Description:** 65 year-old male, baseline serum (S.) creatinine (Cr) 1.0 mg/dl, was admitted after incidental discovery of elevated Cr (4.6 mg/dl). He was non-oliguric and denied any acute events/symptoms other than incarceration 1 year back. He had known history of alcoholism, diabetes, hypertension, extrahepatic biliary excision and Roux-en-Y hepaticojejunostomy (2003) for cholangiocarcinoma. His only medication was entacaponce and atorvastatin. On admission, he was alert but with complaints of abdominal pain, nausea, vomiting, and jaundice for 1 week. Urine analysis revealed a urine specific gravity 1.016, microscopic hematuria, and proteinuria. Serum calcium, phosphorous, and urine calcium/creatinine (Ca/Cr) ratio was 14 g/g with a bland urine sediment on microscopy. She had hypoproteinemia, mildly elevated AST/ALT, LDH, triglycerides and ferritin, positive ANA, and depressed C3 and C4 levels. All Other serologies were normal. She had a decrease in her Hgb and platelets during the course of illness. Renal ultrasound was unremarkable. Kidney biopsy showed glomeruli with prominent infiltrating monocytes/histiocytes, endothelial swelling, and foot process effacement, most consistent with histiocytic glomerulopathy. Over the course of 2 weeks, in the absence of immunosuppressive therapy, we witnessed spontaneous resolution of her symptoms and nephrotic syndrome. DISCUSSION: HGP is typically associated with HPS and can occur in the setting of acute viral infection, autoimmune disease, or malignancy. Our patient did not meet the current diagnostic criteria for HPS on presentation. This is the first reported case of HGP with nephrotic syndrome, occurring without definitive evidence of HPS, with an extremely short self-limiting clinical course.

**Discussion:** The response to ACTH treatment in this case with post-transplant recurrent FSGS was not satisfactory. Early initiation of plasma exchange is necessary to remove circulating permeability factors. Further research is necessary to determine if ACTH may be a useful therapy in patients with recurrent FSGS.

**PUB539**

**Treatment of Recurrent Focal Segmental Glomerulosclerosis (FSGS) in a Post Kidney Transplant Recipient with Adrenocorticotrophic Hormone (ACTH) Gel**

**Jose F. Ramirez-Porres, 1 Amr El-Husseini Mohamed, 1 Virginia Correa, 2 Nada AlSayadi.**
1 Medicine, Univ of Kentucky, Lexington, KY; 2 Pathology, Univ of Kentucky, Lexington, KY; Transplant, Johns Hopkins, Baltimore, MD.

**Introduction:** ACTH has shown efficacy in idiopathic FSGS and other glomerulopathies. The data on using ACTH to treat recurrent FSGS post renal transplantation is limited. This case report describes our experience using ACTH in treating recurrent FSGS in a live donor kidney transplant.

**Case Description:** A 38 year old male who underwent live-related kidney transplant secondary to primary FSGS, presented with elevated creatinine, microscopic hematuria and nephrotic range proteinuria approximately two months after transplant. Serum creatinine increased to 1.8 mg/dl from a baseline of 1.3 mg/dl. Spot urine protein creatinine ratio (UPCR) was 2.5 mg/mg.

**Graft biopsy revealed findings suggestive of vasculitis and early recurrent FSGS.** P-ANCA and C-ANCA serologies were negative. Patient received 3 days high dose pulse intravenous steroids, 3 months of oral cyclophosphamide then switched to Rituximab therapy due to lack of response. Serum creatinine went up to 3.34 mg/dl and UPCR to 6.1 mg/mg. A second graft biopsy revealed only recurrent FSGS. ACTH 40 units subcutaneous twice a week was a started and then increased to 80 units subcutaneous twice a week. Four weeks after initiating a repeat serum creatinine was 2.25 mg/dl and UPCR decreased to 4.2 mg/g. Three months later serum creatinine increased again to 3.5 mg/dl and UPCR increased to 6.2 mg/mg. A third graft biopsy revealed more advanced recurrent FSGS so every other day plasma exchange was started and Achtar gel was continued along with mycophenolate mofetil and prograf. Kidney function continued to decline slowly with progressive rise of serum creatinine to 4.5 mg/dl and UPCR persisted around 6 gm.

**Conclusion:** The response to ACTH treatment in this case with post-transplant recurrent FSGS was not satisfactory. Early initiation of plasma exchange is necessary to remove circulating permeability factors. Further research is necessary to determine if ACTH may be a useful therapy in patients with recurrent FSGS.

**PUB538**

**Bile Cast Nephropathy Complicating Primary Sclerosing Cholangitis**

**Sang Jo Han, Hong Joo Lee.**
Dept of Nephrology, Seoul Red Cross Hospital, Seoul, Republic of Korea.

**Introduction:** Bile cast nephropathy (BCN), a condition of renal dysfunction in the context of cholestatic liver dysfunction is not uncommon. While the exact etiology remains unknown, BCN is presumed to be secondary to multiple concurrent insults to the kidney including direct toxicity from bile acids, obstructive physiology from bile casts, and systemic hyperfusion from vasodilation. Primary sclerosing cholangitis (PSC) is a cholangiographic diagnosis of unknown cause and long-standing, progressive course, leading to cirrhosis and requiring orthotopic liver transplant. The association with BCN and PSC has been reported previously in very limited number of cases.

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

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PUB541

Rapidly Progressive Glomerulonephritis: Cause or Consequence of Developing Posterior Reversible Encephal!opathy Syndrome

Giovanna Y. Arteaga Muler, Lilia Maria Rizo Topete, Allina Primavera Flores Mendoza, Elisa Maria Guerrero Gonzalez, Jose Guadalupe Martinez Jimenez, Concepcion Sanchez Martinez, Jesus Cruz Valdez. Nephrology, José Eleuterio Gonzalez of the Autonomous Univ of Nuevo Leon, Monterrey, Mexico.

Introduction: Rapidly progressive glomerulonephritis is characterized by quick deterioration of renal function. Early diagnosis and immunosuppressive therapy plays a key role in kidney survival. More than half of these cases advance into end stage renal disease, this group of diseases are at risk of developing posterior reversible encephalopathy syndrome (PRES). PRES consists of acute neurological symptoms caused by endothelial dysfunction, which results in vasogenic cerebral edema mainly in white matter, generated in most cases by severe changes of hypertension, but 15-20% of patients have normal or low blood pressure, so it has been attributed to direct endothelial damage caused by immunosuppressant drugs, preeclampsia, and autoimmune disease. Diagnosis is based on clinical presentations, radiological findings in posterior brain and the pattern of the frontal sulcus as well as their reversibility.

Case Description:

Discussion: Kidney injury is present in at least 55% of PRES cases. Its association is affected by accompanying presence of hypertension or autoimmune disease, as we can see in case 1 which presented with severe hypertension. Of the established risk factors for PRES both cases present autoimmune disease, kidney injury and the use of immunosuppressive therapy. It is important to define if rapidly progressive kidney dysfunction, systemic involvement of base illness, age and gender could be considered independent risk factors for developing PRES. Prospective studies that determine associations, manifestations and prognosis must be continued so that a risk scale can be established which can determine if the sum of these factors increase the risk of developing PRES.

PUB542

Air Embolism: A Rare Complication of Tunneled Dialysis Catheters

Trevor R. Smith, Josephine Abraham. Nephrology and Hypertension, Univ of Utah, Salt Lake City, UT.

Introduction: Air embolism is a feared complication of hemodialysis, typically associated with the dialysis procedure itself. Here we report a case of air embolism associated with tunneled dialysis catheter placement.

Case Description: A 60 year old male with ESRD from polycystic kidney disease (PKD) presented to the hospital with a bleeding left upper extremity AVF and found to have MSSA bacteremia. A temporary dialysis catheter was inserted without complication. The patient was found to have MSSA endocarditis by echocardiogram, with a large vegetation on the mitral valve. The patient underwent ligation of the brachiocephalic fistula due to friable vessel tissue. He subsequently underwent placement of a tunneled dialysis catheter. In the recovery unit, the patient had an acute onset of right sided weakness and slurring of speech. A head CT revealed air in the left frontal and parietal lobes. Echocardiogram with agitated saline contrast demonstrated a large left to right shunt that did not augment with Valsalva maneuver, which is suggestive of an intrapulmonary shunt. The patient was started on high flow oxygen. It was determined that he was a poor candidate for hyperbaric therapy due to his history of COPD and metastatic squamous cell lung cancer. The family then decided to undergo aggressive medical care and patient died a few hours later.

Discussion: Air emboli can occur at various stages of dialysis catheter use: insertion, manipulation, use or removal. Complications of air emboli depend on the vascular source of the embolization. Typically, use of veno-venous dialysis catheters will result in pulmonary manifestations of air embolization, characterized by dyspnea, tachycypnea, wheezing, rales or respiratory failure. In the present case, the patient exhibited signs of arterial embolization with neurologic compromise. This venous to arterial shunting can be due to a patent foramen ovale, ventricular septal defect, or presence of a pulmonary arteriovenous malformation (AVM). In this patient, he was suspected of having an AVM as a consequence of untreated lung cancer. Although rare, air embolism can cause sudden symptoms of decompenstiation and the risk of air embolization should be considered when using dialysis catheters.

PUB543

Seronegative Renal Limited Lupus Nephritis

Amit K. Rajput, Paisit Paeucksakon, Paul Persad, Roy Zent. Vanderbilt Univ Medical Center.

Introduction: Lupus Nephritis (LN) is a common manifestation of systemic lupus erythematosus (SLE) that often presents early in the disease process. However, previous case reports discuss a specific patient population (typically females, childhood to middle age) that demonstrate LN without meeting American College of Rheumatology (ACR) criteria and have negative serologic markers. Here, we discuss a unique presentation of seronegative LN in an elderly Caucasian male.

Case Description: A 69 year-old male with chronic kidney disease stage 3 from longstanding hypertension was referred to Nephrology for a persistent acute kidney injury (AKI) and new onset hematuria. The patient was admitted three months prior to presentation for altered mental status, attributed to severe sepsis from S. pneumoniae pneumonia. The hospital course was complicated by oliguric AKI (Cr 3.0mg/dL from baseline 1.2mg/dL), hypertensive urgency, and hematuria that was attributed to traumatic foley insertion. Despite clinical improvement, the patient had unmitting AKI and hematuria along with newly discovered 7.96g proteinuria. Serologic work up, including ANA, Anti-DNase B, ASO titers, Anti-Smith, Anti-dsDNA, SLEP/F/PEP, ANCA, RF, HIV, Hepatitis Panel, and cryoglobulins were negative. However, the patient was found to be hypocomplemenemic (C3: 48mg/dL, C4: <8.0mg/dL), prompting a renal biopsy. Pathology demonstrated classic full house immunofluorescence staining with Focal Proliferative Immune Complex Glomerulonephritis and mild-to-moderate arterioponerosis. The patient was treated with cyclophosphamide IV once monthly for six months along with a prednisone taper. Six months after initiation of treatment, the patient is showing full recovery to baseline (Cr 1.2mg/dL and 0.2g proteinuria).

Discussion: LN is a serious complication of SLE with rapid progression to end-stage renal disease (ESRD) if not diagnosed and treated in a timely manner. Prompt recognition and initiation of treatment are essential for reducing morbidity and mortality. As evident by our patient, relying on ACR classification criteria or serologies alone to diagnose LN can lead to delays in treatment, with an increased risk to ESRD progression.

PUB544

A Venous Anomie Stenosis at Costo-Clavicular Junction (CCJ)

Lisa Giovanni, Walter Morale; Gianni Cappelli. Surgical, Medical and Dental Dept of Morphological Sciences, Section of Nephrology, Univ of Modena and Reggio Emilia, Modena, Italy; Dept of Nephrology and Dialysis, Cannizzaro Hospital, Catania, Italy.

Introduction: Central venous stenosis (CVS) is a frequent complication in hemodialysis (HD) patients. Venous obstruction at the costoclavicular junction (CCJ) requires a different approach beyond PTA and stenting.

Case Description: A 82ys-old man on HD with left radio-cephalic arterovenous fistula (AVF) presented severe edema of AVF arm. Ultrasound (US) did not show significant venous stenosis. TC showed a severe stenosis of the left brachiocephalic vein so we performed multiple PTA and placing of a 16x60-mm stent. Unfortunately, edema recurred and MS-TC showed an instant-stenosis by left clavicle bony hypertrophy. Vascular surgery performed one third anterior claviculectomy. After surgery for persistent intra-stent stenosis of left brachiocephalic vein we placed 16x40-mm intra-stent Wall Stent Boston stent successfully. After 5 months patient was referred from peripheral dialysis unit for edema and distal ischemic lesions. US showed a decreased flow rate, significant stenosis of cephalic vein, thrombosis of basilic vein and ischemic steal syndrome. We performed endovascular closure of AVF with endoprosthesis 6mm/Viahan in radial artery.

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

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Discussion: PTA and stenting are the primary option for treating stenosis surrounded by soft tissue. Venous stenosis adjacent to the CCF poorly respond to PTA/stenting, and, generally, require bony decompression for long-term patency. On our experience, the surgical decompression allowed secondary stent placing intra-stent successfully. The long time duration of venous hypertension may cause irreversible arterial microcirculatory stasis and ischemic steal syndrome. Our experience highlights the importance of early diagnosis of CCF venous stenosis and a multidisciplinary approach for its treatment.

PUB545
IgA Dominant Methylcellulose-Sensitive Staphylococcus aureus-Associated Rapidly Progressive Glomerulonephritis

Amit K. Rajput, Agnes B. Fogo, Paul Persad, Raymond C. Harris. Vandersbilt Univ Medical Center.

Introduction: Post-infectious glomerulonephritis (GN) typically refers to poststreptococcal GN, often seen after the infection has resolved. However, an uncommon entity has been demonstrated in the middle aged and elderly patient populations, in which active staphylococcal infections are associated with progressive renal failure. We present a case of rapidly progressive glomerulonephritis (RPGN) from an active Methylcellulose-sensitive staphylococcus aureus (MSSA) infection.

Case Description: A 72 year-old male with chronic kidney disease stage 3 from long-standing diabetes mellitus type 2 (DM2) was receiving nafcillin IV for a left foot diabetic ulcer with superimposed cellulitis (no osteomyelitis), which was complicated by oliguric acute kidney injury (AKI) with a serum creatinine 5.7mg/dL (from baseline 1.9mg/dL) and new onset nephritis. Investigation revealed MSA septicaemia, with the left foot wound as the infection source. During evaluation, the patient’s renal function declined precipitously, warranting an urgent renal biopsy and initiation of renal replacement therapy (RRT). Pathology demonstrated glomerular proliferation and exudative and fibrinoid glomerulonephritis with IgA and C3 dominant deposits, characteristic of an infection-associated GN, in addition to mild-to-moderate diabetic nephropathy. The patient underwent urgent left below-the-knee amputation for infection source control, but despite intervention, renal function did not recover. The patient was deferred to stage renal failure (ESRD) and passed two months later from a non-renal related illness.

Discussion: As poststreptococcal GN, staphylococcal-associated GN presents with concurrent infection. Although the mechanism remains unclear, it is postulated that the infection provides an antigen to which an immune complex is formed and deposited in the glomerulus. Staphylococcal infections seem to be associated with IgA dominance on immunofluorescence, compared to IgG dominance in poststreptococcal GN, with skin wounds as the most common infection source. Furthermore, previous analysis suggests a correlation with underlying diabetic nephropathy and worse renal prognosis, as evident with our patient.

PUB546
Severe, Refractory Hypokalemia in a Patient with Systemic Lupus Erythematosus Receiving Cyclophosphamide

Ali Iqbal, Mohammed Hadi Tawhari. Nephrology, McMaster Univ, Hamilton, ON, Canada.

Case Description: We describe a 42-year-old female patient with a history of systemic lupus erythematosus who presented with severe, refractory hypokalemia following cyclophosphamide therapy. She was diagnosed with lupus at age 14 and previously had class III lupus nephritis treated with cyclophosphamide years prior to this admission. She was then maintained on mycophenolate and hydroxychloroquine with a normal eGFR and minimal proteinuria over next few years. She then developed steroid refractory musculoskeletal and cutaneous manifestations, eventually leading to the initiation of cyclophosphamide. Following her fifth infusion of cyclophosphamide, she presented to her community hospital with weakness, nausea and hypokalemia ranging from 1.5 to 2.5 mmol/L. Her relevant home medications included furosemide, metolazone, dexamethasone, and hydroxychloroquine. During her hospitalization, she required transfer to the intensive care unit for an episode of torsades de pointes due to hypokalemia. Her diuretics were held and she was started on parenteral and enteral potassium supplementation. 24 hour urine collection demonstrated urinary potassium of 147 mmol (225-125 mmol), normal urine calcium, magnesium, sodium, and total volume of 6.1 L. Serum bicarbonate was 30 mmol/L (22-29 mmol/L), with elevated supine serum renin and normal aldosterone levels. She was placed on indomethacin, amiloride, spironolactone and ranitidine in an attempt to reduce urinary potassium losses. Despite a histamine H1 antagonist to be administered intravenously over six months and was seen in consultation by nephrology, rheumatology, and endocrinology. She was eventually diagnosed with an acquired Bartter like syndrome either secondary to cyclophosphamide toxicity due to an antibody mediated phenotype. Given the possibility of an antibody-mediated etiology, a trial of IVIG was initiated followed by a trial of plasma exchange consisting of 7 sessions over a two-week period. Her potassium did seem to improve and stabilize following plasma exchange. She eventually discharged home about a month later on about 100 mEq per day of potassium supplementation, amiloride, ranitidine, as well as spironolactone.

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PUB547
A Case of Antithyroid Drug-Induced Double ANCA-Positive Vasculitis

Mihoko Shikata, Fumihiko Furuya, Kenichiro Kitamura. Third Dept of Internal Medicine, Univ of Yamanashi, Chuo, Yamanashi, Japan.

Introduction: Antithyroid drugs are shown to induce antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). While both methimazole (MMI) and propylthiouracil (PTU) are potential causes of AAV, the incidence of PTU-induced AAV is reported to be higher than that of MMI-induced AAV.

Case Description: A 68-year-old woman was admitted to our hospital because of acute kidney injury. She was diagnosed with Graves’ disease and had been treated with MMI for 18 years. On admission, she presented proteinuria and microscopic hematuria, and both MPO- and PR3-ANCA were positive. Since MMI-induced AAV was suspected, MMI was discontinued right after the admission. Kidney biopsy revealed pauci-immune crescentic glomerulonephritis. Although intravenous methylprednisolone pulse therapy (1000mg/day for 3 days) followed by oral prednisolone 10mg daily was initiated, her renal function was exacerbated and hemodialysis was started. Thereafter, urine volume was gradually increased and her renal function was recovered. Following the discontinuation of MMI, serum levels of PR3-ANCA were rapidly normalized and those of MPO-ANCA were decreased before the initiation of steroid therapy.

Discussion: We report a case of MPO-induced double ANCA positive vasculitis with acute kidney injury that was successfully treated with immunosuppressive agent. PTU has been demonstrated to produce multiple antigens including MPO-ANCA and PR3-ANCA. Antithyroid drug-induced AAV usually occurs in patients with Graves’ disease who are resistant to drug treatment. Previous reports suggested the possibility that repeated exposure to the drug might trigger the development of drug-induced ANCA vasculitis. In the current case, the discontinuation of ANCA in MPO-ANCA were decreased before the initiation of steroid therapy.

PUB548
A Rare Case of Hodgkin Lymphoma Complicated with Membranous Nephropathy in a Young Male Patient

Naomi Matsuo, Hideki Inoue, Yutaka Kakizoe, Yuichiro Izumi, Takashige Kuwabara, Masataka Adachi, Yushi Nakayama, Masashi Mukoyama. Nephrology, Kumamoto Univ Hospital, Kumamoto, Japan.

Introduction: The most common glomerulopathy associated with Hodgkin lymphoma (HL) is minimal change nephrotic syndrome, but other types of glomerulopathy including membranous nephropathy (MN) have rarely been reported. We here report a case of HL complicated with MN, who responded well to the treatment with chemotherapy and radiotherapy.

Case Description: A 16-year-old man was admitted to our hospital due to proteinuria and hematuria. His serum creatinine level was 0.63 mg/dL and urinary protein excretion was 2.18 g/g creatinine. Renal biopsy revealed MN (stage II). In the immunofluorescence study, IgG4 was most strongly stained for IgG subclass analysis; there was no evidence of glomerulopathy associated with amyloidosis or paraproteinemia. Only partial remission of proteinuria was obtained despite the treatment with 40 mg/d of oral prednisolone. Four months after starting oral corticosteroid therapy, slightly enlarged lymph nodes were noticed above the collarbone. Lymph node biopsy showed lymphocyte-depleted classical HL (stage II). He was treated with four cycles of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) chemotherapy along with radiotherapy, and a complete hematologic response was achieved. Then, the patient showed drastic reduction in proteinuria after an effective treatment of HL.

Discussion: The association between MN and malignancy has well been documented, but MN associated MN has rarely been reported. Remission in glomerular disease was achieved in accordance with hematologic remission by chemotherapy and radiotherapy, suggesting a causal relationship between the two diseases.

PUB549
Drug Induced Antineutrophil Cytoplasmatic Autoantibody Vasculitis Secondary to Propylthiouracil

Elizabeth Upton, 1 Harsharan Kaur Singh,2 William Franklin Pendergraft. 1 UNC Kidney Center; Univ of North Carolina, Chapel Hill, NC; 2Div of Nephrology, Univ of North Carolina, Chapel Hill, NC.

Introduction: We describe a case of a 72-year-old male who developed antineutrophil cytoplasmatic autoantibody (ANCA) vasculitis after treatment with propylthiouracil (PTU) for hyperthyroidism.

Case Description: A 72-year-old male with a ten-year history of hyperthyroidism treated with PTU presented for evaluation of acute renal failure. On routine labs, he was noted to have renal insufficiency with creatinine 2.4 mg/dL, rising to 4.4 mg/dL on recheck from a baseline of 1.1-1.3 mg/dL. Urine microscopy revealed dysmorphic red blood cells and administration of PTU altered the MPO configuration induces the antigenicity. In our current case, prolonged administration of PTU alters the MPO structure surrounding the heme iron and the changes in the heme moiety may affect the antigenicity of MPO. The long-term use of propylthiouracil (PTU) are potential causes of AA V , the incidence of PTU-induced AA V
Discussion: ANCA vasculitis is an autoimmune disorder affecting small vessels caused when autoantibodies to myeloperoxidase or proteinase 3 induce a systemic inflammatory response. Minocycline, hydralazine, levamisole-contaminated cocaine, and PTU are the most common drug culprits. PTU induced ANCA vasculitis typically manifests as a pauci-immune and crescentic necrotizing glomerulonephritis associated with high titer MPO-ANCA positivity. PTU or one of its metabolites may bind to MPO in neutrophils, creating a systemic immunogenic response. Permanent cessation of the offending agent is essential to treatment. Pulse dose steroids, plasma exchange, and immunotherapy are also indicated. Further studies are needed to elucidate the mechanism of autoimmunity in all forms of drug-induced ANCA vasculitis in order to more effectively develop targeted therapies.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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1030A
performed with hypernatremia and markedly elevated urinary sodium levels despite volume expansion with thyroid and mineralocorticoid hormone replacements (day 9). The development of signs of volume overload on day 22 prompted the discontinuation of saline infusion but the hypernatremia and the natriuresis worsened (day 26). This clinical presentation is compatible with the RSWS, rarely diagnosed after cisplatin therapy. Our patient seemed to have developed a sodium tubular reabsorptive defect that persisted after a month of a single dose of cisplatin. This syndrome should be included in the differential diagnoses of hypernatremia associated with cisplatin-based chemotherapy.

Funding: VA Support

PUB555

Tacrolimus Induced Thrombotic Microangiopathy: Everolimus Is Not the Answer

Reem Daloul, Tarek Alhamad, Rowena B. Delos Santos, Daniel C. Brennan, Thin Thin Maw. Div of Renal Transplant, Washington Univ School of Medicine, Saint Louis, MO.

Introduction: Post-transplant calcineurin inhibitor (CNI) induced thrombotic microangiopathy (TMA) is a reported complication associated with poor graft outcomes. Management is based on reduction of CNI or use of alternative agents including mammalian target of rapamycin inhibitors (mTORI).

Case Description: Clinical case: A 35-year-old Caucasian female with end stage renal disease presumed secondary to congenital nephrotic syndrome underwent a deceased donor kidney transplant with thymoglobulin induction. Maintenance therapy consisted of tacrolimus, mycophenolate mofetil, and prednisone. On post-operative day three, she developed acute kidney injury associated with hemolytic anemia and thrombocytopenia in the context of an acute rise in tacrolimus level. Kidney biopsy showed acute tubular injury and one granuloma with fibrin thrombi. C4d staining was negative and no donor specific antibodies (DSA) were identified. Renal function, hematoglobin, platelets, and lactate dehydrogenase recovered gradually mirroring the decrease in CNI which was changed to everolimus. Two weeks after discharge, patient presented with wound dehiscence, infection, acute renal failure, and recurrence of hemolytic anemia and thrombocytopenia. Repeat graft biopsy showed diffuse TMA, interstitial hemorrhage, and negative C4d staining. DSA remained negative. Everolimus was switched to belatacept along with weekly eculizumab. Patient remained anuric and repeat graft ultrasound was concerning for renal vein thrombosis. Surgical exploration showed a non-viable ischemic graft that was resected without evidence of residual viable graft in situ. Genetic testing for complement mutation was negative.

Discussion: CNI induced TMA might reflect an endogenous predisposition to TMA even with a negative testing for genetic mutations. Bearing this in mind, it is advised to avoid mTORIs which carries a similar propensity to induce TMA. Belatacept appears to be a reasonable alternative in such situations.

Funding: VA Support

PUB556

Case Report: Collapsing Glomerulopathy Associated with Systemic Lupus Erythematosus

Sergio A. Trevino Manillo, Daphne Harrington Knicely. Div of Nephrology, Johns Hopkins Univ School of Medicine, Baltimore, MD.

Introduction: Collapsing glomerulopathy (CG) is most often associated with HIV. However, CG can also occur in the absence of HIV infection. CG is a rare cause of end stage renal failure and aggressive treatment, suggesting a potential life-long complication of cocaine-induced vasculitis.

Case Description: A 38-year-old male, milk vendor by occupation was admitted at our hospital, as end stage renal disease of unknown etiology on maintenance hemodialysis from past one year. Patient underwent live donor transplant in January 2016, mother as donor. He was started with corticosteroids, Tacrolimus and Mycophenolate sodium. He had stable renal functions with range of serum creatinine between 0.9 to 1.2 mg/dl and adequate serum tacrolimus levels. Five months post transplant patient presented with local redness without pain, tenderness and without local rise of temperature, three to five centimeters from pubic symphysis. His serum creatinine was 1.2 mg/dl and his tacrolimus level at cohort presentation was 4.7 mg/L. Ultrasound and non contrast CT abdomen showed a subcutaneous abscess 3.0x2.0x4.2 cm (25cc) below the suture scar. Evaluation of aspirate showed acid fast bacilli on Ziehl Neelsen stain and culture grew rapidly growing atypical mycobacteria (species identification pending). Patient was initiated on anti tubercular treatment. Currently patient is doing well, with resolution of local signs and symptoms.

Funding: VA Support

PUB557

Rapidly Growing Mycobacteria Causing Subcutaneous Abscess in a Case of Renal Allograft: A Case Report

Abhishek Goel, Tushar A. Dighit, Atul Sajigure, Atul Mulay, Charan Bhadrappa Bale, Ashwini Sharma, Jayraj Korpe, Nileshe Shinde. Nephrology, Dr. Y D Patil Medical College, Pune, Maharashtra, India.

Case Description: A 38-year-old male, milk vendor by occupation was admitted at our hospital, as end stage renal disease of unknown etiology on maintenance hemodialysis from past one year. Patient underwent live donor transplant in January 2016, mother as donor. He was started with corticosteroids, Tacrolimus and Mycophenolate sodium. He had stable renal functions with range of serum creatinine between 0.9 to 1.2 mg/dl and adequate serum tacrolimus levels. Five months post transplant patient presented with local redness without pain, tenderness and without local rise of temperature, three to five centimeters from pubic symphysis. His serum creatinine was 1.2 mg/dl and his tacrolimus level at cohort presentation was 4.7 mg/L. Ultrasound and non contrast CT abdomen showed a subcutaneous abscess 3.0x2.0x4.2 cm (25cc) below the suture scar. Evaluation of aspirate showed acid fast bacilli on Ziehl Neelsen stain and culture grew rapidly growing atypical mycobacteria (species identification pending). Patient was initiated on anti tubercular medication- Isoniazid, Pyrazinamide, Ethambutol and Levofloxacin. As per the AFB culture report, linezolid and clarithromycin were added in addition to previously mentioned anti tubercular treatment. Currently patient is doing well, with resolution of local signs and serum creatinine of 1.2 mg/dl.

Funding: VA Support

PUB558

Reduction of Serum Free Light Chains Not Apheresis Use May Be the Major Determinant of Improved Renal Function in Light Chain Nephropathy

Dawson Dean, Richard N. Hellman. Dept of Medicine, Div of Nephrology, Indiana Univ, Indianapolis, IN.

Introduction: Acute renal injury (AKI) due to light chain nephropathy (LCN) is common in multiple myeloma (MM) and its presence a major prognostic factor as it is recovery from AKI. The role of Apheresis in the management of AKI due to LCN is uncertain with some studies showing no effect and some showing improvement of renal function and less need for renal replacement therapy if free serum light chains (SLC) are reduced by more than 50%.
Dapsone Induced Vertigo, a Forgotten Side Effect


Introduction: Ecstasy or 3,4-methylenedioxymethamphetamine (MDMA) has both stimulant and hallucinogenic effects. It is commonly abused, including 39% of college students in the United States, causes euphoria and increased energy. The minor adverse effects of Ecstasy are dry mouth or sweating. Rare but lethal side effects include serotonin syndrome, hyperpyrexia, severe rhabdomyolysis, symptomatic hypotension, acute kidney injury and multi-organ failure.

Case Description: 18 y/o male presented after a seizure. He had used Ecstasy 4 hrs prior. Physical exam revealed high grade fever, hypotension, tachypnea and tachycardia, dilated reactive pupils, no response to noxious stimuli. Labs revealed AKI, lactate acidosis, hyperkalemia, hyperphosphatemia, hyperuricemia and severe rhabdomyolysis. He was treated with cooling blankets and aggressive IV fluids. He was later started on CRRT. He developed fulminant hepatic failure within 24 hrs of presentation. He had severe hypocalcemia which was treated with aggressive calcium replacement. He underwent a right orthotopic liver transplantation. He later developed persistent hypercalcemia, with evidence of calcium deposition in muscles on imaging studies. It did not respond to IV fluids, furosemide and pamidronate initially and required intermittent hemodialysis. He had full renal recovery by week 12 of hospitalization. He required daily normal saline and furosemide for 4 more weeks before serum calcium normalized.

Discussion: Ecstasy causes release of serotonin, dopamine and norepinephrine into the central nervous system and inhibits serotonin re-uptake which could cause serotonin syndrome. MDMA toxicity, unlike other drugs abuse, is not dose dependent. Direct toxicity on the kidneys is unclear. MDMA associated AKI is reported to be secondary to rhabdomyolysis due to seizures, hyperthermia and serotonin syndrome. There is no specific antidote. The mainstay of treatment is aggressive management of these complications. The persistent hypercalcemia in our case could have been due to sustained release of the calcitriol from the affected tissues. The likely reason was initial movement of calcium into the injured muscles in rhabdomyolysis resulting in hypocalcemia which was treated with aggressive calcium replacement.

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Underline represents presenting author.
1032A
A Case of Acute Interstitial Nephritis Secondary to Novel HCV Treatment Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (PrOD) 

Ravindra Krishna Komanduri, 1 Nelson P. Kopyt, 1 Ravindra Bullu. 1 Medicine, Lehigh Valley Hospital, Allentown, PA; 1 Medicine, Lehigh Valley Hospital, Allentown, PA; 1 Medicine, Lehigh Valley Hospital, Allentown, PA.

Introduction: A 66 year old AA male with history of CKD Stage IV (presumed secondary to DM and HTN) and HCV, diagnosed at pre-Transplant evaluation, developed Acute Kidney Injury. Admission creatinine [Cr] was 5.57 mg/dl, with baseline 3.28 mg/dL. He presented with symptoms of generalized weakness, fatigue, and edema. PrOD was started approximately five days before admission. He denied any symptoms of rash, fever, chills, nausea, vomiting, or diarrhea, and initially was treated for pre-renal azotemia with intravenous fluid hydration (IVF).

Case Description: Point of care urinalysis was bland, with minimal proteinuria and negative for blood, leucocyte esterase or nitrites. His fractional excretion of sodium (FE Na) was 2. With renal improvement to baseline after stopping PrOD a biopsy was not performed nor was he treated with steroids. After renal recovery, he was successfully treated with ledipasvir/sofosbuvir without complications.

Discussion: PrOD is classically seen with drugs such as Proton Pump Inhibitors, antibiotics, and NSAI-D. This is likely one of the first cases of AIN seen with PrOD. Although his urine was bland, the elevated urine and peripheral eosinophils combined with temporal relationship of therapy makes AIN the most likely diagnosis. With renal improvement to baseline after stopping PrOD a biopsy was not performed nor was he treated with steroids. After renal recovery, he was successfully treated with ledipasvir/sofosbuvir without complications.

PUB566

Symptomatic Hypermagnesemia in Normal Kidney Function with Colonic Cleansing Agent Yoo Jin Lee, Yang Wook Kim, Bongsoo Park, Sihyung Park. Internal Medicine, Haemaeundae Paik Hospital, Busan, Republic of Korea.

Introduction: Hypermagnesemia is an uncommon clinical situation if the intragastric magnesium administration and decreased renal function do not exist. Most of reported cases of hypermagnesemia were related with laxative abuse and impaired renal function. Magnesium containing bowel cleansing agents are widely used before colonoscopy without specific complications. However, we experienced a symptomatic hypermagnesemia with normal renal function after using bowel cleansing agent.

Case Description: A 74-year-old man with normal renal function complained about lethargy and motor weakness after taking bowel cleansing agent containing 14 gram of magnesium before colonoscopy due to hematochezia. His magnesium level was 3.52 mEq/L. Hypermagnesemia is caused by increased gut absorption of magnesium due to organic obstruction or decreased renal function. We did not find any plausible cause of hypermagnesemia. He was treated with bowel enema and intravenous calcium. As magnesium levels declined, his general medical condition improved and his electrocardiogram changes were normalized.

Discussion: The present case suggests that severe hypermagnesemia can occur in the absence of pre-existing renal dysfunction with gastrointestinal diseases. We should be cautious in prescribing drug for colonoscopy if the colonic obstruction is suspected.

PUB567

Bile Cast Nephropathy: A Potential Cause of Acute Kidney Injury in Hyperbilirubinemia Mitchell Pitlick, Lisa M. Antes, Prerna Rastogi. Univ of Iowa, Iowa City, IA.

Introduction: Acute kidney injury (AKI) in the setting of liver disease is frequently a functional, hemodynamically mediated injury. However, studies have proposed that bile casts can cause tubular injury through obstructive and direct toxic effects, a pathologic entity recently referred to as bile cast nephropathy. We present two cases of patients who developed AKI in the setting of hyperbilirubinemia, both of whom showed bile casts on kidney biopsy.

Case Description: Case 1: 37 y/o male admitted to the hospital with altered mental status and diffuse jaundice. Labs: BUN 38 mg/dL, creatinine 3.8 mg/dL, total bilirubin 27.9 mg/dL, AST 166 U/L, ALT 166 U/L, GGT 1044 U/L. U/A: 2+ bilirubin, urobilinogen, and granular casts. Aggressive treatment for alcoholic hepatitis was started with prednisolone. His creatinine peaked at 11.1 mg/dl on day 9. Kidney biopsy showed orange-brown casts in proximal tubules. He required transient dialysis. His creatinine and bilirubin trended down. He was discharged on day 34.

Case Description: Case 2: 87 y/o male admitted to the hospital with progressive jaundice and pruritus, on Augmentin for an ear infection. Labs: BUN 29 mg/dL, creatinine 15.4 g/dl, total bilirubin 27.9 mg/dL, direct bilirubin 17.7 mg/dL, AST 36 U/L, ALT 37 U/L, ALP 349 U/L. He was treated supportively for drug-induced liver injury. Creatinine and bilirubin peaked at 1.2 mg/dL and 73,000 U/L on day 14. UA: 2+ bilirubin, urobilinogen, and granular casts. Kidney biopsy showed yellow-green casts in proximal tubules. His creatinine and bilirubin trended down without aggressive therapy or dialysis. He was discharged on day 18.

Discussion: Bile cast nephropathy is an important pathologic entity that may account for renal dysfunction in some patients with liver disease. As reported in some cases this is associated with severe elevations in bilirubin, as in our cases, and improving renal function with improvement in the cholestasis.

PUB568

Salicylate Toxicity Can Cause Rhabdomyolysis and Sepsis Like Syndrome-A Case Report Anjushree Kumar, Pooja Budhiraj. Nephrology, Kansas Univ Medical Center, Kansas City, KS.

Introduction: Rhabdomyolysis is characterized by myocyte membrane rupture with release of intracellular contents which include creatine phosphokinase, lactate dehydrogenase, aldolase, myoglobin, purines, potassium and phosphates. We describe a case where patient had rhabdomyolysis and sepsis like syndrome from salicylate.

Case Description: A 41 year old female transferred from a local medical history was brought to emergency room because of altered mental status.She was febrile of 102 F, tachycardia of 121, tachypneic at 32 and hypotensive with blood pressure of 70/50. She was intubated for airway protection and started on pressors and antibiotics. Laboratory on presentation, Patient was started on hemodialysis within few hours of admission for salicylate toxicity. After 1 hour of completion of hemodialysis, salicylate level decreased to 13 and then to 8.4 mg/dL of hospitalization. Patient developed oliguric acute kidney injury on D2 with elevated CPK. She was started on hemodialysis three times/week and CPK decreased to below 5,000 on D6. Patient was off pressors on D2 and all cultures were negative. Patient was discharged with twice weekly hemodialysis as outpatient. Her kidney function recovered in about 4 weeks with no further need of hemodialysis.

Discussion: The exact mechanisms by which salicylates cause muscle necrosis is unknown. But, it is thought that uncoupling of oxidative phosphorylation by salicylates leads to increase heat production which enhance permeability of muscle enzymes into circulation. Also Salicylates suppress cyclo-oxygenase pathway and lead to breakdown of arachidonic acid via lipoxigenase pathway leading to formation of leukotrienes, which has muscle damaging effects. Salicylate toxicity should be considered as cause of rhabdomyolysis and differential diagnosis of septic shock especially in patients who have no obvious source of infection.

PUB569

Polymavirus Nephropathy in Native Kidneys of an Immunocompetent Patient Yoo Jin Lee, Yang Wook Kim, Bongsoo Park, Sihyung Park. Internal Medicine, Haeundae Paik Hospital, Busan, Republic of Korea.

Introduction: Polymavirus nephropathy has emerged as an important cause of graft loss in kidney transplant recipients. Polymavirus rarely affects the native kidneys of an immunocompetent individual. Until now, polymavirus nephropathy in native kidneys of an immunocompetent individual has not been reported, as far as we know.

Case Description: A 73 year old male with a remote history of chronic kidney disease came to be evaluated for the cause of azotemia. He was a hepatitis B carrier and had not been treated for hepatitis B. Serum creatinine was 2.85 mg/dL. His urinalysis revealed red blood cells, 0–2/high...
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are desirably performed.

underlying dangers to this kind of procedure. We think this is important information for

more and more young females to opt for this procedure. What are not depicted are the

dose prednisone 20 mg to 40 mg per day. Since being on a higher dose of prednisone, her

increasing from 8.2mg/dl to 10.5mg/dl. She presented once with lethargy and creatinine

nephritis. But over the past few months, she started to develop hypercalcemia with calcium

has been followed in our renal clinic for few years and currently in remission for lupus

hospitalizations due to dehydration and hypercalcemia over the past few months. She

continued treatment of his infection, his clinical symptoms improved and he was discharged

Discussion:

Case Description: A 36 year old lady with history of hypertension, systemic

lupus erythematous, class IV and V lupus nephritis, CKD stage 3, who had multiple

hospitalizations due to dehydration and hypercalcemia over the past few months. She

has been followed in our renal clinic for few years and currently in remission for lupus

nephritis. But over the past few months, she started to develop hypercalcemia with calcium

increasing from 8.2mg/dl to 10.5mg/dl. She presented once with lethargy and creatinine of

2.5 when her serum calcium was 14. Work up for the hypercalcemia showed that 1.25

Vitamin D was 90. Of note, she had silicone injection to her buttocks 1.5 years ago. On

imaging, her subcutaneous fat of the buttocks and hips demonstrate extensive abnormality

including calcifications and nodular soft tissue densities. She was then started on a higher
dose prednisone 20 mg to 40 mg per day. Since being on a higher dose of prednisone, her

serum calcium levels subsequently improved to 9.4mg/dl and she is been in this for more than

1 year now.

Discussion: While the social media highlights this cosmetic effect, it encourages more and more young females to opt for this procedure. What are not depicted are the underlying dangers to this kind of procedure. We think this is important information for not only the nephrology but entire medical community as more and more of these procedures are desirably performed.

Hypercalcemia due to Calcitriol Secondary to Silicone Injection Butt Augmentation

Pawar

Introduction: Buttock augmentation and implants are the fastest growing type of cosmetic surgery in 2015, according to American Society of Plastic Surgery with close to 15,000 procedure performed in U.S. only. While the incidence of this is rising, more and more complications are now been uncovered secondary to this type of procedure. One of the rare but lethal complication is severe hypercalcemia mediated by excessive calcitriol (1, 25 Vitamin D) production from the granulomatous inflammation. We are reporting a very rare and interesting case of such entity.

Case Description: A 36 year old lady with history of hypertension, systemic lupus erythematous, class IV and V lupus nephritis, CKD stage 3, who had multiple hospitalizations due to dehydration and hypercalcemia over the past few months. She has been followed in our renal clinic for few years and currently in remission for lupus nephritis. But over the past few months, she started to develop hypercalcemia with calcium increasing from 8.2mg/dl to 10.5mg/dl. She presented once with lethargy and creatinine of 2.5 when her serum calcium was 14. Work up for the hypercalcemia showed that 1.25 Vitamin D was 90. Of note, she had silicone injection to her buttocks 1.5 years ago. On imaging, her subcutaneous fat of the buttocks and hips demonstrate extensive abnormality including calcifications and nodular soft tissue densities. She was then started on a higher dose prednisone 20 mg to 40 mg per day. Since being on a higher dose of prednisone, her serum calcium levels subsequently improved to 9.4mg/dl and she is been in this for more than 1 year now.

Discussion: While the social media highlights this cosmetic effect, it encourages more and more young females to opt for this procedure. What are not depicted are the underlying dangers to this kind of procedure. We think this is important information for not only the nephrology but entire medical community as more and more of these procedures are desirably performed.

Monoclonal Gammopathy of Renal Significance in Light Chain Deposition Disease

Gheorghe Ciprian Cazan,1 Ketki K. Tendulkar.1 Nephrology, UNMC, Omaha, NE;1Nephrology, UNMC, Omaha, NE.

Introduction: Light chain deposition disease may have an indolent presentation and a high clinical suspicion is needed for an early diagnosis. We present the case with worsening kidney disease in the setting of a normal UA, SLEP, UPEP and an abnormal K/L ratio.

Case Description: 55-old Caucasian male with HTN and a baseline creatinine of 1.1 mg/dl, was referred due to an increase in serum creatinine level to 2.84 mg/dl within 8 months from his last documented baseline creatinine. He started on lisinopril 10 mg daily 2 weeks earlier and was taking meloxicam 15 mg daily for OA radiculopathy. UA was negative for proteinuria or hematuria and further investigations revealed normal urinary Pr/Cr ratio, Alb/Cr ratio and renal ultrasound. After discontinuing lisinopril and meloxicam and with better control of his blood pressure, his renal function slightly improved with creatinine nadir of 2.2 mg/dl within 6 weeks. He had a kidney biopsy that was significant for focal global glomerulosclerosis, tubular atrophy and interstitial fibrosis 70%, weak linear staining for Kappa light chain. SLEP and UPEP were normal but Serum free light chains were remarkable for Kappa 530 mg/L, Lambda 19 mg/L(ratio-27.89). Bone marrow biopsy - mild hypocellularity 10%, 5% plasma cells and 1.69 % cytoplasmatic kappa expression. It was considered as a Monoclonal Gammopathy of Renal Significance but no definite criteria were remarkable for Kappa 530 mg/L, Lambda 19 mg/L (ratio-27.89). Bone marrow biopsy - mild hypocellularity 10%, 5% plasma cells and 1.69 % cytoplasmatic kappa expression. It was considered as a Monoclonal Gammopathy of Renal Significance but no definite criteria were necessary for further treatment. He underwent active surveillance with persistent normal UA, SLEP and stable kappa lambda chain ratio for 5 months. When his GFR started to decline, repeat bone marrow biopsy - unchanged, renal biopsy - brighter staining for kappa light chain.

Discussion: Light chain deposition disease can occur in any organ but renal involvement is present in 93-100% of the cases, a high suspicion is needed if a normal UA and no other explanation. There is a strong association between hematologic response to chemotherapy and renal outcome.

Therapeutic Plasma Exchange for Acute Disseminating Encephalomyelitis following Legionnaires’ Disease

Latoya L. Brathwaite,1 Paras Dodhia,1 Charuhas V. Thakar.1,2 Dept of Nephrology and Hypertension, Univ of Cincinnati, Cincinnati, OH;1Renal Section, Cincinnati VA, Cincinnati, OH.

Introduction: Acute disseminating encephalomyelitis (ADEM) is an immune-mediated demyelinating disorder of the brain and usually occurs within 2 to 30 days after an antibiotic challenge. Neurological symptoms of Legionnaires’ disease range from headache and lethargy to encephalopathy.

Case Description: A 50-year-old male transferred to ICU from other institute with hypoxic respiratory failure secondary to legionella pneumonia. He was diagnosed with legionella pneumonia based on urine antigen and was treated with Azithromycin for 14 days. His hospital course was complicated by oliguric AKI to septic acute tubular necrosis and rhabdomyolysis and required renal replacement therapy. His creatinine increased from 1.1 mg/dl on admission to peak Cr of 4.5 mg/dl. On hospital day 16, noted to be less responsive with significant change in mental status. Exam was significant for increased tone and clonus in all 4 extremities with no response to verbal or tactile stimuli. MRI brain was notable for mixed pattern of diffusion signal involving both cerebral hemispheres and extending into basal ganglia and internal capsules. Also EEG showed an evidence of status epilepticus and was started on Levitiracetam and Fosphenytoin. In view of concern for hemorrhagic variant of ADEM, he was started on therapeutic plasma exchange (TPE) with 5% albumin. He received 5 sessions of TPE and noted to have significant improvement in neurological signs. After TPE, he was alert, awake and following commands and was moving all 4 extremities.

Discussion: Legionnaires’ disease is the systemic disease associated with Legionella infection with significant extra pulmonary manifestations including renal failure and neurological abnormalities. This case highlights successful use of TPE in management of hemorrhagic variant of ADEM.

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Underline represents presenting author.

1034A
Diagnosis Challenges in the Setting of Acute Kidney Injury and Thrombotic Microangiopathy

**Introduction:** Thrombotic Microangiopathy can present in numerous ways, including Acute Renal Failure, and has several causes including Thrombotic Thrombocytopenia Purpura, Malignant Hypertension, Diabetic Haemolytic Uremic Syndrome and the ultra-rare atypical Haemolytic Uraemic Syndrome. In our current case, eALUS allows the opportunity to treat with Eculizumab but it can be a difficult diagnosis to make, owing to a lack of tests.

**Case Description:** We report a 38 year old male presenting with headache, nausea and mild hematuria. Past medical history included hypertension for 5 years and obesity. Blood pressure at presentation was 220/110 mmHg. Biochemical tests showed a plasma creatinine of 83 μmol/L, and raised bilirubin / LDH. Haematological tests demonstrated a platelet count of 65, haemoglobin of 11.9, and a blood film with red cell fragments. ECG suggested left ventricular hypertrophy. Percutaneous renal biopsy demonstrated features consistent with a thrombotic microangiopathy, although a lack of vascular intimal thickening that would be expected with hypertensive disease. Case Description: Haemodialysis was started within 48 hours for fluid overload, whilst antihypertensive medications were introduced, resulting in an improvement in platelet count but no renal recovery. The presumed diagnosis was Thrombotic Microangiopathy resulting from Malignant Hypertension. Diurethelial Haemolytic Uremic Syndrome (HUS) was also considered, whereas ADAMTS13 testing excluded Thrombotic Thrombocytopenia Purpura. Genetic testing for eALUS was requested to exclude an underlying complement defect. This revealed a heterozygous deletion encompassing the CFH locus, extending to CH1R1, hereby producing a hybrid regulatory gene. This variant causes complement dysregulation and eALUS, the final diagnosis in this patient.

**Discussion:** Our case highlights difficulties in the diagnosis and management of Thrombotic Microangiopathy, with the need to consider eALUS. This allows treatment with Eculizumab and the opportunity for genetic screening of family members.

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Rapid and Progressive Glomerulonephritis Associated with Sweet Syndrome

**Introduction:** Rapid and Progressive Glomerulonephritis Associated with Sweet Syndrome

**Case Description:** A 42 year female presented with an erythematous lesion on the leg associated with easy bruisibility since her return from Africa, few days ago. This was followed by ulceration and inabality to ambulate due to requiring debriding and empiric antibiotics for necrotizing fasciitis. Her clinical course was complicated by non-oliguric acute kidney injury (AKI) and respiratory failure. Laboratory investigation revealed leukocytosis (24.9), anaemia (Hgb 6.7), and AKI (Scr 0.62 to 1.44). She had ANA positive, in addition to decreased complement levels with negative ds-DNA or anti-smith antibodies. Skin biopsy exhibited acute inflammatory infiltrate involving the epidermis, dermo-epidermal junction, extending to the hair follicles. Direct immunofluorescence presented fibrillary staining with anti-DNA complement 3 and anti-protein antigens in the superficial dermis, findings compatible with Sweet Syndrome. Her urinalysis was significant for hematuria with red blood cell casts and proteinuria of around 1gm/day. Patient was hypotensive and unstable for renal biopsy. In addition to antibiotics, patient also received pulse dose of steroids along with immunosuppressive therapy with prednisone 100mg. After two weeks, the patient experienced normalization of her creatinine and resolution of proteinuria.

**Discussion:** Sweet Syndrome, also referred to as acute febrile neutrophilic dermatosis, is a rare disease process affecting predominantly females aged 30-50 years of age. Sweet Syndrome can manifest as kidney disease, specifically mesangiocapillary glomerulonephritis including urinalysis abnormalities (hematuria and proteinuria). Systemic corticosteroids remain the gold standard of treatment. In our patient, constitutional symptoms resolved within 72 hours, followed by clearance of skin lesions in 3-9 days. Corticosteroids were gradually tapered over the course of 2-6 weeks. Clinical and diagnostic acuity along with rapid implementation of treatment remain the mainstay of approaching a patient with Sweet Syndrome for favorable results.

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Impact of Hypotonic Fluid on Prevalence of Sodium Disturbances in Children Hospitalized for Treatment of Surgical Conditions

**Introduction:** Pediatric surgical patients are at risk of developing hyponatremia, which can lead to cerebral edema, seizures and death, making fluid management in pediatric surgical patients an important topic. The aim of this study is to evaluate the differences in the prevalence of sodium disturbances in pediatric surgical patients between hypotonic (HT) and isotonic (IT) fluid were included. Hyponatremia was defined by: mild if Na 130-135 mEq/L, moderate if Na 125-129 mEq/L and severe if <125 mEq/L. Age, sex, length of HT fluid administration and length of hospital stay (LOS) for HT and IT patients was studied. Comparisons were made using Chi-square test and t-tests for unpaired samples.

**Results:** 16 of 68 patients (23.5%) with an average age of 6.0±0.6 y/o had mild hyponatremia. Average sodium level for the IN group was 132±0.4 mEq/L, and the NN group had an average of 138±0.3 mEq/L. No cases of moderate or severe hyponatremia were noted in either groups and no cases of hyponatremia occurred. Out of 16 IN patients, 5 were female (31.3%) and 11 were male (68.8%) with no statistical significance (p=0.5). The IN group had a lower average age (6±0.6 years) than the NN group (8±0.7 years), with no statistical difference in average age (p=0.09). The LOS for the IN group was longer (5.3±0.6 days) than the NN group (4.6±0.2 days). The IN group had a higher incidence of HT fluid administration for the IN group was longer (3.6±0.5 days) than the NN group (2.5±0.2 days), with statistical significance (p=0.01).

**Conclusions:** In our study, mild hyponatremia was prevalent at an overall rate of 23.5% in pediatric surgical patients. The prevalence of hyponatremia was higher in males compared to females. The IN group also had a lower average age than the NN group. Hyponatremia was associated with an increased length of HT fluid administration and longer LOS.

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

Underline represents presenting author.
Conclusions: M/S HN in cancer patients is largely untreated. While some form of end of life or comfort care frequently accompanies M/S HN, the majority of patients in our study lived in excess of three months. The potential exists to improve patient care and outcomes by actively treating HN.


PUB580
Cost Analysis of Treatment of Hyperkalemia with Standard Therapy Compared to the Cation Exchanger Patiromer Maria T. Story,1 Prakash M. Nadkarni,1,2 Bradley S. Dixon,1,2,3 Larna A. Noureddine,1,5 Internal Medicine, Univ of Iowa Hospitals and Clinics, Iowa City, IA; 1Inst for Clinical and Translational Science, Univ of Iowa Hospitals and Clinics, Iowa City, IA; 2Nephrology, Univ of Iowa Hospitals and Clinics, Iowa City, IA; 3VAMC, Iowa City, IA;

Background: Current treatment (tx) of hyperkalemia (HK) is time consuming and costly. Here, we analyzed how the cost for treating HK might change with the use of patiromer.

Methods: We performed a single center, retrospective analysis of current tx costs for HK versus projected costs of tx with patiromer. Adult patients with a serum potassium (K) ≥6.0-6.4 mEq/L (a range used in published studies of patiromer) were identified from the electronic medical record. The cost for medications, emergency department (ED) visits, hospitalizations, dialysis, and physician charges were obtained from hospital pharmacy and accounting. All costs for outpatient encounters for hospitalizations due to fluid overload are common in hemodialysis (HD) patients. We aimed to utilize clinical data sources to develop and test predictive models (PMs) that can identify HD patients with a high probability of multiple fluid overload related hospitalizations in the next 12 months.

Methods: We analyzed patient data from the Fresenius Medical Care Data Warehouse from April 2013 to Mar 2015. Various PMs were developed for prediction of ≥3 fluid overload related hospital admissions in the next 12 months, and included the generalized linear model, partitioning and regression trees, artificial neural networks, and generalized additive model (GAM). In all, 11,062 of cleaned clinical records on 33 variables was utilized for development of the PMs. Variables included data on patients’ history of fluid overload related hospital admissions, demographics, morbidities, laboratories, and other parameters. Of the entire study dataset, 70% was randomly selected for PM development and prediction accuracy of the PMs was tested with the remaining 30%. The area under the receiver operating characteristic curve (AUC), sensitivities and specificities were investigated to determine the PMs’ performance. The sensitivities and specificities were derived by taking the maximum of the Youden index to determine the optimal cutoff value.

Results: The GAM had the highest performance, with an AUC of 0.86 (95% CIs 0.83-0.90), sensitivity of 73% (95% CIs 65-81%), and specificity of 83% (95% CIs 82-84%) for the PM utilizing a 30% test dataset.

Conclusions: Testing of the developed PMs demonstrates that predictive analytics utilizing clinical data can assist in identifying patients with a high probability for being admitted to the hospital for fluid overload related complications.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB583
Can Urine pH Predict Plasma pH in ICU Patients with Abnormal Plasma Bicarbonate Levels? Navneet Kaur, Jesse M. Goldman. Internal Medicine, Div of Nephrology, Drexel Univ College of Medicine, Philadelphia, PA.

Background: Physicians are often called upon to interpret the acid-base status of critically ill patients demonstrating abnormal venous plasma bicarbonate values. It is hypothesized that when plasma bicarbonate concentration is either above or below normal, an arterial blood gas is absolutely necessary to obtain a plasma pH and calculate the acid-base condition of an individual patient. Since the kidney is a major sensor and
regulator in maintaining acid-base balance, we wondered whether urine pH might reliably predict arterial pH and thereby (in the right circumstances) correlate with arterial pH, avoiding need for an arterial blood gas specimen.

Methods: We performed retrospective chart review on 181 patients admitted to intensive care units at our institution from September 2013 to September 2014 to identify patients with a urine pH and an arterial blood gas performed within 24 hours of each other. Of the 181 patients screened, 41 patients met this criterion. We reviewed serum chemistries, urinalyses and blood gases to assess for correlation between urine and plasma pH. We excluded patients with normal serum bicarbonate and patients receiving renal replacement therapy.

Results: Among the 41 patients, only 10 patients (24%) showed successful correlation between urine and serum pH. No correlation was noted in the remaining 31 patients. Within our cohort of 41 patients, 10 had cirrhosis, 5 had urinary infections, 4 with gastrointestinal bleeding, 7 were ventilator dependent.

Conclusions: On our retrospective chart review of 41 critically ill patients, only 11 patients showed correlation between the urine and blood pH and 31 patients did not demonstrate a useful correlation. Among patients admitted in the intensive care units at our institution, there is a high frequency of sepsis and acute renal failure. In the setting of acute renal failure, there is poor function of renal tubules, not allowing appropriate compensation by the kidney and inability to maintain the acid base status as predicted. Our research supports the need for obtaining a blood pH specimen to interpret the acid-base status in critically ill patients with abnormal plasma bicarbonate values.

PUB584

Not Serum Potassium Level, but Serum Creatinine Level Has More Impact on Clinical Judgement for Emergent Dialysis for Severe Hyperkalemia

Background: Hyperkalemia is a relatively common problem in hospitalized patients. However, management of hyperkalemia has been traditionally based on the physician’s judgement, or institutional protocols, and treatment pattern for hyperkalemia is not well studied. The aim of the present study is to determine overall practice pattern of treatments for severe hyperkalemia, and clarify the most influential factor for emergent HD in hospitalized patients.

Methods: We analyzed clinical and biochemical parameters of all hyperkalemic patients admitted to St.Luke’s Int Hosp in Tokyo over a 10-year period (2006-2016). Hyperkalemia is defined as serum K+>6.5 mEq/L anytime in hospitalization. Dialysis patients and pediatric patients were excluded.

Results: There were 883 patients who met the criteria for this study. Serum K+ ranged from 6.5 to 17 mEq/L. The mean serum K+ was 7.1±0.9 (mean±S.D.) mEq/L. The mean age was 69.1±15.6 yr, the male ratio was 56.3%, the mean serum creatinine level was 2.8±3.1 mg/dl, and the average urine output per day was 820±1034 ml. Insulin plus dextrose was the most commonly used emergent therapy (41.3%), followed by calcium gluconate (29.8%), sodium bicarbonate (22.7%), loop diuretics (12%), albuterol (1.8%), and sodium polystyrene sulfonate (1.5%) on the day the hyperkalemia was recorded. 89.9% of patients underwent emergent HD. On univariate analysis, patients treated with emergent HD had significantly higher serum creatinine than patients without emergent HD (8.0±4.9 vs 2.8±3.1, P<0.01). Multivariate logistic regression analysis identified high serum creatinine to be independently associated with emergent HD (odds ratio=1.31, P<0.01). No other higher serum K+ nor higher urine output was associated with emergent HD.

Conclusions: Emergent treatment for severe hyperkalemia in hospitalized patients was performed successfully. Of interest, emergent HD is prescribed more frequently for the patients with worse kidney function. This implies that not serum K+ level, but serum creatinine level has more impact on clinical judgement for emergent HD.

PUB585

Evidence-Based Management of Hyperkalemia: A Systematic Review

Background: Hyperkalemia (HK), defined as elevated serum potassium levels of >5.0 mmol/L, is a potentially life-threatening condition that can occur in patients with impaired renal function. To support evidence-based treatment, we conducted a systematic literature review (SLR) to identify studies on the efficacy or safety of interventions for managing HK.

Methods: We searched MEDLINE, EMBASE, CDSR, CENTRAL and DARE for RCTs, non-RCTs or observational studies investigating the efficacy or safety of pharmacological or non-pharmacological interventions for the treatment of prevention of HK.

Results: Database searches identified 848 unique records of which 151 were selected for full-text review. 126 publications from database searches and 30 additional publications from hand-searches were included for a total of 21 RCTs, 26 non-interventional non-RCTs and 34 observational studies. Of these, 16 RCTs, 20 intervention non-RCTs and 10 observational studies reported results in patients with renal dysfunction. Key interventions investigated in the RCTs across all patient populations included the newer treatments sodium zirconium sulfonate (SPS/CPS; 2 RCTs) and combinations of temporizing agents (eg. insulin, salbutamol; 6 RCTs). RCTs of key interventions on renal dysfunction patients included zinc and patrimor (2 RCTs each), SPS/CPS (2 RCTs) and temporizing agents (5 RCTs). Among the 126 publications, 30 were identified, especially in high-risk patients with renal dysfunction. This lack of evidence is associated with unclear treatment recommendations for renal patients with HK.

Conclusion: The majority of patients with HK are treated with combination therapies, including saturated solutions, intravenous insulin and dopamine. However, there is a lack of evidence-based treatment recommendations for renal patients with HK. Further studies are required to determine the most effective treatment options for these patients.

Funding: Pharmaceutical Company Support - AstraZeneca Ltd

PUB586

Identification of Potential Pediatric Hyponatremia Cases in Three Large United States Patient Databases

Background: Hyponatremia (HN), defined as a plasma sodium concentration less than 135 mmol/L, is one of the most commonly encountered electrolyte disorders; however clinically relevant hyponatremia requiring medical intervention is less common. Clinical trials are ongoing to evaluate pharmaceutical treatments for sodium correction among pediatric patients and large retrospective patient databases may be useful in evaluating the feasibility of conducting such trials. Our objective was to estimate the occurrence of pediatric HN patients using retrospective patient databases.

Methods: Three large US databases (OptumClininformatics and Truven MarketScan Commercial claims data from 2010-2014, and the Humedica Electronic Health Records database from 2010-2013 covering approximately 12, 43, and 12 million members, respectively) were used to identify potential pediatric HN patients. Patients receiving ≥1 dose of tolvaptan with International Classification of Diseases, 9th Edition (ICD-9) code of 276.1 (hyponatremia, hypo-osmolality) in primary or secondary diagnosis fields were identified as potential HN cases. Among patients in the Humedica database, serum sodium values of <130 mmol/L in the inpatient or outpatient setting were used in addition to ICD-9 codes to identify potential cases with HN.

Results: On our retrospective chart review of 41 critically ill patients, only 11 patients showed correlation between the urine and blood pH and 31 patients did not demonstrate a useful correlation. Among patients admitted in the intensive care units at our institution, there is a high frequency of sepsis and acute renal failure. In the setting of acute renal failure, there is poor function of renal tubules, not allowing appropriate compensation by the kidney and inability to maintain the acid base status as predicted. Our research supports the need for obtaining a blood pH specimen to interpret the acid-base status in critically ill patients with abnormal plasma bicarbonate values.

PUB587

Utilization of Tolvaptan and Associated Budget Impact among Hospitalized Heart Failure Patients with Hyponatremia

Background: Hyponatremia (HN), defined as plasma sodium concentration less than 135 mmol/L, is a commonly encountered electrolyte disorder in hospitals. Given the increasing pressures for cost containment, hospitals aim to consider the budget impact of treatments used in the inpatient setting during formulary policy-making. Fluid restriction and treatments such as tolvaptan (a vasopressin V2-receptor antagonist) are used for the treatment of clinically significant hyponatremia and euvolemic HN. Our objective was to describe utilization patterns of tolvaptan and evaluate the budget impact among hospitalized heart failure (HF) patients with HN in the real-world inpatient setting.

Methods: A retrospective database analysis was conducted using the Premier inpatient database representing 700 US hospitals from 1/1/2011 through 12/31/2014 to identify patients with a discharge diagnosis of HN (ICD-9 276.xx) and a secondary diagnosis of HF (ICD-9 276.1x). Utilization patterns of tolvaptan and costs incurred were analyzed using descriptive statistics. Budget impact of tolvaptan use was presented per HF-related inpatient visit with codes for HN.

Results: A total of 23,842 inpatient visits were identified with a discharge diagnosis of HN and codes for HF. Among these visits, 935 or 3.9% visits had evidence of tolvaptan use. Inpatient visits with tolvaptan use had a mean length of stay of 11.5 days (median 9) and the average cost of inpatient care for these visits included intensive care unit (ICU) services over the duration of the entire hospitalization. Inpatient stays with HF and HN with evidence of tolvaptan use cost an average of $26,955 (median $14,075) whereas mean costs related to tolvaptan use were $981 (median $480). The budget impact associated with tolvaptan use was $38.4 per HF-related inpatient visit with secondary diagnosis codes for HN (Mean cost of tolvaptan treatment per visit*Number of visits with tolvaptan use/number of HF-related inpatient visits with codes for HN).

Conclusions: Tolvaptan utilization in the inpatient setting is associated with a marginal budget impact in terms of all HF-related hospital visits with codes for HN.

Descriptive Analysis of Patients Receiving Tolvaptan in the Inpatient Setting


Background: Hyponatremia (HN), defined as a plasma sodium concentration less than 135 mmol/L, is one of the most commonly encountered electrolyte disorders in hospitals. Fluid restriction and treatments such as tolvaptan (a vasopressin V2-receptor antagonist) are used for correction of clinically significant hyponatremia and enuretic HN. Lack of consistent guidelines for the management of HN result in high variability in treatment patterns. Our objective was to conduct a descriptive analysis of patients receiving tolvaptan in the inpatient setting.

Methods: Analysis was conducted using the Premier Inpatient database representing 706 United States hospitals from 1/1/2011 through 12/31/2014. Inpatient visits with use of tolvaptan were described in terms of patient demographic and clinical characteristics, length of inpatient stay, occurrence of HN (ICD-9 276.1x), heart failure (ICD-9 428.x, HF), syndrome of inappropriate antidiuretic hormone secretion (ICD-9 253.8x, SIADH), and other commonly occurring discharge diagnoses.

Results: A total of 11,744 inpatient stays were identified with evidence of tolvaptan use – patients had a mean age of 68 years (median 69 years) and 45.7% male. Among these inpatient visits, 6,647 (56.5%) had ICD-9 codes for HN, 4,063 (34.5%) had codes for HF, and 4,704 (40.0%) had codes for SIADH in any diagnosis field. In terms of discharge diagnosis, the most commonly codes were for SIADH (15.4%), 9.9% for HN and 9.8% of patients had HF. Septicemia (2.5%), pneumonia (2.4%), and rehabilitation procedures–non-specific (2.3%) were other commonly occurring discharge diagnosis in patients prescribed tolvaptan. Admission weight of patients receiving tolvaptan was 10.6 (median 81 days).

Conclusions: Tolvaptan use was associated with varying diagnosis codes with the majority relating to HN, SIADH, and HF. Discharge diagnosis for those prescribed tolvaptan varied widely potentially reflecting the variability in the use of treatment in the inpatient setting or low rates of coding HN at discharge.

Funding: Pharmaceutical Company Support - Otuka PDC

Hyponatremia Rarely Associated with Preeclampsia

Tokameh Entezari, Internal Medicine, 1, Reno, NV.

Background: Introduction:Severe hyponatremia is a rare complication of preeclampsia and only handful cases have been reported in the literature. Early diagnosis and treatment are vital to reduce maternal and fetal morbidity and mortality.

Case: A 25 years old primiparous woman 27/5 weeks pregnant admitted with new onset of dyspnea on exertion, lower extremity edema and labile hypertension. No prior diagnosis of preeclampsia and no known medical history.

Initial serum sodium was 127 with normal TSH and cortisol level. Total urine protein was up to 6 grams in 24 hours and urine Na was 23. BP was 160/80 and improved with escalating doses of labetalol and nifedipine. Fluid restriction was attempted with limited success initially improving sodium to 130 and later dropped down to 125. At this time, she was 28 weeks and received betamethasone for accelerating fetal lung maturation and 4,704 (40.0%) had codes for SIADH in any diagnosis field. In terms of discharge diagnosis, the most commonly codes were for SIADH (15.4%), 9.9% for HN and 9.8% of patients had HF. Septicemia (2.5%), pneumonia (2.4%), and rehabilitation procedures–non-specific (2.3%) were other commonly occurring discharge diagnosis in patients prescribed tolvaptan. Admission weight of patients receiving tolvaptan was 10.6 (median 81 days).

Conclusions: Tolvaptan use was associated with varying diagnosis codes with the majority relating to HN, SIADH, and HF. Discharge diagnosis for those prescribed tolvaptan varied widely potentially reflecting the variability in the use of treatment in the inpatient setting or low rates of coding HN at discharge.

Funding: Pharmaceutical Company Support - Otuka PDC

Clinical Features and Extracorporeal Management of Reported Acetylsalicylic Acid Exposures in the United States

Sara Tavernier Burgard, Meghan A. Jobson, Michael Emmett, William Franklin Pendergraft. 2, 3 UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC; 1UNC School of Medicine, Chapel Hill, NC; 2Nephrology, Baylor Univ Medical Center, Dallas, TX.

Background: Acetylsalicylic acid (ASA, aspirin) is a common analgesic ingredient found in most household medicine cabinets in the US. It has been an important cause of intentional and unintentional poisonings since its discovery. Toxicity can result in several mechanisms, including acid-base, renal, cardiac, and central nervous system depression. The objectives of this study were to identify differences in intentional and unintentional poisonings, to identify features unique to cases resulting in death, and to review trends in extracorporeal management of poisonings.

Methods: We used the National Poison Data System to perform a retrospective analysis of reported cases of ASA exposures alone from January 2006 to December 2014. Outcomes were assessed by case intentionality and severity.

Results: There were 85,470 cases of ASA ingestions resulting in 165 deaths. Individuals more likely to experience major effects or death were older and male, and presented with more severe symptoms requiring higher levels of care. Patients who were intubated and mechanically ventilated were more likely to die.

Conclusions: Deaths due to ASA exposure are rare. Of 165 patients who died, only 27% received hemodialysis which continues to be underutilized in management of severe overdoses resulting in major effects or death. Analysis of geographical differences revealed a paucity of dialytic intervention in west south central region of the United States 21% as compared to other regions 27-43% in those with major effects or who died. The decreased utilization of dialysis did not correlate with fewer nephrologists. Standardized management recommendations are made through state or regional poison control centers, thus differences in hemodialysis utilization are unlikely due to differences in management but may be due to underrecognition of severe acetylsalicylic acid poisoning. These data suggest that these regions might benefit from increased public health efforts to limit poisonings and education about prompt management of severe poisoning.

Funding: NIDDK Support

Fabry Disease Screening, Report of a Mexican Hemodialysis Center


Background: Fabry disease (FD) is secondary to a mutation of the gene encoding the enzyme α-galactosidase (α-GAL A) located on the chromosomes X. This genetic disorder is cause of chronic kidney disease. The purpose of the study was to determine the prevalence of FD patients of a hemodialysis center in Mexico.

Methods: Men and women over 16 years diagnosed with CKD in hemodialysis (HD) were included. FD patients with previously diagnosed discarded. December 2015 to March 2016 after the patients signed consent on information, determination of enzyme activity of α-GAL A was performed using fluorescence in dried blood filter for men; for cases with α-GAL activity was decreased to levels determined GB3 molecular analysis also search for mutations in the gene encoding FD. For women only we made the search for gene mutations. Descriptive statistics were performed with absolute frequencies and inferential; SPSS version 22 was used.

Results: 324 patients were evaluated. A mutation in any woman diagnosed. 98 males had levels of enzyme activity of α-GAL A decreased, all GB3 with normal levels. 3 patients positive for gene sequencing GAL were detected. The median age of patients was positive 36 years with a median time of diagnosis of CKD 5 years. Prior to the diagnosis of FD in this study, recorded the cause of CKD was unknown in 2 patients, 1 secondary to diabetic nephropathy. The average level of α-GAL A and Lyso-GB3 was 0.93 ± 1.01 mmol/l/h and 1.43 ± 0.19 mg/l, respectively in patients with FD mutation. There were differences between patients with normal α-GAL A levels when compared with patients who had diminished α-GAL A with and without mutation levels.

Conclusions: This is the first report of the prevalence of FD in HD patients in Mexico. We found a prevalence of 0.9%, being higher than that reported in published studies (0.2-0.3%). Regarding the decline in activity levels of α-GAL A mutation found in this series, doubt about this series unrelated to factor was found. These cutoff levels may not be standardized in our population, so it requires validation of this methodology in Mexican population.

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

Association between the Regulatory Polymorphisms of Organic Anion Transporter 1 (OAT1) and Chronic Kidney Disease

Chiao-Yin Sun, NTU, NTU, Taipei, Taiwan.

Background: Organic anion transporter 1 (OAT1, SLC22A6) was a prototype of OATs, and played central roles in the renal secretion of organic anions. Accumulated evidences indicated that OAT1 had critical roles in kidney injury by mediating organic anionic toxins accumulation in kidney. This study aimed to analyze the 5 regulatory region polymorphisms (rSNP) in human OAT1, and possible associations with chronic kidney disease (CKD) clinically.

Methods: A case-control study including normal subjects and CKD patients with age and sex match was designed (n=162 for each group). In vitro studies were performed to define the possible mechanisms of rSNP of OAT1 on the OAT1 expression.

Results: Results of direct sequencing (-1 to -1196 region) showed that CKD patients had higher frequency of -475 rSNP (T>T-G) than normal subjects (14/162 vs. 2/162).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Luciferase activity assay resulted showed that OAT1 promoter with -475 rSNP had higher promoter efficiency than wild type significantly. ChiP and LC/MS/MS analysis results showed that there were 26 proteins up-regulated and 74 proteins down-regulated by -475 mutant. Hepatoma-derived growth factor (HDGF), a transcription repressor, was noted among these down-regulated protein targets. The Southern-Western blot assay also revealed that -475 mutant had decreased HDGF binding than wild type. HDGF over expression significantly attenuated OAT1 expression in renal tubular cells.

**Conclusions:** Our study results suggested that OAT1 rSNP might associate with chronic kidney disease clinically. The renal tubular cells with -475 rSNP had increased OAT1 expression, which results in increasing organic anion toxin transportation into cells. Cellular accumulation of organic anion toxins caused cytotoxicity, and resulted in chronic kidney injury. 

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

**PUB593**

*Serum lncRNA Expression Profile of Type IV Lupus Nephritis Patients Quiling Fan, Dept of Nephrology, The First Hospital of China Medical Univ.*

**Background:** To evaluate the specificity of expression patterns of circulating long noncoding RNAs(lncRNAs) in class IV lupus nephritis (LN).

**Methods:** Total RNAs were purified from plasma of 3 different LN patients, 3 SLE patients, and 3 healthy controls. We screened lncRNAs expression profiles though the Arraystar Human IncRNA Microarray version 3.0.

**Results:** 8822 IncRNAs, 9886 mRNA were statistically significantly differentially expressed in LN (p<0.05). compared with the control healthy patients, 4603 IncRNAs , 4581 mRNAs were increased, 8407 IncRNAs , 6403 mRNAs were decreased in LN; 593 IncRNAs, 375 mRNAs were increased, 462lncRNAs, 200 mRNAs were decreased in SLE; compared with SLE, 6462 IncRNAs, 4523 mRNAs in LN were increased, 8969 IncRNAs, 6766 mRNAs were decreased in LN. Among healthy controls, 56 IncRNAs, 56 mRNAs were progressively reduced.

**Conclusions:** Gene ontology results suggested that the primary biological processes of these genes were involved in regulation of immune responses, cytokine production, cell differentiation, proliferation, apoptosis, cell cycle, cell adhesion, and metabolic process. IncRNA TCONS_00019182 locate in chr11p15.5, have significantly differentially expressed in LN vs SLE and SLE vs N, may play a role in development of SLE.

**PUB594**

*Is It Time to Re-Visit Aluminum Binders in Our Elderly Patients? Jack Rubin, Los Alamitos, CA.*

**Background:** Patients ingest phosphate binders to mitigate metabolic bone and atherosclerotic disease. In the U.S. the most potent of least expensive agents (1)(Daugirdas JT et al, Semin Dial 2011 24(1):41-49) were marginalized due to concerns of aluminum toxicity. All the products substituted were more expensive. Was this a mistake? In patients with limited life expectancy, aggressive phosphorus binders control may lead to increased costs and pill burden without improvement in survival.

**Methods:** We identified our hemodialysis patients 65 and older treated at 7 units - 5 DaVita, 1 Fresenius and an independent. Daily phosphate binder pill burden was counted using their April 2016 medication list. Costs of medications were calculated using prices listed in the Medical Letter 1483. We assumed phosphate binder potency to be as elaborated in ref 1. We estimated survival in "years to live" for each patient by age cohort as described in the USRDS 2013 report (Vol2, table 6.4). The potential decrease in pill burden using an aluminum binder was estimated by dividing the total number of pills standardized to the potency to calcium acetate by 1.5.

**Results:** There were 47 patients made up of 27 male and 20 female patients. The mean age (yrs) ± standard deviation (SD) was 75.7 ± 8.1, median 74. The mean calcium was 9.2 mg % ± SD 0.8, median 9.3. The mean phosphorus was 5.7 mg % ± (SD) 5.9, median 4.9. The mean albumin was 3.6 g % ± (SD) 0.5, median 3.7. The estimated survival was 3.6 years (yrs) ± (SD) 0.9, median 3.8. There were 6 patients not using a phosphate binder. There were 18 patients exclusively using Fosrenol (Calcium Acetate), 5 using Phoslo plus Renvela (Sevelamer), 15 exclusively Renvela, 1 exclusively using Fosrenol (Lanthanum carbonate), 2 exclusively Auryxia (Ferric citrate) and 1 using 3 agents including Auryxia. The mean pill burden among those taking binders was 7.± (SD) 4, median 6 and the estimated cost/ dose $31 ± (SD) 30, median 17. Aluminum hydroxide substitution was calculated to yield a pill burden of 5 ± (SD) 4, median 5, with the cost under $2 a day.

**Conclusions:** When treating patients with limited life expectancy wherein development of aluminum toxicity is a non issue, if phosphate control is deemed helpful, using aluminum binders to decrease pill burden and costs seems reasonable.

**PUB595**

*Hyperparathyroidism in Elderly Patients with Chronic Kidney Disease Rosilene M. Elias,1 Rosa M.A. Moyses,2,3 Nephrology, Univ de Sao Paulo, Sao Paulo, SP, Brazil; 4Univ Nove de Julho (UNINOVE), Sao Paulo, SP, Brazil.*

**Background:** As the world's population ages, the incidence of chronic kidney disease (CKD) is growing. Since older patients mostly present decreased renal function, there is an ongoing debate regarding whether high levels of PTH would be related to aging or to renal function. Here, we have tested the hypothesis that secondary hyperparathyroidism is frequent among CKD elderly patients and that this population require higher levels of vitamin D than young patients.

**Methods:** This is a cross-sectional analysis of stage 3 CKD patients, in ambulatory patients from a Tertiary Academic Hospital. Elderly patients (age ≥ 65 years, N=518) were compared to a 1:1 sex- and eGFR-matched sample of young patients (age < 65 years), to assess demographic and biochemical differences collected from electronic charts.

**Results:** Elderly patients presented lower phosphate, and higher levels of serum calcium and parathyroid hormone (PTH). Elderly patients with hyperparathyroidism presented low levels of 25(OH)D Vitamin D.

**Conclusions:** Hyperparathyroidism (PTH > 65pg/ml) was 1.6 fold more common in elderly patients, which was dependent on age, eGFR, calcium, phosphate, low levels of 25(OH)-Vitamin D and furosemide use.

**PUB596**

*Longitudinal Association between Kidney Function and Mortality in the Very Old Paula Ferreira Orlandi,1 Climeu Mello Almada-Filho,2 Mayssa Seabra Cendoroglo,3 Ricardo Sesso.4 Nephrology Div, Univ Federal de Sao Paulo, Sao Paulo, Sao Paulo, Brazil; Geriatrics and Gerontology Div, Univ Federal de Sao Paulo, Sao Paulo, Sao Paulo, Brazil.*

**Background:** The association of CKD, older age and mortality among individuals older than 80 years is not well defined. This study evaluates the association between kidney function and mortality in a prospective cohort of community-dwelling very old individuals according to different levels of eGFR and albuminuria.

**Methods:** A total of 231 independent individuals aged ≥80 yr from Sao Paulo, Brazil were recruited and followed by an average of 3.1 years. All underwent a hand-grip test, the ‘mini-mental’ cognitive test and laboratorial assessments, including standardized serum creatinine and urinary albumin to creatinine ratio (ACR). Main outcomes were ESRD and death. Creatinine based CKD-EPI equation was used to estimate eGFR.

**Results:** Participants were predominantly white (67%), female (70%), with median age of 84 years. At baseline, 45% had eGFR<60ml/min/1.73 m2, 12.9% had eGFR<45ml/ min/1.73m2 and 19.5% had ACR>30mg/g. None developed ESRD. Participants with eGFR<45ml/min/1.73m2 or ACR>30mg/g (n= 61) presented higher rates of death (8.5 deaths per 100 persons-year (p-y), 95% CI: 5.2 to 13.9) compared to those with eGFR higher than 45ml/min/1.73m2 and ACR lower than 30mg/g (4.2 deaths/100 p-y; 95% CI: 2.8 to 6.4) (p =0.033). The eGFR threshold of 60ml/min/1.73m2 combined with ACR lower or greater than 30mg/g was not associated with different mortality rates: 4.6 deaths/100 p-y
Factors Predicting Mortality in Hemo dialysis Patients over 65 Years Old  

**Background:** Patients starting dialysis are increasingly elderly and with high morbidity and mortality. Knowledge of prognostic factors in end-stage renal disease patients has improved dialysis management and should be considered when starting renal replacement therapy (RRT).

**Methods:** The aim of this retrospective study was to analyze the outcomes of 208 incident dialysis patients over 65 years old. Possible predictors of mortality, included in multivariable Cox analysis were age, sex, ischemic heart disease (IHD), congestive heart failure (CHF), cancer, chronic pulmonary disease, urgent dialysis, catheter as vascular access (CV), serum albumin, peripheral vascular disease, smoking, dementia and performance status.  

**Results:** Cohort mean age was 75 years. Survival rate at 6 and 36 months was 88 and 61%, the main cause of death was infection (40 and 55%), followed by cardiovascular death (35 and 29%) and cancer. Kaplan-Meier analysis showed that age was significantly associated with mortality at the 36 (p=0.007) but not at 6 (p=0.3) months. Independent predictors of mortality detected by multivariable cox regression model considering all causes, infection or CV are represented below.

<table>
<thead>
<tr>
<th>6-month mortality (all causes)</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVC</td>
<td>2.67</td>
<td>1.99-6.53</td>
<td>0.031</td>
</tr>
<tr>
<td>Albumin&lt;3.5</td>
<td>4.78</td>
<td>1.86-12.28</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Conclusions:** Predictors of mortality varied with time on RRT. Early mortality was associated with hypoalbuminemia and CVC, and with age only being predictor of infection related early death. Our data may contribute in the decision making process about RRT indication and timing in the elderly.

**PUB595**

Anemia Is an Independent Risk for Reduced Physical Function in Elderly Patients With Chronic Kidney Disease  

**Background:** Recently the prevalence of sarcopenia defined as reduced muscle strength and function has been increasing and considered as a risk for poor prognosis in elderly patients with chronic kidney disease (CKD). In this study, we investigated the risk factor of physical function in predialysis CKD.

**Methods:** We conducted a cross-sectional study based on data of 134 outpatients of our hospital who are older than 60 years and estimated glomerular filtration rate (eGFR) is under 60 ml/min/1.73m². Besides baseline laboratory data and muscle mass, physical and cognitive function were examined. We used skeletal mass index [SMI: muscle mass (kg) / height (m)²] and handgrip strength (4mWS) (units: kg) to assess physical function. We compared the variables in those with 4mWS < 10.5 kg/m² in male and < 8.5 kg/m² in female and in those with lower. Student t or chi-squared test were used for comparison and logistic regression were used to conduct multivariate analysis.

**Results:** Mean age was 77 ± 7.12 years old, 100 out of 134 patients were male. The average eGFR was 28 ± 12 ml/min/1.73m², and 57 (42.5%) patients have diabetes mellitus. CKD stage G3 accounted for 44.7%, G4 41.7%, G5 12.6%. Slower 4mWS was associated with older age, lower hemoglobin (Hb; 12.0 vs 10.35 g/dl), higher blood urea nitrogen, higher inorganic phosphorus, lower activated vitamin D, higher urinary albumin and protein. On the other hand, serum albumin, inorganic phosphorus was correlated with SMI. Multivariable logistic regression analysis identified that Hb was the only independent risk factor for slower 4mWS (RR: 2.909, 95% CI: 1.77-7.170). When stratified by CKD stage, only age was associated with 4mWS in CKD stage G3, but in CKD stage 4-5, Hb was the only significant factor (RR: 4.634, 95% CI: 1.396-16.437).  

**Conclusions:** Our study suggests that reduced physical function is associated with anemia. In elderly CKD patients, this association is especially strong in advanced CKD.

**PUB600**

The Clinicopathologic Characteristics of the Very Elderly Chinese Patients with Kidney Disease  

**Background:** Data regarding renal disease with pathology in the very elderly (age ≥80 years old) Chinese is extremely limited. The aim of this study was to examine clinicopathologic presentations in the very elderly patients who underwent renal biopsy and the complications.

**Methods:** From May 2012 to March 2016, the patients who underwent renal biopsy from our hospital were screened. The very elderly patients (age ≥80 years old) were enrolled in the observed group. Their data were compared with the control group (patients aged 65-70 years old) over the same period. The clinical and pathological classifications of the two groups were analyzed.
Results: 33 patients (24 males, 82.7±19 years) were in the observed group and 108 control (67 males, 71.5 years) were in the control group. Compared with the control group, the observed group showed lower eGFR (48.8±27.7 vs. 74.7±44.8 mL/min.1.73m², p<0.05). And there was no significant difference in blood pressure, serum albumin, proteinuria of 24 hours, hemoglobin, creatinine and lipids. Primary glomerulopathy or pathological diagnoses were not found and angiography of ATG (β=0.45, p=0.042) and prorenin levels (β=0.085, p=0.01), respectively.

Conclusions: A decrease in prorenin and ACE levels and an increase in ATG, AngII and ATIR levels in the kidney occur in dialysis patients and these changes may be associated with intrarenal RAS activation and renal damage.

Funding: Government Support - Non-U.S.

PUB603

Platelet-Activating Factor Induces Transcription of Heparin-Binding Epidermal Growth Factor-Like Growth Factor through β-Adrenergic Activity in MDCK Cells Keisuke Sugimoto,1 Tomoki Miyazawa,1 Kohki Miyazaki,1 Takuji Eni,1 Hidehiko Yanagida,2 Mitsuru Okada,1 Raymond C. Harris,3 TsukaSA Takemura.1 1Pediatrics, Kindai Univ Faculty of Medicine, Osaka, Japan; 2Pediatrics, Kindai Sakai Hospital, Sakai, Osaka, Japan; 3Nephrology & Hypertension, Vanderbilt Univ School of Medicine, Nashville, TN.

Background: Various cytokines and growth factors promote cell proliferation and vascularization in glomerulonephritis. Platelet-activating factor (PAF) is a phospholipid activator/mediator which promotes cell growth as well as secretion of inflammatory cytokines and growth factors, stimulates secretion of heparin-binding epidermal growth factor-like growth factor (HB-EGF), which fosters tissue recovery from renal tubular disorder and some types of glomerulonephritis. Since the nuclear factor involved in HB-EGF production and secretion is unclear, we investigated involvement of PAF stimulation in HB-EGF gene expression and details concerning nuclear factors using MDCK II cells.

Methods: After cells were treated with PAF plus inhibitors and cell extracts were obtained, Northern blotting and electrophoretic mobility shift assays (EMSA) were performed.

Results: PAF enhanced HB-EGF mRNA expression in a dose- and stimulation-duration-dependent manner. PAF-induced NKβ DNA-binding by NKβ and HB-EGF mRNA expression were inhibited in the presence of PAF receptor antagonists (L-659989 or WEB 2086) while mRNA expression and DNA-binding activity of NF-κB were inhibited dose-dependently by PDTC, an NF-κB inhibitor.

Conclusions: PAF is involved in gene control in MDCK cells, activating NKβ binding, and strongly inducing HB-EGF gene expression.

PUB604

Evaluation of Factors Associated with Central Venous Catheter and Immature Arteriovenous Fistula Use at Initial Dialysis Ken J. Park,1 Michael. Thorp,2 Eric S. Johnson,2 Ning Smith.3 1Kaiser Permanente Northwest, Milwaukie, OR; 2Kaiser Permanente Center for Health Research Northwest, Portland, OR.

Background: Patients with end stage renal disease (ESRD) have high mortality rate thought related to use of central venous catheters (CVC) for initial dialysis. We sought to examine factors associated with CVC use and presence of immature fistula (AVF) at initial dialysis.

Methods: Retrospective cohort of incident hemodialysis patients from large HMO who started dialysis between 1/1/04 to 1/1/14 (n=918). Variables recorded included age, gender, race, diabetes, peripheral vascular disease, congestive heart failure, grade of proteinuria (divided into <0.2 g/m, 0.2-0.5 gm, 0.5-3.5 gm, and >3.5 gm), length of predialysis nephropathy care, number of hospitalizations predialysis over 2 year period, early history of acute kidney injury, and timing of AVF placement. Primary outcome was presence of CVC at initial dialysis. Secondary outcome was presence of immature AVF at initial dialysis. Multivariable logistic regression model was used to evaluate factors associated with outcome.

Results: At initial dialysis, CVC was used in 36% and CVC was used in 64% of the cohort. Higher odds of CVC use was associated with increased hospitalizations (OR 1.07) while increased length of predialysis care was associated with lower odds of CVC use (OR 0.98). Female gender was associated with higher odds (OR 1.7) of immature AVF at initial dialysis as was shorter time of AVF placement pre dialysis. Grade of proteinuria was associated with both CVC use and presence of immature AVF at initial dialysis. Patients with proteinuria between 0.5-3.5 g/m had the lowest odds for starting dialysis with CVC or immature AVF.

Conclusions: Grade of proteinuria was associated with both use of CVC and presence of immature AVF at initial dialysis. Increased predialysis hospitalizations and shorter predialysis nephropathy care was associated with increased odds of CVC use but not with presence of immature AVF. Female gender and delayed timing of AVF placement was associated with increased odds of immature AVF use.

PUB605

Haemodialysis Vascular Access: Current Practices amongst Indian Nephrologists Dinesh Bansal,1 Eric S. Chemla,2 Vijay K. Kher,2 Vivekanand Jha,3 Debusish Banerjee.1 1PGIMER Chandigarh; 2St. Georges Hospital London; 3MEDICITY Delhi.

Background: Despite the growing number of patients receiving haemodialysis (HD) in India, little is known about vascular access practice. We document use and cost of different vascular accesses as reported by practicing Indian Nephrologists.
Methods: A web-link for a national online survey was emailed to 920 Indian nephrologists in Jan-Feb 2016. A total of 388 (42.1%) completed the survey. 98.5% of whom were responsible for managing dialysis patients, and 98% in hospitals.

Results: At start of RRT, 65% of the patients had HD, 8% PD, 10% kidney transplantation and 20% conservatory care. 48% patients were self-paying, 26% had employer reimbursement and 23% had private insurance. According to 59% responders, >75% of patients started dialysis with uncuffed catheter. Less than a quarter patients started dialysis with fistula [82% nephrologists], graft [99% nephrologists] or tunneled catheter [90% nephrologists]. Among the prevalent haemodialysis patients, over half of the patients dialysing with fistula [79% nephrologists], rather than uncuffed catheters [15% nephrologists] or grafts [11% nephrologists]. 16% reported at least one catheter related sepsis in more than ½ of patients. Placement of uncuffed catheter cost <$US150 in 92% facilities, whereas the cost of placing a tunneled catheter was estimated at >$300 by about half. An AVF could be created for <$150 in the practice of 40% nephrologists, and <$300 in 90% centres. 35% of nephrologists reported grafts were not placed at their institute and the cost, where available, was >$500. 46% nephrologists had access to pre-dialysis clinics, <30% to vascular access program, <17% conducted regular audits of vascular access audits. 98% responders were willing to participate in projects related to vascular access or dialysis audits.

Conclusions: The survey demonstrates that most patients are self-paid, start HD with uncuffed temporary catheters, with poor access to predialysis care and vascular access team. There are more fistulae in prevalent patients. The survey highlights the suboptimal vascular access care in haemodialysis patients and the need for pre-dialysis clinics, vascular access services and registry audits.

PUB606
Cross-Sectional Study Demonstrating Arteriovenous Fistula Failure Is Not Associated with Age, Comorbidity, Previous Access or Anatomical Location
Viwaavan Mahalangisivam, Amrita Ramnarine, Veronica Smith, Pamela Ayling, Abdelgalil Abdelrahman Ali. Dept of Nephrology, Broomfield Hospital, Chelmsford, United Kingdom.

Background: Arteriovenous fistula is the preferred form of vascular access for haemodialysis. However, it is associated with failure rates of up to 49% at two years. Several factors are considered to be responsible for this which may influence surgical access planning. The UK Renal Association published a guideline encouraging best practice access formation.

Methods: We retrospectively audited 107 fistulae formed at our centre between April 2014 and October 2015. Data was collected for variables including age, sex and comorbidity, as well the anatomical location of the fistula and previous access. Data was analyzed to assess whether variables were associated with an increased risk of fistula failure.

Results: Our audit demonstrated a fistula failure rate of 17.7% with 14 out of 71 (19.7%) failed radiopaque fistulae and 5 out of 35 (14.3%) failed brachiocephalic fistulae. There was no statistically significant correlation between sex, comorbidity, anatomical location, the use of dominant arm or previous access with an increase in fistula failure. Further subgroup analysis was performed after separating radiopaque and brachiocephalic fistulae. Neither age nor comorbidity were shown to be associated to significantly increase the risk of failure in either of these groups.

Conclusions: Fistula failure rate at our centre is in keeping with rates documented in the literature. We demonstrated that factors such as sex, comorbidity and anatomical location are not associated with increased rate of fistula failure. We would therefore advocate that fistulae are created with the patient's understanding fistula formation and advice given to patients.

PUB607
Patency of Translumbar Percutaneous Catheter for Hemodialysis, Experience of Our Center: Instituto Mexicano del Seguro Social, Specialty Hospital “La Raza” Mexico City, Mexico Juan Carlos Garcia Yanez, Guillermo Jimenez. Nefrologia, Inst Mexicano del Seguro Social, Ciudad de Mexico, Mexico.

Background: In Mexico we do not have reliable statistics which is the first access of patients starting renal replacement therapy. Over 80% of patients in the United States start haemodialysis therapy with a tunneled catheter (CT). (1) The renal replacement therapy based on Hemodialysis requires placement and maintenance of vascular access that allows adequate flow. It is ideal using an arteriovenous fistula (AVF) due to the low rate of complications that offers handling. However, many patients start (23-63%) or continue their treatment (23-41%) through tunnelled central venous catheters and non-tunneled. Chronic use of these central catheters cause, as an inevitable consequence, vascular stenosis generation exhaustion, intrathoracic thrombosis or associated infection. (3-4). In the following complication of superior vena cava stenosis. When the availability of vascular access for haemodialysis fistulae and vascular prostheses, catheters for hemodialysis, jugular femoral and subclavian is exhausted, it is mandatory to find alternative vascular approach more complex, requiring more technical and advanced technological tools, the experience of our center in placing Translumbar vascular access (AVT) guided by fluoroscopy to a median of 1 year in which the first catheter is reported.

Methods: A retrospective study on an electronic database of AVT placed in our hospital was performed successful survival analysis catheters placed one year of the first catheter was used. The procedure to patients with evidence angiography was performed by bilateral central venous obstruction.

Results: The total number of patients undergoing the procedure were 12, of which 8 were men and 4 were women, the average age is 41 years. The median survival of vascular access is 168.5 days. One patient died from causes attributable to the placement of vascular access.

Conclusions: According to these results the placement of percutaneous vascular access of hemodialysis guided by fluoroscopy through Translumbar approach has proven to be a good alternative for patients with depletion of common vascular access before any surgical intervention.

PUB608
A Modified De Novo Insertion Technique for Catheter Replacement in Elderly Hemodialysis Patients: A Single Clinic Retrospective Analysis
Li Hua Wang, Fang Wei, Ai Li Jiang. 1 Dept of Kidney Disease and Blood Purification Centre, Inst of Urology & Key Laboratory of Tianjin, Tianjin, China; 1Dept of Kidney Disease and Blood Purification Centre, Inst of Urology & Key Laboratory of Tianjin, Tianjin, China; 1Dept of Kidney Disease and Blood Purification Centre, Inst of Urology & Key Laboratory of Tianjin, Tianjin, China.

Background: For patients who rely on a Tunneled cuffed catheter, replacement or retrieval is typically necessary. We recently performed a novel de novo insertion technique for catheter replacement in our practice. As the technique has not yet been studied comprehensively, we performed a retrospective study to evaluate the safety and efficacy of de novo placed catheter without delay for catheter replacement in elderly hemodialysis patients.

Methods: A retrospective review of 164 elderly patients was conducted during a period of three years. There were 84 patients in study group, as well as an 80 patient control group, who had catheter replacement by guidewire exchange technique. Clinical follow-up data was collected.

Results: All catheters were placed successfully. The mean survival time per catheter was 641 catheter days (study group) and 485 catheter days (control group).

PUB609
Effects of Vascular Access Care on Hospitalization Rates in Hemodialysis Patients
Sheetal Chaudhuri, 1 Hao Han, 2 Marta Revirigre-Mendoza, 1 Sophia Rosen, Karen G. Butler, Jane Brzozowski, 1 John W. Larkin, Elsie Koh, 2 Gregory Miller, 2 Melvin Rosenblatt, 1 Murat Sor, 2 Len A. Usvyat, 1 Frankfurt W. Maddux, 2 Fresenius Medical Care North America, Waltham, MA; 2Fresenius Vascular Care, Trevyn, PA.

Background: Hemodialysis (HD) patients at Fresenius Medical Care North America (FMCNA) can choose to receive outpatient vascular access (VA) care from Fresenius Vascular Care facilities (FVC). We investigated if hospitalization rates in HD patients receiving VA care from FVC differ from those receiving VA care from other providers that were either non-FMCNA affiliated or receiving VA care at VA facilities.

Methods: We analyzed data from 4,691 HD patients treated by FVC during entire calendar year 2014. We matched 4,691 control patients exactly by concurrent year of FVC versus Fresenius Vascular Care facilities (FMCNA) can choose to receive outpatient vascular access (VA) care from Fresenius Vascular Care facilities (FVC). We investigated if hospitalization rates in HD patients receiving VA care from FVC differ from those receiving VA care from other providers that were either non-FMCNA affiliated or receiving VA care at VA facilities.

Results: The primary patency rate of 30 days were 97.7% (study group) and 82.5% (control group), respectively. The episode of catheter infection was similar in both groups (p=0.586), but the case of catheter dysfunction was significantly lower in study group compared to control group (p=0.003).

Conclusions: The de novo placed cather without delay technique for catheter replacement near the pre-existing venotomy site is safe, and boasts similar infection rates with lower dysfunction rates compared to tunneled catheter insertion by guidewire exchange technique.

Funding: Private Foundation Support
Outpatient Vascular Access Care Is Associated with Improved Access Sustainability in Hemodialysis Patients

**Background:** In hemodialysis patients, arteriovenous fistula/graft (AVF/AVG) complications are common, life threatening, and can require intermittent catheter exposure. Fresenius Medical Care North America (FMENA) patients can choose to receive outpatient vascular access (VA) care with Fresenius Vascular Care (FVC). We investigated if FVC VA care is associated with improvements in AVF/AVG sustainability, as compared to matched patients receiving care mainly through hospital VA providers or no care at all.

**Methods:** Data from 4,691 FVC HD patients during 2014 was analyzed. Control patients (n=4,691) were matched exactly by year of FVC care, state, gender, race, and access type, and nearest neighbor propensity score matching for age, dialysis vintage, albumin, body mass index, and Kt/V. A sub-analysis was performed on 4,376 FVC patients with preexisting AVF/AVG. Duration of AVF/AVG use was calculated by percent of AVFs/AVGs with a stop date in 2015, as well as, mean enrollment average days from Jan 1, 2014 to right AVF/AVG stop date; an imposed stop date of Jan 14, 2016 was used if none was recorded.

**Results:** We observed that there were 3% fewer patients requiring AVF/AVG removal/abandonment when enrolled in FVC (p<0.001), and on average FVC patients used their AVF/AVG 2.33 days longer than controls (p<0.001). FVC patients had a nonsignificant reduction of 8% in the admission rate (p=0.6; Figure 1: C) hospital days were 12% lower for FVC patients with an AVF/AVG (p<0.001; Figure 1: D).

**Conclusions:** The study results suggest that outpatient VA care at FVC is associated with lower hospitalization rates in HD patients, compared to controls. Further studies are needed to confirm these results.

*Funding:* Pharmaceutical Company Support - Fresenius Medical Care North America

**PUB610**

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*Funding:* Pharmaceutical Company Support - Fresenius Medical Care North America

**PUB611**

The Transluminal Interventional Therapy on Heterotopia of Internal Jugular Vein Cuffed Tunneled Catheter

**Background:** To summarize the transluminal interventional therapy on heteroptia of internal jugular vein cuffed tunneled catheter.

**Methods:** We retrospectively analyzed the clinical data, transluminal interventional therapy and results of 11 patients who had heteroptia of internal jugular vein cuffed tunneled catheter.

**Results:** In 11 patients, 9 patients had no central vein stenosis. Two patients whose right internal jugular vein cuffed tunneled catheter in aygossy vein were adjusted without smooth guide wire. Seven patients whose left internal jugular vein cuffed tunneled catheter in left brachiocephalic vein were adjusted by help of smooth guide wire. Two patients whose right internal jugular vein cuffed tunneled catheter pulled back to right internal jugular vein had right brachiocephalic vein stenosis. They had right internal jugular vein catheterization before. The cuffed tunneled catheter was placed after pertaneous transluminal angioplasty of right brachiocephalic vein stenosis. There were no severe complications in 11 patients.

**Conclusions:** The transluminal interventional therapy on heterotopia of internal jugular vein cuffed tunneled catheter was effective and safe.

**PUB612**

Analysis of the Effects on Two-Locus Puncture Thrombolytic Therapy for Artificial Vascular Thrombosis by Using Urokinase

**Background:** To analyze the effect of two-locus puncture thrombolytic therapy for the treatment of arteriovenous graft (AVG) thrombosis by using urokinase.

**Methods:** Two positioning near arteriovenous anastomosis were selected as the centripetal puncture points, then the AVG was treated with 5000 U/ml urokinase, which was repeatedly pumped through the scalp needle, meanwhile the low molecular weight heparin could be used as an auxiliary drug. After treatment, the result of the patients with AVG ultrasound, blood routine examination, coagulation indicator, biochemical criterion were compared with that before treatment, and the adverse reactions were observed at the same time.

**Results:** Observation of AVG thrombosis (n = 30), AVG usage time was 6 months to 5 years, and thrombus formation time was 3 h to 48 h. Among 30 cases of patients with thrombolytic therapy by two-locus puncture, 26 cases obtained successful thrombolyis (86.7%), with average time of thrombolysis (4.74±2.31) h and average urokinase thrombolytic dosage (35.5±5.5 millionU). There was no significant difference in age, dialysis age and AVG usage time between success group and failure group. The success of the treatment was related to the thrombus formation time and the status of venous terminal flow (P=0.05). Before and after thrombolytic therapy, there was no significant difference in hemoglobin, platelet, prothrombin time (PT), thrombin time, activated partial thromboplastin time (APTT), fibrin protein, glutamic-pyruvic transaminase, serum albumin and total bilirubin. The slight rise of APTT and PT was considered as the application of low molecular weight heparin.

**Conclusions:** The two-locus puncture thrombolytic therapy using urokinase discontinuously and repeatedly has a high success rate, which can reduce the temporary catheter and surgical reconstruction as well as their associated complications. It has a high clinical value, as the ideal choice for the thrombolytic treatment of AVG thrombus formation, especially for basic-level hospitals.

**PUB613**

Financial Impact of Catheter Malfunction in Dialysis

**Background:** Catheter malfunction and infection are major causes of morbidity and mortality in dialysis patients. It also is a financial burden on the health care system and adds to the costs of providing dialysis. Kidney Dialysis Outcomes Quality Initiative (KDOQI) guidelines list catheter malfunction as blood flow less than 300 mL/min during the first 60 minutes of hemodialysis. Intrinsinc thrombus and biofilm formation or fibrin sheath formation are major contributors to catheter malfunction. Mechanical disruption of the fibrin sheath is commonly used to tackle the problem, with variable success. If catheter malfunction cannot be successfully resolved by this method, exchange of catheter is commonly used with attendant cost and potential risk to the patient.

**Methods:** We describe 2 patients with ESRD on maintenance hemodialysis, in whom catheter dysfunction required catheter exchange (CEX) every 3-4 weeks over a 6 month period. A decision was made for weekly instillation of thrombolytic (tPA) into each port which resolved the issue.

**Results:** Since the initiation of tPA use, neither of the two patients has required catheter exchange as opposed to every 3-4 week exchange earlier in their course. In addition to the obvious clinical benefit to the patients, the economic impact of this intervention with weekly instillation of tPA is huge. Considering a conservative estimate of $1,900 per CEX, the cost difference between the two options is tremendous. Please see table 1 below.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of Exchanges</th>
<th>Time period</th>
<th>Number of CEX-Post weekly tPA installation</th>
<th>Additional cost in the time period($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>r1</td>
<td>11</td>
<td>April 2015-February 2016</td>
<td>0</td>
<td>20,000</td>
</tr>
<tr>
<td>r2</td>
<td>6</td>
<td>Feb 2015-January 2016</td>
<td>0</td>
<td>11,400</td>
</tr>
</tbody>
</table>

In addition, there is the disadvantage of loss of productivity secondary to time lost due to the procedures, which was not assessed in our evaluation.

**Conclusions:** We recommend using weekly tPA protocol in patients with catheter dysfunction before proceeding with catheter exchange, especially in those individuals requiring frequent exchanges. This needs to be explored by further randomized controlled studies and more characterization of the patient population.
PUB614

Management of Right Atrial Thrombi Complicating Use of Tunneled-Cuffed Catheter in Hemodialysis Hongliu Yang,1 Tiantie Cui,2 Ping Fu.1 Nephrology, West China Hospital, Sichuan Univ, Chengdu, China; Nephrology, West China Hospital, Sichuan Univ, Chengdu, China; Nephrology, West China Hospital, Sichuan Univ, Chengdu, China.

Background: Catheter-related right atrial thrombosis (CRAT) is a rare as well as underreported but potentially life threatening complication of tunneled-cuffed catheter (TCC) in hemodialysis (HD) patients. There is no current guideline for the management of this complication. Thus, we aimed to explore the optimal treatment of HD patients with CRAT and evaluate their outcomes.

Methods: We reviewed hospital records of 20 HD patients dialysed through TCC with diagnosis of CRAT from March 2013 to August 2015 and followed through 31 May 2016. Once CRAT was diagnosed, TCCs were exchanged over a guide-wire in situ with reposition of the catheter tip.

Results: During the follow up, 3 patients died: 2 of gastrointestinal massive hemorrhage and 1 of acute myocardial infarction. 4 patients suffered from pulmonary embolism but none of them died. There was no death directly attributed to CRAT. Resolution of CRAT was observed in 2 patients and size of thrombi decreased in 12 patients.

Conclusions: Regular maintenance HD through replaced catheter with reposition of catheter tip and oral anticoagulation may be a successful management in HD patients suffered from CRAT. Nevertheless, prospective studies are needed to identify risk factors of development and to determine the optimal management of CRAT in HD patients.

Funding: Government Support - Non-U.S.

PUB615

Superior Cava Vein Syndrome due to Catheter-Related Thrombosis Treated with Angiojet Rheolytic Thrombectomy Michele Ferrannini,1 Alessia Centi,1 Paola Tatangelo,1 Eleonora Bernabei,1 Gianluca Smedile,1 Roberto Cancellieri,2 Marco Guazzaroni,2 Roberto Palumbo,3 Nephrology and Dialysis Dept, St. Eugenio Hosp., Rome, Italy; Radiology Dept. St. Eugenio Hosp., Rome, Italy; Vascular Surgery Dept, St. Eugenio Hosp., Rome, Italy.

Background: The rescue of the vascular access is mandatory in hemodialysis. In literature it is know the efficacy of mechanical thrombectomy devices for arteriovenous (AV) fistula thrombosis, but few data about the superior caval or brachiocephalic veins percutaneous declotting. We report 9 cases of superior cava vein syndrome (SCVS) due to central venous catheter-related central vein thrombosis, 8 of which treated with Angiojet™ rheolytic thrombectomy (RT).

Methods: 9 dialyzed patients (3 male) were admitted with SCVS. All of them had long term central venous catheter (f-CVC), 7 in right and 2 in left Internal Jugular Vein (IJV). Angio-Tc scan showed SCV complete obstruction in 1 case and subocclusions in 3 cases, 8 occlusions or subocclusions of brachiocephalic veins. In all cases the I-CVCs were enveloped into the clot. In one case we desisted to treat because of the complete occlusion of SCV and brachiocephalic veins, the presence of efficient collateral circulations and the dangerous comorbidity of patient. In the others, we performed a double jugular and femoral vein approach: in the first we inserted a guide into f-CVC just before its removal, in the second we inserted an other guide; this second one was captured by a goose-neck catheter introduced in jugular vein and then dragged out of jugular vein own, to obtaining a unique guide from femoral to jugular vein. From femoral approach, the RT was performed with Angiojet system.

Results: The initial technical success to recanalize cava and brachiocephalic vein was 100%. In all cases adjunctive procedures were performed: balloon angioplasty (8 patients, 12 vessels), and stent placement (3 patients, 6 stents). No pulmonary embolism occurred; in one case a hemotransfusion was performed for haemolysis; bradyarrhythmias and thoracic pain occurred in two cases. The patency at 6 months was 87.5% (7/8 patients).

Conclusions: In our experience Angiojet RT is an useful tool in cases of SCVS due to f-CVC complications.

PUB616

A Timely Catheter Removal Program Decreases the Time to Hemodialysis Access Appointments and Catheter Exposure Time Michele Inglese,1 Dugan Maddux,1 Karen G. Butler,1 Valead Latifi,2 Yue Jiao,3 Sheetal Chaudhuri,1 Hao Han,1 Jerry Damon Jusperson,1 Marta Reviriego-Mendoza,1 John W. Larkin,1 Len A. Usyvat,1 Sandra Bodin,1 Margaret Milford,1 Franklin W. Maddux,1 Fresenius Medical Care North America; Fresenius Vascular Care.

Background: In hemodialysis (HD) patients (Pts), the transition from a central venous catheter (CVC) to a permanent dialysis vascular access (VA) reduces the risk of negative outcomes. We implemented a pilot Timely CVC Removal Program (TCRP) and analyzed its impacts on the time to VA appointments, VA surgery, CVC removal, and the total CVC exposure time.

Methods: We deployed the TCRP in 8 Fresenius Medical Care North America clinics, and analyzed VA-related data from HD Pts for the months of August 2015 and May 2016. TCRP includes care coordination between HD clinic staff, vascular access experts (VAEs), interventionalists, and surgeons. Weekly clinic reports were generated and included metrics for all CVC Pts regarding dates of VA appointments, VA surgery, and CVC removal, as well as, total CVC exposure time for each clinic and the Pt population. The “time to” metrics denoted in Figure 1 were utilized to investigate the areas of performance associated with the TCRP.

Results: Overall, we studied data from 144 Pts. After 10 months of the TCRP, we observed notably lower median time from the CVC insertion to the VAE appointment. Despite this, there was an increased time from the VAE appointment to the VA surgeon appointment. The median total CVC exposure time for the clinic and Pt population was found to be lower 10 months after implementation of the TCRP (Figure 1).

Figure 1

Conclusions: Our findings suggest the TCRP hastens placement of a permanent VA in HD Pts and reduces total CVC exposure. Tracking “time to” metrics was beneficial in identifying areas for improvement, which further enhancements of TCRP might be able to address.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB617

Health Economics of Arteriovenous Fistulas (AVFs) among U.S. Hemodialysis Patients Mae Thamar,1 Timmy C. Lee,2 Monnie Wasse,3 Marc H. Glickman,4 Qian Zhang,5 Daniel Gottlib,7 Scott Toner,5 Timothy A. Pfleiderer,5,6 MTPPI,7 Univ of Alabama,8 [frm]Northwestern Univ; RenalCare Associates; Protein Therapeutics Inc; Sentara CarePlex Hospital.

Background: Despite the importance of vascular access (VA) for adequate hemodialysis, few studies have examined real world costs related to long-term VA management. To address these gaps, we use national claims data to examine per patient VA costs over a 2.5 year period for different clinical outcomes of AVF use, patency and abandonment.

Methods: Observational intention-to-treat principle guides this retrospective study using Medicare claims to identify all incident elderly HD patients from 2010-2011 who underwent AVF creation. Using a multidisciplinary expert panel, we identified VA-related diagnostic, imaging, endovascular, surgical, infection, hospitalization and anesthesia codes to calculate total VA costs. The impact on costs of timing of AVF placement was also examined. Total per patient VA costs were calculated for all patients and for subsets based on AVF outcomes prior to use or during the 1st year after AVF creation: 1) no interventions; 2) any intervention to achieve or maintain patency; and 3) AVF abandonment. Patency loss and AVF use were defined using procedure, diagnosis and V (vascular) codes which indicate VA type in use each month. Results: Preliminary results suggest total Medicare costs for VA management were substantial and account for a significant portion of reported ESRD expenditures. Results also suggest that AVF patients with no loss of patency in year 1 have significantly lower 2.5 year VA costs compared to patients with loss of primary or secondary patency in year 1 (final results will be presented at ASN for Table 1).

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

1044A
Table 1. VA-related per patient per year (PYP) costs for incident Medicare HD patients in 2.5 years following AVF creation.

<table>
<thead>
<tr>
<th>AVF cohorts</th>
<th>No Intervention</th>
<th>Intervention</th>
<th>Abandonment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unassisted use</td>
<td>Primary unassisted patency</td>
<td>Assisted Use</td>
<td>Loss of primary patency</td>
</tr>
</tbody>
</table>

mean, median, 25th and 75th percentile costs

Conclusions: Improvements in processes of care and technologies to enhance AVF use and patency should result in less morbidity with the potential for significant cost-savings. Funding: Pharmaceutical Company Support - Proteon Therapeutics Inc

PUB618
The Effect of Extended Antibiotic Prophylaxis on Infection in Vascular Access Intervention Therapy

Marcus Ichinoo, Namiko Kobayashi, Yohei Kono, Ayumu Nomizu, Yoshitatsu Ohara, Yutaro Mori, Shotaro Naito, Takayuki Toda, Noriaki Matsui, 1 Nephrology, Tsuchiura Kyodo General Hospital, Tsuchiura, Ibaraki, Japan; 2Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Vascular access is the lifeline for hemodialysis patients, and Vascular Access Intervention Therapy (VAIIT) has improved the quality of life of such patients. However, the efficacy of extended antibiotic prophylaxis of bloodstream infection among patients treated with VAIIT remains unknown.

Methods: We performed a retrospective study. To clarify whether antibiotic prophylaxis is effective or not, we reviewed the records of 487 procedures of VAIIT between 2011 and 2015 performed in our hospital. Selection of patients who required VAIIT received prophylaxis was at discretion of the doctor attending the case. We evaluated the association between prophylaxis and incidence of infection by logistic regression analysis.

Results: The 487 procedures of VAIIT (419 stenosis cases, 68 thrombosis cases) involved 260 men (53.5%), and 227 women (46.5%), with a mean (SD) age of 70.2 (11.0) years. 220 patients received prophylaxis, and 267 patients did not. The duration of the VAIIT procedure (34 vs. 31, p = 0.28), the types of VA (arteriovenous fistula 211 vs. 258, p = 0.675), complication of diabetes (81 vs. 109, p = 0.367), between the two groups were not significantly different. In logistic regression analysis, the incidence of infection after VAIIT, defined as hyperthermia (greater than 101 degrees F), was not significantly different between both groups (1 case in prophylaxis group, none in non-prophylaxis groups, odds ratio 1.005 [95% CI 0.996 – 1.014]).

Conclusions: In VAIIT, antibiotic prophylaxis does not influence rates of infection. Future prospective, randomized studies with a larger number of catheters are needed to confirm or refute these results.

PUB619
Gender Differences in Catheter Use over Hemodialysis Vintage: Results from the Monitoring Dialysis Outcomes Initiative (MONDO) Alice Topping,1 Xiaoling Ye,2 Jochen G. Raimann,3 Frank van der Sande,4 Adrian M. Guinsburg,2 Bernard Canaud,2 Xiaoqi Xu,4 Albert J. Power,3 Neil D. Duncan,7 Jeroen Kooman,4 Len A. Usavyt,2 Peter Kotanko,1,4 Maria E. Ferris,7 'Renal Research Inst, New York, NY; 2Fresenius Medical Care EMEA, Bad Homburg, Germany; 3Imperial College, London, United Kingdom; 4University of Amsterdam, Netherlands; 5Fresenius Medical Care North America, Waltham, MA; 6Fresenius Medical Care Asia Pacific, Hong Kong; 7Univ of North Carolina Chapel Hill, 7Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Vascular access (VA) is an essential component to successful and efficient hemodialysis (HD). Catheter use is associated with higher mortality rates in HD patients (Xue et al, 2003). Previous research has highlighted differences in VA type by gender (Marcus et al, 2007), but have not compared catheter use over HD vintage across regions (rgs).

Methods: Prevalent patient(s) in MONDO from 2006-2010 were analyzed for differences in catheter use by gender at HD initiation, and at one yr and three yr vintage. For pts beginning HD with a catheter, time to arteriovenous fistula (AVF) use was compared by gender overall and for each rg using the Wilcoxon-Mann-Whitney (WMW) test.

Results: There were 62,431 pts at baseline, 48,618 at one yr and 9,098 at three yr vintage eligible for analysis. Overall 59.2% of males (M) and 63% of females (F) initiated by gender overall and for each rg using the Wilcoxon-Mann-Whitney (WMW) test.

Conclusions: Gender differences in catheter use in all rgs, with F having higher catheter rates. While we observe some variation in size of effect, efforts to reduce catheter rates should take gender inequalities into consideration.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

PUB620
Overlapping of Second Stent Placement between Previous Migrated Stent and Elastic Recoil of Rt. Brachiocephalic Vein Stenosis due to Rt. Thyroid Mass: Case Report

Jin Ho Lee, Heeryong Lee, Joon Seok Oh, Dongyeol Lee, Yong Ki Park, Yong Hun Sin, Seong Min Kim, Joong Kyung Kim. Internal Medicine, Bongseong Memorial Hospital, Busan, Dong-Gu, Korea.

Background: Central vein stenosis (CVS) is commonly associated with arteriovenous fistula for hemodialysis. CVS associated with morbidity, hospitalization and morbidity. Endovascular intervention should be considered to management of CVS, as such balloon angioplasty, stent deployment. Especially, stenting at refractory CVS was choice of treatment. We announced a case that overlapping another stent between previous migrated stent and refractory CVS compressed by thyroid mass.

Methods: 75-year-old woman with advanced DM nephropathy on hemodialysis. Rt. Brachiocephalic AVF op was done at Jan, 2016. Rt. arm swelling and delayed hemostasis was occurred at POD 60days. We decided percutaneous transluminal angioplasty (PTA). Significant Rt. brachiocephalic vein (>80%) stenosis was presented. Despite of 12mm balloon angioplasty (MUSTANG®), stenosis (70-80%) was remained (Fig.1, Fig.2, Fig.5). To find reason of elastic recoil, enhanced chest CT was performed. CT shows Rt. brachiocephalic vein was compressed by thyroid mass (3.4 X 2.7mm), Rt. brachiocephalic artery and 1st rib (Fig.4). Then, stent (WALLSTENT®), 14mm X 4cm was placed at stenotic lesion because of high radial resistive strength (Fig.5). Immediate technical success was achieved. But, ipsilateral arm edema was occurred 3days after intervention. In central venography, stent was migrated into SVC and Rt. brachiocephalic vein stenosis was remained (Fig.6). Stent (EPIC®, 14mm X 4cm) was overlapped between CVS and migrated stent (Fig.7). Arm swelling was disappeared.

Results:

PUB621
Arteriovenous Fistulae Provides Superior Patency and Survival over Arteriovenous Graft

Harcadesh Nandakaban, Ananthakrishnanuram N. Aravindan, Govind Surya Narayanan, Stephen T. Spicer, Imelda De Guzman, Jeffrey Wong. Renal Unit, Liverpool Hospital, Sydney, NSW, Australia.

Background: Review of permanent hemodialysis (HD) access creation in our institution and their outcomes. Arteriovenous fistulae (AVF) and arteriovenous graft (AVG) primary and secondary patency as well as overall vascular access survival was analysed over the study period.

Methods: A retrospective review of vascular access database over a 3 year period with additional data obtained from the electronic medical record (emR). Student’s t-test, Chi-square test, ANOVA and Kaplan-Meier survival analyses were used and significance for p<0.05.

Results: From 1st April 2013 - 31st March 2016, 177 permanent vascular accesses were created in 159 unique patients: 157 AVFs and 20 AVGs. Patient characteristics: average age 58 yrs; males 67%; diabetes 63%; coronary disease 34%; pre-op tunneled catheter (TVC) use (52%); and seen in pre-dialysis clinic 58%. Pre-dialysis review was associated with reduced TVC use 8% vs. 45%. 60% of all access worked, 14% failed to work despite intervention with no difference between AVF & AVG, and 26% were not used by study end. Primary patency of AVF was superior to AVG with a median period of 279 vs. 135 days (p<0.05). Gender, surgeon or access location had no influence. Overall secondary patency at 2 years was 68%. AVFs had superior mean survival to AVGs of 849 vs. 422 days (p<0.05). The presence of: diabetes, coronary disease, access location or side, or operating surgeon did effect secondary patency rates. Assisted access use within 3 months was 14%, and 41% at 6 months.

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

Underline represents presenting author.

1045A
Conclusions: AVF were the predominant vascular access created. AVF have a superior primary and secondary patency rate to AVG that is not affected by the patient comorbidities, location of access placement or surgeon. Pre-dialysis clinic has a positive impact in reducing patient TVC exposure. There were low rates of early use of vascular access.

PUB622
Ultrasound and Color Doppler in Hemodialysis Patients for the best Management of Vascular Access
Federico Nalesso, Sara Samoni, Alessandra Brendolan, Claudio Ronco. IRRI - International Renal Research Inst Vicenza, IRRIV - San Bartolo Hospital, Vicenza, Italy.

Background: Vascular access is a key determinant in adequate extracorporeal purification in CKD patients. Arterio-Venous Fistula and Graft are subject to complications such as ematoma, blood effusions and other injuries during the cannulation procedures. These complications may be avoided by the use of Ultrasound and Color Doppler during the cannulations and the pre-cannulation mapping of the access. In case of complications in the vascular access a single needle is frequently required to obtain the extracorporeal circulation despite of reducing the KTV and the total ultrafiltration.

Methods: We performed a complete Ultrasound and Color Doppler evaluation in all hemodialysis patients before the first access use. In case of difficult procedures of vascular access cannulation and after the report of abnormalities at the physical examination the ultrasound guide cannulation was performed. In our center we started to use this protocol of US analysis from the second part of 2012. (Figure 1)

Results: During our period of observation the total amount of complications drastically decreased progressively as attested by the total percentage of single needle use compared to the total amount of treatments performed

<table>
<thead>
<tr>
<th>YEAR</th>
<th>SINGLE NEEDLE TREATMENTS % OF TOTAL HD TREATMENTS</th>
<th>TOTAL US-CD EXAMINATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>7,5</td>
<td>20</td>
</tr>
<tr>
<td>2012</td>
<td>3,9</td>
<td>186</td>
</tr>
<tr>
<td>2013</td>
<td>3,7</td>
<td>290</td>
</tr>
<tr>
<td>2014</td>
<td>2,8</td>
<td>686</td>
</tr>
<tr>
<td>2015</td>
<td>1,6</td>
<td>802</td>
</tr>
</tbody>
</table>

Conclusions: Ultrasound and Color Doppler is a useful technique that can be performed at bedside reducing the complication related to the cannulations of vascular access. The vascular mapping before the first cannulation allow to determine the best sites to put the needles avoiding injuries and complications that can require the single needle use.

PUB624
Characteristics of High-Dose Hemodialysis Patients: A Systematic Review

Background: Conventional hemodialysis (CHD) (i.e., 4-hour session 3 times/week) is the most common dialysis regime. High-dose hemodialysis (high-dose HD) (i.e., more frequent and/or longer sessions), has been associated with a 30-45% improved survival rate vs. CHD in large observational studies. Patients on high-dose HD have better blood pressure control, improved quality of life and decreased left ventricular mass. However, the characteristics of patients who may benefit from high-dose HD have not been identified. This systematic review aims to summarize high-dose HD patient characteristics.

Methods: Medline and Embase were used to identify randomized controlled and observational clinical studies evaluating the high-dose HD regime (i.e., no 2-day gap without dialysis; short-daily-/24 sessions of ≥2 hours/week, nocturnal: ≥3.5 sessions of ≥6 hours/week; standard Kt/V ≥3.0). To be included, a study had to have at least 20 patients and published in English language between January 2000 and March 2016. Two independent reviewers selected studies and data extraction was performed.

Results: After screening 91 full text articles (total 3,652 citations), only 13 met the eligibility criteria (2,907 hemodialysis patients - 1,088 on high-dose HD: 509 at home; 579 in-center). High-dose HD patients were generally young (mean age range: 43±2 to 58±18.9 years), mostly men (66%-72%), Caucasian (34%-88%), and mean BMI ranging from 21.5±2.9 to 29±14.85 kg/m². The most commonly reported causes of ESRD were diabetes (6%-77%), diabetic neuropathy (27%-36%), glomerulopathies (12%-41%), and polycystic kidney disease (4%-22%). Only 1 study reported a Charlson Comorbidity Index Score (CCI) of 3.2 ± 0.4 for high-dose HD patients. When a short daily regimen was used, patients performed 6-7 sessions/week of 1.5-3 hours/session. For nocturnal dialysis regimen, patients performed 5-6 sessions/week of 6-8 hours/session. The standard Kt/V ranged from 3.24 to 5.86 per week.

Conclusions: Based on the literature, the target patients for a high-dose HD regime are generally young Caucasian males. In addition, underlying causes for ESRD like polycystic kidney disease are more frequent in high-dose HD patients compared to CHD.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

PUB625
Hypertension (HTN) in High School Students (stu): Genetic and Environmental Factors: The Empowerment of Dietary Salt Intake
Roberto Bigazzi,1 Stefano Bianchi,1 Salvatore Lenti,2 Roberto Burano,3 Giada Santini,1 Francesca Nistri,1 Chiara Bilanceri,1 Elisa Poderelli,1 Silvia Campatelli,1 Vito M. Campese.3 Nephrology, ASLNOVOEST Toscana, Livorno, Italy; 2Medici per San Ciro, Grottaglie, Italy; 3Nephrology, USC, Los Angeles.

Background: Due to the epidemic of obesity, the prevalence of HTN is increasing among children. Identification of pre-HTN at this age is important to implement lifestyle interventions. The aim of this study is to evaluate 3,000 high school stu in 3 regions of Italy (IT); in the north, in the center and in the south to 1. Determine the prevalence of obesity

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
and HTN; 2. Perform genetic analyses to determine a link between specific polymorphisms and HTN; 3. Assess the effect of a new adherence program and HTN; 4. Examine whether dietary markers and inflammation and oxidative stress are linked to HTN and CV risk in st with selected genotypes. 

Methods: So far, we have enrolled 753 stu (394 in central and 359 in south IT). Here we present the preliminary data related to the first year of the study focusing on the relationship of dietary Na and intake with HTN. 

Results: The average age was 16.4±1.4 yr; 42.7% M and 49.7% F. In central IT, the average BMI was 21.8±0.5; waist circumference 75.5±9.6; 8.2% of stu were overweight and 2.7% obese. In south IT, the average BMI was 22.5±0.6; 19% of stu were overweight and 6 % obese (P<0.01 compared with central IT). The average UNa was 144±5.5 and UK excretion 44±8,3mEq/g creatinine. (P< 0.01 compared with central IT). Among groups of overweight or obese stu, 85.4% were obese or overweight. Of interest, of stu from hypertensive parents was lower (p=0.02) than those from normotensive parents. 

Conclusions: Our data indicate that: 1) overweight and obesity are more common among children from south than central IT; 2) salt intake is higher in south than central IT; 3) UK excretion is low both in central and south IT suggesting that adherence to a Mediterranean diet is currently not applied. 4) The surprising reduced dietary salt intake among children and HTN; 2. Perform genetic analyses to determine a link between specific polymorphisms and HTN; 3. Assess the effect of a new adherence program and HTN; 4. Examine whether dietary markers and inflammation and oxidative stress are linked to HTN and CV risk in st with selected genotypes. 

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Funding: Government Support - Non-U.S.

PUB626

Renal-Artery Stenosis and Renal Impairment after Renal Denervation Biplanar Angiography and Treatment: The First Experience in Pediatric Nephrology, Bahrain Specialist Hospital, Bahrain.

Background: The prevalence of hypertension (HT) in children and adolescents has increased markedly over the last 20 years, primarily as a result of the obesity epidemic. Because an increased blood pressure (BP) in kids adults into adulthood and possibly causes increased cardiovascular morbidity, it is considered standard of care to measure BP in pediatric practice. However in 2013, the US Preventive Services Task Force (USPSTF) concluded that there are inadequate data to support routine BP screening in asymptomatic children. The potential adverse consequences of screening for high BP in pediatric patients has not been addressed. The objective of this study was to assess the psychological impact of a diagnosis of HT in children and adolescents.

Methods: Patients, age 10-21 yr old, with a diagnosis of HT and their parents were eligible for inclusion. They were recruited in the Fink Ambulatory Care Center or the Bellevue Nephrology Clinic. A 9-question Hypertension Quality of Life Questionnaire was developed to evaluate emotional, performance, and interpersonal aspects of well-being. The primary outcome measure was the total and three subdomain scores in the child version of the survey, based on a 5-point Likert scale. Child and parent scores were compared for inter-rater reliability using intraclass correlation and psychosocial burden of a diagnosis of HT.

Results: There were 20 participants, 14M:6F, mean age 15.6±2.1 yr, 11 White, 3 Black, 4 Hispanic and 2 Other. 16 subjects were in middle or high school and 4 attended college. The parents were married in 14, divorced in 2, or single in 4 cases and in 17 families at least 1 parent attended college. 9 participants were receiving antihypertensive drugs. The survey was completed 2.6±2.8 yr after the diagnosis of HT was made. The mean total score was +0.4 units (P=0.75). The mean emotional subscore was -0.95 units (P=0.10) and 15 (75%) had a negative score. There were no significant differences between the participant current responses.

Conclusions: Our findings suggest that there may be adverse psychological consequences of being given a diagnosis of high BP, especially in emotional status, in adolescents and young adults. Further work is needed to address this issue.

Funding: Clinical Revenue Support

PUB629

Psychological Impact of a Diagnosis of Hypertension in Pediatric Patients Howard Trachtman, Laura Jane Pehrson, Suzanne M. Vento, Laura Malaga-Dieguex, Nigel Madden. Pediatrics, NYU Langone Medical Center, New York, NY.

Background: The prevalence of hypertension (HT) in children and adolescents has increased markedly over the last 20 years, primarily as a result of the obesity epidemic. Because an increased blood pressure (BP) in kids adults into adulthood and possibly causes increased cardiovascular morbidity, it is considered standard of care to measure BP in pediatric practice. However in 2013, the US Preventive Services Task Force (USPSTF) concluded that there are inadequate data to support routine BP screening in asymptomatic children. The potential adverse consequences of screening for high BP in pediatric patients has not been addressed. The objective of this study was to assess the psychological impact of a diagnosis of HT in children and adolescents.

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Funding: Clinical Revenue Support

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

Underline represents presenting author. 1047A
Ankle Brachial Index and Glomerular Filtration Rate as Predictors for Independent Mortality All Causes in Patients with Hypertension Arterial Systemic Franklin Correa Barcellos,1,2 Annelise Reges,1 Gabriela Araujo Duarte,1 Alexia Schuch,1 Mateus De Mamann Vargas,1 Jamile Gardin Dos Santos,1 Luiza Morrone Gastaud,1 Mariestra Bohlke,1 Medicine School, Univ Catholic of Pelotas, Brazil;2 Medicine Faculty, Univ Federal of Pelotas, Pelotas, Brazil.

Background: High blood pressure, chronic kidney disease(CKD), and peripheral arterial disease (PAD) are predictors of mortality in the general population. It has been suggested that patients with arterial hypertension, glomerular filtration rate (GFR) < 60 ml/min/1.73m2 and PAD diagnosed by the ankle brachial index (ABI) < 0.9 also suffer increased mortality rate.

Objective: Identification of predictors of mortality from all causes in a sample of patients with hypertension.

METHODOLOGY: Cohort study that followed non-diabetic patients with hypertension, include variables gender, skin color, age, blood glucose, lipid profile, ABI and GFR calculated from serum creatinine(CKD-Epi-formula) The association between potential predictors and mortality were evaluated using logistic regression.

RESULTS: The sample of 150 subjects had age (mean / SD) of 65.05 (10.88) years, 36.7% male, 67.9% white and 43.0% patients with chronic kidney disease, were accompanied by an average of 2.82 (0.73) years. There were a total of 18.16% deaths in the follow-up period. Presence of CKD (OR 5.38; 95% CI 1.07 to 27.08, P = 0.04) or decreased GFR (OR 0.95 95% CI 0.91 to 0.99; p = 0.01) and ITB reduced (OR 0.02 95% CI 0.01 to 0.57, p = 0.02) were independent predictors of death during follow-up. Ten of the 13 deaths occurred in patients with CKD.

CONCLUSIONS: Reduction in GFR, as the lowest ITB has been associated with increased mortality in the general population. This study confirms the prognostic impact of these variables also among non-diabetic elderly patients with hypertension.

Single-Pill Irbesartan/Amlodipine Combination Therapy Improves Clinic and Home Blood Pressure Profiles in Hypertensive Patients with Chronic Kidney Disease Kouichi Tamura, Ryu Kobayashi, Hiromichi Wakui, Masato Ohswa, Kengo Azushima, Kazuzhi Ueda, Sona Haku, Kotoro Haruhara, Kohji Ohki, Sho Kinguchi. Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Kanagawa, Japan.

Background: Accumulating evidence indicates that appropriate blood pressure (BP) control is essential to inhibit renal deterioration and to prevent cardiovascular complications in hypertensive patients with chronic kidney disease (CKD). In this study we examined the efficacy and safety of single-pill irbesartan/amldipine combination therapy for 12 weeks in hypertensive CKD patients, by evaluating self-measured home BP profile.

Methods: Hypertensive patients with CKD who have already been treated with antihypertensive therapy comprised of renin-angiotensin system inhibitors or calcium channel blockers were eligible for this study if they could not achieve the target BP (clinic systolic BP≤ 130 mmHg and/or diastolic BP≤ 80 mmHg). After the run-in period, eligible patients were given a single pill of irbesartan/amldipine tablet for 12 weeks. Clinic BP and home BP profiles as well as parameters of vascular function were evaluated at baseline and after the protocol therapy. Self-measured home BP values were obtained upper arm cuff oscillometric device with a memory-equipped system (HEM-7080IC, Omron, Kyoto, Japan).

Results: 20 patients were enrolled and assigned to the single-pill irbesartan/amldipine combination therapy for 12 weeks. Combination therapy for 12 weeks significantly decreased clinic BP and home BP (home morning BP; baseline vs 12 weeks, 150±16:85±10 mmHg vs 133±12:76±9, P<0.01). In addition, the combination therapy significantly decreased within-visit variability of clinic BP and day-by-day variability of home BP after 12 weeks treatment. Concerning parameters of vascular function, the combination therapy significantly improved central systolic BP, AI, baPWV and CA VI.

Conclusions: The results of present study suggest that the single-pill irbesartan/amldipine combination therapy may exerts beneficial effects on clinic and home BP profiles including BP variability and vascular function, in addition to BP lowering, in hypertensive CKD patients.

Variability of Circadian Blood Pressure Differentiates Hypertensive Kidney Damage from Chronic Glomerulopathy Arkadiusz Lubas, Grzegorz Kade, Stanislaw Niemczyk. Internal Diseases Nephrology and Dialysis, Military Inst of Medicine, Warsaw, Poland.

Background: Unknown medical history, well-controlled hypertension and clinically latent stable chronic kidney disease (CKD) make it difficult to recognize the initial etiology of kidney damage. The aim of the study was to investigate whether echocardiography or blood pressure profile could help in differentiating between hypertensive nephropathy (HN) and glomerulonephritis (GN) related CKD.

Methods: Sixty nine patients (9 F; 60 M; age 54.3±14.1) with stable CKD (CKD-EPI 53.2±20.9 ml/min/1.73m2) and a history of hypertension (44 with HN) were enrolled in the study. Serum Creatinine (Cre), Cystatin C (Cys), echocardiography and ABPM were tested. Renal function was estimated according to Cre and Cys based on CKD-EPI formula.

Results: Groups with HN and GN did not differ in renal function, systolic, diastolic and mean arterial blood pressure (BP), pulse pressure, left and right ventricles dimensions, as well as left ventricular hemodynamic parameters (E/E', ejection fraction, stroke volume). Patients in HN group were older (age 57.5±13.2 vs 48.6±14.1 years; P>0.01) but had lower to norma blood pressure mean BP/DN (11.2±38.5 vs 16.0±5.8%, P=0.01) and depression of morning BP-profile (PMS) (12.8±10.1 vs 18.5±7.6 mmHg; p=0.02). Diagnosis of HN correlated with age (r=0.31), PMS (r=-0.30), DN (r=-0.47) and stroke volume (r=0.25). After adjusting to the age, in logistic regression, only DN was significantly connected with likelihood of HN (r=-0.084; OR 0.919; 95% CI 0.847-0.997; p=0.04). In ROC analysis DN ≤ 10% recognized HN with specificity of 88%, and sensitivity of 40% (p=0.01).

Conclusions: Nondipping pattern of blood pressure promotes recognition of hypertensive nephropathy rather than glomerulonephritides as the etiology of chronic kidney disease.

Funding: Government Support - Non-U.S.
Finger Arterial Pressure as Index of Impaired Vessel Wave Reflection and Peripheral Vascular Disease in Hemodialysis Patients  
Gaetano Alfano, Francesco Fontana, Gianni Cappelli. Dept of Surgery, Medical and Dentistry, Univ of Modena, Modena, Italy.

**Background:** Nexfin monitor evaluates continuous and non-invasive measurement of arterial blood pressure (BP) through finger-cuff technology; it reconstructs brachial arterial pressure (BP) analyzing peripherally changes of systolic and diastolic wave reflections. It was validated against the auscultatory method using sphygmomanometer but aim of our study is to evaluate Nexfin in maintenance hemodialysis patients (HD).

**Methods:** Forty-homodynamically stable HD underwent serial measurement of Nexfin arterial pressure (NAP) and BAP before HD-sessio. BAP was taken in the upper arm by oscillometric sphygmomanometer.

**Results:** Patients mean age was 68.9±14.9 years, being 65% > 65 yrs and 29% > 75 yrs; 27% of pts were diabetic. Bland-Altman analysis comparing NAP measurements with BAP revealed: a mean bias±LA of 15.3±39.8 mmHg (29% error) for systolic BP, a mean bias±LA of 0.9±20.34 mmHg (32% error) for diastolic BAP and a mean bias of 4.5±11.34 mmHg (26% error) for MAP. Nexfin had poor accuracy in the reconstruction of diastolic and mean BP and extremely inaccurate for systolic BP.

**Table 1. Comparison of BAP versus NAP**

<table>
<thead>
<tr>
<th>No. of patients: 40</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BAP</td>
<td>mmmHg</td>
<td>122.3</td>
<td>82.7</td>
</tr>
<tr>
<td>R²</td>
<td>0.93</td>
<td>0.44</td>
<td>0.44</td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bias</td>
<td>mmmHg</td>
<td>15.1</td>
<td>4.57</td>
</tr>
<tr>
<td>SD of bias</td>
<td>mmmHg</td>
<td>17.8</td>
<td>10.89</td>
</tr>
<tr>
<td>Lower LA</td>
<td>mmmHg</td>
<td>-16.6</td>
<td>-16.77</td>
</tr>
<tr>
<td>Upper LA</td>
<td>mmmHg</td>
<td>56.2</td>
<td>21.92</td>
</tr>
<tr>
<td>Percentage error</td>
<td>%</td>
<td>29</td>
<td>33</td>
</tr>
</tbody>
</table>

**Conclusions:** In healthy subjects can evaluated CVR with genetic test, carotid echography and eucardioscopy. This CVR is associated with metabolic parameters (especially glucose, triglicerides and uric acid). Intima media thickness measure in left carotid and renal function with CKD-EPI, is better associated with genetic test CVR calculated.

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**PUB636**

Denosumab Induced Severe Symptomatic Hypocalcemia in a Patient with Normal Renal Function  
Ashwin Reddy Ganta, Dept of Nephrology, Archbold Memorial Hospital, Thomasville, GA.

**Background:** A 69 y/o Caucasian female was referred to our clinic for resistant hypocalcemia with panic attacks over the past 18 months. She complained of severe anxiety symptoms with significant impairment of QOL and was on Buspirone and Aripiprazol with some relief. Her PMH was significant for HTN and Osteoporosis. Her medications included OTC Vitamin D and Calcium Supplements. Her physical examination was significant for Osteopenic signs and a positive Trouseau sign. Her lab work done a few months ago prior to this presentation was significant for Low Calcium (5.6 mg/dL), Low Ionized Calcium (3.5 mg/dL) with normal albumin and Serum Creatinine (0.7 mg/dl) and Cr Clearance 92 ml/min. Her 25(OH) Vit-D level was low (23 ng/ml) with elevated 1,25(OH) Vit-D levels (144 ng/ml and PTH elevated at 399 pg/ml (Normal 15-65 pg/ml). Her magnesium level was normal. On further questioning, patient admitted that received 4 doses of Prolia (Denosumab) for Osteoporosis over the last 2 years. Her hypocalcemia was attributed to Denosumab and her elevated PTH level was most likely compensatory. She has been initiated on high dose Vitamin D analog and elemental Calcium therapy and is doing better.

**Discussion:** Denosumab is a fully human monoclonal antibody that inhibits bone resorption by binding to receptor activator of Nuclear Factor kB Ligand (RANKL). CKD stage IV/V, Male sex and Malignancy have been found to be risk factors for Denosumab induced symptomatic hypocalcemia and mild non symptomatic hypocalcemia has been reported as a side-effect as well. Based on Pubmed review, to our knowledge this is the first case report of Denosumab induced hypocalcemia in a patient with normal renal function and no known malignancy.

With Denosumab use increasing due to the side effects with Bisphosphonate use, physicians need to be aware of the potential severe side-effects with Prolia.

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**PUB637**

Incidence and Prevalence of Hypomagnesemia in the Intensive Care Units  
Satyam Patel, Maria V. DeVita, David Selzer, Michael F. Michels. Nephrology, Lenox Hill Hospital, New York, NY.

**Background:** The incidence and prevalence of hypomagnesemia in the critical care setting have both been reported as high as 65%. However, a substantial amount of data is from outside the United States and more than 10 years old. This present study evaluates the incidence and prevalence of hypomagnesemia in the intensive care setting.

**Methods:** A prospective, observational study was done on consecutive patients admitted to medical and surgical intensive care units at a tertiary hospital. Each patient’s chart was reviewed for magnesium (Mg) level and medications in the ICU for up to 7 days. Hypomagnesemia was defined as 1.6 meq/L.

**Results:** To date, of the 157 patients reviewed, 108 patients had Mg measured on Day 1. In this cohort, the prevalence of hypomagnesemia was 18/108 = 16.7% (95% CI: 10.2-25.1). Among the 90 patients who had a normal Mg the 1st day, 6 patients did not have Mg level measured during the remainder of their ICU stay, while 84 patients had Mg measured on at least one occasion from day 2 to day 7. Among these 84 patients, 2 patients developed hypomagnesemia at day 2 and no patient developed hypomagnesia at day 3 or later. Therefore, the estimated incidence of hypomagnesemia is 2/84 = 2.4% (95% CI: 0.3-8.3). Interestingly, 77 patients had at least one Mg supplementation, for a total of 114 supplements administered; the average Mg level at which supplementation occurred was 1.7 mg/dL, indicating that most patients are supplemented prior to actually reaching a low Mg level. There was not enough evidence to conclude that other selected factors, such as diuretics, PPIs, and antibiotics were associated with hypomagnesemia. The only comorbidity associated with hypomagnesemia was a history of DVT/PE (62.5%) compared to patients without DVT/PE (15.0%) (p = 0.005).
Our study indicates that social support from a spouse/partner, family, friends, or caregivers has the potential to affect outcomes, but has not been widely investigated. We studied if the social support type is associated with dialysis Pts achieving mineral bone disorder (MBD) laboratory goals.

**Methods:** We analyzed data from Jan 2014 to Dec 2015 on 185,131 Pts at Fresenius Medical Care North America who completed the social work assessment questionnaire. We studied responses to the question “when you have a big problem, can you usually rely on?”, which has choices for support types including: “no one but myself”, “support from my spouse/partner”, “a member of my family”, “a friend/neighbor”, or “on health staff/community resource/church”. We compared support types to the proportion of Pts meeting mean 6 month laboratory goals for calcium (Ca) $\pm 0.10$ mg/dL, phosphate (PO4) $\pm 3.5-5.5$ mg/dL, and intact parathyroid hormone (iPTH) $\pm 150-600$ pg/mL prior to completing the questionnaire.

**Results:** We observed Pts that received social support from a friend/neighbor or nobody had a distinguishably lower proportion of Pts meeting PO4 goals, as compared to other support types. Pts who received support from a spouse/partner had slightly more Pts meeting goals for iPTH versus other support types. Almost all Pts achieved Ca targets with no remarkable differences between types of support (Figure 1).

**Conclusions:** Our study indicates that social support from a spouse/partner, family member, or health staff/community resource/church may result in better control of PO4 levels, as compared to support from a friend/neighbor or no one. This may be indicative of improved adherence to PO4 binders with improved social support.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

---

**Table 1**

<table>
<thead>
<tr>
<th>Parameter estimate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.018</td>
</tr>
<tr>
<td>BMI</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoke</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**R**$^2$ = 0.53

**Conclusions:** This is the first clinical study in a dialysis population identifying smoke as a factor negatively affecting osteocalcin levels.

**PUB641**

**Tailoring Phosphate Binders to Patients’ Needs: Outcomes of a Short Term Pilot Study of a New Web-Based Tele-Medical Device for Smartphones and Tablets (P-MED)**

**Giuseppe Rombo**

**Luca Neri**, **Alice Fattori**, **Elisa Ottone**

**Unit of Nephrology, Ospedale Di Varese, Varese, Italy;** **Univ of Milan, Milan, Italy**

**Background:** Non-adherence to phosphate binders hampers clinical outcomes and increases costs. We assessed the suitability of a new tele-medical device (P-MED) designed to help nurses personalize clinical decisions and improve patient’s adherence. We assessed outcomes of P-MED usage in clinical practice over a 2-month follow up.

**Methods:** P-MED allows to record, view and integrate data on phosphorus lab values, medical prescriptions, p-binders dose, dietary habits, and the 8-item Morisky’s adherence scale. The daily interview is administered via a computer assisted system selecting the most informative question based on previous patients responses. Based on p-binders dose equivalence charts and nutritional charts, P-MED calculates and displays binding needs and the “calcium carbonate 1000 mg” equivalent dose (CC1000-ED) taken by the patients in the day preceding each interview. The pilot study took place in a single center in Italy from April to June 2016. Nurses were allowed to take as many interviews as deemed appropriate,
and encouraged to negotiate adjustments to medication dose based on phosphorus dietary intake with patients. Key clinical trajectories have been evaluated with random intercept generalized models.

**Results:** Ten nurses voluntarily elected to participate in the study and 63 patients took part to the study. During the 2-month follow up 84 adherence interviews and 380 dietary interviews occurred. Baseline characteristics and clinical outcomes are reported in figure 1.

**Conclusions:** The application was well accepted by nurses and patients as showed by the high usage frequency. Despite non statistically significant the improvement in clinical outcomes and the reduction in medication usage is sizeable and merits further investigation in longer term and larger clinical studies.

**PUB642**

**Quality of Mineral Bone Disease Care in Non-Dialysis Chronic Kidney Disease: Results of a Multi-Centre Audit and Survey Questionnaire in the Irish Health System** Muhammad Umair Sharif,1,2 Mohamed Elsayed,1,2 Ahmed Alghali,1,2 Mohammed A. Kaballo,1,2 John P. Ferguson,1 Xia Li,1,3 Austin G. Stack,1,2,3 ‘Graduate Entry Medical School (GEMS), Univ of Limerick, Limerick, Ireland; 2Dept of Nephrology, Univ Hospital Limerick, Limerick, Ireland; 3Health Research Inst (HRI), Univ of Limerick, Limerick, Ireland; 4Health Research Board (HRB) Clinical Research Facility, National Univ of Ireland, Galway, Ireland.

**Background:** Chronic Mineral Bone Disease (MBD) is the most prevalent complication of Chronic Kidney Disease (CKD) and contributes to multiple adverse clinical outcomes. We sought to describe the prevalence, disease characteristics and quality of care of CKD-MBD in non-dialysis Irish CKD population. Parallel to this audit we explored the opinions and attitudes of Irish nephrologists, and their adherence to guidelines.

**Methods:** Data were captured on several aspects of outpatient MBD care in 530 non-dialysis CKD patients from nephrology clinics across 6 Irish health regions. Correspondingly, the survey questionnaire captured the attitudes of nephrologists on use of clinical guidelines and thresholds for intervention. Descriptive statistics and comparisons across groups were made using chi-square, ANOVA and logistic regression.

**Results:** The overall prevalence of CKD-MBD was 48%. The rate of MBD testing increased from 41% in Stage 3 to 88% in Stage 5. Overall 91% of patients’ in Stage 3-5 had optimal phosphate control (Phosphorus <4.6 mg/dL). Among 9% patients with hyperphosphataemia, calcium-based binders were the preferred first-line treatment. The opinion of nephrologists varied widely on the threshold for binder initiation, choice of second line binder as well as the desired target for optimal control. The most frequently used guidelines were from UK Renal Association (41%).

**Conclusions:** Although control of MBD is generally good in the Irish Health system, residual deficits exist. Low treatment and testing rates didn’t correspond to nephrologists’ opinions, which varied widely. Variability in clinical practice may in part be due to these differences and may contribute to differential outcomes. Knowledge of these differences will serve as a useful starting point in seeking consensus for the production of national standards.

**PUB643**

**Is There Really an Correlation between Serum Soluble Klotho Levels and Survival in Maintenance Hemodialysis Patients** Jie Ma, Xuemei Li, Yang Yu. Nephrology Dept, Peking Union Medical College Hospital.

**Background:** Transmembrane α-Klotho (TM-Klotho) expressed in renal tubules, is a cofactor for FGF23-receptor. Circulating soluble-α-Klotho(sKlotho) results from TM-Klotho, the extracellular domain of α-Klotho can be cleaved and released into various extracellular fluids, such as blood. Decreased TM-Klotho, prevents actions of FGF23 and lessens circulating sKlotho. Thus, levels of sKlotho could represent a marker of CKD-MBD, also possibly plays a role in determining the risk of mortality in some populations. The relationship between the level of serum soluble α-Klotho and overall mortality in hemodialysis patients is unclear yet.

**Methods:** We prospectively followed a cohort of 119 maintenance hemodialysis patients for 30 months in Peking Union Medical College Hospital dialysis center. We assessed the level of the soluble α-Klotho and FGF23 of these patients. Cox regression models were used to analyze the relationships between the primary outcomes (death) and the serum soluble α-Klotho and FGF23 levels.

**Results:** A total of 119 cases were enrolled this study, male 59, female 60, age 19-90years, mean age 59.3years, with duration of dialysis for10-95 months. The mean serum sKlotho level and FGF23 level were no significance different between two groups of HD patients.

<table>
<thead>
<tr>
<th></th>
<th>Dead HD Patients</th>
<th>Survival HD Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klotho (pg/mL)</td>
<td>285.07±156.56</td>
<td>239.22±201.93</td>
<td>0.397</td>
</tr>
<tr>
<td>FGF23 (pg/mL)</td>
<td>435.05±649.46</td>
<td>3968±348.64</td>
<td>0.222</td>
</tr>
</tbody>
</table>

Also we did not find any correlation between soluble-α-Klotho and FGF23 and all-cause mortality.

**Conclusions:** We suspect that there may not be an correlation between serum soluble Klotho levels and all-cause mortality in maintenance hemodialysis patients.

**PUB644**

**High-Resolution Magnetic Resonance Imaging to Assess Bone Microarchitecture in Patients with Chronic Kidney Disease** Ashish K. Sharma,1,2 Nigel David Toussaint,1,2 Grahame J. Elder,3,4 Stephen G. Holt,1,2 Patricia L. Robertson,3,2 Peter Robert Ebeling,3,2 Paul A. Baldock,1,3 Chanthi S. Rajapakse,1,3 Rosemary Masterson,1,2 Royal North Shore Hospital, North Sydney, Sydney, NSW, Australia; 3Health Research Board (HRB) Clinical Research Facility, National Univ of Ireland, Galway, Ireland; 4University of Melbourne, Parkville, VIC, Australia; 5Westmead Hospital, Westmead, NSW, Australia; 6Garvan Inst of Medical Research, Sydney, NSW, Australia; 7Monash Health, Clayton, VIC, Australia; 8Univ of Pennsylvania, Philadelphia, PA.

**Background:** Renal osteodystrophy (ROD) affects bone quantity and quality and is associated with increased fracture risk. Screening for ROD is hindered by inadequacy of current diagnostic methods. Bone biopsy is invasive and infrequently performed routinely. High-resolution magnetic resonance imaging (HR-MRI) is a new technique to assess trabecular and cortical microarchitecture. We aimed to validate HR-MRI assessment of bone structure compared to histomorphometry and micro-CT of bone biopsies from kidney transplant recipients.

**Methods:** A total of 104 patients were enrolled to the study. One sub-cohort of 14 patients underwent micro-CT scanning. Patients of C1-3 tibia HR-MRI scans and iliac crest bone biopsies were performed in 10 transplant recipients at transplantation. Structural parameters of biopsies were analyzed by histomorphometry and 3D micro-CT. Measurements included trabecular bone volume (TV/BV), thickness (TbTh), number (TbN), separation (TbS), mean cortical thickness (CtTh) and porosity (%Ps). Bone mineral density (BMD) was measured by peripheral quantitative computerized tomography (pQCT, radius) and dual energy x-ray absorptiometry (DXA, hip).

**Results:** Associations were determined by analysis with Spearman’s rank correlation coefficients.

**Conclusions:** Micro-CT histomorphometry correlates to tibial HR-MRI for trabecular indices and to hip DXA for cortical indices. HR-MRI and DXA combined with biochemical turnover markers may provide rapid, accessible information to guide management of ROD.

**PUB645**

**Does Potassium Citrate Have Equivalent Therapeutic Effect in Patients with Diabetes?** Kimberly Maciokle, Kristina L. Penniston, Leema M. John, Sara Best. Dept of Urology, Univ of Wisconsin School of Medicine & Public Health.

**Background:** Diabetes (DM) increases the risk of stone formation. Patients with and without DM may have both acidic urine and low citrate but with different etiologies. Potassium citrate therapy (KCit) is used to alkalize urine and raise citrate, but its efficacy in patients with DM, whose urinary derangements may be more significant, has not been assessed. We compared changes in 24hr urine parameters after KCit in stone formers with and without DM.

**Methods:** We identified 32 patients (16 with DM who had 24hr urine results pre- and post-KCit. Changes in urinary risk factors between patients with and without DM were evaluated.

**Results:** Age and BMI were similar between groups (58 vs 55 y, p=0.39, 35.3 vs 31.5 kg/m2, p=0.25). Median time between starting KCit and the follow-up urine collection was 173 and 300 days (DM vs non-DM, p=0.13). 24hr urinary parameters were similar between groups before KCit. All patients were deemed to be compliant with KCit. Changes in group means for 24hr urine parameters are shown in the table.

<table>
<thead>
<tr>
<th></th>
<th>Patients with DM</th>
<th>Patients without DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cit (mg/d)</td>
<td>95</td>
<td>126</td>
</tr>
<tr>
<td>pH</td>
<td>5.90*</td>
<td>6.40</td>
</tr>
<tr>
<td>K (mEq/d)</td>
<td>20*</td>
<td>13</td>
</tr>
<tr>
<td>SS Br</td>
<td>0.09</td>
<td>0.66*</td>
</tr>
<tr>
<td>SS UA</td>
<td>-0.68*</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*Statistically significant change (p<0.05) pre- vs post-KCit.

**Table 1 : Mean change in urinary risk factors after initiating KCit**
Neither group achieved a statistically significant rise in citrate after initiating KCi. The path DM experienced a significant rise in pH. A significant proportion of patients without DM achieved therapeutic levels of citrate (>320 mg/d) with KCi (81%, p<0.028). Brushtie supersaturation (SS) rose significantly only in patients without DM after initiating KCi. Uric acid SS decreased in both groups but was significant only in patients with DM. Other changes in 24h urine were statistically similar regardless of DM status.

Conclusions: The effect of KCi on 24hr urine risk factors for stone formation is similar in patients with and without DM. Patients with DM may experience a greater improvement in urine pH than patients who do not have DM and may do so without risking a rise in brushtie SS.

PUB646

Addressing an Unmet Need in Patients with Secondary Hyperoxaluria

Sagar U. Nigwekar,1 James E. Lingeman,2 Louis Brenner,1 Danica Grujic,3 Annamaria T. Kausz.1 1Div of Nephrology, Massachusetts General Hospital, Boston, MA; 2Dept of Urology, Indiana Univ, Indianapolis, IN; 3Allena Pharmaceuticals, Newton, MA.

Background: Kidney stones are common, and secondary hyperoxaluria (2HOx) is a known risk factor. However, randomized controlled trials (RCT) of 2HOx are rare, and little is known about dietary oxalate intake and its correlation to 24h urinary oxalate (UOx) excretion. Here we present characteristics of patients with 2HOx enrolled in two Phase 2 double blind, placebo-controlled RCTs of ALLN-177, a novel oral, crystalline enzyme therapy that specifically degrades oxalate in the GI tract, decreasing the amount available for absorption. Our prior trials demonstrated that ALLN-177 reduced 24h UOx in both healthy volunteers and patients with 2HOx.

Methods: In Study 649, 42-60 subjects are being randomized to receive 1500, 3000 or 7500 units of ALLN-177 or placebo TID with meals x 7d, then cross over to an alternate arm for 7d. In Study 713, 44 subjects are being randomized to receive 7500 units of ALLN-177 or placebo TID with meals x 28d. Subjects remain on their usual diet, monitored with dietary recalls throughout the study. The primary efficacy assessment is based on mean change in 24h UOx.

Results: To date, 30 and 13 subjects have enrolled in Study 649 and 713, respectively. Across both studies, mean age is 60 years, 74% are male and 26% have 2HOx from bariatric surgery or inflammatory bowel disease. Subjects report on average ~6 stones in the past 5 yrs. Nearly 75% of subjects received some guidance to modify dietary intake. Entering the study, mean (SD) dietary intake of oxalate was 351 (435) mg/d, calcium 981 (578) mg/d, and fluids 3.9 (1.3) L/d. Mean (SD) excretion of UOx was 77 (32) mg/d, calcium 248 (178) mg/d and citrate 738 (576) mg/d; urine volume was 2.4 (0.76) L/d.

Conclusions: The characteristics of subjects enrolled in ALLN-177 clinical trials highlight the need for an effective therapy for 2HOx. Despite adequate fluid intake and dietary guidance, patients have excess oxalate in their diet, remain hyperoxaluric, and have recurrent kidney stones. Results of these Phase 2 studies will provide further confirmation of the efficacy and tolerability of ALLN-177 for treating 2HOx.

Funding: Pharmaceutical Company Support - Allena Pharmaceuticals

PUB647

Follow-Up of HD Patients Receiving sVDRA for Prevention and Treatment of SHPT: An Observational Study (P12-314)

Evren E. Ensoy,1 Hasan Koc,2 Hasan Hoser,3 Yalcin Akdag,4 Cemaliye Kendir.5 1Adeniz Univ Medical School, Antalya, Turkey; 2Hayat Dialysis Center, Istanbul, Turkey; 3Cinar Dialysis Center, Katahya, Turkey; 4Larende Dialysis Center, Karaman, Turkey; 5Besyuzver Sahaf Hospital, Istanbul, Turkey.

Background: Secondary hyperparathyroidism (SHPT) is caused by decreased calcitriol synthesis, phosphate (P) accumulation and hypocalcemia during chronic kidney disease (CKD). The aim of this study was to evaluate monthly changes of iPTH and other major mineral bone marker levels in hemodialysis (HD) patients with SHPT receiving paricalcitol.

Methods: 493 (F/M 243/250) adult hemodialysis (HD) patients, who were selected from 22 HD units in Turkey; receiving sVDRA treatment; with iPTH>300 pg/mL, Ca<10.2 mg/dl and P<6 mg/dl, were included in this multi-center, national, prospective, observational study. Efficacy, safety and adverse events information on sVDRA treatment were collected by monthly visits along with iPTH, Ca, P and hsCRP values for 12 months. Mortality data was collected 6 months after the end of study.

Results: The mean age and duration of CKD Stage 5 were 58.3±15.8 years and 6.2±5.5 years, respectively; HD duration was ≤1 year in 14.4%, whereas longer than 3 years in 59.2% of subjects. Dialysate Ca concentrations were 125 mmol/L in 77.1% of patients. As of the 12th month, no statistically significant changes have been observed in Ca and hsCRP levels (p>0.05) (Figure 1) and iPTH values were decreased from 646±424 pg/mL to 473±387 pg/mL (p<0.001). There were clinically insignificant increases in P and albumine levels at 12th month compared with the baseline (p=0.017 and p<0.003 respectively).

Conclusions: Our study has shown that, paricalcitol, in addition to successful iPTH control, had favorable effects on serum Ca and P, which are consistent with previous studies. Increased serum albumin levels at Month 12, may be related to nutritional factors.


PUB648

Effects of Parathyroidectomy on Blood Bone Markers and Heart Rate Variability in Stage 5 Chronic Kidney Disease Patients

Ningning Wang, Huimin Chen. Dept of Nephrology, First Affiliated Hospital with Nanjing Medical Univ, Nanjing, China.

Background: Attenuated heart rate variability (HRV) is associated with cardiovascular autonomic nerve disorders. No study has investigated the correlations between blood bone markers and HRV in chronic kidney disease (CKD), especially in secondary hyperparathyroidism (SHPT) patients.

Methods: We performed cross-sectional and prospective studies.

Results: Compared with controls, baseline circulating levels of phosphorus, iPTH, (7-84)PTH as bone remodeling regulators, (2)bone-specific alkaline phosphatase (BAP), representing bone formation; (3) tartrate-resistant acid phosphatase (TRACP-5b), indicating bone resorption; (4) bone-derived hormone, fibroblast growth factor 23 (FGF23) and its cofactor Klotho.

Results: Compared with controls, baseline circulating levels of phosphorus, iPTH, (7-84)PTH, BAP, TRACP-5b, and FGF23 were increased, while Klotho and wPTH/ iPTH were decreased in CKD patients. Baseline plasma wPTH, (7-84)PTH, TRACP-5b, and FGF23 levels were associated with HRV in CKD. In parathyroidectomy (PTX) group, baseline and postoperative changes of bone markers which predicting the normalization of HRV were shown in table 1.

Bone parameters included (1) intact parathyroid hormone (iPTH), whole PTH (wPTH), and (7-84)PTH as bone remodeling regulators, (2) bone-specific alkaline phosphatase(BAP), representing bone formation; (3) tartrate-resistant acid phosphatase(TRACP-5b), indicating bone resorption; (4) bone-derived hormone, fibroblast growth factor 23(FGF23) and its cofactor Klotho.
Dependent Improved HRV variables | Independent bone markers variables
---|---
Δmean 24h heart rate | Δ(7-84)PTH
Δmean normal-to-normal R-R intervals | (7-84)PTH
Standard deviation of the normal-to-normal R-R intervals | TRACP-5b
Arêt mean square of differences between adjacent normal R-R intervals | ΔiPTH
Aposturation of adjacent R-R intervals differing by >50 ms over 24 h | ΔiPTH
Δvery-low frequency | TRACP-5b
Δlow frequency | TRACP-5b
Δhigh frequency | TRACP-5b

Conclusions: In CKD, (7-84)PTH, TRACP-5b, wPTH, and FGF23 predict imbalances of cardiovascular autonomic nervous system. We offer novel insights into the relationship between bone resorption and cardiovascular disease in CKD.

Funding: Government Support - Non-U.S.

PUB649

Does Combination of Cinacalcet with Paricalcitol in Secondary Hyperparathyroidism Treatment Make Sense? | Jacek P. Zawisza,1 Wojciech Marcinkowski,1,2 Jolanta Małyszkow,2 Jack S. Małyszkow,2 Teresa Dryl-Rydzynska,1 Tomasz R. Prystacki.1 1 Fresenius Medical Care Polska S.A., Poznan, Poland; 2Second Dept of Nephrology and Hypertension with Dialysis Unit, Medical Univ of Bialystok, Bialystok, Poland; 3Department of Nephrology with Dialysis Unit, Medical Univ of Bialystok, Bialystok, Poland; 4Fresenius Nephrocare Polska sp. z o.o., Poznan, Poland.

Methods: The study included 64 hemodialysis patients aged 19-90, average PTH 930pg/mL/1440pg/mL (2718±516pg/mL, median 784pg/mL). Paricalcitol included in an initial dose of approximately 48mcg/month (5-180mcg/month depending on the initial iPTH level). 16 patients were additionally administered with cinacalcet (0.6mg/kg/day initially). Results: Paricalcitol impact on the concentration of iPTH, corrected calcium and alkaline phosphatase activity is shown in table 1.

Paricalcitol significant effect significantly on the corrected calcium concentration. Cinacalcet had also a similar effect on PTH level. In both groups effect on serum calcium and phosphate was observed. In both groups baseline iPTH corrected Ca (mg/dL) were 9.5±0.7 and 9.7±0.5, respectively. In both groups post-repletion iPTH, corrected calcium and alkaline phosphatase activity was 9.4±0.7 and 9.9±0.6, respectively. The combination of paricalcitol and cinacalcet does not improve the results of the treatment. The combination of paricalcitol and cinacalcet does not improve the results of the treatment. However, possible combination of two drugs may be considered in case of hypocalcemia, but cost-effectiveness should be taken into account.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

PUB650

Effect of GFR on a Novel Assay of Calcification Propensity in Chronic Kidney Disease | Bernhard O. Bielesz,1 Thomas Johannes Reiter,1 Rodrigo Marcelescu,2 Andreas Gleiss,3 Marija Bojic,1 Daniel Cejka.1 1Medical Univ of Vienna, Div of Nephrology and Dialysis, Vienna, Austria; 2Medical Univ of Vienna, Dept of Laboratory Medicine, Vienna, Austria; 3Elsabethinen Hospital, Div of Nephrology, Transplantation, and Rheumatology, Linz, Austria; 4Medical Univ of Vienna, Center for Medical Statistics, Informatics, and Intelligent Systems, Vienna, Austria.

Methods: Propensity of serum for calcification was determined by measuring the propensity of serum for calcification. The combination of paricalcitol and cinacalcet does not improve the results of the treatment. However, possible combination of two drugs may be considered in case of hypocalcemia, but cost-effectiveness should be taken into account.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.

1053A
Vitamin D: A New Marker for Acute Kidney Injury Progression

Jeanne Kamal,1 Christine Boumidri,2 Patricia Nasi,3 Joseph Saabiyi,1 Lara El Khoury,1 Firas Safa,1 Julie Zaidan,1 Rania El Maïs,1 Suzanne E. El Sayegh,3 Elie El-Charabati,2 1Internal Medicine Dept, Staten Island Univ Hospital, Staten Island, NY; 2Gastroenterology Dept, Univ of Missouri, Columbia, MO; 3Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, China.

Background: Acute kidney injury (AKI) is a common and serious complication occurring in 5-7% of hospitalized patients. Markers helping in the early recognition of patients at risk are still lacking. Low levels of vitamin D and its metabolites occur in AKI. This raises the interest of studying vitamin D as a predictor of AKI outcome.

Methods: Patients admitted to SIUH with AKI and a normal baseline GFR (>60) were enrolled. All patients had their serum creatinine (SCr) checked within 24 hours of admission (D0) and 3 days after (D3) and Vitamin D levels (25 hydroxyvitamin D; 1,25 hydroxyvitamin D) at D0, Vitamin D was collected at D3 for the patients who remained in AKI and not for those who recovered (50% decrease in SCr or return to baseline).

Results: 56 patients in AKI were enrolled. 37 were men, mean age of 64,6 and BMI of 31.1 22 (39.3%) were diabetic and 34 (60.7%) were hypertensive. 35 (56.4%) patients recovered from AKI and 21 (43.6%) remained in AKI at D 3. 1,25 DihydroxyVitamin D levels was significantly higher in patients whom kidney function improved (43.63 vs 30.1; p=0.036). There were no significant findings with respect to 25hydroxyvitamin D (19.51 vs 18.86; p=0.77).

Conclusions: 1,25 DihydroxyVitamin D is the active metabolite of vitamin D. High levels of Calcitriol were associated with clinical improvement of AKI. A possible explanation of the low levels in kidney disease is probably due to the suppressed renal 1α-hydroxylase activity in contrast to 25-hydroxyvitamin D which levels reflect the total body stores of vitamin D. Higher Calcitriol level is a marker of better outcome in AKI. Could supplementing patients in AKI with Calcitriol be an intervention helping in their recovery?

PUB653

Serum 1, 25-Dihydroxyvitamin D and Clinical Characteristics of End Stage Renal Disease Patients: A Cross-Sectional Study

Jing Liu, Juanwei Yang, Center of Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Most patients with end stage renal disease (ESRD) have vitamin D deficiencies, especially calcitriol deficiencies in both active (1, 25-dihydroxyvitamin D, 1, 25(OH)2D) and inactive vitamin D (25-hydroxyvitamin D, 25(OH)D). Most of the previous studies examined the inactivated form; however, the serum level of activated form and its role in ESRD patients were largely unknown. In this study we tested the levels of 1, 25(OH)2D in serum and evaluate their relations with clinical characteristics of ESRD patients.

Methods: This cross-sectional study enrolled a cohort of 709 ESRD patients on maintenance hemodialysis for at least 6 month, who came from two different hospitals. The serum concentration of 1, 25(OH)2D was measured by liquid chromatography mass spectrometer. Clinical covariates, including sex, age, dialysis duration were recorded. Serum concentrations of intact PTH (iPTH), calcium, phosphate, fibroblast growth factor 23 (FGF23) and alkaline phosphatase (ALP) were examined. Correlative artery calcification score (CACS), left ventricular ejection fractions (LVEF) and bone density were also measured.

Results: The serum levels of 1, 25(OH)2D were markedly decreased in hemodialysis patients (105.28 ± 65.74 pg/ml) compared with healthy control (110.70 ± 25.17 pg/ml; p<0.001). According to the quartile of serum 1, 25(OH)2D levels, the hemodialysis patients were divided into three groups. The serum FGF23, LVEF and blood flow rate were significantly different among these three groups. However, no statistical differences were found in age, dialysis duration, serum iPTH, ALP and CACS. Nevertheless, no significant difference in serum 1, 25(OH)2D levels was found in patients with or without active Vitamin D supplementation (66.24±5.48 pg/ml vs. 65.23±4.85 pg/ml; P>0.05). Moreover, lower serum 1, 25(OH)2D was significantly associated with incidence of osteodystonia and skin itching (P<0.05).

Conclusions: ESRD patients have active vitamin D deficiency. It seemed that increased metabolism is unknown and warrants further investigation.

PUB654

Does the Treatment for Secondary Hyperparathyroidism in End-Stage Kidney Disease (ESKD) Benefit Phosphorus Metabolism?

Joaquin Bautista, Fernando Tornerro, Serenius Gatiu, Jose A. Herrero, Marisol Poma Tapia, Amia Shabaka, Virginia Lopez de la Manzanara Perez, Fabio Proacceini, Mauricio Alejandro Miranda Cam, Ana Sanchez Frutcuo. Nephrology, Hospital Clinico San Carlos, Madrid, Spain.

Background: The rationale for increased PTH observed in patients with end-stage kidney disease is probably the increase in urinary phosphorus excretion. For the treatment of secondary hyperparathyroidism (SHP), most of the current clinical practice guidelines recommend lowering PTH levels. However, control of PTH could be accompanied by a decrease in the urinary phosphorus excretion and an increase in its serum concentration. Our goal was to evaluate the influence of PTH reduction on urinary phosphorus excretion in patients with ESKD.

Methods: We analyzed 64 patients with ESKD, 33 males, mean age 69.3±12.9 years, diagnosed with SHP with PTH-lowering treatment (59 with paricalcitol, 5 with cinacalcet). We evaluated epidemiological factors, renal function, calcium and phosphorus metabolism parameters before and after treatment. Patients with other therapeutic modifications that could have influenced calcium and phosphorus metabolism were not included.

Results: After treatment, we observed a significant decrease in PTH levels (from 385.3±135.1 pg/ml to 311.3±25.6 pg/ml; P<0.001), an increase in serum phosphorus levels (from 4.35±1.01 to 4.65±1.01; P<0.001). There was also a significant decrease in phosphorus excretion, measured both as 24-hour phosphaturia (from 582.5±29.2 mg/24 h to 528.2±28.1 mg/24 h; P=0.024), and as fractional excretion of phosphorus (from 47.9±18.1% to 44.2±22.2%; P=0.029), and parallel to this, an increase in tubular reabsorption of phosphorus (from 91.4 ± 21.5% to 95.3±2.1 %; p=0.029). Regarding renal function, we observed an increase in serum creatinine (from 3.7±1.04 mg/dl to 4.03±1.17 mg/dl; P=0.005), associated to a decrease in the glomerular filtration rate measured by CKD-EPI (from 16.3±0.7 ml/min to 14.6±0.6 ml/min; p=0.002). No significant differences were found in terms of levels of serum calcium and vitamin D.

Conclusions: The treatment for SHP in patients with ESKD can have a detrimental effect on serum phosphorus levels, increasing them by reducing its urinary excretion.
Results: Molecular characterization showed 5 patients with COL4A5 mutations and one probably autosomal recessive Alport syndrome.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Sex</th>
<th>Mutation</th>
<th>Retina</th>
<th>Renal state at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5020166</td>
<td>M</td>
<td>COL4A5 L1469R</td>
<td>Macular holes OU</td>
<td>SCr 1.0 mg/dl</td>
</tr>
<tr>
<td>2017006</td>
<td>M</td>
<td>COL4A5 Y1597X</td>
<td>Macular holes OU</td>
<td>Transplanted</td>
</tr>
<tr>
<td>2224004</td>
<td>M</td>
<td>Likely autosomal recessive</td>
<td>Macular holes OU, retinal flecks</td>
<td>SCr 1.0 mg/dl</td>
</tr>
<tr>
<td>2163001</td>
<td>M</td>
<td>COL4A5 G1205S</td>
<td>Macular holes OU</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>2198001</td>
<td>M</td>
<td>COL4A5 1981+3 g&gt;t</td>
<td>Macular hole OD</td>
<td>Not on dialysis</td>
</tr>
</tbody>
</table>

Macular holes developed either early or late in the course of Alport syndrome. Renal phenotypes varied from COL4A5 mutations causing a severe (Y1597X, G1205S, 1981+3 g>t), uncertain (COL4A5 3218+1 g>t), or late onset (COL4A5 L1469R) renal phenotype. One patient comes from a family that appears autosomal recessive by pedigree analysis and by segregation of chromosome 2 haplotypes. Whole exome sequencing of this kindred is currently under way.

Conclusions: Giant macular holes occur occasionally in Alport syndrome, much more commonly than in the general population. They are not confined to a single mode of inheritance nor to COL4A5 mutations that cause a severe renal phenotype.

PUB660

The Novel Arg646Gly SLC4A41 Mutation Is Responsible for Distal Renal Tubular Acidosis Joaquin T. Calado, Sandra Brun, Cataria Sofia Almeida Silveira, Ana Santos, Fernando E.B. Nolasco, E. ToxOmics, NOVA Medical School, Lisbon, Portugal; 2Nephrology, CHLC, Lisbon, Portugal; 3Nephrology, Hospital de Santo Espírito, Angra, Portugal; 4Genomed, IMM, FML, Lisbon, Portugal.

Background: The C/HCO3– exchanger (eAE1), encoded by SLC4A41, is differentially expressed in the erythrocyte and kidney. The full transcript (eAE1) has a structural role in the red cell, while the shorter isoform (kAE1) is essential for renal acidification. SLC4A41 mutations can account for hemolytic anemia or distal renal tubular acidosis (dRTA). Since mutations that give rise to spherocytosis/ovalocytosis are different from those responsible for dRTA, the occurrence of a dual hemolytic and dRTA phenotype is extremely rare. The few cases reported involve mostly a compound heterozygous condition for the c.4400-408 allele, leading to autosomal dominant southeast Asian ovalocytosis (SAO), together with a reduced number of mutations responsible for recessive isolated dRTA.

Methods: We report a 53 years old male of southeast Asian ancestry presenting with severe hydropsplenia (1.7 mmol/L) and a non-anion gap metabolic acidosis, with normal renal function and persistent alkaline urine. Nephrocalcinosis was documented by ultra-sound, recovered calcify was shown to be made of calcium phosphate and a diagnosis of dRTA was established. In spite the lack of anemia, an abdominal ultra-sound revealed cholelithiasis and cavierous transformation of the portal vein. Additional workup characterized a Coombs’ negative chronic hemolysis displaying the typical findings of spherocytosis in the blood smear together with hémossiderosis in liver biopsy.

Results: Sanger sequencing of SLC4A41 identified 3 heterozygous variations: the c.1199_1225del27 (4400-408), the c.1666A>G (p.Lys556Glu), known to be in linkage with the former, and the c.1936G>C (p.Arg646Gly) mutation. This latter allele is not found within the 1000 Genomes Project or the Exome Aggregation Consortium and is predicted to be pathogenic by in silico analysis.

Conclusions: The current report broadens the spectrum of SLC4A41 mutations associated with dRTA and suggests this novel Arg646Gly mutation, in addition of being a codominant allele for the dual phenotype, may act as a recessive allele for isolated dRTA.

PUB661

Hereditary Transthyretin Amyloidosis and Kidney Injury Asuncion Ferrer-Nadal, Cristina Gallego, Manuel Rayo, Mercedes Uson, Antoni Figuerola, Carles Montala, Cristina Descals, Tomas Ripoll, Juana Nuñez, Hernan Andreu, Eugenia Cisneros-Barroso, Juan Buades, Dept. of Nephrology, Hospital Son Llátzer, Palma de Mallorca, Baleares, Spain; 2D. Internal Medicine, H. S. Llátzer; 3Neurology, H. S. Llátzer; 4Neurophysiology U., H. S. Llátzer; 5Cardiology, H. S. Llátzer; 6D. Gastroenterology, H. S. Llátzer.

Background: Transthyretin-associated amyloidosis (ATTR) is a common autosomal-dominant form of amyloidosis frequently associated with the substitution of methionine for valine at position 30. Mallorca represents one of the most important focus of ATTR in the world. Kidney disease has been reported in Portugal as a result of renal deposition. They identified one third of patients with proteinuria and 10% progression to End Stage Renal Disease (ESRD).

Methods: Retrospective and prospective study of renal disease development in ATTR V30M. The assessment included clinical and laboratory tests in blood and urine. Chronic kidney Disease (CKD) was considered as a glomerular filtration measured by MDRD formula of 6 variables and Cistatine C.

Results: 155 ATTR V30M carriers were recruited at the Hospital Son L.Látzer among 2002 and 2016. Mean age at the onset was 48.64 years (SD 16.2), median 46.5 (IQR 35.2-62.7). 52% male. 36 cases (23.2%) presented CKD with MDRD < 60 ml/min and 22 (14.2%) with severe CKD (<30 ml/min). Cistatine C formula showed a significant increase
of CKD in this group of patients. 80% of patients developed proteinuria (73% < 500 mg and 27% > 1g/24h). Only 4 patients with severe CKD developed nephrotic proteinuria. Liver transplantation was achieved in 53 patients (34.2%). 20 (12.9%) patients died during the study period.

**Figure 1. Clinical outcomes according to Level of Proteinuria (cutoff 1 g/24h)**

**Conclusions:** We observed 2 different phenotypes of ESRD, one proteinuric and another not proteinuric, suggesting that the patients develop ESRD by totally different, pathophysiologic mechanisms. MRDR formula underestimates CKD in this group of patients.

**PUB662**

**Clinical Utility of Medical Exome Sequencing/Whole Exome Sequencing in the Diagnosis of Genetic Renal Diseases**

Takuro Takenouchi,1,2 Midori Awazu,3 Kenjiro Kosaki,1 \1Center for Medical Genetics, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan; \2Pediatrics, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan.

**Background:** Recently, genetic causes have been identified in various renal diseases thanks to the advent of next generation sequencing (NGS). We evaluated the clinical utility of NGS among patients who presumably have genetic renal diseases on clinical grounds.

**Methods:** The probands and their parents were recruited through the Japanese nationwide undiagnosed disease program, Initiative on Rare and Undiagnosed Diseases (IRUD). Whole blood was collected from them after informed consent. Comprehensive genetic diagnosis was performed by whole exome sequencing (WES). Variants detected by the sequencer were filtered on quality, frequency, segregation pattern, previous reports, and genetic function and were confirmed by Sanger sequencing.

**Results:** 27 families with clinical diagnosis of genetic renal diseases were recruited based on positive family history or co-occurrence of extrarenal abnormalities. Ten were diagnosed as having congenital abnormality kidney and urinary tract (CALKUT), 11 presented with ciliopathy phenotype, 2 had VATER association, and others were chronic kidney disease (CKD) with extrarenal abnormalities. We confirmed 12 types of genetic diagnosis in 13 probands: Compound heterozygous mutations in MKKS, UBE3B, CC2D2A, C5, and BBS10, a homozygous mutation in RPGRIP1L, heterozygous mutations in WAS, AGT, RET, PKD1, and JAG1, and a hemizygous mutation in OFD1.

**Conclusions:** Comprehensive genetic testing allowed genetic mutations in 13 of the 27 families (48.2%). These detection rates were comparable to that reported in the previous reports. Identification of precise genetic cause could contribute to medical management of the patients. An illustrative case was a patient with clinical diagnosis of CKD and thrombocytopenia. He was demonstrated to have WAS mutation through WES. The WES result made renal biopsy unnecessary. In addition, bone marrow transplantation was suggested to be effective. Further analyses are needed for unresolved families.

**PUB663**

**Targeted Next Generation Sequencing of Alport Syndrome in Japan**

Tomohiko Yamamura,1 Kandali Nozu,1 Shogo Minamikawa,1 Takeshi Ninnoji,1 Yuko Shimadou,2 Koichi Nakano,1 Kazumoto Umesaki,3,4 Pediatrics, Kobe Univ Graduate School of Medicine, Kobe, Japan; \1Pediatrics, Wakayama Medical Univ, Wakayama, Japan.

**Background:** Alport syndrome (AS) is a hereditary disease caused by mutations of COL4A3/COL4A4/COL4A5 genes. In recent years, comprehensive genetic analyses using next generation sequencer (NGS) are available for diagnosis of many genetic diseases. Comprehensive analyses such as whole genome sequencing or whole exome sequencing are very expensive. In contrast, targeted next generation sequencing using a custom panel is cost-effective and expedient if this method is applied to appropriate patients.

**Methods:** 40 patients suspected of having AS from their clinical findings and renal pathological findings or family histories were studied. Mutational analyses were performed using the targeted sequencing panel including 44 genes causing AS, other inherited glomerulopathies and X-linked kidney diseases.

**Results:** 32 patients (80%) were genetically diagnosed with AS by targeted next generation sequencing. 19 patients were diagnosed with X-linked AS (XLAS) caused by mutations of COL4A5 gene and other 13 patients were autosomal dominant AS caused by mutations of COL4A3 gene (5 patients) or COL4A4 gene (8 patients). Of the remaining 8 patients, one patient was diagnosed with XLAS caused by deep intronic mutation using cDNA analysis. One patient was diagnosed with Dent disease caused by mutations of CLCN5 gene and another patient who showed lamellation of the glomerular basement membrane (GBM) was diagnosed with Pierson syndrome caused by mutations of LAMB2 gene.

**Conclusions:** Our results suggest that targeted next generation sequencing is a useful diagnostic tool for patients clinically suspected of having AS. In addition, it was revealed that some other inherited glomerulopathies with GBM changes or X-linked nephropathies can be diagnosed as AS by clinical findings, therefore this method is crucial for the accurate diagnosis of inherited kidney diseases.

**PUB664**

**Development a Method of Estimating Salt Intake by Self-Completed Questionnaire for Japanese Patients**

Mari Odamaki,1 Eiko Kawakami,1 Hiromichi Kumagai,1 Yoshiko Tsumura,2 Akihiko Yato,2 Hideo Yasuda,2 Yoshioide Fujigaki,3 Akira Hishida,6 \6Dept of Health and Nutritional Sciences, Tokoha Univ, Hamamatsu, Japan; \1Dept of Clinical Nutrition, Univ of Shizuoka, Shizuoka, Japan; \2First Dept of Medicine, Hamamatsu Univ School of Medicine, Hamamatsu, Japan; \3Blood Purification Unit, Hamamatsu Univ School of Medicine, Hamamatsu, Japan; \4Dept of Internal Medicine, Teikyo Univ School of Medicine, Tokyo, Japan; \5Nephrology, Yaizu City Hospital, Yaizu, Japan.

**Background:** It is important to know daily salt intake for hypertension treatment. We developed a method of estimating salt intake by self-completed questionnaire for Japanese patients.

**Methods:** We recruited 650 (male: female=237:413) people who agreed to participate in this study. We made a list of food which is eaten by Japanese people in their usual diet. We divided the food into seven groups by salt content per serving. We made a self-completed questionnaire to ask how often they consume each group of food per week. From this questionnaire we estimated daily salt intake in each person. In parallel, we calculated salt intake by measuring salt in the urine collected for 24 hours. Using the result of calculated salt intake, we evaluated the accuracy of the estimation method.

**Results:** A significant positive correlation was found between estimated salt intake by questionnaire and calculated salt intake by 24 hours urine collection (r=0.3, p<0.0001, y=0.382x+5.23). On eleven people, we made the estimation and calculation of salt intake twice, before and after the instruction of salt restriction. The change of the salt intake in each person estimated agreed well with the calculated one. The average decrease in 1.0g of salt intake estimated by the questionnaire corresponded to the decrease in 1.2 g of salt intake calculated by 24 hours urine collection.

**Conclusions:** The questionnaire we developed is useful for estimating salt intake in Japanese and for evaluating the effects of salt restriction instruction.

**PUB665**

**Nutritional Assessment of Haemodialysis Patients**

Muhammad Nauman Hashmi,1 Waad Alshazly, Hamza Raza, Fayer Alhejaili. \1Haemodialysis, King Abdullah International Foundation for Haemodialysis, Riyadh, Central, Saudi Arabia.

**Background:** Malnutrition is a strong predictor of mortality in Haemodialysis patients. Several Scoring systems have been used previously but either they were on non-renal patients or include costly investigations or more subjective rather than objective.

**Methods:** This is prospective analysis of maintenance Hemodialysis patients over period of 12 months in a single centre. This analysis was carried out from June 2015 till May 2016 inclusive. The study included 5 objective assessments (Body Mass index, No of years on HD, Serum Albumin, Ferritin & Co-morbidities). 1 Subjective assessment of Functional capacity was included in this scoring system. Parameters were evaluated every 3 months. Co-morbidities (Diabetes Mellitus, Ischemic Heart disease, Cerebrovascular disease and Hypertension–Every co-morbidity was given 1 score).

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass Index</td>
<td>&lt;20</td>
<td>18-19.99</td>
<td>16-17.99</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Functional capacity</td>
<td>Normal</td>
<td>Occasional difficulty</td>
<td>Difficulty with Independence</td>
<td>Bed/Chair bound</td>
</tr>
<tr>
<td>No of years on Hemodialysis</td>
<td>&lt;1</td>
<td>1-3</td>
<td>3-4</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>≤25 gm/l</td>
<td>26-35 gm/l</td>
<td>36-45 gm/l</td>
<td>&gt;45 gm/l</td>
</tr>
<tr>
<td>Ferritin</td>
<td>≤700 mcg/l</td>
<td>701-800 mcg/l</td>
<td>800-1000 mcg/l</td>
<td>&gt;1000 mcg/l</td>
</tr>
<tr>
<td>Co-Morbidities(D,HTN,CVA,HIC)</td>
<td>1 Co-morbidity</td>
<td>2 Co-morbidities</td>
<td>3 Co-morbidities</td>
<td>4 Co-morbidities</td>
</tr>
</tbody>
</table>

Maximum score is 18. Patients scoring ≥8 were categorised as high risk &<8 as low risk. Total no of patients present throughout assessment 174.

**Results:** We identified 12,10,11 &11 no of patients scoring ≥8 score in every quarterly assessment during 12 months. There were 6 patients constantly present in high risk group. In High risk group 3 patients died. Low risk group had 1 mortality during this study.

**Conclusions:** Nutritional Assessment plays key role in management of Hemodialysis patients and this scoring system we are able to identify patients as high and low risk groups. This tool helps to identify at risk patients so that timely measures are taken to improve patient survival. This scoring system is cost effective and convenient. Our analysis suggests that it is reliable and we will continue to monitor patients with help of this tool to get more data over coming years.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Protein Energy Wasting in Predialysis Patients

**Background:** Evaluating nutritional status is important for prevention of protein energy wasting (PEW). Objective: Prevalence of PEW in predialysis patients on first visit to a nephrologist.

**Methods:** Three day dietary intake of 484 CKD stage 3 and 4 patients. ISRN nutrition criteria used for diagnosing PEW.

**Results:** Serum albumin was 3.77±0.83 (males) and 3.68±0.81 g/dL (females). As appetite, BMI and income decreased dietary protein and energy intake decreased significantly.

**Average Dietary Intake**

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Energy kcal/kg</th>
<th>Energy deficit</th>
<th>Protein g/kg</th>
<th>Protein deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>male</strong></td>
<td>17.2±8.29</td>
<td>17.78±8.29</td>
<td>0.66±0.28</td>
<td>0.09±0.28</td>
<td></td>
</tr>
<tr>
<td><strong>female</strong></td>
<td>16.8±7.66</td>
<td>18.12±7.66</td>
<td>0.64±0.30</td>
<td>0.11±0.30</td>
<td></td>
</tr>
</tbody>
</table>

**Dietary Intake Based on Appetite**

<table>
<thead>
<tr>
<th>N%</th>
<th>Normal 52.8%</th>
<th>Underweight 15.0%</th>
<th>Severely Underwrt 32.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy kcal/kg</td>
<td>17.2±9.0 Deficit</td>
<td>17.0±10.0 Deficit</td>
<td>15.9±11.1 Deficit</td>
</tr>
<tr>
<td>Protein g/kg</td>
<td>0.5±0.4 Deficit</td>
<td>0.5±0.4 Deficit</td>
<td>0.5±0.4 Deficit</td>
</tr>
</tbody>
</table>

**Based on Income groups**

<table>
<thead>
<tr>
<th>High Middl(17.2%)</th>
<th>Low Middl (53.5%)</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy kcal/kg</td>
<td>17.0 (10.07±313.99)</td>
<td>15.0 (9.18±47.396.15)</td>
</tr>
<tr>
<td>Protein g/kg</td>
<td>0.5±0.4 (0.1)</td>
<td>0.5±0.4 (0.1)</td>
</tr>
</tbody>
</table>

Appetite correlated with energy, protein, BMI with energy and GFR (p < 0.001). Carbohydrate intake was not significantly different between the groups. Significant difference between income groups in BMI (P < 0.000), energy (p < 0.019), protein (p < 0.031), albumin (p < 0.001). Prevalence of PEW based on energy was 91%, protein 57%, BMI 56.6%, and appetite 69.2%.

**Conclusions:** Dietary counseling can help preserve nutritional status. Appetite, BMI and income are markers of PEW in CKD.

PUB667

Which Inflammatory Biomarkers Are Associated with Diabetic Kidney Disease?  

Flavia Bob,1 Romulus Timar,1 Daniel F. Lighezan,2 Geta Bujor,1 Mircea Munteanu,1 Florica Gadalean,2 Adelina Mihaescu,1 Bogdan Timar,1 Diana Lighezan,1 Sagren Pillay,1 Adalbert Schiller.1 1Internal Medicine 2, Univ of Medicine and Pharmacy, Timisoara, Romania; 2Internal Medicine 1, Univ of Medicine and Pharmacy, Timisoara, Romania; 2Biochemistry, Univ of Medicine and Pharmacy, Timisoara, Romania; 3Medical Informatics, Univ of Medicine and Pharmacy, Timisoara, Romania.

**Background:** Inflammation is associated with patients with chronic kidney disease (CKD) with an increased mortality. However, there is still uncertain if the characteristic of the inflammatory biomarkers are prominently involved in CKD. In the present study we tried to compare the role played by two of these markers (interleukin-6 and C-reactive protein - CRP) in patients with diabetic kidney disease (DKD).

**Methods:** We performed this study on 52 patients with diabetes mellitus (DM) (13 patients with DM without renal involvement and 39 patients with DKD - with eGFR <60 ml/min or urinary albumin/creatinine ratio > 30 mg/g), with a mean age of 64.16 ± 7.35. In all patients we performed, using standard methods the following: serum creatinine, CRP, serum calcium, phosphorus, iPTH, urinary albumin/creatinine ratio, while IL6 was performed using ELISA method.

**Results:** IL6 levels were compared between patients with diabetes mellitus and patients with diabetes mellitus and CKD. The mean levels of IL6 were 10.74±7.43 pg/ml vs. 5.7±6.3 pg/ml, p < 0.02, but no difference regarding CRP. We found no also statistically significant correlation between the two markers of inflammation (CRP and IL6): r = -0.187, p = 0.27. There were also no statistically higher levels of IL6 or CRP with albumin/creatinine ratio, serum calcium, serum phosphorus or iPTH.

**Conclusions:** In our study we found that the two inflammation markers studied – CRP and IL-6 showed different patterns of evolution, with an increase of IL-6, and not CRP, in patients with DKD.

**Funding:** Government Support - Non-U.S.
Attitudes and Opinions of Canadian Nephrologists Toward Continuous Quality Improvement Options

Background: Accountability and public reporting are increasingly prominent in health care. At the present time, quality improvement in Canadian nephrology is based on reporting of facility-wide performance. The objective of the study was to determine the attitudes and opinions of nephrologists towards a potential shift of improvement efforts from facility based to the individual physician level.

Methods: A pilot tested, web-based instrument was used to administer a survey to 330 nephrologists across Canada, through the Canadian Society of Nephrology (CSN).

Results: Out of the initial 320 eligible nephrologists contacted, 137 nephrologists responded (43%). Amongst all respondents, 48% agreed or strongly agreed that “there is significant variation in physician performance in my facility”, 79% agreed or strongly agreed that “there are quality metrics that nephrologists should be responsible for”. More than 80% agreed or strongly agreed that “there are some appropriate and valid measures that should form a basis for CQI activities”, 82% agreed or strongly agreed to “receive a confidential, personalized score card reflecting my individual patient care”. Only 30% agreed or strongly agreed that “public reporting of physician performance is likely to improve patient outcome”. Of note, compared to staff nephrologists, medical directors were twice as likely to agree or strongly agree that “shifting from program to physician level measurement and reporting is likely to improve care”. Leadership level physicians were more likely to support this shift. As modern medicine evolves towards more accountability and public reporting, the nephrology community must grapple with how to adapt to these trends and apply those methods that are validated and proven to improve patient care outcomes and outcomes.

Primary Care Providers’ (PCPs) Perceptions of Medication Safety in Chronic Kidney Disease (CKD)

Background: Renal clearance and potential nephrotoxicity makes medication safety in CKD a unique challenge, particularly among PCPs managing the complex multi-morbidity of CKD patients.

Methods: We conducted 4 qualitative focus groups of PCPs (n=32) across 4 US metro areas to assess their views of medication management in CKD. Participants were asked: “What aspects of medication safety are the most [and least] challenging for you and why?”; “Please describe resources, tools, or features of your practice that make it easy for you to address medication safety.”; “What would you find helpful in addressing medication safety for your patients with CKD?” Focus group content was transcribed, and relevant concepts were identified.

Results: PCPs identified patient-level barriers to medication safety including lack of awareness of nephrotoxins such as NSAIDs and non-disclosure of their over-the-counter use. For example “if they don’t think they don’t see this [NSAID use] as an issue and I take care of a lot of people who are educated and you would think explaining all this they get it. They don’t get it half the time because their kidneys don’t bother them.” PCPs described inadequate knowledge of recommended dose adjustments in CKD, stating “I always forget like some antibiotics you actually have to adjust and I always forget which ones it is...” Difficulties managing polypharmacy and pain were identified as common challenges: “The guy has severe arthritis taking a lot of pain medicine that affects the kidneys. Then what are your alternatives? That’s my problem.” PCPs described facilitators of CKD medication safety such as educational materials to increase patient NKAID risk awareness, routine integration of pharmacists in CKD care, and utilization of electronic decision support tools.

Conclusions: Interventions targeting patient awareness of adverse renal effects of medications and enhancement of clinical medication safeguards using pharmacists and decision support tools may improve CKD medication safety in primary care.

Funding: NIDDK Support, Private Foundation Support

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

1058A

vs 35.46±11.73±p(0.01), TNF-β 25.42±5.72% vs 32.72±7.18% (p(0.034), Muscle Mass% 35.65±0.96 vs 32.08±0.71, BF% 26.06±16.84±2.17 vs 5.50±2.22 (p(0.000), HB 12.04±1.39 vs 13.12±1.42 (p<0.000), albumin4.15±0.72 vs 3.99±0.50 (p<0.019), prealbumin 26.46±7.15 vs 24.02±6.76 (p<0.003), CRP 0.96±2.22 vs 1.64±2.52 (p<0.010).

Conclusions: 1. Monitoring the nutritional state in CKD units favoured the maintenance of a greater percentage of normo-nourished patients was observed in CKD patients with differences in biochemical parameters, body composition and Mls scale.

PUB672

Inferior Vena Cava Index: A Bedside Method for Dry Body Weight Assessment in Critically Ill Haemodialysis Patients

Mostafa Abd-Elsalam Abd-Elkhalak, Mansoura Nephrology and Dialysis Unit, Mansoura Medical School, Mansoura, Dakhla, Egypt.

Background: Assessment of dry body weight in emergency conditions is still a matter of mystery. Central venous pressure is accurate but invasive. We try to find a simple non invasive method for assessment of dry weight in critically ill haemodialysis patients.

Methods: This is prospective observational study conducted on 45 haemodialysis patients referred to Mansoura Nephrology and Dialysis Unit from emergency hospital. The candidates for this study were seeking for urgent haemodialysis using temporary central intravascular access. Abdominal ultrasonography for assessment of IVC index was done immediately after dialysis session with measurement of the IVC trough temporary central haemodialysis catheter. Pearson correlation between central venous pressure as an invasive maneuver to assess dry weight in haemodialysis patients, IVC maximum diameter in deep inspiration and IVC index was done.

Results: Pearson correlation between CVP and IVC maximum diameter in deep inspiration and IVC index revealed a statistically significant positive correlation between CVP and IVC maximum diameter (ρ= -0.411, p<0.005) and a statistically significant positive correlation between CVP and IVC (R= 0.483, P=0.001). Multiple linear regression analysis (table 1) for CVP values as the dependent variable and both the IVC maximum diameter in inspiration and IVC index as independent variables was done using the step wise procedure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C.V.P</th>
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<tbody>
<tr>
<td>IVC (mm/m2)</td>
<td>r</td>
</tr>
<tr>
<td></td>
<td>p</td>
</tr>
<tr>
<td>INSPMax</td>
<td>r</td>
</tr>
<tr>
<td></td>
<td>p</td>
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</table>

The procedure selected the IVC index as the best independent predictors for CVP value (R2=0.233, p=0.001).

Conclusions: Bedside sonographic measurement of inferior vena cava index which is simple, quick and non invasive method could be used as a reliable and accurate method for assessment of dry weight in critically ill chronic renal failure patients.

PUB673

Concomitant Use of Vancomycin and Contrast Exposure and AKI: Quality Improvement Program

Muhammad Muneeb1, Farah Dadabhoy1, Thakrar V. Thakrar1, Agrawal Bernard, Carina Estrella, Varun Agrawal, Bernard G. Jaar, Michael J. Choi, Raquel C. Greer. NKF Education Committee, New York, NY.

Background: Supratherapeutic Vancomycin (Vanc) is known to cause tubular toxicity leading to acute kidney injury (AKI). Intensive Vanc dosing and radio-contrast exposure are frequently needed together, for diagnosis and treatment in patients with high morbidity. Thus, a known event that reduces glomerular filtration rate (eGFR) can result in supra-therapeutic Vanc levels, resulting in AKI. In a prior institution wide trainee survey (ASN 2015), 60% providers were uncomfortable with Vanc dosing and depended on pharmacy protocols.

Methods: We describe two case-reports, which led to the development of a Quality Improvement Program (QIP) to reduce kidney adverse events due to exposure to concomitant nephrotoxins.

Results: We noted two cases of AKI to be associated with Vanc dosing protocol and contrast exposure. Patient-1 (33 yo male) and Patient 2 (59 yo male) were admitted for contrast exposure. Both patients were discharged with partial renal recovery. Patient-1 (33 yo male) and Patient 2 (59 yo male) were admitted for contrast exposure. Both patients were discharged with partial renal recovery.
results in relative overdosing of Vanc for an average daily eGFR. In collaboration with pharmacy service, following recommendations are being adopted when implementing Vanc dosing protocol: 1. Alert to pharmacy of concomitant orders of nephrotoxins; 2. Modify Vanc dose; 3. Use frequent level monitoring.

Conclusions: Cases identified a current gap in drug safety; and multi-disciplinary QI programs in high risk patients could reduce AKI and associated morbidity.

PUB674
Native Kidney Biopsies: Complications and Yield: A Quality Improvement Initiative Mahwash Kamal, Karthikeyan Meganathan, Kotagal Shashi Kant. Kidney and Hypertension, Univ of Cincinnati, Cincinnati, OH.

Background: The kidney biopsy is the gold standard in the diagnosis and management of many renal diseases. Sample size is critical for the diagnosis of most renal pathologies. We performed a three year retrospective review to analyse our experiences with the complications and diagnostic yield of native kidney biopsies and their impact on patient safety.

Methods: Native kidney biopsies were identified on the basis of pathology coding between January 2013 and December 2015. A biopsy sample was defined as adequate when it had at least 10 glomeruli for light microscopy and sufficient tissue for electron microscopy and immunofluorescence. Complications were defined as minor and major. Minor complications included bleeding requiring monitoring and no intervention. Major complications included bleeding requiring intervention, nephrectomy and death.

Results: We performed 64 native kidney biopsies in 3 years. 47(73.4%) biopsies were performed by interventional radiologists and 17(26.6%) were performed by nephrologists. (69.4%) patients had complications; 2 had minor and 4 had major. 33(51.5%) biopsies were adequate and 31(48.5%) were not adequate. There were only 3(4.7%) biopsies in which the pathologist was unable to provide any diagnosis. We found a higher likelihood of inpatient biopsies to be performed by IR. Rising creatinine increases the odds of biopsy to be performed by IR. Rising creatinine also increases odds of complications. Statistically significant difference for complication rates was not found with differences in gender, BMI, clinical setting, operator, age, kidney size, blood pressure and hemoglobin. Statistically significant difference for biopsy adequacy was not found with differences in BMI, operator or kidney size.

Conclusions: Our complication rates were comparable to other centers, however our biopsy sample adequacy was lower. Measures proposed to improve biopsy sample adequacy in our institution include: 1) changing biopsy needle size from 18 gauge to 16 gauge; 2) Visualizing all specimens under direct microscopy for sectioning; 3) identifying operators on the basis of experience and interest and designating them as the preferred operators for native kidney biopsies.

PUB675
Preventing Contrast-Induced Nephropathy in Patients with Renal Disease in a Nephrologic Day Hospital Nurin Rodriguez Mendiola, Maite Rivera, Victor Burgueria, Estefania Yerovi, Martha Elizabeth Diaz, Jose L. Teruel, Fernando Liano. Nephrology. Hospital Ramón y Cajal, Madrid, Spain.

Background: The best established treatment for the prevention of CIN is intravenous hydration. Traditional regime consist of fluid volume loading before and after intravascular contrast media (CM) administration, which requires the patient to be admitted to hospital. We analyse the efficacy of intravascular hydration with n-acetyl-cysteine (NAC) in only one dose before CM administration, in an ambulatory way.

Methods: From January 2013 to December 2014, 97 patients with preexisting impairment of renal function (GFR<60 ml/min/1.73 m2) (table 1) received our preventive scheme prior to intravenous radiographic contrast media.

<table>
<thead>
<tr>
<th>Patients characteristics</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>66±13(range 23-89)</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>76/24</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>81</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>36</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>27</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>3.9±2.9</td>
</tr>
<tr>
<td>Charlson index punctuation</td>
<td>5.8±2.7 (range 2-12)</td>
</tr>
<tr>
<td>ARB/ACE receivers (%)</td>
<td>58</td>
</tr>
<tr>
<td>Chronic kidney disease stages</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
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<td>5</td>
<td>35</td>
</tr>
</tbody>
</table>

All the imaging tests were computed tomography (CT) with 100 cc of iohexol as contrast media (concentration of 350 mg/ml). Imaging tests were programmed in the afternoon. During the morning patients were fluid loaded with 1000 cc isotonic saline solution with intravenous formulation of 2 grams of NAC post CM fluid infusion was not given. This treatment was administrated in the day hospital of Nephrology department, with no need of patient’s admittance. Serum creatinine was measured before and within 10 days of exposure to intravascular CM.

Results: Contrast induced nephropathy was defined as an increase of 25 % in serum creatinine level from baseline (K/DOQI definition). With this criteria just 4 patients showed the rise in serum creatinine and three of them required treatment.

Conclusions: Intravenous saline solution with NAC precontrast, without infusion postcontrast, is shown to be effective in reducing the risk of CIN in patients with a preexisting renal dysfunction undergoing contrast CT scan. This is administered in ambulatory nephrologic day hospital, what avoids complications associated to hospital admittance and reduces costs.

PUB676

Background: Hyperkalemia (Potassium > 6.0 mmol/L) is a common, potentially life-threatening emergency among hospitalized patients. Most patients at our institution are not routinely evaluated prior to initiation of treatment. Only 85% of patients with a serum potassium value above 6.5 mmol/L had an ECG. Most patients (82.1%) treated with calcium gluconate did not have ECG changes nor did patients treated with insulin and dextrose (68.5%). There is minimal data to guide management of hyperkalemia and common treatments can have serious adverse effects.

Methods: We reviewed the literature to evaluate the safety and efficacy of treatments for hyperkalemia and developed a protocol for management. The protocol incorporates the severity of hyperkalemia, physical examination, ECG findings, renal function as measured by urine output and diastolic status, presence of conditions which could rapidly raise potassium levels and other variables into a stepwise approach. The protocol is currently being piloted among patients admitted to our nephrology service.

Results: Initial results document that since the protocol was implemented, acquisition of ECGs in patients with hyperkalemia improved from 88.4% (61/69) to 100% (11/11). The number of patients unnecessarily receiving calcium gluconate decreased (46.4% (32/69) to 10% (1/10)) as did the utilization of the insulin and dextrose (68.5% (24/35) to 0% (0/9)).

Conclusions: Our initial results show that implementing a standardized evidence-based protocol for management of hyperkalemia can improve the treatment of patients by reducing unnecessary treatment and improving monitoring. Our goal is to continue to revise the protocol and eventually distribute it to the rest of the hospital.

PUB677
The Comfort Status after Renal Biopsy Hair-Qun Li,1 Wenbo Zhao,1 Geng-Xi Sun,2 Tan-Qi Lou.1 The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; 2Guangzhou Hexian Memorial Hospital, Southern Medical Univ, Guangzhou, Guangdong.

Background: Renal biopsy (RB) is an important auxiliary examination. It is helpful to identify the pathological types, guide treatment and learn prognosis of kidney disease. Because of strictly confined in the bed within 24 hours after RB, patients often have the physiological and psychological discomfort. The purpose of this study was to investigate the comfort status of patients after RB.

Methods: Renal biopsy (RB) is an important auxiliary examination. It is helpful to identify the pathological types, guide treatment and learn prognosis of kidney disease. Because of strictly confined in the bed within 24 hours after RB, patients often have the physiological and psychological discomfort. The purpose of this study was to investigate the comfort status of patients after RB.

Results: The GCQ scale scores increased gradually with the time after RB. The total GCQ score was 68.3±5.42 in the 6 hours and 85.2±6.3 in the 24 hours. The scores of physiological and psychological discomfort. The purpose of this study was to investigate the comfort status of patients after RB.

Conclusions: Our initial results document that since the protocol was implemented, acquisition of ECGs in patients with hyperkalemia improved from 88.4% (61/69) to 100% (11/11). The number of patients unnecessarily receiving calcium gluconate decreased (46.4% (32/69) to 10% (1/10)) as did the utilization of the insulin and dextrose (68.5% (24/35) to 0% (0/9)).

Conclusions: Our initial results show that implementing an evidenced-based protocol for management of hyperkalemia can improve the treatment of patients by reducing unnecessary treatment and improving monitoring. Our goal is to continue to revise the protocol and eventually distribute it to the rest of the hospital.

PUB678
Improving Quality of Care in Acute Kidney Injury and Continuous Renal Replacement Therapy: From Clinical Practice Guidelines to Quality Measures Rhea Bhargava,1 Sairasad Narasingam,1 Himmat Grewal,1 Reem Mustafa,2,3 1Dept of Internal Medicine, Univ of Missouri- Kansas City; 2Dept of Nephrology and Hypertension, Univ of Missouri- Kansas City; 3Dept of Internal Medicine, Saint Vincent Hospital, Worcester, MA.

Background: Monitoring quality in health care is of vital significance to avoid preventable medical errors and to improve the quality of health care which is delivered. There is wide variation across the globe in the care of patients with acute kidney injury
(AKI) and who are receiving continuous renal replacement therapy (CRRT). Clinical practice guidelines are available for patients with AKI and for patients who are receiving CRRT. We wish to present potential quality measures and their level of adaptation by health care delivery organizations.

**Methods:** Databases of Acute Dialysis quality initiative (ADQI) and Kidney Disease Improvements Global Outcomes (KDIGO) were reviewed for clinical practice guidelines and potential quality measures prescribed by them for patients with AKI and for those needing CRRT. Then a search was done to determine whether these were endorsed by National quality forum (NQF) and Centers for Medicare and Medicaid services (CMS).

**Results:** Clinical practice guidelines and management of AKI and guiding CRRT are available from both ADQI and KDIGO. These include factors affecting CRRT - patient selection, timing for initiation, insertion site of the dialysis catheter, risk of infection, type of anticoagulation, bleeding risk among others and AKI-definition and diagnosis.

No clinical practice guidelines were being used as quality measures from the National quality forum (NQF) or as Centers for Medicare and Medicaid services (CMS) core measures.

**Conclusions:** Wide scale use of quality measures are needed to monitor and thereby standardize and improve quality of health care delivery to patients with AKI and patients needing CRRT. NQF and CMS core measures do not currently contain measures pertaining to quality for AKI and CRRT populations. Incorporating them could lead to increased adherence to clinical practice guidelines and provide a much needed framework to improve the care for the AKI and CRRT populations in the hospital.

**PUB679**

**Defining the Optimal Method to Monitor Albuminuria Over Time in Toddlers**  
Sofie Van den Belt,1 Valentina Grechi,2 Dick de Zeeuw,3 Hiddo Jan Lambers Heerspink.4 Clinical Pharmacy and Pharmacology, UMCG, Groningen, Netherlands; 2Pediatric Nephrology, UMCG, Groningen, Netherlands.

**Background:** Microalbuminuria can also be found in toddlers. This could have important consequences for understanding pathophysiology and guiding possible treatments. In adults, the guideline for establishing and monitoring microalbuminuria over time recommends to use first morning void (FMV) urine samples collected over three consecutive days. Since such a guideline is absent in toddlers, we tested several urine collection strategies for albuminuria measurement in toddlers.

**Methods:** A FMV urine sample and random daytime urine sample were collected on three consecutive days at week 0 (period 1), week 4 (period 2) and week 8 (period 3) in toddlers aged 12-48 months. Urinary albumin (U_AcR) and albumin:creatinine ratio (U_AcR) were assessed. Intra-individual coefficient of variation (CV), calculated as the standard deviation divided by the geometric mean of U_AcR or U_AcR, was determined using only the first U_AcR or U_AcR measurement of each study period and secondly using all three U_AcR or U_AcR measurements per study period.

**Results:** A total of 38 toddlers (mean age 28.4 months, SD 10.6, 64% male) were included. The geometric mean U_AcR was 5.0 mg/L in the FMV and 5.2 mg/L in the random daytime sample. U_AcR was 13.3 mg/L and 18.6 mg/L, respectively. The lowest intra-individual CV was observed when U_AcR was measured in FMV over three consecutive days (table).

| Table: Within individual Coefficient of Variation in albuminuria |  |
|---|---|---|---|---|---|
| Single urine sample per period | FMV sample | Daytime sample | U_AcR | 46.3%* | 72.7%  |
| Three urine samples per period | FMV sample | Daytime sample | U_AcR | 49.4% | 69.8%  |

* p<0.009 single FMV U_AcR; p=0.02 vs single FMV U_AcR. ** p=0.004 vs daytime single U_AcR  

**Conclusions:** These data suggest that U_AcR should be measured in FMV urine samples over three consecutive days to assess and monitor (micro)albuminuria in toddlers.

**PUB680**

**L-Carnitine Replacement Improves Proximal Tubular Function in Patients with Fanconi Syndrome**  

**Background:** Hereditary nephrotic syndrome (HNS) is a rare renal genetic disorder that presents in early children and lead to end stage kidney disease (ESKD). We aim to describe their genotypic spectrum.

**Methods:** We identified 10 children with HNS presented between 2013 and 2015 in a single centre, where genetic testings and clinical courses were reviewed.

**Results:** Three have PLCE1 mutation, three WT1, two NPHS1, one LAMB2, and one has putatively pathogenic variants at DGKE, KANK1 and PA2X.

**PUB681**

**Genotypic and Phenotypic Specturm of Hereditary Nephrotic Syndrome in a Single Saudi Center**  
Majed Aloufi, Naif Fahad Abdulmajed, Abdulmonnad Mohammad Alghamdi, Saeed Al Alghwery, Saeed Ali Alzahrani. Pediatric Nephrology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.

**Background:** Hereditary nephrotic syndrome (HNS) is a rare renal genetic disorders that present in present in early in life and lead to end stage kidney disease (ESKD). We aim to describe their genotypic spectrum.

**Methods:** We identified 10 children with HNS presented between 2013 and 2015 in a single centre, where genetic testings and clinical courses were reviewed. Our result is biased by small sample size, therefore a large national multi-center study is needed, as well as going further toward a national registry of those cases of HNS.

**PUB682**

**GFR-Estimation Using Serum Creatinine Is Not Affected by Corticosteroid Therapy**  
Emilien Bakker,1 Joanna Van Wijk,1 Isabelle Hubeck,2 Arend Bokkenkamp,1 Berend Koenen.1 Nephrology, VUMC, Amsterdam, Netherlands; 2Clinical Chemistry, VUMC, Amsterdam, Netherlands.

**Background:** Glucocorticosteroids (GCS) are widely used in patients with kidney disease. While the effect of GCS is well characterized for endogenous GFR markers as serum creatinine, cystatin C, β2-microglobulin and β-trace protein, little is known about their effect on serum creatinine (sCr) the standard endogenous parameter for GFR estimation. Aims: To study the effect of GCS on the relationship between sCr and GFR measured by single injection inulin clearance (Cin).

**Methods:** Retrospective analysis of estimated GFR using the pediatric Schwartz equation (eGFR) and simultaneous Cin. Paired analysis of 22 children with and without GCS (median prednisone dose 35.5 mg/d). Cross-sectional study in 50 nephritis patients with similar characteristics, 31 of which received long-term GCS (median dose 12 mg/m²/d, median GFR 97.3 ml/min/1.73m²). The difference between eGFR and Cin (AGFR) was used to assess the interaction between creatinine and GCS using non-parametric tests and linear regression analysis for paired and cross-sectional data respectively.

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

**Underline represents presenting author.**
Results: There was no significant difference in AGFR by paired analysis:

<table>
<thead>
<tr>
<th>Age (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>&lt; 59 years</td>
<td>0.010</td>
</tr>
<tr>
<td>60-69 years</td>
<td>0.545</td>
</tr>
<tr>
<td>70-79 years</td>
<td>0.120</td>
</tr>
<tr>
<td>≥80 years</td>
<td>0.186</td>
</tr>
</tbody>
</table>

These findings were confirmed by stepwise multivariate regression analysis in which only age was retained in the final model. 

Conclusions: Data in dogs and man indicate that GFR increases in glucocorticoid excess. In the present study this was corrected for by using AGFR as indicator of a potential GCS effect on the performance of serum creatinine as marker of GFR.

Conclusions: 

In the dosage studied, GCS do not interfere with the use of scGFR as an endogenous marker of GFR.

Funding: Clinical Revenue Support

PUB683

Lack of Correlation between Changes in Ejection Fraction and Weight in Patients with Heart Failure Treated with Peritoneal Dialysis


Background: There is mounting evidence on the beneficial effects of peritoneal dialysis (PD) as an alternate therapeutic modality in patients with chronic heart failure (HF) and fluid overload, in the absence of end stage renal disease (ESRD). Improvement in left ventricular ejection fraction (LVEF) is one of the most frequently reported benefits of PD in this patient population. It is unclear whether the observed amelioration in cardiac function is correlated with correction of hypervolemia and lowered end-diastolic left ventricular pressure or due to less well understood mechanisms.

Methods: Available data from clinical trials of PD in HF performed between January 2000 and March 2016 that included more than 10 patients were selected and reviewed. Those studies evaluating the impact of PD on LVEF and volume status (assessed through changes in weight) in non-ESRD patients were included. Pertinent data were extracted and using Pearson product-moment correlation, the degree of linear dependence and correlation between these two variables was determined.

Results: Nine studies with a total of 426 participants were included. The mean age was 71.5 years, and the mean LVEF and weight before PD were 36% and 70.9 Kg respectively. There was substantial variation in the reporting time point for cardiac function and weight. LVEF changes ranged from -1 to +8.2 % (mean 3.6 ± 2.8) and weight changes ranged from -8.3 to +2 Kg (mean -2.56 ± 3.1). There was no correlation observed between changes in LVEF and weight (r=0.08, 95% CI of Correlation -0.62 to 0.70).

Conclusions: Currently available evidence suggests that changes in cardiac function and weight do not correlate in chronic HF patients who undergo PD. Hence, effective fluid removal and optimization of hemodynamics status via a left-shift on the Frank-Starling curve is unlikely to be the sole mechanism underlying improvement in left ventricular systolic function. Future studies are needed to clarify whether other proposed PD-specific factors, such as reduction in neurohormonal activation or removal of inflammatory mediators may play a role in this setting.

PUB684

Early and Late Patient Outcomes in Urgent Start Peritoneal Dialysis: A Matched Case-Control Study

Emily J. See, Yeong Jee Cho, Carmel M. Hawley, Lauren Jaffey, David W. Johnson. Dept of Nephrology, Princess Alexandra Hospital, Australia.

Background: Significant interest in the practice of urgent start peritoneal dialysis (USPD) is mounting internationally. Although several observational studies have supported the safety, efficacy and feasibility of this approach, little is known about the early complication rates and long-term technique and peritonitis-free survival of USPD compared to conventional start peritoneal dialysis (CSPD).

Methods: This single-centre, matched case-control study evaluated patients commencing peritoneal dialysis (PD) between 2010 and 2015. USPD patients, defined as needing to commence PD within 2 weeks of catheter insertion, were matched 1:3 with CSPD controls. The primary outcomes were early complications, both following catheter insertion and PD start (within 4 weeks). Technique and peritonitis-free survival were secondary outcomes.

Results: 104 patients (26 USPD, 78 CSPD) were included (mean age 50.9±14.1yr, 63% male). USPD patients were more likely to be referred late (73 vs 1%, P<0.01), initiate PD in the intensive care setting (95 vs 4%, P<0.01), and be prescribed lower initial exchange volumes (1.0L vs 2.0L, P<0.01). USPD patients experienced more frequent leaks post-catheter insertion and catheter migration post-PD start. There were no significant differences in overall or infectious complications, or technique or peritonitis-free survival between the groups.

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

1061A

Pubmed ID: 27352765

PUB685

Tenckhoff Catheter Removal Is Not Mandatory in Tuberculosis Peritonitis

Patients on Continuous Ambulatory Peritoneal Dialysis

Qi Jian, Wan Jie, Rong Yang, Wu Ming, Wan Jie, Shuang He. Dept of Nephrology, The First Affiliated Hospital of Shenzhen Univ, Shenzhen Second People’s Hospital, Shenzhen, Guangdong, China.

Background: The prevalence and prognosis of tuberculosis peritonitis (TBP) among continuous ambulatory peritoneal dialysis (CAPD) patients are not well known in China. Whether the Tenckhoff catheter must be removed or not in TBP patients remains controversial. Our aim is to report a single-center experience in the management of TBP on CAPD patients.

Methods: This is a single-center case cohort study. 178 CAPD patients followed up in our center from 1997 to 2015 included. IFN-γ, IFN-γ (PB+P8.10), IFN-γ(P8.10)(ELISpot) in blood and peritoneal effluent fluid were examined in the clinical suspicious TBP patients to confirm the diagnosis, respectively. Anti-tuberculosis combined with CAPD treatment were given to the confirmed TBP patients. Clinical and laboratory data were assessed at the 0 month, 3 th month, 6 th month and 12 th month of the follow-up, respectively.

Results: Only one 39-year old woman with severe thalassemia and without extraperitoneal tuberculosis was diagnosed TBP. The prevalence of TBP in the present study was only 0.56%, which accounted for 0.9 % of all peritonitis episodes. The incidence of TBP was 1/806 months. Fever was normal five days after the initiation of anti-tuberculosis treatment. Other clinical and laboratory data were gradually improved during follow-up. The complications such as intestinal obstruction, peritoneal-wall fistula were not found. The Tenckhoff catheter was in perfect function during the whole follow-up.

Conclusions: The incidence and prevalence of TBP among CAPD patients are rare in this single China center. TBP should be considered in CAPD patients with neutrophilic sterile peritonitis with no response to antibiotic medications. The severe anemia may be the key factor for TBP in this patient. Tenckhoff catheter removal is not mandatory in TBP patients receiving anti-tuberculous therapy.

PUB686

The Evaluation of Balance and Fall Risk in Patients with Peritoneal Dialysis: Cross-Sectional Controlled Study

Runya Ozelsancak,1 Pinar Doruk Analan,2 1Nephrology, Baskent Univ Faculty of Medicine, Adana Medical and Research Center, Adana, Turkey; 2Physical Medicine and Rehabilitation, Baskent Univ Faculty of Medicine, Adana Medical and Research Center, Adana, Turkey.

Background: This study aimed to compare the balance parameter, and fall risk between patients on peritoneal dialysis (PD) and healthy subjects. It was also aimed to determine whether there is a correlation between biochemical parameters with fall risk and balance assessments in PD patients.

Methods: We evaluated 58 patients on PD treatment (PD Group ) and 75 healthy subjects (Control Group) for this cross-sectional controlled study. Balance parameters and risk of fall were measured by using Tetrax® Interactive Balance System. All participants were also evaluated via Berg Balance Scale (BBS) to determine dynamic and functional balance status. These variables were compared between two groups. Duration of PD, Kt/Vurea and serum biochemical parameters were recorded in patients on PD. Correlation analysis between these parameters and balance measurements were made in patients on PD.

Results: The mean age of PD and Control Groups were found 54.2±12.16 and 50.38±12.11 years respectively. No statistically significant difference was found between the two groups in terms of the sociodemographic features. Fall risk of PD Group was significantly higher than healthy controls (p=0.00005) according to Tetrax measurement, but BBS score was similar (p=0.05) between two groups. Age of PD patients was negative correlated with BBS (r=-0.433). Risk of fall was positive correlated with BMI (r=0.339). Blood glucose, BUN of PD patients were positively correlated with balance parameters. There was no statistically significant correlation between duration of PD and Kt/Vurea with balance parameters and the risk of fall.

Conclusions: Balance is impaired in patients undertreatment of PD. Fall risk may be evaluated using Tetrax® Interactive Balance System instead of BBS in those patients. BMI and age affect the balance and fall risk. Biochemical parameters are not correlated of balance and risk of fall except BUN and glucose. Duration of PD and Kt/Vurea do not affect balance system.
Microparticle Formation in Peritoneal Dialysis  
Rima Abou Arkoub,1,2,3 Shareef Akbari,2 Susy Sun,2 Mercedes N. Munkonda,2 Swapnil Hiremath,2 Brendan Mccormick,1,2 Marcel Ruzicka,1,2 Dylan Burger,1 1 Div of Nephrology, The Ottawa Hospital; 2 Kidney Research Centre, Ottawa Hospital Research Inst.

Background: Injury to the mesothelial layer of the peritoneal membrane during peritoneal dialysis (PD) is implicated in loss of ultrafiltration capacity but there are no validated biomarkers for mesothelial cell injury. Microparticles (MPs) are 0.1-1.0 μm vesicles shed from the cell surface following injury. Our laboratory and others have previously reported that MPs are sensitive markers of tissue injury in hypertension, hyperlipidemia, and diabetes however there are no studies examining the formation of MPs in the peritoneal cavity during PD.

Methods: We examined MP levels in peritoneal dialysis effluents by electron microscopy, nanoparticle tracking analysis (NTA), flow cytometry, pro-coagulant activity, and Western blot. PD effluents (Dianeal® 4.25%) were collected during a peritoneal equilibration test at 0 hours, 1 hour, 2 hours, and 4 hours dwell.

Results: NTA identified particles in the size range of 30-900 nm, with a mean of ~240 nm. MP levels increased in a progressive, non-linear manner and there was approximately a 4-fold increase in MP levels at 4 hours (P<0.01, n=6). Electron microscopy confirmed size and morphology of vesicles consistent with characteristics of MPs as well as the presence of mesothelin on the surface. Western blot analysis of the MP fraction also identified the presence of mesothelin after 4 hours suggesting that MPs found in PD effluents arise, at least in part, from mesothelial cells.

Conclusions: Our results show that MPs are formed and accumulate in the peritoneal cavity during PD, possibly as a stress response. Assessing levels of MPs in PD effluents may be useful as a biomarker for peritoneal membrane damage.

The Opinion of Nephrologists Regarding Quality Management in Peritoneal Dialysis – The Network-Based Conjoint Analysis Study  
Hisako Yoshida,1 Kazuhiro Tsuuryu,2 1 Clinical Research Center, Saga Univ Hospital, Saga, Japan; 2 Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: In Japan, peritoneal dialysis (PD) is selected as the mode of renal replacement therapy in less than 10% of incident end-stage kidney disease patients, in spite of some medical and social benefits of PD have been revealed. One of the reason might be that quality of life of patients is considered difficult for a number of doctors and health care staffs. In the present study, we conducted a questionnaire study to elucidate the opinion of nephrologists regarding PD management using a network clustering-based conjoint analysis method.

Methods: The 34 simulation cases were created to quantify the relative importance of 9 hypothetical patient attributes, including 1) age and living, 2) sex and self-management, 3) blood pressure, volume status and dialysate types, 4) primary disease and cardio-cerebrovascular disease, 5) PD vintage, 6) peritoneal equilibration test, 7) residual renal function and mineral and bone disorders, 8) peritonitis, and 9) anemia. These attributes were extracted using network clustering method which were significantly associated with outcomes defined transfer to hemodialysis or death, in actual 105 PD patients observed from May 2006 to November 2014. The sample size was calculated according to precedent studies (Whitman CB, et al. Clin J Am Soc Nephrol, 2013). In the present study, participants completed 34 tasks with 5 alternatives and 5 levels, producing a sufficient sample size of 15.

Results: Sixteen nephrologists in Kyushu University Hospital were participated in this study. Attribute of “blood pressure, volume status and dialysate types” was the most important factor for nephrologists’ evaluation of management in PD patients, which accumulated the 41.5% of decision making, followed by “peritonitis” (13.0%). According to the utility scores of these clinical factors, sustained volume overload and repeated peritonitis had an impact on the opinion of the nephrologists regarding quality management in PD.

Conclusions: For nephrologists, volume overload and peritonitis might be considered important factors to maintain PD.

Bedside Peritoneal Dialysis Catheters for the Management of Refractory Ascites: A Multi-Centre Experience  
Reid Whirlock,1,2 Paul Kometani,1,2 Navdeep Tangri,1,2,3 Claudio Rigatto,1,2,3 Jay P. Hingwalla,1,4 Sean Armstrong,1,2 1 Chronic Disease Innovation Centre, Seven Oaks General Hospital, Winnipeg, MB, Canada; 2 Community Health Sciences, Univ of Manitoba, Winnipeg, MB, Canada; 3 Medicine, Univ of Manitoba, Winnipeg, MB, Canada; 4 Nephrology, Health Sciences Centre, Winnipeg, MB, Canada; 5 Nephrology, St Boniface General Hospital, Winnipeg, MB, Canada.

Background: Refractory ascites is when fluid recurrently accumulates in the peritoneal cavity, and is a common complication of liver cirrhosis. It can result in symptoms of malnutrition, respiratory distress, and ascites-related complications. PD with a peritoneal catheter has been used to manage refractory ascites since its approval by the FDA in 2010. We have collected basic demographic and comorbidity data on these patients in addition to complications of the procedure and outcomes such as peritonitis and survival. 

Results: We have placed 29 PD catheters for the sole indication of refractory ascites since 2010. There were no inpatient complications with the insertion procedure itself. Our patients had a mean age of 64 years and 52% were male. The reasons for ascites in each patient included cirrhosis (14), malignancy (10), heart failure (4) and other (1). The median survival time from the time of insertion was 56 days. In a total person-time at risk of 302 months, only 1 infection of peritonitis was detected. There were no cases of peritonitis among those whose ascites was caused by cirrhosis.

Conclusions: Bedside PD catheter insertion by trained operators appears to be a safe, effective option for the management of refractory ascites. Prospective, randomized trials are needed to assess survival, quality of life and patient satisfaction metrics for this palliative procedure.

Factors of the PD Patient that Affect the Period of the First Incidence Peritonitis  
Won Min Huang, Se-Hee Yoon, Sung-Ro Yun. Dept of Nephrology, Konjyung Univ Hospital, Daegugon, Republic of Korea.

Background: PD peritonitis is the most important cause of failure of peritoneal dialysis and the times of first incidence of peritonitis are not the same on all patients. And there are very few studies on the factors that affect the time of manifestation of the first incidence of peritonitis. So, through this Study we will try to examine the clinical and environmental factors that affect the time of manifestation of the first incidence of peritonitis and the effect of the first manifestation of peritonitis on the survival of patients.

Methods: Retrospective researches have been executed on the basis of the medical records on the occurrence of peritonitis, clinical factors (cause of ESRD, BMI, serum albumin, hemoglobin, accompanying diseases and microbiologic cause) and environmental factors (gender, age, residence, educational level and whether employed or not) of these study subjects. Factors that affect the time of the 1st manifestation of peritonitis were analyzed by conducting multivariate analysis on the aforementioned factors. The subjects were divided into the ‘early peritonitis group’ and the ‘late peritonitis group’ on the basis of 6 months as the standard time of manifestation of peritonitis since the commencement of dialysis in order to comparatively analyze the prognosis of the patients.

Results: 478 patients over the age of 18 years who continued to undergo peritoneal dialysis for more than 90 days after having commenced peritoneal dialysis during the period from January 2008 to December 2015 were chosen as the subjects of this study. In this study, two environmental factors, namely, the residence and the level of education, affected the time of manifestation of the first incidence of peritonitis on patients. In addition, the early peritonitis group had a higher incidence of manifestation of peritonitis with longer periods of hospitalization.

Conclusions: Therefore, it is anticipated that delaying the manifestation of the 1st incidence of peritonitis through management and provision of education for the peritoneal dialysis patients would be helpful to the patients not only from the perspective of the prognosis but also save them from long pricy hospitalization.

Molecular Hydrogen Dissolved Dialysate Suppresses Iron Induced Peritoneal Mesothelial Change in Rat Models  
Wan-Jun Zhu,1,2 Ayano Gibo,1 Shigeru Kabaayama,2 Masaaki Nakayama,1 1 Dept Kidney and Hypertension, Osaka Medical Univ, Fukushima, Japan; 2 Medical Device, Nikon Trim, Osaka, Japan.

Background: Free iron induces oxidative stress by Fenton reaction and causes peritoneal mesothelial injury consequently. Molecular hydrogen (H2) has anti-oxidative and inflammatory effects in biological way. This study is to clarify whether H2 could protect peritoneal mesothelial injury by iron.

Methods: SD male rats (n=10, 8wks old) were divided into two groups: Fe and H2-Fe (H2Fe) group. Rats were subjected to intraperitoneal injection of peritoneal dialysate (20ml/daily) for ten days; dialysate contained 0.05M FeCl3 in Fe group, and with that 0.8-1.0 ppm H2 in H2Fe group, respectively. Peritoneal membrane thickness and shedding loss (mass of mesothelium) were analyzed with Masson Trichrome staining pictures. Immunohistochemistry staining was performed for determining proliferative changes (Ki67), apoptosis (m30cyto) and EMT (vimentin). Real time PCR were performed in collected surface cells to analyzed wound healing, inflammation related cytokines.

Results: There were significant differences between the two groups, in peritoneal thickness (H2Fe vs. Fe: P=5.3:5.7 x 60.9:3.1 mm; p<0.05), and in shedding cells analysis 2.4±1.5 vs. 28.9±7.1%; p<0.05). In regards to surface immunostaining positive cells, there were significant increases in Ki67 (0.010±0.002 vs. 0.004±0.001/mm; p=0.05), and decreases in m30cyto (0.018±0.004 vs. 0.013±0.002/mm; p<0.05) in H2Fe as compared to Fe group, respectively, while the level of vimentin were found in vimentin. Real time PCR showed that, expressions in H2Fe were significantly lower as compared with Fe group, in TNFα (0.6±0.2 vs. 6.3±3.1; p<0.05), and IL1b (0.2±0.2 vs. 4.2±1.8; p<0.05), while they were higher in TGFβ (5.5±2.1 vs. 6.0±0.1), Fibronectin (5.5±2.1 vs. 1.4±0.3) and CTGF (4.2±1.3 vs. 2.5±1.3).

Conclusions: Molecular hydrogen could ameliorate oxidative/inflammatory peritoneal injury induced by iron, through the mechanisms such as, suppression of apoptosis, and enhancing regenerative process of mesothelial cells.

PUB869
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Low Protein Diet in Early Years of PD Initiation Leads to the Preservation of Residual Kidney Function in Peritoneal Dialysis Patients Mitsutaka Nakahigashi, TakanoBU692bu Imada, Ichiro Shoji. Second Depart of Internal Medicine, Kansai Medical Univ, Hirakata, Osaka, Japan.

Background: In peritoneal dialysis patients, dietary protein restriction is recommended 0.9-1.2 g/kg/day in Japan. This recommendation is based on the effect of the protein leakage into the dialysis fluid and nutritional status. However, it is not discussed in terms of residual kidney function and few reports examined the protein restriction effects on residual kidney function. This study aimed to evaluate the protein restriction effects on the residual kidney function in peritoneal dialysis patients.

Methods: A total 29 PD patients (15 males, mean age of 53 years old) who visited our hospital between January 2006 and May 2015 were enrolled. We evaluated the relationship between the residual kidney function and clinical parameters in peritoneal dialysis patients over three years after the initiation of peritoneal dialysis. The study protocol was reviewed and approved by the Ethics Committee of Kansai Medical University.

Results: In multivariate analyses, decreases in residual Kt/V from first PET to second PET were most associated with nPCR at first PET (r=0.319, P<0.021). Next, to define the effectiveness of protein-restricted diet in PD patients, we conducted a sub-analysis by dividing the patients into two groups: those with nPCR < 0.8 and those at first PET or second PET. The group of strict dietary restriction of nPCR < 0.8 slowed the decline of residual renal function compared with that of nPCR of ≥0.8, without worsening indicators of nutrition and arteriosclerosis, for example albumin and skeletal muscle rate. Conclusion: Our observations indicated that decreases in residual renal function were more pronounced with nPCR and strict dietary restriction of less than 0.8 nPCR, which in the predialysis level, may postpone reduction of residual renal function without causing malnutrition, during early years of PD initiation.


Background: Rhabdomyolysis results from injury to skeletal muscle and leakage of intracellular contents such as creatine kinase (CK). It may lead to nephrotoxicity, myalgias, muscular weakness and possible electrolyte abnormalities. Little information is available regarding rhabdomyolysis in peritoneal dialysis (PD) patients. We aimed at analyzing its incidence and possible determinants in this population.

Methods: We performed a retrospective analysis of the 115 patients in our PD program in December 2015, reviewing demographic, clinical and laboratory information dating from the last 4 months. All patients had recent results of CK, myoglobin and aldolase.

Results: Mean age was 53.5 years (±14.0), 54.8% of the patients were men and 71.1% were taking statins. Median values for CK, aldolase and myoglobin were 111 (IQR 78-188) U/L, 5.5 (IQR 4.5-7.7) U/L and 254 (IQR 184-409) ng/mL respectively. Only 7.8% of the patients had all markers within the reference range; 31.3% had 2 and 13% had the 3 markers above the normal range. CK correlated well with the other 2 markers (r=0.497 for aldolase and r=0.771 for myoglobin; p<0.00). CK had a positive correlation with the Adragao vascular calcification score (r=0.24; p=0.01), systolic blood pressure (r=0.21; p=0.03), total body water measured by bioimpedance (r=0.34; p=0.00), body mass index (r=0.23; p=0.04) and negative correlation with serum calcium (r=-0.29; p=0.00). Men had a higher CK than women (median value 144 vs. 88; p=0.00). No significant relationships were found between CK and age, diabetes, use of statins, vitamin D analogs, cinacalcet, phosphate binders, erythropoiesis-stimulating agent, renin-angiotensin system blockers, serum phosphaturia, calcium, B-natriuretic peptide, dialysis efficiency by Kt/V or being on continuous ambulatory peritoneal dialysis vs. automatic peritoneal dialysis.

Conclusions: Higher calcification scores were associated with an increased risk for rhabdomyolysis in PD patients, maybe due to tissue hypoxia. Statins were not associated with rhabdomyolysis in our population and seem to be safe, although this is a cross-sectional analysis.

Identifying Urine Microbiome in Patients Receiving Peritoneal Dialysis Ehsa Georges, Holly J. Kramer, Vinod K. Bansal, Julia Schneider, Michael Zillioux, Kavitha Vellanki. Dept of Nephrology and Hypertension, Loyola Univ Medical Center, Maywood, IL.

Background: No data exists on urinary microbiome in peritoneal dialysis (PD) patients. The aim of this pilot study is to identify urinary microbiome and correlate with urinary symptoms in patients receiving PD.

Methods: Patients who were 18 years and older and receiving PD at our institute are included. Patients who received antibiotics within 4 weeks or had an episode of peritonitis 8 weeks prior to enrollment were excluded. 10 cc of random mid-stream urine is collected using routine sterile techniques. 16S rRNA gene sequencing is used to identify bacteria that are not routinely cultivated by clinical microbiology laboratories. Demographic and clinical characteristics are collected from electronic medical records.

Results: Of the 25 PD patients, 5 are excluded (3 patients were on antibiotics and 2 refused).9 of the 20 remaining patients with native urine output are included in the study. Baseline characteristics are shown in table 1.

<table>
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<th>Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only</th>
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<tr>
<td><strong>Table 1: Baseline Characteristics of Study Population in Patients who have urine output (n=9)</strong></td>
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<tr>
<td><strong>Mean age in years</strong></td>
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<td><strong>Sex (M:F)</strong></td>
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<td><strong>Race</strong></td>
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<td><strong>Diabetes</strong></td>
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<td><strong>History of peritonitis (over the last year)</strong></td>
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<td><strong>History of abdominal surgery</strong></td>
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<td><strong>Type of transporter</strong></td>
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<td><strong>Mean dialysis vintage time in years</strong></td>
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There is wide variation in the urinary microbiome. Strepococcus is the predominant bacteria in 3 patients (2 female and one male), lactobacillus in one female and prevotella in another male patient. 3 patients have no predominant bacteria. Nighturia (waking up more than once in the middle of the night to urinate) is predominant in males PD patients compared to females (80% vs. 25% respectively). The sample size was too small to make any meaningful correlation between urinary microbiome and urinary symptoms.

Conclusions: Urinary microbiome varies in each patient and further research is needed to delineate its role urinary tract symptoms in PD patients with native urine output.


Background: Hypoalbuminemia is associated with mortality in peritoneal dialysis (PD) patients and may result from malnourishment, non-nutrition factors or PD-related factors such as protein loss in the effluent. We aimed to study determinants of serum albumin in a PD population.

Methods: 115 patients in our PD program in December 2015 entered this cross-sectional analysis. Current therapy, PD modality, clinical data, serum markers dating from the last 4 months were recorded.

Results: Mean age was 53.5 (±14.0) years, 54.8% of the patients were men and only 25.4% had normal serum albumin. The remaining had serum albumin < 4g/dL, in 39.8% of cases < 3.5g/dL. Median protein losses were 18.0 (IQR 12.3-24.5)g/day. Serum albumin had a significant negative correlation with age (r=-0.19; p=0.047), C-reactive protein (r=-0.19; p=0.04), B-natriuretic peptide (r=-0.20; p=0.03) and extracellular/intracellular water ratio by bioimpedance (r=-0.33; p=0.00). A positive correlation was found with urine output (r=0.27; p=0.00), hemoglobin (r=0.21; p=0.03), serum calcium (r=0.25; p=0.01), potassium (r=0.20; p=0.03) and sodium (r=-0.22; p=0.02). Hypoalbuminemia was significantly more frequent among patients on automatic peritoneal dialysis (APD) vs. continuous ambulatory peritoneal dialysis (CAPD) (3.48±0.54 vs. 3.78±0.48 g/dL; p=0.00) diabetes (3.42±0.54 vs. 3.77±0.48 g/dL; p=0.00), those who had a weekly Kt/V under the target of 1.7 (3.42±0.69 vs 3.69±0.45 g/dL; p=0.04) or an Adragao vascular calcification index > 2 (3.46±0.47 vs. 3.80±0.50 g/dL; p=0.00). Dialysis vintage, use of icosdenixin, protein losses in the effluent, body fat measured by bioimpedance and serum phosphate were not significantly associated with serum hypoalbuminemia.

Conclusions: We found important correlations between hypoalbuminemia and inflammation, markers of volume overload and factors possibly associated with a higher comorbidity burden and worse condition such as diabetes, vascular calcification index, less efficient dialysis and being on APD.


Background: Body composition in the literature compares hemodialysis and peritoneal dialysis, an uneven comparison. We analyzed differences in body composition after a transition from Continuous ambulatory(CAPD) to continuous automatic peritoneal dialysis(APD).

Methods: We performed multiple frequency bioelectrical impedance analysis (InBodyS10, InBodyCo) and standard laboratories in patients with CAPD at baseline and 1 month after transition to APD.

Results: Twenty subjects are described, 12 men and 8 women, median age 28 years (22.15-40), height 163cm(157.25-165). Median and IQR along with Wilcoxon rank test for related samples were performed. We found statistical significance in EBW-TBW ratio in favor of APD, and increase in albumin and hemoglobin.
PUB697

Telemedicine in the Provision of Remote Peritoneal Dialysis Care: Preliminary Results

Vinay Narasimha Krishna, Russell Griffin, Michael Louis Smith, Eric L. Wallace, Nephrology, Univ of Alabama, Birmingham, AL; 2Epidemiology, Univ of Alabama, Birmingham, AL; 3Alabama Dept of Public Health, Montgomery, AL.

Background: Geography may pose a significant barrier in delivering peritoneal dialysis (PD) care to remote underserved populations leading to low utilization rates and poor outcomes. Telemedicine as a replacement for a face-to-face visit may serve as a solution to overcome geographic barriers in delivering PD care.

Methods: A telemedicine network was established through collaboration with Alabama Department of Public Health. PD patients living in a county different from the University of Alabama (UAB) Home Dialysis Unit were included in the study. A single cohort cross-over design was adopted. Patients started with 6 standard in-person (SOC) visits followed by 2 quarterly SOC visits, followed by 2 telemedicine visits. Kidney Disease Quality of Life (KDQOL-36) and the Illness Intrusiveness Ratings Scale (IIRS) were administered three times in the SOC and telemedicine arm. Telemedicine visits included interactive videoconferencing, physical exam including auscultatory exam using bluetooth enabled stethoscopes, and exit site examination using a handheld high definition camera. Labs were drawn at county health departments and shipped to a central lab. Dialysis flow sheets were faxed at the time of telemedicine visit.

Results: To date 12 telemedicine visits have been completed in 4 different counties/patients. The average physician encounter time was 8 minutes longer for telemedicine versus SOC visits (p<0.05). An average of 162 miles and 142 minutes of driving time was saved per telemedicine visit. Preliminary analysis showed the largest improvement was in SF12 physical component of the KDQOL-36 which increased an average of 5 points. IIRS scoring showed a 4 point average improvement (decrease) of 7.6 points when comparing telemedicine to SOC visits. All patient concerns were successfully addressed over telemedicine.

Conclusions: Telemedicine visits, although more time consuming for the physician, saves patients substantial driving time and trends towards improvement in quality of life for PD patients who live in a county different from the UAB Home Dialysis Unit. Funding: Pharmaceutical Company Support - Baxter Healthcare Corp

PUB698

Cat in the Bag

Naseem H. Siddiqui, Nephrology, Apex Medical Group, Knoxville, TN.

Background: A 33 year old white male, suffering from ESRD secondary to Diabetic Nephropathy and has been on Peritoneal Dialysis. Presented with abdominal pain, nausea, vomiting, elevated temperature and cloudy fluid.

Methods: Patient was initially started on IP Vancomycin and Fortaz. His PD fluid showed evidence of Peritonitis with an increased WBC count and the PD culture showed Pasteurella Multocida Infection. After the PD culture results came back, the patient was then switched to Fortaz alone for a period of 14 days. Patient completely recovered from Peritonitis. Pasteurella Multocida Infection comes from cats and dogs. Patient was quizzed about having a cat or dog and confessed that he had acquired a cat therefore his Peritonitis was a result of the cat being handled by him. Therefore he was asked to find another home for the cat.

Results: The patient completely recovered from Pasteurella Multocida Infection.

Conclusions: Pasteurella Multocida Peritonitis is very rare but does occur. We should be screening patients with regard to having pets in the house before starting PD and be vigilant that they do not acquire and handle pets while they are on PD program.

PUB699

Prediction of the Mortality Risk in Peritoneal Dialysis Patients: Machine Learning Approach Using a Prospective Cohort in Korea

Kyoung Don Yoo, Junhyung Noh, Hajeong Lee, Dong Ki Kim, Chun Soo Lim, Shin-Wook Kang, Chul Woo Yang, Yong-Lim Kim, Gunhee Kim, Jung Pyo Lee, Yong Su Kim, Dongguk Univ Gyeongju Hospital, 1College of Engineering, Seoul National University, 2Sejong National University College of Medicine; Yongsei Univ; 3Catholic Univ; Kyungkook National Univ.

Background: Peritoneal dialysis(PD) has several benefits for ESRD patients compared to hemodialysis in terms of residual renal function, reducing cardiovascular complications, improving quality of life. However, survival benefit was not consistently shown in each subgroup.

Methods: A total of 1,730 PD patients in the Clinical Research Center for ESRD prospective cohort from Aug 2008 to Dec 2014 were enrolled to this study. Mortality risk model was validated by the individual learning algorithms such as survival tree (DT), ridge/lasso/Cox regression, and ensemble learning algorithms such as survival bagging and random forest.

Results: We analyze records of 1,127 prevalent and 603 incident PD patients, among which we use 21 independent attributes to learn our models including. The mean age was 52.7 years, and 57.4% were men. Survival tree algorithm had presented the most accurate prediction model, and it outperforms a conventional method such as Cox regression (Concordance index 0.802 vs. 0.745, respectively). Among various survival DT models, Charlson Comorbidity index(CCI) was selected for the best predictor of mortality. If PD patients with high CCI (≥4) were more than 70 years old, survival hazard ratio (HR) was predicted as 4.61 compared to overall study participants(C-index 0.802). In patient under 70yrs old, if serum uric acid at dialysis initiation is 7.5 mg/dl or more, the survival HR is decreased from 0.19 to 1.88. Survival HR is only 0.104, if CCI is 2 or less at the same age. Consequently, low risk patients whose CCI 3 or 4 were depend on serum BUN level and phosphorus level for survival HR (C-index 0.802).

Conclusions: We propose machine learning based models with estimated-death risks for presenting more accurate than conventional models. In our final model, age at dialysis initiation and CCI were interleaved as notable risk factors for mortality in Korean PD patients.

PUB700

Microbiology and Outcomes of Peritoneal Dialysis Peritonitis in a Korean Medical Center

Jung-Woo Noh, Eunjuung Kim, Dong Ho Shin. Div of Nephrology; Hallym Univ Medical Center, Seoul, Korea.

Background: Knowledge on microbiologic profiles and antibiotic resistance patterns are important to guide treatment for peritoneal dialysis (PD) peritonitis. Changes in prevalence of etiologies have been reported. We analyze the incidence of peritonitis, causative pathogens, antibiotic resistance of commonly isolated pathogens and clinical outcomes.

Methods: We enrolled 321 patients on PD between January 2000 and December 2014. The endpoints analyzed were resolution, catheter loss, death due to peritonitis and shift to hemodialysis.

Results: There were 237 episodes of peritonitis in 138 of 321 patients over a cumulative follow-up period of 1205.5 patient-years. The overall rate was 0.40 episodes/patient-year. Gram- cocci were identified in 122 (51.5%) episodes, whereas Gram- bacilli were isolated from 67 (28.3%). Methicillin-resistant Coagulase-negative staphylococci (CoNS) was the most common isolate. Methicillin susceptibility was observed in 16 of 41 (39%) due to CoNS and 21 of 39 (53.8%) due to S.aureus. The ceftazidime susceptibility rate was 79.1% among Gram- bacilli, 88.5% among E.coli, 88.9% among Klebsiella spp., 33.3% among P. aeruginosa, 8.1% among Acinetobacter spp. The resistance rate was higher among P. aeruginosa than among E.coli (p=0.01). Episodes of Enterococcus spp were 65 (26.9%) in the follow-up period of 1205.5 patient-years. The overall rate was 0.20 episodes/patient-year. The main empirical antibiotic regimens were i.p. cefazolin plus ceftazidime could be acceptable regardless of antibiotic resistance.
Methods: All patients admitted in our PD center from January 1, 2003 and December 31, 2015, were evaluated. Peritonitis failure was defined as the switch from PD to hemodialysis therapy. Kaplan-Meier curves and the log-rank test were used to evaluate mortality and technique failure, and Cox proportional hazards model was used to identify factors associated with outcomes.

Results: A total of 633 patients [58.9 (44.7-68.2) years, 49% male, 33% diabetes] were analyzed. The peritonitis rate in the last 5 years was 1 episode every 34 months. During this period, 213 (34%) patients died: 101 (47%) from cardiovascular events, 64 (30%) from infectious complications not related to therapy and 27 (13%) from infectious complications related to therapy. Technique failure occurred in 204 (32%) patients especially due to peritonitis (51%). One-year and 5-year patient survival were 85% and 42%, respectively, and 1-year and 5-year technique survival were 83% and 51%, respectively. In Cox analysis, age (HR=1.045, C95% 1.034-1.055; p<0.001) and diabetes (HR=1.636, C95% 1.246-2.149; p=0.001) were associated with mortality, while age was inverse associated (HR=0.991, C95% 0.982-0.999; p=0.037) with technique failure.

Conclusions: Non-modifiable risk factors such as age and diabetes were the important determinants of survival in a larger PD center. The low peritonitis rate observed in this population seem to be not sufficient to avoid transfer to hemodialysis, suggesting that management of this infection should be more effective.

PUB702
Procalcitonin Is Not a Superior Biomarker for Peritoneal Dialysis Peritonitis Jae Seok Kim, Jae Won Yang, Byoung Gun Han, Min Keun Kim, Minseok Eom, Seung-OK Choi. 1 Internal Medicine, Yonsei Univ Wonju College of Medicine, Wonju, Republic of Korea; 2 Pathology, Yonsei Univ Wonju College of Medicine, Wonju, Republic of Korea.

Background: Peritonitis is a common complication in peritoneal dialysis (PD). Procalcitonin is a useful biomarker for bacterial infection. We aim to investigate the utility of procalcitonin in PD peritonitis.

Methods: This study included thirty-three PD peritonitis episodes for the periods of total 450 days and peritostol analysis from seven patients without peritonitis. We investigated clinical characteristics and inflammatory markers including serum and PD effluent levels of procalcitonin at the time of initial visit and discharge.

Results: The mean of dialysis vintage in the patients with peritonitis was 1774.4 days, incidence of total peritonitis during their PD periods: 4.3 times, interval from symptom onset to visit; 13.6 hours, duration of intra-peritoneal antibiotic treatment; 8.2 days, and interval from clinical improvement to recurrence; 80.7 days. Initial serum procalcitonin increased to 402.2±278.4 pg/mL (mean±SEM, <50 pg/mL in healthy people). PD effluent procalcitonin increased compared with in control group, but not significantly (72.6±38.6 vs. 14.7±3.8 pg/mL; p=0.503). The serum procalcitonin decreased to 132.5±63.2 pg/mL with clinical improvement but not significantly (p=0.267), and the PD effluent procalcitonin decreased 37.6±16.3 pg/mL, but not significantly (p=0.378).

Conclusions: Procalcitonin showed the tendencies corresponding to clinical course of PD peritonitis, but not statistical significances. We believe that procalcitonin is not a superior biomarker in PD peritonitis compared with other existing markers.

PUB703

Background: Blood pressure control is important for the reduction of cardiovascular risk. We report results of home blood pressure recordings obtained by patients and entered into a remote, PD cycler-embedded, interactive cloud-based platform (Sharesource) with blood pressures collected at home using validated home BP monitors Sharesource enables retrieval of clinical data on blood pressure and dialysis performance remotely and automatically via the Internet network. The data is collated at a server and is presented to the clinical team via an interactive "dashboard".

Methods: Patients at a single centre were changed from conventional automated peritoneal dialysis (APD) to an APD device with embedded remote monitoring features (Claria-Sharesource) in Oct. 2015. Patients were instructed to record daily blood pressures at home using the Omron M10-IT home bp monitor. Readings were then entered by the patient into the Sharesource at the start of each dialysis session. Omron blood pressure monitor data were retrieved and processed by a bespoke data management system.

Results: 4 patients had recorded and entered daily blood pressure via Sharesource for 4 months, a total of 487 days of readings. The blood pressure data was retrieved for the same period from the Omron/Proton blood pressure collection system and compared to the corresponding month of sharesource blood pressure results.

Conclusions: Mean retrieved home blood pressure was significantly higher. Inaccuracies were also apparent. Protocols and education are required to maintain data quality. Further development of the technique (eg Bluetooth enabled pressure monitors) may minimise input error.

PUB704
Peritoneal Dialysis Associated Peritonitis in the Elderly: Clinical Characteristics, Outcomes and Prognostic Factors Chen Yu, Yue Chen. Nephrology, Tongji Hospital, Shanghai, China.

Background: To investigate the clinical characteristics, outcomes and prognostic factors of peritoneal dialysis associated peritonitis (PDAP) in the elderly.

Methods: We conducted a retrospective cohort study including all peritonitis episodes cases in peritoneal dialysis (PD) patients at a single center from January 2012 and December 2015. Demographic data, clinical data at admission, causative organisms and drug resistance were collected. The outcomes of patients were recorded at the time of 4 weeks after the completion of antibiotic therapy. Treatment failure included death or removal of PD catheter for peritonitis episodes.

Results: 129 episodes of peritonitis occurred in 87 PD patients including 61 elderly patients and 26 younger patients. The proportion of elderly patients with diabetes was higher (P<0.001). The incidence of primary glomerular diseases (PGD) was lower in the elderly (P<0.001). The levels of serum albumin (Salb), blood urea nitrogen, serum creatinine and uric acid were lower in the elderly (P<0.005). There was minor difference in spectrums of causative organisms from effluents between the elderly and younger. The proportion of Enterococcus species to gram-positive bacteria was lower in the elderly (P<0.029). The occurrences of outcomes were similar in the elderly and younger. More WBC counts in effluent on d5, lower Salb and fungal or polymicrobial infections were associated with treatment failure.

Conclusions: The elderly PDAP patients were more likely to have diabetes as a comorbid disease and had worse nutritional status. The outcomes of the elderly were comparable to those of the younger. The treatment response for PDAP caused by fungi or polymicrobe was challenging in the elderly.

PUB705
How Far We Can Go: Extremes of Body Mass Index in Peritoneal Dialysis Youngdanghar Akula, 1 Sohail Abdul Salim, 1 Betzaida Rodriguez, 2 Lajos Zsom, 2 Tibor Fulop, 3 Mehul P. Dixit. 4 Div of Nephrology, Univ of Mississippi Medical Center, Jackson, MS; 5Div of Hospital Medicine, Univ of Mississippi Medical Center, Jackson, MS; 6Dept of Surgery, Div of Transplantation, Univ of Debrecen, Debrecen, Hungary; 4Div of Pediatric Nephrology, Univ of Mississippi Medical Center, Jackson, MS.

Background: The State of Mississippi leads the nation in the epidemics of obesity and, with the rising tide of chronic kidney disease, inevitably the need for renal replacement therapy (RRT) in many overweight subjects. The feasibility of peritoneal dialysis in extremely obese subjects is well not understood.

Methods: We reviewed our peritoneal dialysis (PD) unit for extremely obese subjects (body mass index [BMI] >40 kg/m²) and evaluated their biochemistry and PD adequacy parameters, in comparison with those with normal weight individuals (BMI 20-25). Results were expressed with means (SD) and percent (%); between-group comparison was performed with independent sample t-test.

Results: We observed six subjects with BMI > 40 kg/m²: mean weight was 134.7 (SD±12.5) kg, body length 174.8 (11.8) cm with BMI 44.3 (SD±4.2) kg/m² [range: 40.2-51.6]. Age was 39.3 (7.6) years with PD vintage 15.8 (16.2) months; all African-American and using cycler-assisted peritoneal dialysis. Weekly Kt/V measured 1.8 (0.18), creatinine clearance 90.1 (46.4) liter/L/1.73 m²/week with total exchanged volume 12.2 (3.5) L. Residual urine output (RUO) measured 708 (501) mL and residual creatinine clearance 48.5 (44.3) L/week/1.73 m². The lean (n=20) subjects had mean weight of 66.5 (9.8) kg and BMI 23.3 (1.4) kg/m². While both weight and BMI differed significantly (p<0.0001), weekly global and residual creatinine clearance and RUO did not. Exchanges volumes were larger (p<0.04) and Kt/V smaller (p<0.007) in the obese subjects. None of the serum biochemistry parameters were significantly different between the subgroups.

Conclusions: Successful PD appears feasible even in massively obese subject and provides RRT access when no arteriovenous fistula available.
**PUB706**

A Simplified Method to Measure GFR in Swine by the Plasma Clearance of Iohexol: Conclusions C. García-Contreras, Marta Vazquez, Sergio Luiz Lima, Susana Astiz, Antonio Gonzalez-Bulnes, Esteban Porrini. 

**Background:** There is no definitive method to measure GFR in swine.

**Methods:** We used two groups (testing and validation), of 8 adult ibertian pigs each in which 10 ml of iohexol (0.47 g) was injected intravenously (marginally auricular vein) and blood samples were collected at 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 and 420 minutes (orbital sinus). Iohexol plasma clearance was measured by two-compartment model (CL2-reference method) using all the samples and by one-compartment model (CL1) using the last six.

**Results:** Plasma clearance calculated by CL1 lead to a ±30% overestimation of CL2. A correction formula (CLr = -47.909 + (1.176xCL1) - (0.00063968xCL1^2)) was created to recalculate CL1. This approach increased the correlation between CL2 and CL1 (R=0.996).

The latter (CL1 and correction formula) was the simplified method (SM). In the validation group, GFR averaged 229.6±6.5 ml/min (CL2) and 276.9±8.3 ml/min (CL1). The recalculation of GFR with the formula lead to 224.7±7.1 ml/min, comparable to CL2. Similar results were observed in the testing group.

**Conclusions:** We offer a simple method to evaluate GFR in conscious swine which does not need urine collection and allows repeating the measurement in the same animal. 

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

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**PUB707**


**Background:** Fatigue is a prevalent and debilitating symptom in patients on hemodialysis but is measured infrequently, inconsistently, and using instruments that may not be valid for this population.

**Methods:** We used two groups (testing and validation), of 8 adult ibertian pigs each in which 10 ml of iohexol (0.47 g) was injected intravenously (marginally auricular vein) and blood samples were collected at 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 and 420 minutes (orbital sinus). Iohexol plasma clearance was measured by two-compartment model (CL2-reference method) using all the samples and by one-compartment model (CL1) using the last six.

**Results:** Plasma clearance calculated by CL1 lead to a ±30% overestimation of CL2. A correction formula (CLr = -47.909 + (1.176xCL1) - (0.00063968xCL1^2)) was created to recalculate CL1. This approach increased the correlation between CL2 and CL1 (R=0.996).

The latter (CL1 and correction formula) was the simplified method (SM). In the validation group, GFR averaged 229.6±6.5 ml/min (CL2) and 276.9±8.3 ml/min (CL1). The recalculation of GFR with the formula lead to 224.7±7.1 ml/min, comparable to CL2. Similar results were observed in the testing group.

**Conclusions:** We offer a simple method to evaluate GFR in conscious swine which does not need urine collection and allows repeating the measurement in the same animal. 

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

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**PUB708**

Comparative Biocompatibility of Polysulfone Hemodialyzers Applied in Different Treatment Modalities: Stephanie Wagner, Katharina Brand, Ursula Kreuzberg, Adelheid Gauly.

**Background:** The biocompatibility profile of two polysulfone hemodialyzers was evaluated based on hemocompatibility markers.

**Methods:** In a prospective randomized crossover study 24 adult patients on online hemodialfiltration (HD) were treated one week each with the dialyzers FX100 on hemodialysis (HD), FX Cordiax 100 on HD and HDF (Fresenius Medical Care, Germany). Linear mixed models were used for inferential statistical analysis including fixed effects for treatment and period and a period effect. Differences for the categorical means at 10 min. and for the whole treatment (area-under-the-curve, AUC), or relative changes from pre- to post-dialysis were analyzed.

**Results:** The complement factors C3a and C5a increased early in the treatment, comparable between FX Cordiax and FX in HD, but less with FX Cordiax HDF, likely due to convective elimination. sC5b9 increased in all three phases with the highest level after 60 min., overall (AUC) it was significantly lower with FX Cordiax HDF than in both HD settings. Leukocytes decreased in the first 10 min. of the treatment, without significant differences at 10 min. and over the entire treatment in all phases. Thrombocytes decreased slightly in all phases in the first 30 min., with FX Cordiax HDF significantly more than with the two HD settings. ATI increased to a different extent towards treatment end, significantly more with FX Cordiax HDF compared to both HD settings. Elastase increased in the first hour with all dialyser/modality settings, the least with FX Cordiax HDF. Kallikrein as a marker of contact activation showed a slight increase at 10 min, but not significantly different by dialyser/modality at 10 min. or overall. Tryptase decreased significantly more with FX Cordiax HDF than with both dialysers in HD. No difference was observed for IgG and HSPR. All adverse events occurring during the study were judged as unrelated to dialyser and treatment.

**Conclusions:** This study confirmed a comparable biocompatibility profile of FX Cordiax and FX. Some differences observed with FXCORDIAx HDF are likely due to convective elimination of middle molecules.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care

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**PUB709**

Intradialytic Hypotension – Can We Reduce the Incidence?: Narayanam Unni VavulliPhillip, Nephrology, Aster Medcity, Kochi, Kerala, India.

**Background:** All attempts should be made to avoid Intradialytic hypotension during maintenance haemodialysis Objectives: To study the incidence of intradialytic hypotension in blood and maintenance haemodialysis, if the Nephrologist makes an assessment of the patient before each dialysis session and decides on the volume of ultrafiltration at each session. All patients were asked about their antihypertensive medications as usual. Pulse rate and blood pressure was monitored every 10 minutes with a Philips multiparameter monitor model Intellivue P5. Intradialytic hypotension was defined as a fall in systolic blood pressure by 20 mmHg or a decrease in mean arterial blood pressure by 10 mmHg, and need for nursing interventions (KDOQI definition). Results: During the study period, 10075 haemodialysis sessions were done in 80 patients (58 males and 22 females). The mean age was 55 years (Range: 24 to 82). Diabetic nephropathy constituted 52% of the cases. Seventy seven patients were hypertensive and the mean BMI was 22.8 (14.1 to 34.6). Diastolic dysfunction on echocardiogram was seen in 74% of patients. The mean intradialytic weight gain was 1.87 kilograms (0.5 to 3.5 kg). The incidence of intradialytic hypotension was 1.55%. Incidence of hypotension was very low in our patients, compared to published reports. Assessment by the Nephrologist before every dialysis session and determination of the ultrafiltration volume at every session is extremely useful to avoid intradialytic hypotension.

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

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**PUB710**

Will Flushing of Normal Saline Reduce the Clotting Incidence during Hemodialysis?: Jafar Al-Said, Leonor Fontanilla. Nephrology, Bahrain Specialist Hospital.

**Background:** Hemodialysis is the main renal replacement mode for ESRD. Clotting is the major technical problem that could affect the blood flow and the clearance. It carries a significant risk for access loss with all its consequences. Proper Anticoagulation is needed to prevent the clot formation and maintain proper hemodialysis clearing. Adding prefilter saline flush to the regular Anticoagulation might reduce the clotting incidence by diluting the blood and facilitating removal of small clots from the filter.

**Methods:** Nine patients from our hemodialysis unit were selected. The recruitment criteria were: patients with chronic kidney disease stage 5 on maintenance haemodialysis from June 2014 to May 2016 were studied. They were dialysed for 4 hours twice a week using a Fresenius Polysulfone dialyser with a surface area equal to 75% of body surface area with Fresenius hemodialysis machine model 4008. The blood flow was kept at 230 to 300ml per minute, with a dialysate flow of 500ml per minute at 37 degree Celsius. A qualified experienced Nephrologist evaluated the patients before each dialysis session and decided on the volume of ultrafiltration at each session. All attempts should be made to avoid Intradialytic hypotension during maintenance haemodialysis Objectives: To study the incidence of intradialytic hypotension in blood and maintenance haemodialysis, if the Nephrologist makes an assessment of the patient before each dialysis session and decides on the volume of ultrafiltration at each session. All patients were asked about their antihypertensive medications as usual. Pulse rate and blood pressure was monitored every 10 minutes with a Philips multiparameter monitor model Intellivue P5. Intradialytic hypotension was defined as a fall in systolic blood pressure by 20 mmHg or a decrease in mean arterial blood pressure by 10 mmHg, and need for nursing interventions (KDOQI definition). Results: During the study period, 10075 haemodialysis sessions were done in 80 patients (58 males and 22 females). The mean age was 55 years (Range: 24 to 82). Diabetic nephropathy constituted 52% of the cases. Seventy seven patients were hypertensive and the mean BMI was 22.8 (14.1 to 34.6). Diastolic dysfunction on echocardiogram was seen in 74% of patients. The mean intradialytic weight gain was 1.87 kilograms (0.5 to 3.5kg.). The incidence of intradialytic hypotension was 1.55%. Incidence of hypotension was very low in our patients, compared to published reports. Assessment by the Nephrologist before every dialysis session and determination of the ultrafiltration volume at every session is extremely useful to avoid intradialytic hypotension. 

**Funding:** Non-U.S.
and venous chambers were monitored by the end of each session by two nursing staff. The session was labeled as negative accordingly: (No clot). (4) Clore present in moderate amount. (2) Sever clotting required changing of the filter and tubing.

Results: Nine patients had 50 HD sessions over two weeks. Five males and 4 females. Mean Age was 62.5 years (SE 7). Mean BMI 22.2 (SE1.3). The access in 24 sessions were cuffed tunneled catheter. In 10 sessions it was an AVF and 10 sessions were performed via AVG. Aspirin was used on a regular daily dose of 81mg by 5 patients. The mean interdialytic wt. gain was 2.3kg (SE 0.13). The mean Heparin dose used per session was 4313 IU (SE 281). Intradialytic hypotension noticed in 4 sessions during the study period. There were no clots in any of the 25 sessions using saline flush and Heparin. However, among the other 25 sessions, with only Heparin, moderate clotting was identified in one session. The difference was not statistically significant.

Conclusions: Using saline in addition to the regular Heparin anticoagulation during hemodialysis did not make a significant difference in regard to the intradialytic clotting incidence. A larger study is required to test the effect of saline flushing as a sole method to reduce clotting in dialysis lines.

PUB711
Reusing Dialysis Catheter Caps

Background: Hemodialysis catheter caps are utilized to secure the venous and arterial ports of the catheter from contamination, prevent blood leak and air embolism. Soaking hemodialysis catheter caps in antiseptic solution to be reused is practiced in our dialysis ports of the catheter from contamination, prevent blood leak and air embolism. Soaking catheter caps with 10% Betadine was described in KDOQI Vascular Access Guidelines in 2000. It is practiced in our dialysis at a tertiary care Dialysis Center, Bahrain Specialist Hospital.

Methods: Five patients using cuffed tunneled catheters as their permanent dialysis access were included from our unit. The duration for the catheters use was between 2-9 months. The catheter caps were reused after each hemodialysis session from the time the catheters were inserted. The caps were soaked in 10% Betadine during the hemodialysis session. The caps were flushed with 9% saline by the end of the session and then used to cover the venous and arterial ports of the catheter. Personal protective equipment was emphasized and monitored as part of our hemodialysis strict infection control policy. During this study, these caps were sent for culture and replaced with new ones. The caps were transferred to the labs in sterile containers. Each Cap was flushed with 1 ml nutrient broth and incubated at 37°C for 24 hours. The broth was subcultures for another 24 hours in different agar plates. Having a positive bacterial culture within 48 hours would indicate a possible contamination to the catheters and thus to the blood.

Results: Table (1) shows the culture report of the catheter caps as well as the duration of use. All cap cultures were negative with no growth regardless of the duration the catheter caps use.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of cap reuse in months</th>
<th>Culture result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Conclusions: Reuse catheter caps after soaking in Betadine solution does not lead to increased risk of contamination, infection or harm to our dialysis patients. It can be followed with strict aseptic technique and proper infection control procedures.

PUB712
Barriers to Reducing Sodium (Na) Intake among Black ESRD Patients
Carla Boutin-Foster, 1 Sania Tahir, 2 Amary V. Patel, 1 Jenna M. George, 2 Subodh J. Saggi. 1 Div of Internal Medicine, SUNY Downstate Medical Center, Brooklyn, NY; 2 Div of Nephrology, SUNY Downstate Medical Center, Brooklyn, NY.

Background: Black patients are 3 times more likely to have ESRD, which places them at risk for adverse cardiac events. A major risk factor is fluid retention and subsequent cardiac events. The objective was to examine outcomes of a standard program to reduce Na intake among ESRD patients cared for in a dialysis unit located in a medically underserved community.

Methods: Outcomes for patients who had elevated inter-dialytic weights (IDWs) and who received an educational program by a registered dietitian were examined. Na intake was calculated using the formula: V = ([Na+]0 - [Na+]1) + (IDW x [Na+]0), where V = total body water. The standard protocol entailed showing patients their actual Na intake, educating them about low Na intakes in traditional meals, and keeping a food log. Final Na intake was calculated at 3-months.

Results: Outcomes were reviewed for 13 patients; all were black; 8 were male; age was 49.6 ± 11.98; all were hypertensive; and 6 were diabetic. An increase in Na intake was observed in 3 patients (7.7 ± 1.3g to 4.2 ± 1.3g, P>0.5). Patients revealed physical and socioeconomic barriers to reducing Na intake. Physical barriers included difficulty seeing salt labels and measuring salt due to visual impairment. Ambulation and dexterity problems limited the ability to prepare meals, resulting in a high consumption of fast-foods. Patients described a lack of social support by family members for preparing low Na meals. Patients revealed physical and dexterity problems limited the ability to prepare meals, resulting in a high consumption of fast-foods. Patients revealed physical and dexterity problems limited the ability to prepare meals, resulting in a high consumption of fast-foods.

Conclusions: Reuse catheter caps after soaking in Betadine solution does not lead to increased risk of contamination, infection or harm to our dialysis patients. It can be followed with strict aseptic technique and proper infection control procedures.

PUB714
Acquired Cystic Kidney Disease in ESRD Patients on Maintenance Hemodialysis at a Tertiary Care Dialysis Center
Syed Rizwan Bokhari, 1 Maria Rizwan Bokhari, 1 Hafiz I. Ahmad, 1 Syed A. Khalid, 1 Muhammad Zaman Khan Assir. 1 ‘Nephrology, AICMC/JHL, Pakistan; 2Radiology, AICMC/ JHL, Pakistan.

Background: Renal cysts are commonly observed in patients on maintenance hemodialysis (HD). Most of these patients are asymptomatic, while some report hematuria and lumbar pain. Its association with renal cell carcinoma is also well known. Frequency of acquired cystic kidney disease (ACKD) is not known in our End stage renal disease (ESRD) population. We studied the prevalence of ACKD and its correlation with patient’s characteristics in our dialysis population.

Methods: Seventy-Four ESRD patients on maintenance hemodialysis at Jinnah Hospital Dialysis center were assessed for the study. Three patients with Autosomal dominant polycystic kidney disease (ADPKD) were excluded. None of the other 71 patients had previously known history of renal cysts. These patients underwent ultrasound examination by consultant radiologist for presence of renal cysts.

Results: Median age of patients was 50 years (range 17-82) and 44 (64%) were male. Median duration on hemodialysis was 4 years (1-12 years). Cause of ESRD was Hypertension (63%) Diabetes mellitus (30%) and obstructive uropathy (7%). Twenty-nine (40%) patients had hematuria C infection. Sixty (85%) patients were on thrice weekly and 11 (15%) were on twice weekly HD. Fifty five (77%) patients had 1 renal cyst, 26 patients had 2-5 renal cysts and 12 patients had more than 5 renal cysts bilaterally. Thirty-five (49%) Patients getting HD for less than 3 years had median of 3 cysts (range 0-15), while remaining patients on HD for more than 3 years had median number of 4.5 cysts (range 0-26). Nine (13%) on HD for less than 1 year had multiple renal cysts (1-4). No significant correlation was found between ACKD and duration of dialysis, frequency of dialysis, age, gender, or co morbidities, Hepatitis C status. None of these patients had evidence of extra renal cysts, retroperitoneal or intrarenal hemorrhage.

Conclusions: No significant correlation between ACKD and duration of hemodialysis was observed while a high frequency of renal cysts was seen earlier (within 1 year of HD). The reason may be the late initiation of HD at a much lower GFR which is a routine in the developing countries.
HYPERPHOSPHATEMIA AND ITS RELATION WITH CAROTID INTIMA THICKNESS IN ESRD PATIENTS

Methods: All 86 ESRD hemodialysis patients in the center were enrolled in the study. Serum phosphate level was measured. Hyperphosphatemia was labelled in accordance with KDOQI guidelines. Carotid intima media thickness was measured by ultrasound using linear transducer by a consultant radiologist.

Results: Mean age of the patients was 47.29±14.7 (ranging: 25-82 years). Thirty-six (63.4%) patients were male. Eleven (19.6%) patients had ischemic heart disease. Nineteen (33.9%) patients had uncontrolled hypertension. Mean carotid intima thickness in patients with and without ischemic heart disease was 1.13±0.5 mm and 0.80±0.24 mm respectively. Mean serum phosphate level was 5.62±1.95 (range: 1.4-10.4 mg/dl). Mean carotid intima media thickness was 0.87±0.34mm in our cohort. Twenty-nine (51.8%) had hyperphosphatemia. Mean carotid intima media thickness in patients with hyperphosphatemia was 0.85±0.34 mm which is similar to those without hyperphosphatemia (P value=0.56).

Conclusions: In our dialysis population hyperphosphatemia, common carotid artery intima media thickness was not observed.

REGULAR TREATMENT WITH HAEMODIALFILTRATION RESULTS IN FEWER HOSPITAL ADMISSIONS THAN HAEMODIALYSIS

Methods: Our findings have provided evidence for the efficacy of HDF in the treatment of peri- dialysis patients. Although HDF is more labor-intensive and expensive than HD, it has been shown to be more effective in the treatment of hemodialysis patients. Therefore, it is important to consider the use of HDF in the treatment of these patients.

Results: The prevalence of malnutrition in dialysis patients was higher than we expected. Serum ferritin is a useful and convenient biochemical parameter for assessing nutritional status in dialysis patients.

Conclusions: The prevalence of malnutrition in dialysis patients was higher than expected. Serum ferritin is useful and convenient biochemical parameter for assessing nutritional status in dialysis patients.

LOW CALCIUM (Ca) BATHS AND RELATION TO INTACT PARATHYROID HORMONE (iPTH) IN PATIENTS WITH NUTRITIONALLY IMPAIRED DIALYSIS

Methods: As a Quality Assurance project we conducted a retrospective, single center study to determine the iPTH response to a lower calcium bath. Three separate study periods employing several low Ca dialysates in the hope of decreasing the net absorption of calcium. As a Quality Assurance project we conducted a retrospective, single center study to determine the iPTH response to a lower calcium bath. Three separate study periods employing several low Ca dialysates in the hope of decreasing the net absorption of calcium. As a Quality Assurance project we conducted a retrospective, single center study to determine the iPTH response to a lower calcium bath. Three separate study periods employing several low Ca dialysates in the hope of decreasing the net absorption of calcium.

Results: As seen on Table 1, we found a tendency for increases in iPTH as the bath concentration was decreased but none of these increases were statistically significant in our small samples. Of interest is that of 6 patients treated with the most substantial drop in Ca bath (2.5 vs. 2.0), 2 developed a decrease in iPTH.
Predictive Value of Histological Acute Kidney Injury Parameters in Implantation Biopsies for Delayed Graft Function

Anke Keilbeck, Tim C. Van Smaalen, Marielle Gelenis, Robert Jan Van Suylen, Floortje Steegh, Maarthen H.L. Christiaans, Ernst van Heurn, Carine Peutz-Kootstra, Pathology, MUMC, Maastricht, Netherlands; Surgery, MUMC, Maastricht, Netherlands; Internal Medicine, MUMC, Maastricht, Netherlands; Pathology, Jeroen Bosch Hospital, ’s-Hertogenbosch, Netherlands; Surgery, AMC, Amsterdam, Netherlands.

Background: Ischemia-reperfusion injury (IRI) in kidney transplantation is an important risk factor for later complications such as delayed graft function (DGF) and reduced graft survival. Clinical parameters such as cold ischemia time (CIT) and donor type are indicative for IRI, however, the additional value of post-reperfusion histology is not known. The aim of this study was to investigate the predictive value of histological parameters of acute kidney injury for DGF.

Methods: The biopsy results of 192 consecutive donor kidney recipients transplanted between April 2003 and December 2009 at the Maastricht University Medical Centre (MUMC) with representative renal biopsy taken 30-60 minutes after reperfusion and a functional graft one year after transplantation were analysed. Biopsies were scored for 5 parameters for IRI known from animal studies: tubular cell necrosis, oedema, loss of brush border, neutrophils in glomerular capillaries and neutrophils in peritubular capillaries (PTC), which were scored in a dichotomous manner.

Results: Donor types were equally distributed in the cohort: 32.8% living donors, 35.4% donors after brain death (DBD) and 31.7% donors after cardiac death (DCD). The incidence of DGF in the cohort was 35%. Tubular cell necrosis was a risk factor for DGF (OR=2.6 (1.4-4.4)). Other histological IRI markers didn’t affect the risk of DGF in addition to the known clinical factors CIT and DCD donor type. Area under the curve of the ROC (0.88 [0.83-0.93]) shows an excellent discriminant power of the model.

Conclusions: This study shows that IRI is already visible in implantation biopsies. Assessment of histological acute kidney injury parameters in the post reperfusion kidney biopsy has added value to predict DGF.

The Change of Fcγ Receptor 1α mRNA in the Graft of Acute Kidney Rejection

Renate Dufour, Dieter Bischof, Oliver Meier, Hendrik Büsscher, Rainer Büscher, Heinrich-Ludwig-University, Department of Nephrology, Pathology, MUMC, Maastricht, Netherlands; Surgery, Maastricht, Netherlands; Pathology, Jeroen Bosch Hospital, ’s-Hertogenbosch, Netherlands; Surgery, AMC, Amsterdam, Netherlands.

Background: In the renal transplantation model, especially after the acute rejection.

Methods: The biopsy results of 192 consecutive donor kidney recipients transplanted between April 2003 and December 2009 at the Maastricht University Medical Centre (MUMC) with representative renal biopsy taken 30-60 minutes after reperfusion and a functional graft one year after transplantation were analysed. Biopsies were scored for 5 parameters for IRI known from animal studies: tubular cell necrosis, oedema, loss of brush border, neutrophils in glomerular capillaries and neutrophils in peritubular capillaries (PTC), which were scored in a dichotomous manner.

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Conclusions: This study shows that IRI is already visible in implantation biopsies. Assessment of histological acute kidney injury parameters in the post reperfusion kidney biopsy has added value to predict DGF.

Proteinuria Associated with mTOR Inhibitor Use in Heart Transplant Recipients

Negiin Aalaei Andabili, Michael Negiin, F. Ali Hameeni, Evgeni K. Sinha, Jane E. Gelone, Aditi Gupta, Abbas Ghaemi, Stephen King, Robert G. Urich, Annalisa B. Young, Ajay G. Yachha, H.L. Sinha, Wineke van Suylen, Van Heurn, Rainer Büscher, Astrid Gelens, Carine Peutz-Kootstra, Pathology, MUMC, Maastricht, Netherlands; Surgery, MUMC, Maastricht, Netherlands; Internal Medicine, MUMC, Maastricht, Netherlands; Pathology, Jeroen Bosch Hospital, ’s-Hertogenbosch, Netherlands; Surgery, AMC, Amsterdam, Netherlands.

Background: Proteinuria is a known complication of mTOR inhibitors in renal transplantation recipients; we sought to determine whether these agents are associated with increased urinary protein excretion in OPT patients.

Methods: This is a retrospective study of adult patients who received OPT at the University of Florida between January 2000 and December 2015. All patients who received mTORi, whether de novo or following conversion from a calcineurin inhibitor regimen, were included. The OPT patients’ clinical and laboratory information were reviewed and relevant data such as renal function and urinary protein excretion were recorded.

Results: There were a total of 411 OPT patients, of which 91 received mTORi (23 sirolimus and 19 everolimus). The mean age of recipients was 47.7 years and 80% were men. mTORi was started de novo in 35% of the patients. The timing of the measurement of proteinuria was highly variable ranging from 4 weeks to 7 years after starting mTORi (median 15.7 months). mTORi therapy was associated with an increase in the urinary excretion of protein in 31% of the patients. The mean albumin/creatinine or protein/creatinine ratios were as high as 1.11 mg/g and 2.5 g/g respectively, and 17% developed nephrotic-range proteinuria. Interestingly, all these patients had negative or unremarkable proteinuria before initiation of mTORi.

Conclusions: To our knowledge, this is the largest study on the impact of mTORi on urinary protein excretion in the setting of OPT. Based on these findings, mTORi use can be associated with development of moderate to severe proteinuria in a significant subset of these patients. Serial assessment of urinary protein excretion should be integrated in the therapeutic protocols that include these agents in OPT. Future studies are needed to determine the risk factors associated with mTORi-related proteinuria and its potential impact on renal and cardiovascular outcomes.

Successful Treatment of Severe Antibody Mediated Rejection in Simultaneous Liver Kidney Transplant: A Case Report

Aditi Gupta, Abhishek Sinha Roy, Anjushree Kumar, Sri G. Yarlagadda, Internal Medicine, Nephrology, Univ of Kansas Medical Center, Kansas City, KS.

Background: Simultaneous liver-kidney (SLK) transplants are often performed in the presence of donor specific antibodies (DSAs) and/or positive cross match. The presence of DSAs is associated with increased risk of antibody mediated rejection (AMR). We report a case of severe AMR resistant to conventional therapy with steroids, plasmapheresis (PP) and intravenous immunoglobulin (IVIG) respond to Eculizumab, a monoclonal antibody against the terminal complement C5.

Methods: A 64-year-old woman with primary biliary cirrhosis and end stage renal disease (ESRD) with ESKD on dialysis and a SLK transplant was referred for AMR. She received induction with anti-thymocyte globulin and solenemod and was maintained on mycophenolic acid, tacrolimus and prednisone. Since she had DSAs, she received PP and IVIG on post-operative day (POD) 1, 3 and 5, and was discharged on POD 6 with a serum creatinine of 0.9mg/dl. However, on POD 8, she presented with anuria, thrombocytopenia and aminotransferase levels. She was treated with eculizumab and antithrombotic therapy. Markers of complement activation were measured before, during and after treatment. She was discharged on POD 17 with a serum creatinine of 0.9mg/dl. She remained anuric after four sessions of PP. She was then treated with eculizumab. Her hemoglobin, platelet count and urine output improved after two doses of eculizumab (POD 12 and POD 19). With improvement in thrombocytopenia, a renal biopsy was performed on POD 17 confirming AMR. There was no evidence of thrombotic microangiopathy in the biopsy.

Results: Serum creatinine started to improve and returned to baseline of 0.9mg/dl by POD 25. She received a total of four doses of weekly eculizumab. After 24 months, her renal function continues to remain stable with a serum creatinine of 0.8-0.9mg/dl and without any detectable proteinuria on dipstick.

Conclusions: SLKs are often performed despite presence of pre-transplant DSAs that are associated with early AMR. Treatment with a monoclonal antibody against the terminal complement C5 can prevent early graft loss from severe AMR.
Association between Kidney Transplantation and Diabetes Management in Recipients with Kidney Failure due to Diabetic Nephropathy

Samyuktha B. and colleagues from the National & Kapodistrian Univ of Athens, Athens, Greece; Georgios Nikolaos Panagiotellis, Panagiotis Pappas, Aliki Ioitaki, Georgios Zavos, John Boletis, and others.

Diseases of Non-Autoimmune Origin of ESRD: Nephritic Syndrome versus Nephrotic Syndrome versus Primary Kidney Transplantation Outcomes among Patients with Different Causes of ESRD

PUB725

Kidney Transplantation Outcomes among Patients with Different Causes of ESRD: Nephritic Syndrome versus Nephrotic Syndrome versus Primary Diseases of Non-Autoimmune Origin


Background: To compare kidney transplantation (KTx) outcomes of patients with different causes of end stage renal disease (ESRD).

Methods: We retrospectively compared the outcomes of KTx recipients with biopsy proven glomerular primary disease (PD), i.e. nephritic and nephrotic syndrome, with those of KTx recipients with PD from non-autoimmune origin. All patients were transplanted during the period 1/1985-1/2015 and had 1 year of follow up post KTx or more.

Results: 180 KTx recipients with biopsy proven glomerular PD were identified, and a control group of 110 patients with PDK, hypoplastic kidneys or obstructive uropathy, as PD were matched. The two groups were similar with respect to baseline characteristics at KTx, but patients with glomerular PD had received more grafts from living donors than the controls (p=0.02), most of them (75.33%) had been transplanted with immunosuppressants prior to KTx (p=0.0001) and had donor specific antibodies (DSA) less frequently.

Conclusions: KTx recipients with a glomerular PD had inferior renal function and worse graft survival, compared to those with a PD of non-autoimmune origin. The difference in graft function and survival remained significant when the analysis was controlled per decade of follow up or was limited to living donor KTx. No differences in KTx outcomes were found between patients with nephritic and nephrotic syndrome as PD.

Early Recurrence of Diabetic Nephropathy in Kidney Allografts

PUB727

Panu Pangpong Hansriwong, Amy K. Mottl, Randal K. Detwiler, and others from the Univ of North Carolina Kidney Center, Chapel Hill, NC.

Background: Although recurrent diabetic nephropathy (rDN) after kidney transplant (KT) is reported in 70% of cases, most patients are diagnosed after 10 years. Early rDN within 5 years of kidney transplant is extremely uncommon.

Methods: Patients' medical records were reviewed for patients who had KT due to diabetic nephropathy at the University of North Carolina Kidney Center from March 2000 to October 2013 were reviewed. All patients received their allograft from non-diabetic donors. Diagnosis of rDN was made based on pathological classification. The recurrence rate of early DN, defined as pathological lesions present within 5 years post-KT, were reported.

Results: Of 156 patients with native DN, 4 patients (2.5%) had early rDN during median follow-up of 1.78 ± 4.57 years. These patients were described in details. Blood pressure and serum glucose were not well-controlled among these patients. HCV seropositivity was present in one patient. Some patients had rDN without significant proteinuria. In contrast, another patient presented with marked proteinuria. His biopsy revealed co-existing focal segmental glomerulosclerosis (FSGS).

Conclusions: To date, it is inconclusive to establish the recurrence rate of early DN after KT. A larger cohort is required to demonstrate the association between clinical characteristics and early recurrent diabetic nephropathy.

Funding: Clinical Revenue Support

Effect of Meeting Brain-Dead Donor Management Goals on the Development of Delayed Graft Function in Kidney Transplant Patients

Stephanie Grondin, Pierre Marsolais, Martin Albert, Anne-Marie Lagacé, Isabelle Houde, Anne Boucher, Dana Baran, Yannick Begin, Melanie Massé, Heloise Cardinal, Josée Boucharé, and others from the University of Montreal, Canada; CHUQ, Canada; 1CUSM, Canada; CHUS, Canada.

Background: A recent US study suggests that meeting several hemodynamic, respiratory and metabolic goals in organ donors (donor management goals, DMG) could reduce the incidence of delayed graft function (DGF) in kidney transplant recipients (KTR).

We determined if DMG goals were met in our kidney donors and how this influenced the incidence of DGF.

Methods: We collected data on consecutive brain-dead donors and corresponding KTx from June 2013 to February 2015. Using guidelines from Transplant-Québec, we evaluated whether DMG were met at donor neurological death (DND), and before organ procurement (OP). We used generalized estimating equations to predict DGF, including DMG parameters and other risk factors for DGF (expanded-criteria donors (ECD), cold ischemia time (CIT), use of Lifeport perfusion, and recipient body mass index).

Results: The 69 consecutive donors had a median age of 50 years (IQR 31.5-62.0), and 36.2% were ECD donors. Mean serum creatinine was 71 (61-91) μmol/L, and Lifeport perfusion was used in 42.2% of cases. The percentages of DMG met increased over time, e.g. central venous pressure (51.2% at DND; 57.9% at OP), urinary output (63.2% at DND; 75.4% at OP) and appropriate use of vasopressors (70.6% at DND; 91.3% at OP). Median CIT was 14 hours (8.0-17.8). DGF, defined as dialysis during the first week after transplantation, occurred in 25.0% of 124 KTR. In univariate analysis, no variables significantly predicted DGF, including mean arterial pressure within targets (OR 0.69; 95%CI 0.30-1.62). However, the use of Lifeport perfusion was significant in multivariate analysis (OR 0.37; 95%CI 0.15-0.93).

Conclusions: Although DMG were met in the majority of our cases, we were unable to show a significant relationship between this achievement and the occurrence of DGF in KTR. This may be due to small sample size and/or the fact that peri-operative and recipient factors may carry more weight in the context of good donor management.
**Thrombotic Microangiopathy after Transplant: Which Is the Role for Eculizumab?**

**Ana Avila**, Eva Gavela, Mercedes Gonzalez, Marco Montomoli, Asunción Sancho, Julia Kanter, Jose F. Crespo, Luis M. Pallardo. *Nephrology, H. Univ Dr Peset, Valencia, Spain.*

**Background:** We describe the prevalence and management of thrombotic microangiopathy (TMA) after transplant.

**Methods:** Retrospective study of the incidence of TMA after kidney transplant from cadaveric donors in our center between January 2010 and May 2016. We reviewed the risk factors associated to TMA, management and the evolution after treatment.

**Results:** 315 kidney transplants were performed. We found 13 TMA cases (4.1%), 8 males. Recipient age was 55 years (r:30-67). Donor age: 42.5 years. Eleven patients presented TMA early after transplant (mean ± SD: 10 ± 3.3). Two patients presented late TMA (7 months and 8 years after transplant). Three patients presented TMA in the context of severe intravascular coagulation, 3 related to AMR, 2 after transplant with a non heart beating donor, 4 to drug induced TMA and one, all HUS relapse. Ten patients presented hematological manifestations and kidney function impairment. A kidney biopsy, performed in 11 patients, showed TMA. ADAMTS13 activity deficiency was ruled-out. The patients were managed controlling TMA risk factors (AMR treatment, drugs withdrawal). Ten required plasma exchange (median 4.5 sessions). In 6/10 patients diagnosed after 2012, after non response to previous measures, eculizumab was started. Mean time to eculizumab treatment was 6 days. A complete hematological response was seen in all of them, but 4 patients lost their grafts. Most of the remaining patients (8/9) improved kidney function (mean GFR 2.45 mg/dL, r:9.5-22) at the end of the follow-up (mean follow-up after TMA was 9.5 months r:1-23). The duration of eculizumab treatment was 133 days (7-240). In 7 patients, a complement system genetic study was performed, showing anti-HF antibodies in one case and CPI mutation in another.

**Conclusions:** TMA is a rare but severe disease that can lead to graft loss or to reduced kidney function. It is associated to several risk factors presented in kidney transplant (AMR, drugs). In patients who do not respond to classic measures (drug withdrawal, plasma exchange) eculizumab can reverse TMA and improve kidney function.

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**Chronic Kidney Disease after Living Kidney Donation: A Single Center Cohort**

Suthanit Laowalert, Pisut Katavej, Yingyos Avihingsanon, Kearkat Praditpornsilpa, Natavudh Townamchai. *Dept of Medicine, Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand.*

**Background:** Post kidney donation outcomes in nonwhite living kidney donors (LKDs) are lacking. This is the first study of Thai population to assess the incidence of chronic kidney disease (CKD) after donor nephrectomy and estimated glomerular filtration rate (eGFR) for donation.

**Methods:** A retrospectively cohort of all 205 LKDs in King Chulalongkorn Memorial Hospital who were followed from 2009-2014 were retrieved to ascertain development of CKD stage 3 or higher. The eGFR was determined by the CKD-EPI.

**Results:** 143 of 205 records were available, mean age at donation was 37.0 years. 18 of 143 (12.6%) had stage 3 CKD after median follow-up duration of 4 years (range 1-17 years). Predonation eGFR was an independent risk factor in developing CKD stage 3. The risk was significantly increased in donors with eGFRs <85 mL/min/1.73m² and eGFRs <85 mL/min/1.73m² compared with eGFRs >90 mL/min/1.73m² (HR 10.3, p<0.05, HR 13.7, p<0.001, respectively).

**Conclusions:** We describe the prevalence and management of thrombotic microangiopathy (TMA) after transplant. The present study clearly establishes that the Luminex DSA crossmatch is helpful for predicting post transplant graft outcome or rejection. The laboratory cut off value of the eGFR for positive DSA was increased from 500 to 1000. Furthermore, the clinical impact of DSA as described in this article should be explored in larger studies to have a better correlation with kidney function.

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**Table 1 Cox proportional hazard analysis of clinical risk factors for development of CKD in 143 LKDs**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio (CI)</td>
<td>P-value</td>
<td>Hazard ratio (CI)</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.57 (0.23-1.47)</td>
<td>0.235</td>
</tr>
<tr>
<td>Age</td>
<td>1.07 (1.029-1.148)</td>
<td>0.003</td>
</tr>
<tr>
<td>Predonation eGFR</td>
<td>17.49 (5.46-56.06)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.107 (0.108-0.108)</td>
<td>0.87</td>
</tr>
<tr>
<td>UPCR</td>
<td>0.107 (0.108-0.108)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

**Age at donation was associated with the development of CKD stage 3 only in univariate analysis (HR 1.09, P<0.003). There were 17 (11.9%) and 3 (2.1%) donors developed hypertension and diabetes mellitus. One donor (0.7%) experienced ESRD.**

**Conclusions:** Incidence of CKD stage 3 and ESRD of kidney donor were 12.6% and 0.7%, respectively. Predonation eGFR<90 mL/min/1.73m² was a strong determinant of development of CKD, which led to the extended thresholds of eGFR for a donor candidate.
transplanted, of which 5 were excluded because of age less than 18 years, acute rejection, or anatomical ureter problems; thus a total of 55 patients were studied. 45% were female and 55% were male.

**Results:** We found that pyuria and bacteruria are unreliable predictors of a true symptomatic urinary infection. 87% of our patient sample had pyuria, of which only 33% developed bacteruria. We additionally found that in patients with bacteruria, 50% developed symptoms that require treatment. Among the patients that require treatment, only 25% had a ureteral stent in place (Figure 1).

**Conclusions:** In summary, our study indicates that ureteral stents post renal transplant do not have a higher incidence of true symptomatic infection or hospitalization compared to patients without a stent. Further studies are useful to confirm these findings.

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**PUB734**

Impact of Conversion from Original MMF to Generic MMF in Kidney Transplant Recipients: A Single-Center Experience

**Haijme Hirano,1 Haruhito Azuma,1 Hideki Matsumura,1 Hideaki Shim,2 Tatsuhiko Mor,1 Akira Ashida,1 Blood Purification Center, Osaka Medical College, Takatsuki, Osaka, Japan; 2Dept of Pediatrics, Osaka Medical College, Takatsuki, Osaka, Japan; 1Dept of Nephrology, Osaka Medical College, Takatsuki, Osaka, Japan.

**Background:** Recently, more and more generic drugs have been used for immunosuppressive drugs in the field of organ transplantation. Some reports have indicated that blood concentration of most generic drugs is difficult to maintain stability, and it may cause the difference in graft survival of transplanted organs between original drugs and generic drugs. In this article, we report the cases could not maintain blood concentration of generic drugs. In this article, we report the cases could not maintain blood concentration of generic drugs of mycophenolate mofetil (MMF).

**Results:** In 4 cases out of 5 cases that we had to change original MMF to generic MMF, there were cases that blood concentration level was not stabilized. There were possibility that the lowered blood concentration level of MMF caused a rejection. In two cases. Mean MMF trough level was decreased from 3.6±1.9μg/ml to 0.6±0.4μg/m. Due to the early detection, it did not become severe or failure of graft function, however, we cannot deny the possibilities that side effects were increased and rejection rose. In these cases, we discontinued to use the generic drugs thereafter due to unstable plasma concentration of MMF.

**Conclusions:** Some reports have indicated that failure to maintain plasma concentration of MMF leads to rejection. Therefore, maintenance of effective plasma concentration and prevention of rejection are essential to long-term graft survival in kidney transplant. Conversion to the generic drug should be used, patients should be closely monitored.

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**PUB735**

Allograft Rejection in the HIV Infected Kidney Transplant Recipient

**Adriana Dejman, Juan E. Kusnir, Juan Camilo Duque Ballesteros, David Roth. Nephrology, Univ of Miami, Miami, FL.

**Background:** Excellent graft survival outcomes have been reported in HIV patients on anti-retroviral therapy with undetectable viral loads and CD4 count >200 at time of transplant. Prior studies also observed higher incidences of acute rejection with limited data on variables that associate with this outcome.

**Methods:** Retrospective chart review for patients with HIV who had a kidney transplant between 2001-2014. A multivariate logistic regression model adjusted for demographics, co-morbidities, induction immunosuppression (IS), chronic IS with steroids, presence of drug-drug interaction (DDI) between protease inhibitors (PI) and calcineurin inhibitors (CNI), type of transplant, initial graft function (immediate/IGF, slow/SGF or delayed/DSG), calculated post-transplantative antibodies (cPRA), histologic type of rejection and donor specific antibodies (DSA) was used.

**Results:** 58 consecutive patients were included and divided into Group A, no-rejection (N=41, 70.7%) and Group B, biopsy proven rejection (N=17, 29.3%). Mean age was 52.1±13.9 years, and 60.3% were female. The prevalence of HCV in KT is about to decrease over time as a result of hepatitis B vaccination and close collaboration between nephrologists and hepatologists.

**Conclusions:** HCV still has significant prevalence in kidney transplant (KT) recipients and is related to poor recipient and graft survival. The new antivirals are leading to a radical change in the problem.

**Methods:** We study HCV prevalence at time of transplant and in follow-up patients, the way RNA+ cases are handled and the results of direct-acting antivirals(DAA).

**Results:** From 1978 to 2015,2015 transplants had been performed in our center. Sorcery was present in 1880 cases,being + in 13.4%.1955 was still being monitored by our service,69.9%were HCV+/RNA+ in 45 cases(3.6%).Of these 45 patients,26 were being treated,6 were about to begin treatment,1 was awaiting a new DAA for low GFR,3 were treated,6 were about to begin treatment,1 was awaiting a new DAA for low GFR,3 were treated,6 were about to begin treatment,1 was awaiting a new DAA for low GFR,3 were treated,6 were about to begin treatment,1 was awaiting a new DAA for low GFR,3 were treated,6 were about to begin treatment,1 was awaiting a new DAA for low GFR,3 were treated.
**PUB738**

**Cost-Effectiveness of Machine Perfusion Use in a Brazilian Kidney Transplantation Program**

Ana Carvalho Matos, Daniel Tavares Malheiro, Silvia Regina Morgado, Eduardo J. Notato, Milton Borrelli, Mario Nogueira Junior, Marcelinho Souza Durao, Lucio Roberto Requeiao-Moura, Alvare Paccheco-Silva. Renal Transplant Unit, Hospital Israelita Albert Einstein, Sao Paulo, Brazil.

**Background:** The incidence of DGF is one of the most important problem in kidney transplantation in Brazil: higher than 60%. Static cold storage (CS) is the standard method of preservation performed by governmental allocation. Our center has used perfusion machine (PM) as preservation method since 02/2013, however we have only used PM after long time in CS. Aim: to determine the relative cost-effectiveness between renal machine perfusion (MP) after long CIT in CS and standard CS preservation.

**Methods:** Probabilistic decision tree was developed to compare MP versus CS and the results and probabilities of our own center were used to construct this model. The model estimated Economic Impact (E=MPcost – CScost) and Incremental Cost-Effectiveness Ratio (ICER=EI/Effectiveness CS/Effectiveness MP). Direct and indirect medical costs were considered and sensitivity analysis was performed with variations of several parameters.

**Results:** MP group had TIF 11 hours longer than CS, despite of this the incidence of DGF (9 vs. 5 days, p<0.001) were reduced significantly, leading to a reduced length of hospital stay (18 vs. 13 days, p<0.001). The mean cost of each transplant was: MP-US$12,588.15 and CS-US$16,660.83. The budget impact was US$-4078.28. ICER for each DGF avoided was US$-226.26. The variables that most impacted the costs were length in hospital and length of DGF.

**Conclusions:** The use of MP after long CS preservation was cost-effective. This is the first economic study performed in Brazil and will enable other transplant centers to decide on incorporating the renal MP as a strategy to prevent DGF and reduce costs.

**PUB739**

**Association of Childbearing Age with Live Birth after Kidney Transplantation: A Retrospective Single-Center Cohort Study**

Yuki Hung-Tien,1,2 Yoshihiro Iwadare,1,2 Seiichiro Yasushi.1,2 Medicine, Toho Univ, Tokyo, Japan.

**Background:** Recipients may be concerned about various aspects of having children. We investigated the association of fertility after kidney transplantation as if fertility is restored. Although the frequency of pregnancy complications should not be long in recipients with live births than those with no live births (14.1 ± 7.1 vs. 9.9 ± 7.3 years, p=0.02) and length of DGF (9 vs. 5 days, p<0.001) were reduced significantly, leading to a reduced length of hospital stay (18 vs. 13 days, p<0.001). The mean cost of each transplant was: MP-US$12,588.15 and CS-US$16,660.83. The budget impact was US$-4078.28. ICER for each DGF avoided was US$-226.26. The variables that most impacted the costs were length in hospital and length of DGF.

**Methods:** The objective of this study was to investigate the risk factor for proteinuria after mTORI treatment in kidney transplant recipients. In univariate analysis, BMI >27 kg/m² (OR=3.111, P<0.047) and hyperlipidemia (OR=3.345, P=0.024) were associated with proteinuria after mTORI use. After adjusting for confounding factors, hyperlipidemia (adjusted OR=3.740, P<0.026) and BMI at 24-26.9 kg/m² (adjusted OR=4.7, P<0.021) were significantly associated with risk of proteinuria.

**Conclusions:** The use of MP after long CS preservation was cost-effective. This is the first economic study performed in Brazil and will enable other transplant centers to decide on incorporating the renal MP as a strategy to prevent DGF and reduce costs.

**PUB740**

**The Risk Factors of Mammalian Target of Rapamycin Inhibitor Associated Post-Transplant Proteinuria**

Lee-Mooi Lim,1 Hsiin-Tien Kuo,1,2,3,4,5 Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan; 1Faculty of Renal Care, College of Medicine, Kaohsiung Medical Univ, Kaohsiung, Taiwan.

**Background:** The Mammalian Target of Rapamycin Inhibitors (mTORI) has been associated with an increased incidence of proteinuria after kidney transplantation as compared to other immunosuppressive agents, yet the precise mechanism remain unclear. The objective of this study was to investigate the risk factor for proteinuria after mTORI treatment in kidney transplant recipients.

**Methods:** A total of 123 kidney transplant recipients following up in a medical center in Southern Taiwan from January 1990 till April 2016 were included. We examined the risk factor for mTORI associated proteinuria using multivariate logistic regression analysis.

**Results:** The mean transplant days before the initiation of mTORI was 638 days. Patients with higher body mass index (BMI) and hyperlipidemia have higher percentage of proteinuria after mTORI use.

<table>
<thead>
<tr>
<th>Adjusted OR (95% CI)</th>
<th>p</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at mTORI use</td>
<td>0.957 (0.917-0.998)</td>
<td>0.042</td>
</tr>
<tr>
<td>Male</td>
<td>1.112 (0.415-2.983)</td>
<td>0.833</td>
</tr>
<tr>
<td>BMI &lt;24</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;24-26.9</td>
<td>4.700 (1.263-17.475)</td>
<td>0.021</td>
</tr>
<tr>
<td>&gt;27</td>
<td>2.918 (0.844-10.088)</td>
<td>0.091</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3.740 (1.67-11.983)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

**Conclusions:** A total of 123 kidney transplant recipients following up in a medical center in Southern Taiwan from January 1990 till April 2016 were included. We examined the risk factor for mTORI associated proteinuria using multivariate logistic regression analysis. BMI >27 kg/m² (OR=3.111, P<0.047) and hyperlipidemia (OR=3.345, P=0.024) were associated with proteinuria after mTORI use. After adjusting for confounding factors, hyperlipidemia (adjusted OR=3.740, P<0.026) and BMI at 24-26.9 kg/m² (adjusted OR=4.7, P<0.021) were significantly associated with risk of proteinuria.
PUB742
Collectin Liver 1 and Collectin Kidney 1 of the Lectin Complement Pathway Are Associated with Mortality after Kidney Transplantation
Julia M. Smedbråten,1,2 Solbjørg Sagedal,1,3 Anders Hartmann,1,3 Steffen Thiel,1
1Dept of Nephrology, Oslo Univ Hospital Ullevål, Norway; 2Faculty of Medicine, Univ of Oslo, Norway; 3Dept of Transplant Medicine, Oslo Univ Hospital Rikshospitalet, Norway; 4Dept of Biomedical, Aarhus Univ, Denmark.

Background: Kidney recipients have significantly higher mortality compared to the general population. The innate immune system may play an important role during periods with suppression of the adaptive immune system. In the present study, the association of two soluble pattern recognition molecules of the lectin complement pathway, Collectin liver 1 (CL-L1) and Collectin kidney 1 (CL-K1), with long-term graft and recipient survival were investigated.

Methods: The levels of CL-L1 and CL-K1 were measured at the time of transplantation in 382 patients (∗177 years) transplanted in 2000-2001. The cohort was subsequently followed until December 31, 2014. Data on patient and graft survival were obtained from the Norwegian Renal Registry.

Results: Both high CL-L1 (∗376 ng/ml) and high CL-K1 (∗304 ng/ml) levels were significantly associated with overall mortality in multivariate COX analyses with HR 1.50, 95% CI 1.09-2.07, p=0.031 and HR 1.43, 95% CI 1.02-1.99, p=0.038, respectively.

Moreover, high CL-K1 levels were significantly associated with cardiovascular mortality. No association between measured biomarkers and death censored graft loss was found. Finally, there was no significant correlation between these two collectins, r=0.83 (95% CI 0.80-0.86).

Conclusions: CL-L1 and CL-K1 were significantly associated with mortality in kidney transplant recipients, when adjusted for other relevant risk factors for mortality. No association with death censored graft loss was found. The levels of those two proteins were significantly correlated.

PUB743
Donor Specific Antibody Kinetics in Patients with Antibody Mediated Rejection Treated with Plasmapheresis and Bortezomib
Lucio Mediated Rejection Treated with Plasmapheresis and Bortezomib

1 (CL-L1) and Collectin kidney 1 (CL-K1), with long-term graft and recipient survival were investigated.

Methods: The levels of CL-L1 and CL-K1 were measured at the time of transplantation in 382 patients (∗177 years) transplanted in 2000-2001. The cohort was subsequently followed until December 31, 2014. Data on patient and graft survival were obtained from the Norwegian Renal Registry.

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Moreover, high CL-K1 levels were significantly associated with cardiovascular mortality. No association between measured biomarkers and death censored graft loss was found. Finally, there was no significant correlation between these two collectins, r=0.83 (95% CI 0.80-0.86).

Conclusions: CL-L1 and CL-K1 were significantly associated with mortality in kidney transplant recipients, when adjusted for other relevant risk factors for mortality. No association with death censored graft loss was found. The levels of those two proteins were significantly correlated.
Early Initiation of ACE Inhibitors in the Post Renal Transplant Period: A Study from a State Run Tertiary Care Centre

**Background:** Angiotsensin converting enzyme inhibitors (ACEI) comprise a drug class that inhibit the effects of angiotensin II. ACEI are well documented to be potent antihypertensives with renoprotective effects but are grossly underutilized in renal transplantation. However, these drugs have been reported to cause elevated potassium and creatinine levels in some renal transplant patients. There have been no reports of prospective studies of ACEI in renal transplant patients in the early post-transplant period. The purpose of this study is to assess the safety of an ACEI class, when started in early post-transplant setting.

**Methods:** We reviewed 84 kidney transplant patients during the period of January 2012 to April 2016 at our Institution. 72 patients were initiated on ACEI therapy, patients who initiated therapy after day 5 and before day 365 of post transplant were included. Recipients were classified into two groups according to the time of ACEI initiation: early (within 6 months post-transplantation) and late (after 6 months after transplantation) group. For each patient, haemoglobin, serum creatinine and potassium serum levels after initiation of ACEI were initiated within six months post-transplantation and in 15 (20.9%) patients ACE inhibitor were initiated, but after six months post-transplantation. There was no statistically significant difference between the two groups related to age or gender and due to the duration of dialysis treatment before the transplantation. Analyzing the Hb, creatinine and potassium serum levels after initiation of therapy with ACEI trough observed period, we did not found any statistically significant difference in all measured parameters between the two groups of patients and also within the same group of patients.

**Conclusions:** ACEI can be used successfully post-renal transplant with beneficial long term impact on renal function. There is need for further randomized controlled studies to see the effect of ACEI on Graft function and its survival.

**PUB747**

Predicting Outcomes in Pediatric Renal Transplant Recipients

**Background:** Pediatric kidney transplant recipients (pKTRs) experience multiple sequelae of their condition, yet an assessment of the cumulative burden and relationship to poor patient outcome is lacking in the literature. Our objective was to develop a composite outcome measure for pKTRs that considers the most common comorbidities and evaluates its ability to predict one poor outcome measure 5 years after transplantation.

**Methods:** We retrospectively reviewed all KTRs at our center from 10/2008 through 2/2015. An optimal outcome composite measure was created consisting of 15 criteria in a binary (0-1) overall composite outcome measure (COKD stage ≥3, using a predicted outcome score <0.5), including histology & immunology (absence of DSAs, no or mild interstitial fibrosis and tubular atrophy, no transplant glomerulopathy, and no history of AMR or ACR), infection (BKV PCR <10,000, CMV PCR <50, no history of PTLD or symptomatic EBV), cardiovascular health (triglycerides <500, LDL <130, BP <90th%ile, fasting glucose <126), and growth (BMI >85th%ile, height z-score >2 SD). We evaluated the ability of this pass/fail criteria to predict poor outcome (patient death, graft failure, and 20% decline in GFR) at years 3 and 5 post-transplant.

**Results:** A total of 37 patients were evaluated at post-transplant year 3 and 32 patients were evaluated at year 5. Subjects having a low outcome score (lower third tertile) at year 1 and year 3 trended towards poor outcome at years 3 and 5 respectively, although potential prediction was not significant. Of the 15 outcome criteria, presence of proteinuria was the only criteria predictive of poor outcome (p<0.05).

**Conclusions:** Proteinuria is predictive of poor outcome in pKTRs in terms of patient death, decreased allograft function, or failure. The use of a composite score consisting of criteria characterizing allograft health and common comorbidities may be predictive of overall outcome, however a larger sample size is needed for validation. Evaluation of risk factors for poor outcomes will allow practitioners to focus clinical outcome improvement efforts.

**PUB749**

Use of Eculizumab for Atypical Hemolytic Uremic Syndrome in Kidney Transplantation - Single Center Experience in Brazil

**Background:** Atypical hemolytic uremic syndrome (aHUS) is associated with a 50% rate of mortality/dialysis dependence at 5 years. Kidney transplantation (KTx) is the best treatment for end stage renal disease (ESRD), but in patient with aHUS recurrence rate >80% has historically discouraged transplantation. Eculizumab has caused a shift in the management of these patients. The drug is not available worldwide.

**Methods:** Case series on aHUS patients using eculizumab either before or after kidney transplantation.

**Results:** Between June 2012 and August 2014, eight patients received eculizumab, being three on a prophylactic basis before KTx, three after KTx due to aHUS recurrence and two after kidney allograft loss. They were mainly women (7/8); 27±14 years old presenting past history of thrombotic microangiopathy in kidney biopsy, microangiopathic anemia (MA) and extrarenal organ damage. Prior to eculizumab all patients received ACWy anti- meningococcal vaccine and antibiotic prophylactic were maintained lifelong. They were divided in three groups- clinical characteristics and outcomes are presented in (Figure 1).

**Conclusions:** Eculizumab, either used for prophylaxis of aHUS recurrence or early after kidney transplantation, allowed good renal function and stable hematological profile. The two patients who did not receive eculizumab in an appropriate time-schedule, lost the allografts. Using eculizumab after renal loss avoided microangiopathic anemia and extrarenal organ damage in this short term follow-up. Death with functioning graft due to pulmonary infection raises awareness of infection risk of eculizumab on top of the current immunosuppression regimen.

**PUB750**

Attitude of Kidney Transplant Recipients about Influenza Vaccination and Preventive Measures: Comparison of 2009 versus 2016

**Background:** An outbreak of influenza A virus H1N1 was identified in Mexico and USA in Apr/09. The government established intensive campaign of diffusion about preventive measures and vaccination. In early 2016, we had another outbreak of influenza but with little diffusion to the population. Aim: to compare the effect of diffusion campaign on kidney transplant recipients’ (KTR) attitude about vaccination and preventive measures during the outbreak in 2009 vs 2016.

**Methods:** During 2009 outbreak, we applied a standardized survey to evaluate: use of flu vaccine the previous winter, during the outbreak and intention to receive it next winter, prophylactic measures during contingency. In May/2016 we apply the same survey to KTR and compared them.

**Results:** We included 131 cases of 2009 and 155 of 2016. In table1 we compare demographic characteristics, vaccination frequency previous and after outbreaks, and use of...
preventive measures. Only 4 cases have had influenza since 2009. In cases with symptoms or direct contact with influenza patients, an increase in use of facial masks was observed. 53 patients had symptoms but didn’t change the attitude to vaccination.

**PUB751**

Urinary Liver Type Fatty Acid Binding Protein and Urinary Albumin Excretion Improvement Prediction of Graft Failure after Renal Transplantation

**Methods:** A longitudinal cohort of 702 stable renal transplant recipients was included from December 2012-December 2014 in Hospital de Especialidades Centro Médico Inst. Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico; Unidad de Investigación Médica en Enfermedades Renales, Inst Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico. The mean age of the subjects was 51.8 ± 8.1 years, 7 Caucasian, 1 African American and 1 Hispanic, and with urinary creatinine clearance measured by urinary collection every 12 hours with estimated creatinine with functioning renal allograft. Primary objective of the study is to compare the mean age 51.8 ± 8.1 years, 7 Caucasian, 1 African American and 1 Hispanic, and with urinary creatinine clearance measured by urinary collection every 12 hours with estimated creatinine with functioning renal allograft. Primary objective of the study is to compare the

**Results:** Participants (57% male, age 53.0 ± 12.7 years) were followed for median 3.1 [2.6–3.8] years. 45 developed graft failure. At inclusion median L-FABP was 2.1 ng/mL [0.9–6.8]. Median UAE was 43.5 mg/24hr [11.0–203.4]. L-FABP correlated with UAE (r = 0.26, p < 0.01) and serum creatinine (r = 0.52, p < 0.01), and UAE with eGFR (r = 0.25, p < 0.01) and serum creatinine (r = 0.35, p < 0.01). Higher L-FABP (HR = 1.78 [95%CI 1.23–2.90] p < 0.01) and higher UAE (HR = 1.89 [95%CI 1.55–5.04] p < 0.01) were independently associated with graft failure. L-FABP and UAE with eGFR (r = -0.25), proteinuria (r = 0.77) and serum creatinine (r = 0.35) (all p < 0.01). Larger study is needed to establish the role of Tryptophan metabolizing enzyme as predictive biomarker for graft survival.IDO 1 may possibly show some association. Corticosteroid sparing immunosuppressant regimen (Tac + MMF + EVL) appear to be as safe as compared to Steroid containing immunosuppressant regimens (Tac + MF + Steroid + EVL).

**Conclusions:** Despite an intention to receive vaccinated next winter increased in 2009 (63.4%), the actual percentage that received vaccine last winter (2015) was substantially reduced (39.4%) despite another outbreak of influenza, most likely due to probably limited to public reporting.

**PUB753**

Comparison of Tacrolimus with Everolimus or Mycophenolate Mofetil or Steroid Regimen and Their Association with Tryptophan Metabolism: A Pilot Study

**Methods:** All patients received induction therapy with Thymoglobulin (3mg/kg). They received Tacrolimus, mycophenolate mofetil, steroid and were randomised into three groups at the end of 3 months. Group 1 (control) patients received Tacrolimus + Mycophenolate/ Steroid. Group 2: Tacrolimus/Mycophenolate Mofetil/Everolimus and group 3: Tacrolimus/ Everolimus/Steroid. Patients were assessed with RFT, Hemogram, Urine R/M, Lipid profile, Blood Sugar levels, Serum Tryptophol/ Everolimus levels. Adverse events such as anaphylaxis, life threatening infections were noted. Tryptophol metabolite measurement was done using Quantitative real-time RT-PCR.

**Results:** Graft survival at one year: Control group 1: 7/11 patients had stable graft outcomes, 1 patient had ATN & 3 were lost to follow up. Group 2: 4/6 patients had stable graft outcomes & 2 had ATN. Group 3: 4/7 patients had stable graft outcome, 1 had ACR+ AMR. Safety: No patient had serious adverse events. One patient with Dyslipidemia was reported in each of the Groups 2 & 3. Funduscopy was noted in group 3. Tryptophol metabolism enzyme levels: Control Group: No changes were seen in various enzymes levels for the 9 patients available. Group 2 & Group 3: Various enzymes showed low expression, but no association was observed with graft survival. Low expression of IDO 1 was observed in 5 patients out of which 4 patients were associated with stable graft outcome & 1 with graft dysfunction. No significant difference was observed in drug levels, Hemoglobin, Creatinine, Lipid profile, Blood Sugar levels, Serum Tryptophol/ Everolimus levels. Adverse events such as anaphylaxis, life threatening infections were noted. Tryptophol metabolite measurement was done using Quantitative real-time RT-PCR.

**Conclusions:** A larger study is needed to establish the role of Tryptophol metabolizing enzyme as predictive biomarker for graft survival. IDO 1 may possibly show some association. Corticosteroid sparing immunosuppressant regimen (Tac + MMF + EVL) appear to be as safe as compared to Steroid containing immunosuppressant regimens (Tac + MF + Steroid + EVL).

**PUB754**

Prevalence and Risk Factors for Post-Transplant Anemia in a Reference Center in Mexico

**Methods:** All the kidney transplants in adult patients (over 16 yrs of age) performed from December 2012-December 2014 in Hospital de Especialidades Centro Médico Nacional de Occidente in Guadalajara were included. We used data collected in our registration program during one year following transplantation. Anemia was defined according the WHO: hemoglobin (Hb) levels <12 g/dl in women and <13 g/dl in men.

**Results:** 505 recipients were included in the analysis, 361 male and 144 female had an overall mean age at transplantation of 29.10 years. Most patients were from living donor (86%). Evolution is shown.

**Conclusions:** Anemia is a common complication after kidney transplantation (KT) and has a controversial impact on graft or patient survival. The aim of the study was to describe the prevalence of anemia before and after KT and to find the characteristics of the patients with anemia.

**Methods:** All the kidney transplants in adult patients (over 16 yrs of age) performed from December 2012-December 2014 in Hospital de Especialidades Centro Médico Nacional de Occidente in Guadalajara were included. We used data collected in our registration program during one year following transplantation. Anemia was defined according the WHO: hemoglobin (Hb) levels <12 g/dl in women and <13 g/dl in men.

**Results:** 505 recipients were included in the analysis, 361 male and 144 female had an overall mean age at transplantation of 29.10 years. Most patients were from living donor (86%). Evolution is shown.

**Parameter** | Baseline | 3 mo | 6 mo | 12 mo
--- | --- | --- | --- | ---
Serum Cr (mg/dl) | 1.1±0.5 | 1.2±0.7 | 1.2±0.8 | 1.3±1.2
Serum Hb (g/dl) | 10.5±2.1 | 12.8±2.0 | 13.6±2.2 | 14.1±2.3
Anemia (yes/no) | (434/71) | (234/271) | (172/333) | (111/394)

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

1076A

Funding: Clinical Revenue Support

**Conclusions:** Our observations suggest that currently used formulae underestimate the renal function in working allograft. The variability is higher in the first few days with rapidly decreasing serum Creatinine. There is a need to develop a new formula to estimate renal function in functioning allografts with rapidly decreasing creatinine.

**Funding:** Clinical Revenue Support
Post-transplant anemia at 1 year

<table>
<thead>
<tr>
<th>Variables that predicted anemia at 12 months (mo)</th>
<th>Yes (n = 113)</th>
<th>No (n = 394)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female recipient (%)</td>
<td>60/76</td>
<td>29/36</td>
<td>.004</td>
</tr>
<tr>
<td>Male donor (%)</td>
<td>56/76</td>
<td>50/29</td>
<td>.475</td>
</tr>
<tr>
<td>Recipient age (years)</td>
<td>56 ± 12</td>
<td>36 ± 11</td>
<td>.027</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>85/87</td>
<td>88/88</td>
<td>.879</td>
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<tr>
<td>Donor type (%)</td>
<td>15/15</td>
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<tr>
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<td>5/5</td>
<td>.639</td>
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<tr>
<td>Deceased donor (%)</td>
<td>59/57</td>
<td>41/44</td>
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<tr>
<td>Maintenance (%)</td>
<td>97/99</td>
<td>95/98</td>
<td>.008</td>
</tr>
<tr>
<td>Tacrolimus (%)</td>
<td>56/56</td>
<td>55/55</td>
<td>.008</td>
</tr>
<tr>
<td>MMF (%)</td>
<td>100/100</td>
<td>100/100</td>
<td>.008</td>
</tr>
</tbody>
</table>

Variables that predicted anemia at 12 months (mo) were Hb at 6 mo and eGFR at 6 mo (RR 1.9 (9.1.6-2.3) p<.001) and RR 1.6 (1.01-1.3) p=.002. Higher baseline Hb level predicted less graft loss (RR 0.6 (0.3-0.9) p=.001) and higher Hb level at 1 year predicted better patient survival (RR 0.6 (0.4-0.8) p=.001).

Conclusions: In contrast with other studies, we had lower incidence of anemia at 1 year. We found relation between graft function and anemia diagnosis. Baseline Hb and at 1 year does impact in graft and patient survival, respectively.

PUB575

Triglyceride Metabolism before and after Meal in Post Kidney Transplant Recipients

Makoto Tsujita,1 Tomoki Kosugi,2 Shiochi Maturaya.1 Transplant Surgery, Nagoya Daini Red Cross Hospital, Japan; 2Nephrology, Nagoya Univ School of Medicine.

Background: Many factors cause dyslipidemia after kidney transplantation. Low density lipoprotein cholesterol (LDL-C) has been focused to reduce cardiovascular disease (CVD), but residual risk factors such as triglyceride (TG), remnant-like lipoprotein cholesterol (RLP-C) or small dense LDL-C (sdLDL-C) are also important to reduce CVD.

Methods: TG metabolism could be evaluated by cookie test. (Endocrine Journal 2006,53(2):173-180) We performed the test for sixty three stable kidney transplant recipients at one year after transplantation in 2014. TG, RLP-C, LDL-C/apoB ratio (substitute for LDL-C) and LDL-C/apoB ratio was associated with TG4h (r=0.30 p=0.009). TG metabolism in non DM group was similar with that in DM group. In EVL group, TGf levels were higher than that in non EVL group (p=0.04).

Conclusions: This study revealed most recipients had some problems with TG metabolism. Any intervention to improve TG metabolism will be needed.

PUB576

Controlled Cardiac Death Donor (cDDC) for Kidney Transplantation: Factors Associated to Best eGFR after 2 Years: Spanish Multicentre SENTRA-GEOADAS Group

Jose M. Portoles,1,2 María Marques Vidas,1,2 Omar Reynaldo Lafuente Covarrubias,1 Erika De Sousa Amorim,1,2 Eva Gavela,1 Paloma Martín Moreno,1 Domingo Hernández,1,2 Francesc J. M. Oliu,1 Isabel Beneyto Castello,1 Julie Pascual,1,2 Nephrology, Hospital Puerta de Hierro. SENTRA / GEOADAS, Majadahonda, Spain; 1Public Health Research Net RedN16/009/009 RETYC ISCIII.

Background: Controlled donation after cardiac death (cDDC) programs are running in some countries for years. National transplant organization (ONT) has developed a nationwide program in Spain from Jan2012 and 45 centers had started by Dec2015. Eighteen centers out of them have joined our study group. We present our preliminary analysis for best eGFR after 2 years.

Methods: Study: Observational prospective multicentre study. Intervention: Kidney transplantation (KTx) from cDDC at joined units. Local centre surgical procedures and IS protocols. Main Variable: Best eGFR along 1st post – TX year as measured by MDRD-4.

Results: Cohort description: 430 grafts were obtained from 215 cDDC. 13 kidneys were discharged for several reasons and 28 implanted out of our group. 389 recipients: 56 years, 69,1% males, 75,6% first KTx, others 2nd KTx. Cold ischemia time (CIT): 12.5h; median warm IT 24min, HLA-mismatch: 4 [0-6]. Immunosuppression: 98.8% induction plus prednisone-MMF-Tacrolimus or mTOR. Graft Function: Primary graft failure (PGF): 3%, delayed graft function (DGF): 49.7% Nadir Cr: 1.5 mg/dl [0.6-3.1]. Best eGFR was 53.5 (24.6) ml/min. For patient with more than 1 year follow-up, best renal function was 55.3 (SD 24.6) ml/min; serum Cr was 2.1 mg/dl at month, 1.8 mg/dl at 3 month, 1.9 mg/dl at 6 month, 1.6 mg/dl at 1 year and 1.6 mg/dl at 2 years. In the multivariate analysis for the probability to reach 1 year best eGFR=50 ml/min after the first cDDC-KTx was associated to lower donor age (<45yrs, OR 2.21 [2.1-2.3]), a shorter CIT (OR 1.04 per hour) and previous treatment (PD vs HD OR 1.9 [1.03-6.3]) but not to HLA-mismatch or DGF.

Conclusions: In contrast with other studies, we had lower incidence of anemia at 1 year. We found relation between graft function and anemia diagnosis. Baseline Hb and at 1 year does impact in graft and patient survival, respectively.
The Epstein-Barr Virus DNA Load in the Peripheral Blood of Transplant Recipients Does Not Accurately Reflect the Burden of Infected Cells

Henri-Jacques Fink, Uta Behrend, Henri-Jacques Delecuelle, Nierenzentrum Heidelberg, Germany; German Cancer Research Centre (DKFZ) Unit F100, Heidelberg, Germany; Dept of Infected CNI nephrotoxicity, Univ of Heidelberg, Heidelberg, Germany; Children's Hospital Klinikum Rechts der Isar, Technische Univ Miinchen, Munich, Germany; Dept of Medicine V, Univ of Heidelberg, Heidelberg, Germany; Dept of Medicine V, Univ of Heidelberg, Heidelberg, Germany.

Background: Transplant recipients frequently evince an increased Epstein-Barr Virus (EBV) load in the peripheral blood. Predicting post-transplant lymphoproliferative disorders is the rationale behind the quantification of the EBV load in the peripheral blood. However, this parameter has shown poor predictive value.

Methods: EBV load was quantified in kidney and stem cell recipients by qPCR. EBV infected cells were determined by in situ hybridisation, lytic antigens by immunostaining. Fluorescence in-situ hybridization (FISH) was used to determine the number of EBV episomes per infected cell. Binding and transformation assays were performed with either plasma or serum.

Results: We quantitated the number of EBV-infected cells in the peripheral blood of 23 transplant recipients and defined the mode of viral infection, latent or lytic. These data indicated that there is no strong correlation between the number of infected cells and the EBV load. This can be explained by a highly variable number of EBV copies per infected cell and by lytic replication in some cells. The plasma of these patients did not contain free infectious viruses. Some of the investigated samples carried a highly variable number of infected cells in active latency. However, a third of the samples expressed neither latent nor lytic proteins.

Conclusions: Patients with an increased EBV load represent a heterogeneous group of patients whose infection cannot be characterized by this method alone. Evaluation of the EBV load is only significant in an increased EBV load, in particular as a predictive marker of PTLD, requires the inclusion of additional investigations, in particular the number of EBER RNA-positive cells.

Evaluation of Efficacy and Safety of a Lower Dose of Thymoglobulin as Induction Therapy in Kidney Transplantation

Isabelle Malbouisson, Mayara Iwani de Paula, Marina Cristelli, Erika Y. Tamashiro, Laila Viana, Juliana Mansur, Helio Tedesco Silva, J. Medina-Pestana. Hospital do Rio - Unifesp, Brazil.

Background: Thymoglobulin® (rATG), a rabbit antithymocyte globulin is the most common induction therapy used in kidney transplantation. Although its use is essential to reduce acute rejection incidence, it is also associated with many infections complications, such as cytomegalovirus (CMV) infection. Objective: To evaluate if a 3 mg/kg single dose of rATG as induction therapy is effective in preventing acute rejection without compromising safety.

Methods: This was a retrospective cohort of 409 patients, whose kidney transplantation was performed from 18-Aug-2014 to 31-May-2015, with a follow-up until 31-May-2016. Before 18-Aug-2014, we used a 6mg/Kg dose of rATG as induction therapy only to sensitized patients (panel reactive antibody-PRA class I or II > 50%) or those with deceased expanded donor. Since then, we changed the induction protocol to a 3mg/Kg single dose of rATG to all transplanted patients. Outcomes evaluated were acute rejection incidence, renal function, graft and patient survival and CMV infection incidence.

Results: A total of 409 patients receiving the new induction protocol were included. Of these, 58% (n=238) were under Tacrolimus, Prednisone and Azathioprine as immunosuppression regimen, comprising transplants of living or deceased standard criteria donors and 42% (n=171) were under Tacrolimus, Prednisone and Myfortic, comprising transplants of deceased expanded criteria donors or sensitized patients. Patients had a mean age of 45.8 ± 12.6 years, 82% had deceased donors, 10% had a PRA class I > 50% and 7% had a PRA class II > 50%. In the Azathioprine group, after one year of follow-up, 8% had biopsy-proven acute rejection and 33% had a CMV infection episode. In the Myfortic group in the same period of follow-up, 6% had biopsy-proven acute rejection and 50% had a CMV infection episode. [table 1] We didn’t use a prophylaxis drug for CMV infection. Our strategy was the preemptive treatment for the patients with positive CMV antigens.

Conclusions: The 3mg/Kg single dose of rATG as induction therapy was associated with a low incidence of acute rejection after one year of follow-up.

The Use of Mammalian Target of Rapamycin Inhibitors (i-mTOR) Could Improve Renal Function in Renal Grafts from Uncontrolled Donation after Cardiac Death Donors (UDCDD)

Maria Molina, Eduardo Gutierrez-Martinez, Enrique Morales, Manuel Praga, Amaudo Andres. Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain.

Background: Ischemia injury in kidneys grafts from UDCDD could produce a poor renal function. Minimized blood levels of CNI associated with i-mTOR therapy could avoid acute rejection and decreased CNI nephrotoxicity. The aim was to describe evolution of renal function before and after CNI minimization associated with conversion from MMF to i-mTOR in a population in renal transplants (RT) from UDCDD.

Methods: All RT from UDCDD received steroids, thymoglobuline, mycophenolate (MMF) and delayed introduction of CNIs(tacrolimus). Blood levels of tacrolimus had to be between 8-10 ng/ml at first months after transplantation. We selected for our study patients in whom the immunosuppression was changed after 3 months of transplantation minimization of tacrolimus blood levels to 5 ng/ml and conversion from MMF to i-mTOR. We evaluated renal function before and after these changes.

Results: Our center have performed 207 RT from UDCDD. Minimization of tacrolimus blood levels (10 to 5 ng/ml) and conversion from MMF to i-mTOR was performed in 46 (22%) cases at 11 (6,32) months from transplantation. Causes of immunosuppression change were: 20 (44%) CNI nephrotoxicity, 14 (30%) neoplasia, 6 (13%) clinical trials, 3 (7%) viral infections, 1 (2%) BK nephropathy, 1 (2%) posttransplantation diabetes and 1 (2%) gastrointestinal intolerance to MMF. The evolution of renal function is showed in Table 1.

Conclusions: Minimization of tacrolimus blood levels and conversion from MMF to i-mTOR in kidney transplant from UDCDD is efficient and safe with low rate of i-MTOR withdrawn and improves renal function.

Prevalence of HLA-DR15 in Lups Kidney Transplant Patients

Maria Izabel Neves da Holanda, Fernanda Paula Feres Rios Da Costa, Alicia Imada, Luiz Fernando Christiani. Nephrology/Kidney Transplant, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil.

Background: Systemic Lupus erythematosus (SLE) is a severe auto immune disease, characterized by involvement of multiple organ systems. Lupus Nephritis is one of the main complications of the disease and is associated with poor survival and high morbidity, particularly for patients who develop end-stage renal disease (ESRD). the cause of the disease is complex and both environmental and genetic factors are involved. recent studies demonstrated that HLA class II genes are consistently associated with SLE susceptibility, especially some alleles of DR-15.

Methods: The aim of this study is to evaluate the association of HLA-DR15 in a Lupus patients that underwent to a kidney transplant between 1981 and 2016 in Bonsucesso Federal Hospital, Rio de Janeiro, Brazil. This is a retrospective study, and the Lupus group was compared with a control group. The control Group was composed with patients with the subsequent transplants in the same year of the lupus patients transplant. The analyses were performed using Chi square test and sps.

Results: Forty-eight patients were included in the lupus group, 41 female patients, 23 white (48%) and 25 african-american. Median age was 31 years old. Thirty one patients in this group was Live donor transplant. The control group was composed by 92 patients, 65 female patients, 43 patients were caucasian, 49 african americans. The median age

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
was 43 years old. The prevalence of undelying diseases were 51 hypertension patients, 5 diabetes, 13 glomerulosclerosis, 12 Polcistic Kidney disease and 10 others. Forty three patients were due to live donor transplant. The HLA DR-15 was present in 16 patients(33%) in the lupus group compared with 15 patients(16%) in the control group (p=0.021).

Conclusions: The association of HLA DR-15 in lupus patients was relevent in this study. Further studies are necessary to evaluate this correlation with lupus nephritits and the progression of this patients after kidney transplant and the graft survival.

PUB763

Graft Survival at 5 Years in Living Donor Renal Transplantation: Does Azathioprin versus MMF Based Immuno Suppression Influence the Outcome? Raju Balasubramaniam, Sivaram Kannan Swaminathan, 2Hemalatha Anantha Kumar Naidu. 1Nephrology, Kaiverry Hospital, Chennai, Tamil Nadu, India; 2Internal Medicine, Madras Medical College, Chennai, Tamil Nadu, India.

Background: Retrospective evaluation of renal transplant outcome at 5 years post transplantation, in live transplant program was analysed.

Methods: Live renal transplant recipients from 1998 to 2007 were included. Cadaver transplantation recipients, who did not follow up and who died prior to 5 years were excluded. Mean age, gender distribution, basic disease, degree of HLA matching, immuno suppression and its influence studied.

Results: 123 patients fulfilled the inclusion criteria -99 men (80.5%) 24 women (19.5%), mean age 38.09 years. Basic disease was Glomerulonephritis in 59(47%), interstitial disease 30 (24.3%), hypertensive nephrosclerosis 20 (16.3%), diabetic nephropathy 12 (9.75%) and 3(2.43%) other diseases. First degree relatives donated in 92 (74.8%) and the rest 31 (25.2%).13 were full house, 69 were haplo identical, 35 mismatches, and 6 were single antigen mismatch. 36 (76%) received cyclosporine, azathioprin and steroids and 34(30%) received cyclosporine, MMF and steroid based immuno suppression. Among those who took Azathioprin 59/86 patients (68.6%) had normal graft function at 5 years and 25 patients (31%) had varying degrees of azotemia (18 patients had creatinine from 1.5-3 mgm%, 7 had creatinine > 3 mgm% and 2 had creatinine > 5 mgm%). The creatinine level at 5 years was 43 years old. The prevalence of undelying diseases were 51 hypertension patients, 5 diabetes, 13 glomerulosclerosis, 12 Polcistic Kidney disease and 10 others. Forty three patients were due to live donor transplant. The HLA DR-15 was present in 16 patients(33%) in the lupus group compared with 15 patients(16%) in the control group (p=0.021).

Conclusions: The association of HLA DR-15 in lupus patients was relevent in this study. Further studies are necessary to evaluate this correlation with lupus nephritits and the progression of this patients after kidney transplant and the graft survival.

PUB764

Malnutrition at the Moment of Kidney Transplantation Is Associated to Worst Long-Term Renal Function Carlo M. Alfieri,1 Maria Teresa Gandolfo, 1Valentina Binda, 1Donata Cresseri, 1Mariarosaria Campise, 1Anna Regalia, 1Francesco Cosa, 1Deborah Mattinanzi, 2Masami Kehata, 2Piergiorgio Messa. 1Nephrology, Dialysis and Renal Transplantation Unit, Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milano, Italy; 2Renal Research Laboratory, Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milano, Italy.

Background: The relationship between weight anomaalies(WA) and kidney transplantation (KTx) dysfunction is debated. Our study performed in KTx patients aims to: calculate the WA in the 1styear of KTx;Evaluate the relations between body mass index(BMI), clinical and biochemical exams;Explore the influence BMI in renal function (RF) variations.

Methods: Routinely evaluations at 1st(T1) and 12th(T12) mths after KTx were performed in 440(M=250; so=48±11 yrs) KTx pts transplanted between 2004 and 2013. Patients were categorized as: malnourished (MN-BMI< 20 kg/m2), normal (N-BMI=20 to <25 kg/m2), overweight (OW-BMI=25-30 kg/m2) and obese (OB>=30 kg/m2) and by median BMI(23kg/m2) in upper(BMI-up) or under(BMI-un) median. Serum creatinine(Cr– mg/dl), 24-hour proteinuria (Prot-U–g/24h) and eGFR (ml/min) were used as RF indicators. RF variation was calculated by T12-T1 values. Delayed graft function(DGF-12% of patients) was defined by the need of dialysis during the week after KTx.

Results: At T1 and T12, 27% and 7% of patients were MN, and 41%, 28% and 4% at T1 and 50%, 39% and 4% at T12 were N, OW and OB resp. (p<0.0001). During the 1styear of KTx, BMI increased (p<0.0001). BMI-T1 correlated with age, systolic blood pressure(SBP), glucose, acid uric, albumin and Hb. No associations with length of hospital stay and DGF were present. At T1 a decline of sCr,stronger in BMI-up (p<0.02) was observed. Of note, only in MN patients the increase of sCr was observed (p<0.0001). At T12 and T12 (p=0.46), with no relation with BMI. BMI-T1 was associated to sCr reduction(p<0.005). In the 1styear of KTx 12 patients (6.0%) underwent dialysis and 2 (OW) died.

Conclusions: In the 1styear of KTx BMI increased, mostly because of a normalization of pretransplant patients. BMI is associated to nutritional parameters and to sCr. No effect of BMI in RF recovery was found, whereas malnutrition seems influence negatively the long term trend of RF.

PUB765

Balloon Dilatation at Ureterovesical Junction Stenosis in Kidney Transplantation Patient by Interventional Nephrologist: 3 Cases Jin Ho Lee, Hee Young Lee, Joon Seok Oh, Dongyool Lee, Seong Min Kim, Yong Ki Park, Yong Hun Sin, Joong Kyung Kim. Internal Medicine, Bongseong Memorial Hospital, Busan, Dong-Gu, Korea.

Background: Hydrourephrosis is one of the etiologies of allorgraft dysfunction in KTP. Urere stone, midureter ischemia, surgical technique error, and the other reasons make the hydrourephrosis. To eliminate the hydrourephrosis due to ureter stenosis, balloon dilatation may be the treatment option. We announced 3 cases of hydrourephrosis due to UVJ stenosis causing graft dysfunction was treated balloon dilatation by interventional nephrologist.

Methods: Case 1: 59-year-old man who underwent KTP at Feb, 1989. His serum creatinine was elevated to 3.2mg/dl. Image modalities show hydrourephrosis and UVJ stenosis(Fig.1). Then, we underwent percutaneous nephrostomy. We inserted guide wire and ballooning(MUSTANG3M, 3.0mm)(Fig.2) was done via PCN site. After that, UVJ stenosis was improved(Fig.3). His serum creatinine was declined to 2.2mg/dl. Case 2: 38-year-old man who underwent KTP with deceased donor at Jan, 2015 was admitted for elevated serum creatinine, from 1.6 to 2.2mg/dl. His CT and abdominal US findings show hydrourephrosis and UVJ stenosis(Fig.4). We underwent cystoscopy and ballooning (MUSTANG3M, 4.0mm) (Fig.5) was done. After that, diameter was increased at stenotic ureter(Fig.6). His serum creatinine was declined to 1.8mg/dl. Case 3: 28-year-old man who underwent KTP with deceased donor at Sep, 2015. At POD 21, graft kidney CT scan shows hydrourephrosis and hydrourerter. His serum creatinine level increased slowly. We performed cystoscopy and ballooning at stenotic lesion. Ballooning was done(MUSTANG3M, 4.0mm and 8.0mm) (Fig. 7, 8, 9). After that, ureter size was normalized(Fig.10).

Results:

Conclusions: UVJ stenosis in KTP patient could be treated by balloon dilatation and DJ catheter insertion by interventional nephrologist.

PUB766

Overcoming of Very High Anti A/B Antibody Titer in ABO Incompatible Kidney Transplantation: Single Center Study Hee Young Lee, Jin Ho Lee, Dongyool Lee, Joon Seok Oh, Yong Hun Sin, Seong Min Kim, Yong Ki Park, Joong Kyung Kim. Internal Medicine, Bongseong Hospital, Busan, Korea.

Background: ABO incompatible KTP is effective way to reduce the shortage of living donor. In some studies, the presence of high titer of anti A/B Antibody was considered to contraindication for ABOi KTP. With the development of desensitization therapy, 512 or more high titer ABOi KTP could perform.

Methods: Eleven patients with end-stage renal failure underwent ABO-incompatible living kidney transplantation. Baseline anti-A/B antibody titer was 577.16(IgG, range; 512–1024) and 192.72(ng/ml, range; 8–512), titer was performed by tube method.
Mean follow-up duration was 41.9 months (range 3–75 months). We had one case of biopsy proven acute cellular rejection, and then we lost the graft despite of rescue therapy. There was no antibody mediated rejection episodes and all patients are alive.

A BO incompatibility

<table>
<thead>
<tr>
<th>ABO Incompatibility</th>
<th>Father</th>
<th>Son</th>
<th>Sister</th>
<th>Brother</th>
</tr>
</thead>
<tbody>
<tr>
<td>A~0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>A~0</td>
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<td>6</td>
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Cases of ABO incompatibility

<table>
<thead>
<tr>
<th>Causative Disease</th>
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<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>MGN</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MPGN</td>
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<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Dialysis vintage(month) 17.5 ± 28.6

Initial isoglutamin titer, IgG(log2) 577.16 ± 207.11 (9.18 ± 0.40)

Initial isoglutamin titer, IgM(log2) 192.72 ± 136.16 (6.10 ± 0.98)

Intra- and extra vascular injury

<table>
<thead>
<tr>
<th>Age(year)</th>
<th>55.7±12.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male: 4</td>
</tr>
<tr>
<td></td>
<td>Female: 7</td>
</tr>
<tr>
<td>Causative Disease</td>
<td>DM: 2</td>
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<td>IgA nephropathy: 3</td>
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<td></td>
<td>MGN: 1</td>
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<tr>
<td></td>
<td>MPGN: 1</td>
</tr>
<tr>
<td></td>
<td>Unknown: 4</td>
</tr>
</tbody>
</table>

We tried plasmapheresis (PP) and IVIG for removal of the anti A/B antibodies before the kidney transplantation and the number of PP was 6.10 ± 0.98. We used Basiliximab, methylprednisolone for induction immunosuppressant and tacrolimus, mycophenolate mofetil, prednisolone for maintenance IS according to desensitization protocol.

Results: Mean follow-up duration was 41.9 months (range 3–75 months). We had one case of biopsy proven acute cellular rejection, and then we lost the graft despite of therapy. There was no antibody mediated rejection episodes and all patients are alive.

Conclusions: Very high Anti A/B antibody titer (>512, IgG, Isoglutamin tube method) in ABOi KTP shows excellent outcomes.

PUB768

Validity of Kidney Donor Risk Index for Prediction of Graft Outcome in Deceased Donor Kidney Transplantation: a Single Center Experience

Background: Donor organ quality is a key determinant of graft outcomes in deceased donor kidney transplantation (DDKT), and several donor quality scoring systems have been proposed.

Methods: To validate the kidney donor risk index (KDRI) for prediction of graft outcome, we screened 134 patients who received DDKTs at Ulsan University Hospital from April 2003 to May 2015. Among them, 91 DDKTs whose KDRI were available were included this analysis.

Results: Median follow-up was 48 months. Mean age of recipients and donors are 47.3 and 42.5 years, respectively. Mean KDRI was 1.31 ± 0.31 (range from 0.68 to 2.23). During follow up, delayed graft function (DGF) and biopsy-proven acute rejection (BPAR) developed for 6 and 16 patients, respectively. One- and 5-year BPAR-free survival was 88.8% and 79.3%, respectively. BPAR-free survival trend was to be higher for DDKTs from donor with KDRI ≤ 1.0 but not statistically significant (P = 0.073), compared to those with KDRI > 1.0. Graft failure occurred to only 2 patients at 5 and 29 months after DDKT, and their KDRI were 1.28 and 1.98, respectively. In multivariate linear regression, DGF (standardized beta = -0.273, P = 0.005), BPAR (standardized beta = -0.261, P = 0.012) and KDRI (standardized beta = -0.521, P < 0.001) were significant predictors of last-visit estimated glomerular filtration rate.

Conclusions: KDRI is an easily applicable scoring system and is a good prognostic tool for graft outcomes in DDKTs.

PUB769

Hair Matters: Underrated Side Effect of Immunosuppressive Therapy

The use of sirolimus in patients with recurrent CMV infection after kidney transplantation: a retrospective case series analysis

Results: Median follow-up was 48 months. Mean age of recipients and donors are 47.3 and 42.5 years, respectively. Mean KDRI was 1.31 ± 0.31 (range from 0.68 to 2.23). During follow up, delayed graft function (DGF) and biopsy-proven acute rejection (BPAR) developed for 6 and 16 patients, respectively. One- and 5-year BPAR-free survival was 88.8% and 79.3%, respectively. BPAR-free survival trend was to be higher for DDKTs from donor with KDRI ≤ 1.0 but not statistically significant (P = 0.073), compared to those with KDRI > 1.0. Graft failure occurred to only 2 patients at 5 and 29 months after DDKT, and their KDRI were 1.28 and 1.98, respectively. In multivariate linear regression, DGF (standardized beta = -0.273, P = 0.005), BPAR (standardized beta = -0.261, P = 0.012) and KDRI (standardized beta = -0.521, P < 0.001) were significant predictors of last-visit estimated glomerular filtration rate.

Conclusions: KDRI is an easily applicable scoring system and is a good prognostic tool for graft outcomes in DDKTs.

Conclusions: Patients with recurrent CMV viremia who are high immunological risk patients or those with anti-viral resistance risk life-threatening infection or sacrifice of the transplant. In our experience the use of an mTORi is a useful strategy in treating recurrent CMV viremia without provoking rejection.

PUB769

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Hemolytic Anemia after Kidney Transplant and Polyclonal Antibodies

Alana L. Rita, Birne, Ivo Laranjan, Sofia Semedo, Filipo, Liliana Maria Goncalves Cunha, Tiago J. Carvalho, Cristina Jorge, Margarida Bruges, Patrícia Matias, Teresita Adragao, André L. Weigert, Domingos Machado.

Nephrology, Hospital Santa Cruz, CHLO, Lisbon, Portugal.

Background: Hemolytic anemia (HA) after renal transplantation (RT) may result from hemolytic-uremic syndrome (HUS), donor-derived antibodies (Ab) against recipient’s erythrocytes or related to calcineurin inhibitors (CNI). However, an association with polyclonal ab (Pabs) has been poorly described.

Methods: We conducted a single-center cohort study to evaluate the incidence of HA in the first 30 days of RT in patients (pts) who randomly received ATG-Fresenius (ATG-F) or Thymoglobulin-Genzyme (TMG-G) between 2009 and 2014/2016. HA was defined as decrease of at least 1 g/dL hemoglobin (Hb) in 24 and haptoglobin <30 mg/dL. Pts with identified causes of HA were excluded.

Results: We enrolled 180 pts; 59% males; mean age 50 ± 11 yrs; Less than 1% was pre-emptive. Six percent obtained a living donor graft and 16% a 2nd RT. Regarding immunosuppression, 58.9% received ATG-F (mean cumulative dose (mCD): 17.9/kg) and 41.1% TMG-G (8.4/kg). Out of 180, 11.7% developed HA. Demographic data, RRT modality and vintage, kidney failure etiology, deceased vs. living organ donor, cold ischemic period, anemia, erythropoietin (EPO) use and blood transfusions (BT) before RT were similar in ATG-F and TMG-G group and in HA and non-HA group (NHA). In HA pts, ATG-F was used in 95.2% (p=0.001) in similar doses to NHA pts. HA group had lower Hb at day 1 (9.8 ± 10.6 g/dL; p=0.023), day 3 (8.3 ± 9.3 g/dL; p=0.003), day 7 (7.9 ± 9.3 g/dL; p=0.001) and day 15 (8.1 ± 9.1 g/dL; p=0.001) after ATG-F/TMG-G use vs. control more BT (median 2 vs. 0.0; p=0.006). Higher EPO dose (1932 vs 1295 UI-week; p=0.005) was needed for identical Hb at day 30. No differences were found concerning serum creatinine, maintenance IMS (CNI, mTor inhibitors, anti-proliferative), HLA-mismatches number, donor specific ab and panel reactive ab percentage. HA group had no irregular ab. Overall, 19% of ATG-F pts developed HA compared to TMG-G (0.01%).

Conclusions: In our study, 11.7% pts developed HA in the first month, 95.2% occurring in the ATG-F group. A prospective study on the influence of different Pabs in HA is needed.

Plasma Exchange by Single Membrane Separation Technique for ABO Incompatible Kidney Transplantation

Joon Seok Oh, Seong Min Kim, Yong Ki Park, Jong Kyung Kim.

Division of Nephrology, Dept of Internal Medicine, Bloomberg Memorial Hospital, Busan, Korea. Division of Nephrology, Internal Medicine, Dongnag Bong Song Hospital, Busan, Korea.

Background: Some variations in plasma exchange technique for antibody reduction was reported, the confusion about both efficacy and safety were added. We had compared the serum fibrinogen changes of patients who received plasma exchange by single membrane separation technique and centrifuge technique during the last 2 years.

Methods: All subjects were received ABO incompatible living donor kidney transplantation in our hospital. 68 times of plasma exchange were carried out at every other day in 13 patients before transplantation, using the COBE ® Spectra apheresis system. 50 times of plasma exchange were performed at every other day in 10 patients before transplantation, using the Prisamflex ® system with TPE 2000 filter. The levels of serum fibrinogen were monitored at pre-exchange, post-exchange one day. In pre-exchange 1.0 time the calculated plasma volume was replaced with an electrolyte solution containing 5% salt-free human albumin or fresh frozen plasma (FFP).

Results: The serum fibrinogen levels (mg/dL) were markedly reduced immediately following the plasma exchange in cases of 5% albumin solution replacement but increased in cases of FFP replacement. And there were not a significant difference of serum fibrinogen changes between the two methods for plasma exchange.

Conclusions: According to our experience in plasma exchange, we could say that it is not different the change of coagulation factor during the plasma exchange by single membrane separation technique with the plasmapheresis by centrifuge technique.

Experience with IL-1 Blockade in Renal Transplant Patients with Gout

Arthritis Vega Goedecke, Marcus Hiss, Hermann G. Haller, Annette D. Wagner.

Dept of Nephrology, Hannover Medical School, Hannover, Germany.

Background: Hyperuricemia and gout are common comorbid conditions experienced by up to 28% of kidney transplant recipients. Reasons for this include reduced excretory renal function, intake of diuretic medication as well as side-effects of immunosuppressant drugs such as calcineurin-inhibitors. Use of selective IL-1 inhibitors shows promising results in the treatment of gout. However, data on the use of IL-1 blockade as treatment for gout in renal transplant patients are limited.

Methods: Here we present our experience with interleukin 1 blockade in 3 patients after renal transplantation with therapy refractory gout arthritis.

Results: Two patients had no gout symptoms since starting IL-1 blocking therapy. One patient suffered from pneumonia. This patient developed hyperuricemia under IL-1 blockade. He was started on rasburicase therapy.

Monitoring of Serum Fibrinogen in Patients with ESRD Undergoing Plasma Exchange by Single Membrane Separation Technique for ABO Incompatible Kidney Transplantation

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Jeon Seok Oh, Seong Min Kim, Yong Ki Park, Jong Kyung Kim.

Division of Nephrology, Dept of Internal Medicine, Bloomberg Memorial Hospital, Busan, Korea.

Aim. To compare the efficacy and safety of plasma exchange by single membrane separation technique and centrifuge technique during the last 2 years.

Methods: All subjects were received ABO incompatible living donor kidney transplantation in our hospital. 68 times of plasma exchange were carried out at every other day in 13 patients before transplantation, using the COBE ® Spectra apheresis system. 50 times of plasma exchange were performed at every other day in 10 patients before transplantation, using the Prisamflex ® system with TPE 2000 filter. The levels of serum fibrinogen were monitored at pre-exchange, post-exchange one day. In pre-exchange 1.0 time the calculated plasma volume was replaced with an electrolyte solution containing 5% salt-free human albumin or fresh frozen plasma (FFP).

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Infections in Kidney Transplant Recipients in the Biggest Transplant Hospital of Mexico (Western National Medical Center, IMSS)

Alejandra Elizabeth Ramirez, Moises Marcial, Marco A. Torres-González, Jose Ignacio Cerrillos, Benjamin Gomez, Petra Martinez.

Nephrology, Western National Medical Center, IMSS, Guadalajara, Jalisco, Mexico.

Background: Infections are a major cause of morbidity and mortality in kidney transplant recipients. Aim. To describe the frequency, risk factors and major clinical syndromes associated to infections in patients renal post-transplant period.

Methods: Retrospective cohort. Medical records of kidney transplant patients who were hospitalized in the department of Nephrology between January to December 2015 and clinical, biochemical and socio-demographical and level of immunosuppression, cultures, kidney function and kind of infections were recorded. All patients over 18 years old, recipients of renal transplant with an infectious processes were included in the statistics analysis.

Results: A total of 1409 kidney transplant patients who were hospitalized in 2015, of these 325 (23%) had infections, the average age was 31.5±10.8 years old, 63% men, 56% transplant from live donor related, 32 of brain death, in 92% of cases received induction therapy. Acute rejection was present in 11%. Presentation of post-transplant infections median was at 4 (2–11) months. Urinary tract infections were the most frequent 54%, Cytomegalovirus 4%, Pneumonia 3%, 2.5% parovirus, 2% polyomavirus, invasive fungal infections 2%, 1% lower respiratory tract infections and 0.6% tuberculosis. Added syndromes whose etiology was infectious origin such as febrile syndrome, diarrhea and febrile neutropenia syndrome which accounted for 3%, 4% and 4% respectively.

Conclusions: Interaction between immunosuppression-infection is the protagonist in renal transplant recipients, related with drugs immunosuppressants, and give us the information to prevent this kind of infections.

**Table 1: Analysis of Prediction of Infections**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>OR</th>
<th>CI 95%</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>AGE</td>
<td>0.86</td>
<td>0.78 – 0.96</td>
<td>0.006</td>
</tr>
<tr>
<td>INDUCTION</td>
<td>5.20</td>
<td>3.70 – 38.78</td>
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<td>ALBUMIN</td>
<td>7.42</td>
<td>1.64 – 33.55</td>
<td>0.009</td>
</tr>
<tr>
<td>TACROLIMUS</td>
<td>0.013</td>
<td>0.001 – 0.120</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

controlled by gender, type donor, risk infectologic
Monoclonal Gamopathy of Undetermined Significance in Kidney Transplant Patients

Gaetano Alfano, Francesco Fontana, Gianni Cappelli.

Background: Monoclonal gamopathy of undetermined significance (MGUS) is an asymptomatic pre-malignant plasma cell disorder; its prevalence in the general population in Italy was reported to be 2.9% increasing with age. MGUS prevalence after kidney transplantation (KT) has been reported in few studies, with conflicting results. We assessed MGUS prevalence in KT recipients at our Center, linked to clinical outcomes.

Methods: We retrospectively reviewed medical charts of patients receiving KT between 1998 and 2015 and assessed MGUS prevalence and its characteristics.

Results: Of 5471 transplanted patients, MGUS was detected in 61 cases. We further analyzed outcomes of patients with postKT stable MGUS compared with a control group matched for sex, age and KT date. In 14 patients MGUS spontaneously disappeared during follow-up, while in 47 remained stable. 42 patients developed MGUS after KT (0.78%) at a median time from KT of 5.2 years. Fifty-two (86%) patients had MGUS the diagnosis before KT. Diabetes mellitus (DM) was present in 73% of patients with MGUS and 28% of patients without MGUS (p<0.01). Anemia was present in 40% of patients with MGUS and 10% of patients without MGUS (p<0.01). Blood count (WBC) were measured by routine methods and NLR calculated accordingly.

Conclusions: In conclusion, we report a high incidence of MGUS after KT, with a younger age at diagnosis compared to general population and with no sex difference. KT patients with MGUS had higher rates of mortality, graft failure, obstructive jaundice, and a significant increase in blood transfusions. NLR was adjusted to potential clinical confounders: Age, sex, diabetes mellitus, hypertension, smoking, LDL- and HDL-cholesterol and CAD.

Gastrointestinal Pathologies in Patients after Successful Renal Transplantation – One Center Prospective Study

Anna M. Dobies,1,2 Alicja Kubanek,1 Marcin Renke,1 Wojciech Wolnycie,1 Lukas Paleniec,1 Ewa Krol,1 Slawomir Lizakowski,1 Przemyslaw Rutkowski,2 Boleslaw Rutkowski,2 Alicja Debska-Sliżen,1 1Dept of Occupational, Nutritional, Metabolic and Internal Medicine, Medical Univ of Gdańsk, Gdańsk, Poland; 2Dept of Nephrology, Transplantology and Internal Medicine, Medical Univ of Gdansk, Gdansk, Poland.

Background: The aim of this study was to evaluate the prevalence of gastrointestinal pathologies in patients after kidney transplantation. Methods: Adult patients after kidney transplantation being under care of Outpatient Department of Nephrology in Gdansk after giving their consent were given questionnaire regarding alarm symptoms and referred for colonoscopy in each patient over 40 years old before the kidney transplantation is performed.

Results: So far the endoscopic examination was performed in 47 patients (31±16) at mean age 59 (range 35-83) years. The examination revealed: gastritis and/or duodenitis in 40 patients, stomach polyps in 6 patients, diverticular colon disease in 18 pts, inflammatory bowel disease in 10, colon polyps in 14 and cancers in 3 patients.

Conclusions: The results indicate that gastrointestinal pathologies are very common in patients after the kidney transplantation. It could be taken into consideration to perform colonoscopy in each patient over 40 years old before the kidney transplantation is performed.

Funding: Government Support - Non-U.S.

mTOR Inhibitors in the Prevention of BK Nephropathy: A Randomized Clinical Pilot Study

Sumit Mohan,1 Mariana C. Chiles,1 Darshana Dadhania,1 Samnang Lee,2 Bekir Tanrıöver,2 Russell J. Crew,2 David J. Cohen.1 1Columbia Univ; 2Univ of Texas Southwestern; Well Cornell.

Background: BK infection is an early and frequent complication of kidney transplantation that often results in graft loss. BK viremia (BKVI) is associated with calcineurin inhibitor (CNI) use while mTOR inhibitors (mTORIS) are associated with lower rates of BKV. mTOR inhibitors have been associated with low rates of BKV. We compare the impact of CNI based IS reduction to mTOR based IS conversion in steroid free transplant recipients.

Methods: The study was a multicenter prospective randomized controlled pilot study with 40 patients (Pts) randomized to reduction of CNI and antimitabolite (MTX) IS or conversion to mTOR and reduction of MPA at the time of BKV detection and started on study intervention once BKV PCR >5000 copies/ml. Primary end point was BKV clearance within 12 months of enrollment and groups were compared with an intent to treat analysis.

Results: Pts (56.7±14.0 yrs, 35% female, 23% Black, creatinine 1.41±0.4 mg/dL) were enrolled after BKV was detected 12.3±14.5 months post-transplant. Pts in the FK and mTOR arm were similar with respect to age (61±14.1 vs 52.4±12.7, p=0.055), gender (30% vs 40%, p=0.51), race (15% vs 30%, p=0.45), creatinine (1.49±0.46 v 1.34±0.40 mg/dL, p=0.30). The FK and BK groups were similar with respect to complete and partial clearance of viremia (70 and 85%, p=0.58 and 70 and 95%, p=0.092, respectively). Pts exposed to mTOR had a shorter time to complete and partial clearance (134±158 and 67±109 days, respectively). Pts in the FK arm appeared to be less likely to reach BK clearance (HR=1.87, 95% CI: 1.90–3.86, p=0.091).

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Conclusions: The results from this study indicate that mTOR IS has potential to be an effective treatment option for BKV. Given the observed effect size, a clinical trial with 90 pts is needed to demonstrate a statistically significant benefit.

Funding: Pharmaceutical Company Support - Pfizer

PUB779

Increase in Epidocardial Fat Impairs the Regression of Left Ventricular Hypertrophy in Kidney Transplantation Recipients

Daniel Constantino Yazbek,1 Aluzius B. Carvalho,1 Cinara Barros de Sá,1 Jose Medina-Pestana,2 Carlos Eduardo Rochitte,2 Raul Santos,2 Maria Eugenia F. Canziani,1 1 Federal Univ of Sao Paulo, 2 Heart Inst (InCor), Univ of Sao Paulo, 3 Hospital Rim.

Background: Epidocardial fat (EF) a component of visceral adipose tissue has been related to increased cardiovascular risk in chronic kidney disease (CKD). Left ventricular hypertrophy (LVH) is associated with high morbidity and mortality in this population and tends to decrease after kidney transplant. The aim of the present study was to investigate the association between changes in EF and left ventricular mass index (LVMI) during the first year after kidney transplant.

Methods: Heart images previously obtained by multislice CT from a randomized, controlled and open-labeled study that tested the effects of statins on coronary calcification in incidents kidney transplant recipients (IKTRs), were evaluated. EF (milliliters) was measured by VtiraCore® software, at baseline and after 12 months. LVMI was calculated by transthoracic echocardiography at the same periods.

Results: A total of 87 KTRs, 62% men, aged 41.0 ±10.1 years, average of 24 (11–49) months on dialysis were evaluated. LVMI was respectively 128.5 ±46.1 g/m² and 102.5 ±33.4 g/m² at baseline and 12 months. A decrease in LVMI was observed in 39 (79%) patients. EF was 318.1 (260.9 – 356.6) and 325.9 (273.0 – 382.3) ml at baseline and 12 months, respectively. In 58 (66%) patients EF progressed during follow-up (EF progressors). These patients, when compared to those in which EF decreased, had a greater increase in body mass index (2.9 ± 2.1 kg/m² vs. 1.3 ± 1.7 kg/m², p<0.001), in serum glucose concentration (6 (3 – 12) mg/dl vs. -1 (9 – 7) mg/dl, p=0.046) and a trend to smaller decrease of LVMI (-18 (-37 – -2) g/m² vs. -42 (-51 – -10) g/m², p<0.09). The lipid profile at baseline and after 12 months, as well as the use of statins were similar between the groups. The general linear model analysis showed that the progressor group had a smaller decrease in LVMI during follow up (for group effect <0.01; p for time-effect=-0.09; p for interaction =0.03).

Conclusions: The increase of EF impaired the regression of left ventricular mass in CKD patients after kidney transplant.

PUB780

Percutaneous Ultrasound Guided Renal Transplant Biopsies Outcomes as Performed by Two Specialties

Camilo Cortes,1 Franco H. Cabeza Rivera,2 Phillip Ruiz,2 Giselle Guerra,2 Adela D. Mattiazi,2 Internal Medicine, Univ of Miami - Jackson Memorial Hospital, Miami, FL; 1 Transplant Nephrology, Miami Transplant Inst - Univ of Miami, Miami, FL; 2 Surgery and Pathology, Univ of Miami, Miami, FL.

Background: Percutaneous ultrasound-guided renal transplant biopsy (US-TB) is the preferred method to assess renal allograft dysfunction. Reported complication rates range from 0.06-13%. We aim to analyze moderate to severe complications related to US-TB when performed either by Interventional Radiology (IR) or Transplant Nephrology (TN) specialists in a teaching hospital.

Methods: We retrospectively reviewed the US-TB performed at our center between Jan 1° 2015 and Dec 31° 2015. Demographic data, blood pressure ≥160/90mmHg, BMI, creatinine, BUN, INR, platelets counts, antiplatelet and/or anticoagulant agents held, biopsy core number, and time of complication were analyzed. Moderate complications were defined as hematoma, hydrenephrosis, arteriogenous fistula (AVF), hemoglobin drop >2 g/dl, and need for blood transfusion. Severe complications were defined as development of Page kidney or need for nephrectomy, hematoma-hydronephrosis and/or AVF all associated with kidney dysfunction.

Results: 222 US-TB were performed in 204 patients; 165 (74%) by IR and 57 (26%) by TN. There was no statistical significance among demographic, clinical and laboratory data.

Acute graft rejection during the study period was similar among the three groups (group 1: 21.5%, group 2: 28.5% and group 3:36.3%, p=0.55). Only 4 out of 25 patients discontinued PLQ; mainly for anemia and leukopenia.

Conclusions: Around 20% of kidney transplant recipients with native kidney lupus nephritis require PLQ after transplant discharge for recurrent lupus symptoms or arthritis. In general, the use of PLQ is safe. Larger studies are needed to determine whether PLQ use protects survival of kidney graft.

PUB782

Incidence of Human Parvovirus B19 Infection in Kidney Recipients

Milagros Melissa Flores Fonseca, Pablo Eduardo Nava Diaz, Celina Margarita Rodriguez, Benjamin Gomez. Nephrology and Organ Transplant Unit, Centro Medico Nacional de Occidente, Guadalajara, Jalisco, Mexico.

Background: Human parvovirus B19 (PVB19) infection is a rare infectious complication in immunosuppressed patients. The only manifestation is usually evidence of persistent and progressive anemia, occurring during the first year after transplantation, during which immunosuppression reaches its maximum state.

Methods: Retrospective analysis, identifying patients with persistent anemia and confirmed PVB19 in Centro Medico Nacional de Occidente (CMNO) between 2013-2015.

Results: 12 Patients with confirmed PVB19 were identified, regardless of gender, where the average age was 25.6 years, none recipients of deceased donors, first trimester was the time line of its presentation.

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

Underline represents presenting author.
Viral infections manifest atypically in renal allograft recipients. Transplant Glomerulopathy: Histological and Electron Microscopy (EM) Predictors for Progressive PUB783

Findings are shown in Table 1. While there were no statistically significant

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<td>3.01-2.0</td>
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<td>Endothelial Swelling present (EM analysis)</td>
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Conclusions: These initial data suggest that a more detailed histological and in particular EM analysis of biopsies with TG may be warranted in order to glean maximum available predictive information from these tissue samples; an important first step towards a more individualized/precision medicine approach to clinical transplantation.

PUB784

Case of Stroke in an Adult Renal Allograft Recipient after Parvovirus B19 Infection Ravindra V. Bhattu,1 Sonali R. Bhattu.2 · Nephrology & Renal Transplantation, DHOOT Hospital, Aurangabad, Maharashtra, India; ‘Internal Medicine, MGM’s Medical College, Aurangabad, Maharashtra, India.

Background: Viral infections manifest very differently in renal allograft recipients because of their immunosuppressed status. Parvovirus B19 infection commonly presents as anaemia. Here we present a rare case of stroke secondary to Parvovirus B19 infection in an adult renal allograft recipient.

Methods: A 35-yr old male with stage V CKD underwent pre-emptive renal transplant with his sister as donor. Immunosuppression used was standard Tacrolimus, MMF and steroids, which was started two days prior to transplant. No induction was used in view of low immunological risk. Post transplant course was uneventful with a rapid graft function achievement. Eight weeks post transplant, patient presented with severe anaemia(Hb 4.6g/dl). Evaluation revealed confirmed presence of Parvovirus, hence IV Immunglobulin therapy was started. He developed headache and visual deficit, to start with, and deteriorated within 72 hrs leading to coma and death.

Results: Serum Iron and B12 studies were normal. Bone marrow trephine biopsy revealed severe suppression of erythropoiesis and marrow was remarkable for scattered large erythroid cells (Glycophorin C and CD 117 expressing cells) with prominent large eosinophilic nuclear inclusions suggestive of Parvovirus infection, which was confirmed by Parvovirus B19 DNA detection by PCR. MRI brain revealed thrombosis of anterior cerebral arteries bilaterally, along with multiple infarcts in frontal areas, caudate nucleus and thalamus.

Conclusions: Viral infections manifest atypically in renal allograft recipients. Parvovirus B19 commonly presents with severe anaemia. To our knowledge this is the first ever case report of stroke secondary to Parvovirus B19 infection in an adult renal allograft recipient. This has to be kept in mind while evaluating neurological syndromes in post-transplant period.

PUB785

Design of a Real World Program to Transition Kidney Transplant Patients from Pediatric to Adult Care Tamar Y. Sprungel, Pat Minshall, Beth A. Vogt, Robert J. Cunningham. Pediatrics, Rainbow Babies and Children’s Hospital, Cleveland, OH.

Background: It is hypothesized that failure of appropriate transition from pediatric to adult care may contribute to the increased risk of graft loss during early adulthood. Few studies have focused on designing a transition program for the non-research, “real world” setting. Most pediatric kidney transplant programs have limited resources to dedicate to a transition program, and may benefit from an easily adaptable program. We set out to design a program to transition kidney transplant patients from pediatric to adult care which will be easily adaptable and require limited resources.

Methods: We performed a thorough literature review of previous studies and guidelines for transitioning patients with chronic disease from pediatric to adult care. We collaborated with adult transplant nephrology physicians and transplant coordinators to ascertain hurdles to patient transition.

Results: We developed a protocol which focuses on helping patients achieve the milestones which are necessary for successful transition. Starting at age 14, readiness for transition is assessed twice yearly through previously published transition questionnaires. Patients complete one survey every 6 months, alternating between two surveys. These questionnaires are designed to be patient-centered goals which are reviewed twice yearly.

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Underline represents presenting author.

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through a transition report card with patients and caregivers. Goals are dependent on patient’s individual abilities and the caregiver’s future expectations. Patients are reviewed among the pediatric and adult providers on a quarterly basis in preparation for transition in order to align care plans between pediatric and adult care. Following transition, patients are monitored more closely for the first year.

Conclusions: We designed a program for transition kidney transplant patients from pediatric to adult care. This program can be easily adapted by most pediatric kidney transplant centers without the need for additional staff. In the future, outcomes, including adherence to appointments, adherence to laboratory testing, graft outcomes, and patient and physician satisfaction may be examined.

PUB786

Rapamycin Induced Minimal Change Disease in a Renal Transplant Recipient: A Case Report
Vasili Pevy, Rush Univ Transplant Program, Rush Univ, Chicago, IL.

Background: Recurrent or de novo minimal change disease (MCD) in a renal transplant recipient represents a rarity. I report an unusual case of Rapamycin induced MCD in a renal transplant recipient eleven years after transplantation.

Methods: A 42-year old African American male with unknown cause of end stage renal disease (ESRD) received cadaveric renal transplant from donor after cardiac death (DCD). His postoperative course was complicated by slow graft function. He received induction immunosuppression with Campath and Solnedrool followed by maintenance immunosuppression with Prograf (FK) and Prednisone. Renal allograft biopsy preformed two years after transplant for evaluation of elevated serum creatinine revealed mild interstitial fibrosis and borderline cellular rejection. He was treated with high dose steroids. Six years later, due to concern for progressive interstitial fibrosis and persistently elevated serum creatinine he was converted from FK and prednisone to Rapamycin and prednisone. Within nine months of this conversion he developed gradually worsening proteinuria from prior baseline of 0.3 g/g, now up to 2.4 g/g with otherwise normal urine sediment. Due to stable renal function and absence of donor specific antibodies (DSA) his renal biopsy was deferred. Eleven years later his proteinuria peaked at 2.5 g/g and he developed mild lower extremity edema prompting repeat renal biopsy. This showed normal glomeruli on light with diffuse foot processes effacement on electron microscopy, consistent with the diagnosis of MCD. Post Transplant Lymphoproliferative Disorder (PTLD) was ruled out based on absence of lymphadenopathy on physical exam and normal thoracic and abdominal computer tomography imaging. Intake of non-steroidal agents was ruled out per history. Conversion of Rapamycin to FK lead to prompt resolution of his near nephrotic range proteinuria.

Conclusions: In conclusion, I report a rare case of Rapamycin induced podocytopathy consistent with MCD.

PUB787

Medium and Long-Term Outcomes following Treatment of Acute Antibody Mediated Rejection Complicating Renal Transplantation - Low Morbidity and Mortality
Leny Hudavani,1 Peter D. Hughes,2 Michael Lian,2 Peggy Teh,2 Marcus B. Tan,3 Susheel Sharma,2 Shlomo J. Cohen,1,2 1Dept of Nephrology, Western Health, Victoria, Australia; 2Dept of Nephrology, Royal Melbourne Hospital, Victoria, Australia.

Background: Antibody mediated rejection (AbMR) carries a high risk of graft loss, & significant treatment related morbidity & mortality. Short-term results have improved with intravenous gammaglobulin (IVIG) & plasma exchange (PEX). Little data exists on long-term outcomes, which were examined in this single centre study.

Methods: Outcomes of 87 patients diagnosed with acute AbMR between Jan 2000 & Dec 2011 were reviewed. Standard treatment included PEX, with 1 or 2 doses of intravenous methylprednisolone & no increase in maintenance immunosuppression.

Results: 91 episodes of AbMR occurred in 87 patients, 56 deemed early(≤90 days post-transplant) & 35 late (>90 days post-transplant). 68 episodes were treated with PEX and IVIG; in addition, 15 received rituximab & 5 bortezomb. Two had Pex alone, IVIG alone (n=10), rituximab alone (n=1). At median follow-up of 63 months post-AbMR, patient & graft survival at 2 years were 98% & 81% & at 5 years were 93% & 65%.

Conclusions: Mortality was low in this cohort of patients with AbMR treated primarily with PEX and without augmented immunosuppression while graft survival was comparable to previously published series using more aggressive therapy.

PUB788

Clinical Outcome of Kidney Re-Transplantation in Comparison with First Kidney Transplantation in Korea: Nationwide Cohort Study
Ji-Yeon Chang,1 Cho Woong Yang,2 Cheol Whee Park,1 Byung Ha Chung,1,2 1Div of Nephrology, Dept of Internal Medicine, Seoul St. Mary’s Hospital, The Catholic Univ of Korea, Seoul, Korea; 2Transplant Research Center, Seoul St. Mary’s Hospital, The Catholic Univ of Korea, Seoul, Korea.

Background: Due to the limitation of the survival of kidney allograft, increasing number of patients needs to take re-transplantation (re-KT) after the first allograft failure. In this study, we investigated the clinical characteristics and clinical outcomes of re-KT recipients in comparison with those of first KT using nationwide registry.

Methods: We retrospectively analyzed 4757 adult kidney transplant recipients(KTR) registered in Korean organ transplant registry database from 2009 to 2012. These cases were divided into 4 groups; first KT (n=2762) and re-KT (n=162) from living donor (LD), first KT(n=1647) and re-KT (n=196) from deceased donor (DD). We compared the clinical outcomes such as early or late biopsy-proven acute rejection and also allograft or patient survival rate across those groups.

Results: Out of total 4,757 KTRs, 348 (7.5%) cases were re-KT. The proportion of DDKT and sensitized patients was significantly higher in re-KT group compared to first KT group (DDKT; 55.4% vs. 37.4%; P<0.05, sensitized patients; 21.6% vs. 3.7%, P<0.05). Especially in LDKT, the proportion of ABO incompatible KT was higher in re-KT group than first KT group as well (18.5% vs. 12.5%; P<0.05). The incidence of early biopsy proven acute rejection (BPAR) was significantly higher in re-KT group than first KT group in DDKT (19.4% vs. 11.3%; P<0.05), but not in LDKT (7.4% vs. 9.0%; P>0.05). Incidence of late BPAR was not significantly different between re-KT and first KT groups both in DDKT (0.6% vs. 2.4%; P>0.05) and LDKT (1.6% vs. 2.6%; P>0.05). In multivariate analyses, re-KT was an independent risk factor for development of early BPAR in DDKT (odd ratio, 1.724; 95% confidence interval, 1.10 to 2.67; P<0.05). However, allograft and patient survival rate were not significantly different between re-KT and first KT group in DDKT and LDKT (P>0.05, for all).

Conclusions: Our study showed that overall clinical outcomes of re-KT was comparable to those of first KT irrespective of donor type.

Funding: Government Support - Non-U.S.
Does Left Ventricular Mass Decrease after Successful Renal Transplantation? An Updated Meta-analysis of Observational Studies

Background: Left ventricular hypertrophy is the hallmark of uremic cardiomyopathy and has been shown to be of prognostic importance in patients after renal transplantation. Several recent studies have evaluated left ventricular mass index (LVMI) in renal transplant recipients with unequivocal results. We therefore performed a meta-analysis of the available evidence to assess the effect of renal transplantation on (LVMI).

Methods: We identified manuscripts using Medline and Scopus databases. The search terms included “left ventricular hypertrophy” OR “left ventricular hypertrophy” AND transplantation. For the final analysis we identified 8 manuscripts comparing LVMI in kidney transplanted patients cross-sectional with healthy controls, 6 manuscripts comparing LVMI in kidney transplanted patients cross-sectional with patients on dialysis, 13 manuscripts longitudinal before and at least 12 months after renal transplantation and 2 studies examining LVMI longitudinally for at least 12 months using a control cohort. Standardized means were computed and a random effect model was used for analysis. A p value of .05, two-sided was considered significant. heterogeneity was assessed using I2 test for heterogeneity and Cochran Q test. Publication bias was tested using funnel-plots. “Comprehensive Meta Analysis V2,” Biostat, Enwellow, USA” was used for analysis.

Results: Compared to healthy controls LVMI was higher in renal transplant recipients (standardized mean difference=-0.584±0.270, p= 0.030; I2= 90%; Q=102.5, p<0.001), but compared to patients on dialysis LVMI was lower (standardized mean difference=-0.44±0.096, p=0.001; I2= 52; Q=6.3, p=0.387). In the studies with longitudinal observation LVMI was decreased after at least 12 months of follow-up (standardized mean difference=-0.43±0.069, p=0.001, I2= 42; Q=20.5, p=0.058).

Conclusions: LVMI decreases after renal transplantation, but remains higher than in normal controls, reflecting a cardiovascular risk that is decreased compared to dialysis patients but remains elevated.

Alterations in Glucose Metabolism in the Waiting List for Renal Transplantation

Background: Post-transplant diabetes (PTDM) is a severe complication after renal transplantation. Some risk factors for PTDM are present before transplantation, including obesity and insulin resistance. However, the role of alterations in glucose metabolism (AGM) i.e. prediabetes and diabetes diagnosed by an oral glucose tolerance test (OGTT) is not completely clear.

Methods: We studied 93 patients on the waiting list, without diabetes (diagnosed by baseline hyperglycemia or the use of medications). All underwent an OGTT and were classified as normal, prediabetes (impaired fasting glucose or glucose tolerance) or occult diabetes (glucose > 200 mg/dl at 120 min). 53 patients were transplanted. OGTT was repeated in 3-4 months after transplantation. Insulin resistance and secretion indexes were calculated (HOMA-R, McAuley, HOMA-sec and insulinogenic index).

Results: OGTTs were abnormal in 29 (31%) patients in the waiting list (22.5% prediabetes, 6.8% DMo). Age was the best predictor of an abnormal OGTT (OR: 1.07, 95% CI 1.01-1.12, p=0.02), age≥ 55 years was the best cut off point to distinguish a pathological OGTT by (Receiver operating curve and Youden index): <55 years, 16,1% prediabetes and 4,8% DMo; ≥ 55 years, 35,5% prediabetes and 16,1% respectively). Age(45±12 vs. 55±9 y), BMI (23±3 vs. 29±4) and HBA1C (4.9±0.3 vs 5.2±0.5%) on waiting list were higher in patients who developed PTDM (p<0.001).

Conclusions: An OGTT with normal glucose tolerance is a simple test to anticipate PTDM risk. Further studies are needed to evaluate the role of glucose metabolism in the waiting list for kidney transplantation.

Association of Blood Pressure Levels and Blood Pressure Variability with Left Ventricular Mass Index in Pediatric Kidney Transplant Recipients

Background: Recent studies suggest that not only blood pressure (BP) levels but also BP variability (BPV) are important for the development of target organ damage and cardiovascular morbidity. We aimed to evaluate the association of BP levels and BP variability with left ventricular mass index (LVMI) in pediatric kidney transplant recipients.

Methods: 32 patients (20 males, mean age 16.0±3.5 years) with a well-functioning graft (GFR=60 ml/min/1.73 m²) who had been performed kidney transplantation (Tx) before 18 years of age were evaluated. Demographic data and medications were noted. Ambulatory BP monitoring (ABPM) and echocardiography were carried out. Standardized mean difference scores (SDS) for 24-h/day/night BP readings were calculated based on normative data. BP dipping and BP loads, BPV parameters [standard deviation (SD) and coefficient of variation (CV)] of 24-h/day ABPM readings and average real variables were recorded from ABPM files. Left ventricular hypertrophy (LVHI) was defined as LVMI>95. percentile for age and gender. Hypertension was classified according to American Heart Association criteria.

Results: The median duration of dialysis before Tx was 2.47 (0-16) years and the follow-up period after Tx was 6.5 (0.3-7.5) years. Immunosuppressive protocol included triple therapy (prednisoloin, MMF and tacrolimus).16 patients were on antihypertensive therapy (calcium channel blockers and/or renin angitensin blockers). A total of 18 patients (56%) had arterial hypertension, 4 patients (43%) had LVHI. Significant correlations were found between ambulatory BP SDS parameters and LVMI whereas BPV parameters were not associated with LVMI. Significant risk factors for LVHI are shown in Table 1.

Conclusions: It is important to note that ambulatory BP levels are strongly associated with LVHI in pediatric kidney transplant recipients.

Post-Transplantation Graft Function Is Associated with Major Cardiovascular Events in Kidney Transplant Recipients: A Multicenter Cohort Study

Background: Reduced kidney function is an independent risk factor for cardiovascular disease in the general population. However, the association between post-transplantation graft function and subsequent cardiovascular disease remains uncertain. Therefore, we investigated the outcomes of transplantation in kidney transplant recipients.

Methods: A total of 2,419 kidney transplant recipients in a multicenter cohort were included to evaluate the effects of post-transplant graft function on major adverse cardiovascular events (MACE: cardiac death, nonfatal myocardial infarction, or coronary revascularization), graft failure, and mortality. Recipients were classified into 3 groups according to their estimated glomerular filtration rate (eGFR): group 1 (eGFR ≥ 60 mL/min/1.73 m², n=1,441), group 2 (30 ≤ eGFR < 60 mL/min/1.73 m², n=907), and group 3 (eGFR < 30 mL/min/1.73 m², n=71). Multivariate Cox hazard model was used to explore the association of eGFR with MACE.

Results: Median age was 42 years and 58.8% were male. Median eGFR was 63.6 mL/min/1.73 m². In 2,419 participants, there were 93 cases of MACE, 214 cases of graft failure, and 76 patient deaths over a median of 6.1 years. The cumulative rates of MACE were higher in the group of lower graft function. In multivariate Cox regression, lower graft function was significantly associated with the occurrence of MACE (hazard ratio 1.5, 95% confidence interval 1.0–2.3, P[hazard]=[hazard]0.04 compared to higher graft function. Additionally, cumulative rates of graft failure and mortality were also significantly higher in recipients with lower graft function.

Conclusions: Post-transplant graft function independently correlates with MACE, graft failure, and mortality, suggesting management of graft function may improve the patient and graft survival and cardiac outcome of kidney transplant recipients.

Kidney Transplant Outcomes in Two Adults with Down Syndrome

Background: There is little literature about renal transplantation in adults with trisomy 21 (Down syndrome). We present the cases of two adults transplanted at different institutions to describe their post-transplant course and outcomes.

Methods: Electronic medical records (2000-present) were reviewed at two institutions to identify adult patients with Down syndrome who had undergone kidney transplant.

Results: Patient 1 is a 45 year old man with insulin dependent type 2 diabetes initiated on hemodialysis in 2010. He underwent kidney transplant in 2014 from a 54 year old woman who died of a stroke. Pre-transplant biopsy showed 7% glomerular sclerosis and 1% interstitial fibrosis. He received standard immunosuppression. Post-operative course was marked by delayed graft function (DGF). Initial biopsy showed acute T cell- and antibody-mediated rejection, as well as thrombotic microangiopathy (TMA). Biopsy POD 27 showed acute tubular injury, resolving inflammation, and TMA with acute and chronic features. Final biopsy at 2 months showed TMA with chronic features, despite switching tacrolimus to cyclosporine. Kidney never functioned, and patient 1 remains on dialysis.

Patient 2 was a 38 year old man at his time of death in 2014. He had ESRD secondary to type 1 diabetes, and was initiated on hemodialysis in 2000. He underwent kidney transplant in 2006 from a 5 year old deceased donor who underwent prolonged reanimation efforts. The postoperative course was notable for DGF, for which the patient received dialysis and thyromoglobin infusion. He was discharged with stable renal function after 2 weeks, and enjoyed excellent renal function for 7.5 years on standard immunosuppression. The patient was admitted from an outside hospital in 2014 with small bowel obstruction and sepis, and subsequently died.
Conclusions: The cases represent extremes of renal transplantation in an adult. Patient 1 remains inactive on the list, with his mother reluctant to agree to another transplant. Patient 2 enjoyed over seven years of stable renal function prior to his death. Taken together the cases underscore the need to evaluate adults with Down syndrome individually for renal transplantation.

PUB795
Surveillance Biopsy Findings with Different Induction Agents in Kidney Transplant Recipients Hector M. Madariaga,1 Cinthia Drachenberg,2 Nadiesa A. Costa,1 Jonathan Bromberg,1 Matthew R. Weir,1 Abdolehra Haritani,1 1Div of Nephrology, Univ of Maryland Medical Center, Baltimore, MD; 2Dept of Pathology, Univ of Maryland Medical Center, Baltimore, MD; 2Dept of Surgery, Univ of Maryland Medical Center, Baltimore, MD.

Background: Surveillance renal transplant biopsies (SBx) could detect subclinical historical changes that could affect graft outcomes. The impact of the induction agent on SBx findings is not well defined.

Methods: We conducted a retrospective cohort study of 466 patients who underwent SBx from 1/2007 to 12/2012, with stable graft function and no proteinuria, and had received induction with alemtuzumab (ALZ) (60%), anti-thymocyte globulin (ATG) (15%) or basiliximab (BBX) (24%).

Results: 410 patients had SBx at 4.0±2.1 and 245 at 13.4± months post-transplant, 228 had both. Mean creatinine was 1.4 and 1.8 mg/dl, respectively.

First Biopsy Findings

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Conclusions: Our study suggests that subclinical histologic changes are not uncommon with modern IS regimens and the prevalence of these findings with ALZ induction was comparable to other induction agents.

PUB796
Incidence of Anti-HLA Antibodies Specific Donor in Kidney Transplant Recipients (KTR) and Its Association with Acute Rejection (AR) on Immunosuppression Schemes with or without Steroids Jorge Andrade-Sierra, Enrique Rojas-Campos, Jose Ignacio Cerrillos, Benjamin Gomez, Luis Alberto Evangelista-Carrillo, Alfonso M. Cueto-Manzano. Nephrology, IMSS, Guadalajara, Jalisco, Mexico.

Background: Antigen-specific humoral and cellular immune mechanisms contribute to an increased number and severe episodes of AR, conditioning chronic damage and graft loss. OBJECTIVE: To compare the incidence of donor-specific HLA-antibodies (HLA-DSA) and its association with AR in KTR on immunosuppression schemes with and without steroids.

Methods: Prospective Cohort, from March-2013 to March-2014, on participants over 18 years of age, first living donor kidney transplant (LDKT) with maintenance immunosuppression after transplantation without steroids compared to those who remained on steroids. All had negative crossmatch (flow cytometry) and anti-HLA antibodies (Lifecodes LifeScreen Deluxe (LMX)) before transplantation.

Results: 77 patients posttransplant were included, 30 without steroids and 47 with steroids. At the end of follow-up the formation of donor-specific HLA-antibodies class I (13% vs 2.1%; p = 0.05) and class II (17% vs 4%; p = 0.06) was higher in the group without steroids and this intervention tended to predict the development of HLA-DSA class II [RR 5.7, CI (0.93 to 34.5); p = 0.06]. A history cellular AR was present in 80% (p = 0.07) in those who formed HLA-DSA class I and 86% (p = 0.03) among class II and was a predictor for antibody class II formation [RR 7.23, CI (1.2 - 44); p = 0.03]. Sixty-two percent of patients with positive HLA-DSA bordering changes for AR corresponded to immunosuppression without steroids.

Conclusions: The HLA-DSA class I and II were present in both groups from the early stages of transplantation, with no significant trend to be higher among those who did not receive steroids. AR predicts production of renal antibody receptors without steroids.

PUB797

Background: HIV-associated nephropathy (HIVAN) is the 3rd cause of ESRD in HIV+ patients. We report 10 HIV+ KTx from HIV- donors.

Methods: In a 4-year period (2009-2013), data from 10 HIV+ KTx was reviewed. Transplant criteria were: undetectable HIV RNA levels, CD4+ count ≥ 200/mm³, stable antiretroviral Rx, and no opportunistic infections. 3 patients had biopsy-proven HIVAN in 1 had IgAN. Of 6 patients presumed to have HIVAN, one had diabetes and one had hepatitis C. Race: Black (9/10), male (7/10), mean age of 49 years. Nine KTx were from a deceased- and 4 from living-related donors. 8 received immunosuppression: induction with basiliximab (n=9) or Thymoglobulin (TGB) (n=1) + tacrolimus (FK) + mycophenolic acid + steroids. KTx on Protease Inhibitors (PI) were switched to a non-PI Rx. Demographics, patient (PS) and graft survival (GS), CD4 and HIV RNA counts, renal function, as well as incidence of acute rejection (ACR), opportunistic infections and cancer were evaluated.

Results: KTx were followed for a mean of 45 months (range 19–77). ACR was diagnosed in 4 patients, most of them severe, with a mean time to first ACR of 117 days (range 6–394), and mostly associated with low or undetectable FK levels. Three KTx had opportunistic infections (1 CMV disease, 1 BK viremia and 1 PCP). Two of them had received TGB for previous ACR. One patient developed colon cancer less than 18 months post KTx. Pre-KTx mean CD4 was 574±150 and 321±170, at last follow up. Low CD4+ levels post KTx were attributed to a patient who had received TGB for ACR and another patient receiving chemotherapy for colon cancer. None of the patients showed reactivation of the HIV virus. Among patients with a functioning kidney, the median serum creatinine was 1.60±0.48 mg/dl with a mean Gllof GFR of 67.2±34.6 cc/min. GS at 1 to 4 years were 96±8%, 80% and 80% and PS were, respectively, 100%, 90%, 90% and 90%.

Conclusions: The use of antirejection Rx does not result in the reactivation of the HIV virus. ACR tend to be severe and associated with suboptimal immunosuppression. KTx is a feasible and safe option for renal replacement in HIV+ patients with equivalent GS and PS to HIV+ KTx.

PUB798
Low Bioavailability Steroids for Treatment of Diarrhea Associated with Mycophenolate in Renal Transplant Recipients Pooja Budhiraja, Charity Thompson, Anna Ilhae. Dept of Transplant, Univ of Kansas, Kansas City, MO.

Background: Mycophenolic acid (MPA) is one of the main immunosuppressant’s used in organ transplants. Diarrhea can be seen in 20% of subjects. Mycophenolic acid-acyl glucuronide is a metabolite of MPA, which causes inflammation and cytokine release and plays major role. Corticosteroids due to anti-inflammatory activity are drug of choice for noninfectious inflammatory colitis. Low bioavailability steroids act locally in the intestine and have minimal absorption into systemic circulation.

Methods: We present cases with MPA induced diarrhea who responded to these. They had no history of IBS, IBD, malabsorption and had never experienced diarrhea. Infectious work up and Celiac disease panel were negative. They had colonoscopy which revealed normal appearing terminal ileum and colonic mucosa. Random biopsies taken from the colon showed acute and chronic inflammation, cryptitis, and focal crypt distortion. Their immunosuppression consisted of Myfortic, Prograf and prednisone. First patient is a 47 year old male with history of kidney transplant in 2014 for PKD. He presented 16 months post-transplant for diarrhea. Patient was having 5-10 episodes of watery diarrhea daily for the last 6 months. The patient was started on budesonide 9 mg once a day and had improvement in diarrhea in 2 weeks. He continued on 4 mg for a total of 6 weeks and then tapered to 4 mg daily with taper over 12 weeks. He has been on budesonide for 8 weeks and denies diarrhea. Second patient is a 63 year old male with history of kidney transplant in 2014 for MPGN. He complained of chronic diarrhea one year post transplant. His baseline creatinine was 2.5mg/dl and he had low TPMT level. He was started on budesonamethasone 2 mg three times a day and reported improvement in symptoms in 2 weeks. It was tapered to 2 mg twice a day at 6 weeks and plan is to taper it over 12 weeks. We will finish the course of oral low bioavailability steroids and observe the patient and repeat colonoscopy in 6 months after they finish treatment.

Conclusions: Oral low bioavailability steroids can improve MPA associated diarrhea and help minimize unnecessary reduction of MPA, help improve compliance and promote long term allograft survival.

PUB799

Background: Multiple arteries exist in almost 30% of these renal grafts, challenging the arterial repair and implantation. The target of this work is to describe an infrequent arterial reconstruction technique on kidneys with multiple arteries.

Methods: 41-year-old male with chronic renal failure with no-filiated etiology is candidate for renal transplantation. Living donor program is accepted. Due to ABO incompatibility both are included in the crossed living donor program. Multi-centric crossed transplant is initiated, and a compatible left renal graft is received. Remarkably, the graft shows 4 renal arteries (3 short primaries and 1 polar) of 3-4 mm diameter. Due to the complexity

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
of the vascular surgery, the previous ex vivo repair is performed. During the ex vivo reconstruction, done with continuous saline infusion (4°C) and Celisor solution, the polar artery is linked, due to the endo-thelial injury during the explant, and the latero-lateral anastomosis of 2 principal arteries is done, creating a common ostium. A gonadal vein patch is created and the two joined arteries and the lower artery is anastomosed separately. The scanner showed a normal expected curves and normal resistance index of the renal arteries. The scanner after two months showed permeable renal arteries without signs of restenosis. After two months, the creatinine value is 1.87 mg/dl with a glomerular filtration rate of 43 ml/min.

**Conclusions:** The use of gonadal vein acting as a Carrel patch is a safe surgical alternative in case of donor with multiple arteries/arteries.

**PUB800**

### Oxidative Stress, and Its Association with Vascular Calcification in End Stage Renal Disease Patients

**Evaluating CTLA-4-Ig and a CXCR4 Antagonist as Potential Treatment Options for Diabetic Kidney Disease (DKD)**

#### Background

Renal inflammation is a hallmark of DKD pathophysiology. CTLA-4 is a co-inhibitory receptor present on activated T and regulatory T cells that blocks co-stimulatory B7-1 and B7-2 ligands on antigen presenting cells, thereby limiting CD28 receptor mediated T-cell activation. Reportedly, soluble CTLA-4-Ig (ababactet) that acts as a B7 ligand trap was shown to reduce proteinuria in FSGS and nephrotic SLE patients. As both B7/CD28 and CXCL12/CXCR4 pathways are concordantly upregulated in human DKD kidney, targeting both pathways simultaneously may result in better efficacy. The CXCR4 antagonism shows greater reduction of albuminuria compared to Lisinopril alone and reduces BUN and serum creatinine levels as a B7 ligand trap was shown to reduce proteinuria in FSGS and nephrotic SLE patients. Methods: We set out to test if targeting B7 molecules with CTLA-4-Ig constitutes a promising therapeutic avenue for treating DKD.

#### Results

There is increased mRNA expression of B7-1 in glomeruli and B7-2 and CD28 in both glomeruli and tubules of human DKD patients. B7-1 and B7-2 mRNA expression are also increased in kidneys of the renin-AAV1 uninephrectomized df/df mouse model. Interestingly, CTLA-4-Ig treatment retarded albuminuria progression in this model compared to the vehicle control, but doesn’t reduce albuminuria from baseline or further reduce albuminuria when added to Lisinopril. Among other inflammatory pathways prominently upregulated in human DKD kidney is the CXCL12/CXCR4 chemokine signaling pathway. CXCL12/CXCR4 engagement activates several signaling pathways (e.g. MAPK, PI3K/AKT, NF-kB and JAK/STAT) and is known to play a major role in cell survival, angiogenesis, inflammation, and mobilization/homing of bone marrow stem/immune cells. As both B7/CD28 and CXCL12/CXCR4 pathways are concordantly upregulated in human DKD, targeting both pathways simultaneously may result in better efficacy. The CXCR4 antagonist alone or in combination with Lisinopril doesn’t impact albuminuria. However, the combination of CTLA-4-Ig + Lisinopril + CXCR4 antagonist shows greater reduction of albuminuria compared to Lisinopril alone and reduces BUN and serum creatinine levels consistent with renal function improvement.

#### Conclusions

We conclude that CTLA-4-Ig has modest preventative effects on albuminuria in a hyperensive model of DKD and requires additional interventions to confer albuminuria reduction.

**PUB801**

### A Time Dependent Analysis of Long-Term Renal Outcome and Mortality among Critical Acute Kidney Injury Patients Receiving Different Dialysis Modality

**Evaluting CTLA-4-Ig and a CXCR4 Antagonist as Potential Treatment Options for Diabetic Kidney Disease (DKD)**

#### Background

Renal inflammation is a hallmark of DKD pathophysiology. CTLA-4 is a co-inhibitory receptor present on activated T and regulatory T cells that blocks co-stimulatory B7-1 and B7-2 ligands on antigen presenting cells, thereby limiting CD28 receptor mediated T-cell activation. Reportedly, soluble CTLA-4-Ig (ababactet) that acts as a B7 ligand trap was shown to reduce proteinuria in FSGS and nephrotic SLE patients. Methods: We set out to test if targeting B7 molecules with CTLA-4-Ig constitutes a promising therapeutic avenue for treating DKD.

#### Results

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#### Conclusions

We conclude that CTLA-4-Ig has modest preventative effects on albuminuria in a hyperensive model of DKD and requires additional interventions to confer albuminuria reduction.

**PUB802**

### Clinical Significance of Different Carnitine Levels in Improving the Prognosis of Hemodialysis Patients

**Clinical Significance of Different Carnitine Levels in Improving the Prognosis of Hemodialysis Patients**

#### Background

Carnitine is a amino acid derivative, which produces energy required for muscle and cell metabolism. It has been suggested that disturbed carnitine homeostasis is harmful in hemodialysis (HD) patients. The aim of this study was to investigate the clinical significance of different carnitine levels in HD patients.

#### Methods

HD patients (n=133) were divided into medication group (received carnitine treatment) and non-medication group. According to patients’ Fc (free carnitine) level, medication group were further divided into three subgroups: Fe90–199µmol/L group, Fe200–299µmol/L group and Fe300µmol/L group. We used non-derivative tandem mass spectrometry to determine carnitine level and observed clinical symptoms, such as weakness, hypotension and muscle cramps during dialysis.

#### Results

The Fe level in non-medication group was significantly lower than that in control group, while the Fe, Ac(a-carnitine) level in medication group were higher than that in non-medication group (P<0.05). Compared with that in non-medication group, symptoms like weakness, hypotension and muscle cramps during dialysis in medication group showed lower (P<0.05). A further intercomparison was made in them and showed the incidence of hypotension and muscle cramps in Fe80–199µmol/L group was lower than that in Fe300µmol/L medication group and non-medication group. The differences were statistical significance.

#### Conclusions

A general lack of carnitine in patients with hemodialysis. L-carnitine can effectively increase the concentration of Fe. We found that appropriate range of free carnitine can improve complications in dialysis, however, beyond certain range could be counterproductive. The proper range of Fe need to be further studied.

**Funding:** Private Foundation Support
Methods: We conducted a retrospective, single-center, cohort study of 1866 adults admitted to hospital with AKI between 2006 and 2011. Serum chloride values during the first 48 hours of ICU admission were collected and analysed for baseline levels, peak levels, and change in the first 48 hours. Adjusted logistic regression analysis was used to examine the association between serum chloride and the incidence of AKI (2012 KDIGO criteria) and ICU mortality.

Results: The incidence of AKI was 56.3% and ICU mortality was 12.8%. The mean (SD) baseline chloride was 106 (7) mmol/L and average peak chloride 106 (7). The mean change in chloride was -2.2 mmol/L, with 12.8% of patients showing an increase within the first 48 hours of admission. An increase in serum chloride was significantly associated with a decrease in AKI and ICU mortality. In multivariate analysis adjusting for age, APACHE II score, ventilation status and pH value, the association remained significant between the serum chloride increase and severe AKI (OR 1.756, 95% CI 1.140-2.706, p=0.0107) and ICU mortality (OR 2.260, 95% CI 1.384-3.69, p=0.0011). There was no significant association between baseline chloride and AKI or ICU mortality.

Conclusions: An increase in serum chloride in critically ill patients during the first 48 hours of admission is significantly associated with the development of severe AKI and ICU mortality, independent of disease severity (APACHE II score). Serum chloride increase may have a deleterious effect on kidney function. Whether this justifies the use of chloride-restrictive fluid strategies requires further evaluation.

Funding: Clinical Revenue Support

PUB806

Case Report of Long-Term Recovery from Advanced Chronic Kidney Disease following Alternative Oxidative Therapy and Supplements Pria Visweewarangal Balakrishnan. Div of Renal Diseases, The Immortality Inst, Houston, TX.

Background: CKD affects nearly 3-20 million people in the US alone and 20-100 million people worldwide. While there are drugs available to slow progression to ESRD, nothing has been shown to absolutely, and consistently, prevent the need for Renal Replacement therapy, when CKD Stage V is attained, or RRT becomes a medical necessity. We hereby report a long-standing diabetic patient with CKD Stage V (who had needed RRT for the past 7 years) and access complications seen in ESRD patients may be related to a set of complications that occur during hemodialysis, such as intradialytic hypotension which is known to occur in relatively large number of dialyzed patients. Analysis will be conducted further to investigate the effect of failing to reach dry weight in a hemodialysis patient on mortality, hospitalization and morbidity, and whether a drop in blood pressure during hemodialysis with or without reaching the dry weight will affect a patient outcome.

Funding: Other NIH Support - Staten Island University Hospital

PUB807

Mortality and Hospitalization in Patients That Fail to Reach Dry Weight Suzanne E. El Savegh, Nabil Zeineddine, Raja Asif Masood, Marco Campitelli, Salim Bou Slaiman, Sandy El Bitar. Internal Medicine, Staten Island Univ Hospital.

Methods: Patients with end stage renal disease have an elevated risk for hospitalization, cardiovascular complications and increased mortality compared with the general population. The high rate of mortality and the high burden of cardiovascular events in ESRD patients might be related to a set of complications that occur during hemodialysis, such as intradialytic hypotension with consequent tissue hypoxia which is known to occur in relatively large number of dialyzed patients. This study was conducted to investigate the effect of failing to reach dry weight in a hemodialysis patient on mortality, hospitalization and morbidity, and whether a drop in blood pressure during hemodialysis with or without reaching the dry weight will affect a patient outcome. (intradialytic hypotension defined based on the KDQOI as “a decrease in systolic BP by 20 mmhg from predialysis to nadir intradialytic levels plus 2 or more responsive measures (solute administered, rate of dialysis decreased or dialysis stopped).

Results: 49 hemodialysis patients (49% males, 51% females. Mean age 60.7 years) with ESRD charts were reviewed, and data from 1763 hemodialysis session was collected; 37.2% (644) of the hemodialysis sessions ended with the patient reaching his dry weight. In 16.4 % (283) of hemodialysis sessions hypotension occurred. 69.4% (n=34) of the studied patients were hospitalized in a one year follow up period. 20.5% (7/34) were hospitalized for a cardiovascular complication (myocardial infarction, CHF exacerbation, or a newly diagnosed angina). 20.5% (n=7/34) were hospitalized for hemodialysis access site complications.

Conclusions: The high rate of mortality and the high burden of cardiovascular events and access complications seen in ESRD patients may be related to a set of complications that occur during hemodialysis, such as intradialytic hypotension which is known to occur in relatively large number of dialyzed patients. Analysis will be conducted further to investigate the effect of failing to reach dry weight in a hemodialysis patient on mortality, hospitalization and morbidity, and whether a drop in blood pressure during hemodialysis with or without reaching the dry weight will affect a patient outcome.

Funding: Other NIH Support - Staten Island University Hospital

Relaxin Reverses Contrast-Induced Human Kidney Proximal Tubular Epithelial Cell Apoptosis by Activation of Akt Signaling Pathway In Vitro Ming Wang, Xiangcheng Xie, Xiao Fei, Nabil Zeineddine, Raja Asif Masood, Marco Campitelli, Salim Bou Slaiman, Sandy El Bitar.

Background: Contrast-induced acute kidney injury (CI-AKI) is a common acute renal failure, which is the third most common cause of hospital-acquired acute renal failure. However, the treatment strategies remain limited. The present study was designed to investigate the impact of relaxin on the contrast-induced cell injury in order to find an effective way to treat contrast-induced acute kidney injury (CI-AKI).

Methods: In this experiment, renal tubular epithelial cells (HK-2) were exposed to isoversol (10 mg iodine/mL) for 0.5 hours. The Relaxin (10ng/mL) was added 1.5 hours before isoversol, as well as the P13K inhibitor LY294002 (50 µM). Then cells were incubated for 24 hours in normal medium. CCK-8 assay was used to measure cell viability. Apoptotic morphologic alterations were observed using Hoescht 33342 staining method. Apoptosis was detected by Annexin V stain. Western blot analysis was employed to measure the expression of pAKTser473, AKT, Cleaved-Caspase3, Bcl-2, Bax, ACTIN protein. Results: Ioversol reduced cell viability of HK-2 cells. Western blot results revealed that the expression of phosphorylated Akt (p-Akt) in cells decreased after exposure to isoversol. Ioversol increased both the activities of caspase-3, and the expression of the Bax protein, while the expression of Bcl-2 protein decreased. As a result the Bax:Bcl-2 ratio was therefore increased after the treatment with isoversol. These effects were reversed when co-treated with relaxin. However, when pre-administration of Akt inhibitor LY294002, the effect of relaxin was blocked, indicating that relaxin can attenuate contrast-induced cell apoptosis by activating Akt signaling pathway.

Conclusions: Our study demonstrated that relaxin attenuated the isoversol induced cell apoptotic injury via activation of P13K/Akt signaling pathway, suggesting that H2 relaxin might play a protective role in the treatment for CI-AKI.

Funding: Government Support - Non-U.S.
chronic glomerulonephritis
chronic hemodialysis
chronic diabetic complications
chemotherapy
chronic heart failure
chronic allograft nephropathy
chronic inflammation
chronic kidney disease
chronic hypoxia

chemokinergic receptor
chemotherapy
chronic allograft failure
chronic allograft rejection
chronic diabetic complications
chronic heart failure
chronic hemodialysis
chronic kidney disease
chronic hypoxia
membranous nephropathy (3550.10), membranoproliferative
glomerulonephritis (N03.6), mesangial proliferative
glomerulonephritis (N03.1), focal segmental
glomerulosclerosis (N03.8), diabetic nephropathy
(905.31), polycystic kidney disease (105.3), lupus
erenphritis (N03.1), hepatitis C virus-related
nephropathy (N04.9), thrombotic microangiopathy
(N17.9), polyarteritis nodosa (N05.0), Goodpasture's
syndrome (N17.0), acute kidney injury (24.1), chronic
kidney disease (24.2), end-stage kidney disease
(24.3), chronic interstitial nephritis (N17.1), acute
interstitial nephritis (N17.0), acute tubular
necrosis (N17.0), chronic tubulointerstitial
nephropathy (N17.2), renal vein thrombosis
(D73.4), renal artery stenosis (D73.5), renal
artery aneurysm (D73.6), kidney transplant
(934.5), urinary tract infection (934.1), bladder
cancer (956.3), prostate cancer (956.4), testicular
cancer (956.5), ovarian cancer (956.6), kidney
carcinoma (956.7), renal cell carcinoma
(956.8), Wilms' tumor (N72.2), nephrotoxic
nephropathy (N17.0), alcohol-related kidney
disease (24.1), ischemic nephropathy (24.2),
diabetes (24.2), hypertensive nephropathy
(24.2), glomerular hyperfiltration (Q90.1),
proteinuria (N02.2), hematuria (N03.0),
chronic kidney disease (24.2), end-stage kidney
disease (24.3), chronic interstitial nephritis
(N17.1), acute interstitial nephritis (N17.0), acute
human leukemia
(24.1), hyperlipidemia
(24.2), LDL cholesterol
(24.2), C-reactive protein
(052.3), homocysteine
(24.1), HbA1c (24.1),
renal biopsy (24.1), C3
(185.6), C4 (185.6),
complement C3 (185.6),
complement C4 (185.6),
C3a (185.7), C5a (185.7),
complement C3a (185.7),
complement C5a (185.7),
proinflammatory cytokines (185.7),
monocyte chemoattractant protein 1 (185.7),
lipid metabolism (185.7),
vasculitis (185.7),
acute kidney injury (24.1), chronic kidney disease
(24.2), end-stage kidney disease (24.3),
chronic interstitial nephritis (N17.1), acute
interstitial nephritis (N17.0), acute tubular
necrosis (N17.0), chronic tubulointerstitial
nephropathy (N17.2), renal vein thrombosis
(D73.4), renal artery stenosis (D73.5),
renal artery aneurysm (D73.6), kidney transplant
(934.5), urinary tract infection (934.1),
bladder cancer (956.3), prostate cancer
(956.4), testicular cancer (956.5), ovarian
cancer (956.6), kidney carcinoma
(956.7), Wilms' tumor (N72.2), nephrotoxic
nephropathy (N17.0), alcohol-related kidney
disease (24.1), ischemic nephropathy (24.2),
hyperlipidemia (24.2), C-reactive protein
(052.3), homocysteine (24.1), HbA1c (24.1),
renal biopsy (24.1), C3 (185.6), C4 (185.6),
complement C3 (185.6), complement C4
(185.6), C3a (185.7), C5a (185.7), complement C3a
(185.7), complement C5a (185.7), proinflammatory
cytokines (185.7), monocyte chemoattractant
protein 1 (185.7), lipid metabolism (185.7),
vasculitis (185.7), acute kidney injury (24.1),
chronic kidney disease (24.2), end-stage kidney
disease (24.3), chronic interstitial nephritis
(N17.1), acute interstitial nephritis (N17.0),
acute tubular necrosis (N17.0), chronic
microalbuminuria
...... TH‑PO004, TH‑PO113, TH‑PO421, TH‑PO425,
mesangial cells
...... TH‑OR091, TH‑OR092, TH‑OR093, TH‑OR101,
veins
...... TH‑PO323, TH‑PO547, TH‑PO550, TH‑PO553,
leptomeningeal
...... TH‑PO550, TH‑PO553, TH‑PO556, TH‑PO559,
epithelial cells
...... TH‑PO550, TH‑PO553, TH‑PO556, TH‑PO559,
mesangial cells
...... OR‑PO031, OR‑PO032, OR‑PO033, OR‑PO034,
mesangial cells
...... OR‑PO031, OR‑PO032, OR‑PO033, OR‑PO034,
mesangial cells
...... OR‑PO031, OR‑PO032, OR‑PO033, OR‑PO034,
mesangial cells
...... OR‑PO031, OR‑PO032, OR‑PO033, OR‑PO034,
mesangial cells
...... OR‑PO031, OR‑PO032, OR‑PO033, OR‑PO034,
pediatric nephrology (continued)................ TH‑PO598,
TH‑PO605, TH‑PO606, TH‑PO607, TH‑PO609,
TH‑PO613, TH‑PO614, TH‑PO615, TH‑PO695,
TH‑PO848, TH‑PO900, TH‑PO916, TH‑PO923,
FR‑OR036, FR‑OR087, FR‑OR088, FR‑OR090,
FR‑OR091, FR‑OR093, FR‑OR094, FR‑PO564,
FR‑PO741, FR‑PO859, FR‑PO1056, SA‑OR004,
SA‑OR007, SA‑PO034, SA‑PO055, SA‑PO098,
SA‑PO171, SA‑PO538, SA‑PO563, SA‑PO564,
SA‑PO652, SA‑PO666, SA‑PO693, SA‑PO700,
SA‑PO851, SA‑PO981, SA‑PO982, PUB128,
PUB161, PUB218, PUB411, PUB444, PUB492,
PUB497, PUB627, PUB629, PUB680, PUB681,
PUB785
pediatrics.................TH‑PO021, TH‑PO306, TH‑PO583,
TH‑PO584, TH‑PO586, TH‑PO604, TH‑PO617,
TH‑PO620, TH‑PO622, TH‑PO673, TH‑PO695,
TH‑PO718, TH‑PO923, TH‑PO1026, TH‑PO1031,
TH‑PO1066, TH‑PO1067, FR‑OR010, FR‑PO1035,
SA‑PO034, SA‑PO275, SA‑PO276, SA‑PO401,
SA‑PO408, SA‑PO501, SA‑PO597, SA‑PO605,
SA‑PO668, PUB035, PUB069, PUB578, PUB586
pericarditis.......................................................FR‑PO033
peritoneal dialysis......................TH‑PO612, TH‑PO613,
TH‑PO737, TH‑PO744, TH‑PO1035, TH‑PO1048,
TH‑PO1149, FR‑OR077, FR‑PO021, FR‑PO908,
FR‑PO929, FR‑PO931, FR‑PO1034, FR‑PO1035,
FR‑PO1037, FR‑PO1039, FR‑PO1040, FR‑PO1042,
FR‑PO1043, FR‑PO1044, FR‑PO1047, FR‑PO1048,
FR‑PO1049, FR‑PO1050, FR‑PO1051, FR‑PO1053,
FR‑PO1054, FR‑PO1055, FR‑PO1056, FR‑PO1057,
FR‑PO1059, FR‑PO1060, FR‑PO1061, FR‑PO1062,
FR‑PO1063, FR‑PO1067, FR‑PO1068, FR‑PO1071,
FR‑PO1072, FR‑PO1073, FR‑PO1074, SA‑OR001,
SA‑OR002, SA‑OR003, SA‑OR004, SA‑OR005,
SA‑OR006, SA‑OR009, SA‑OR010, SA‑OR086,
SA‑PO023, SA‑PO034, SA‑PO037, SA‑PO045,
SA‑PO049, SA‑PO053, SA‑PO069, SA‑PO1004,
SA‑PO1071, SA‑PO1075, SA‑PO1076,
SA‑PO1077, SA‑PO1079, SA‑PO1080,
SA‑PO1082, SA‑PO1084, SA‑PO1085,
SA‑PO1086, SA‑PO1087, SA‑PO1088,
SA‑PO1089, SA‑PO1090, SA‑PO1092,
SA‑PO1093, SA‑PO1095, SA‑PO1096,
SA‑PO1098, SA‑PO1099, SA‑PO1100,
SA‑PO1101, SA‑PO1102, SA‑PO1104, SA‑PO1105,
SA‑PO1106, SA‑PO1110, SA‑PO1111, SA‑PO1112,
SA‑PO1127, SA‑PO1131, PUB117, PUB304,
PUB308, PUB406, PUB426, PUB447, PUB464,
PUB485, PUB552, PUB684, PUB686, PUB687,
PUB688, PUB690, PUB692, PUB693, PUB694,
PUB695, PUB696, PUB697, PUB698, PUB699,
PUB700, PUB701, PUB702, PUB705
peritoneal membrane............. TH‑PO1149, FR‑PO1051,
FR‑PO1062, FR‑PO1066, FR‑PO1072, SA‑OR007,
SA‑PO032, SA‑PO1071, SA‑PO1072, SA‑PO1074,
SA‑PO1076, SA‑PO1077, SA‑PO1078,
SA‑PO1079, SA‑PO1081, SA‑PO1084,
SA‑PO1085, SA‑PO1086, SA‑PO1087,
SA‑PO1088, PUB687, PUB691, PUB694
pharmacokinetics.......................TH‑PO799, FR‑PO841,
FR‑PO1080, SA‑PO501, SA‑PO502, SA‑PO504,
SA‑PO506, SA‑PO507, SA‑PO509, SA‑PO511,
SA‑PO512, SA‑PO514, SA‑PO516, SA‑PO520,
SA‑PO521, SA‑PO525, SA‑PO526, SA‑PO1089,
PUB116, PUB406, PUB407, PUB706
phosphate binders......................TH‑PO563, TH‑PO564,
TH‑PO565, TH‑PO754, TH‑PO903, TH‑PO905,
FR‑PO402, FR‑PO415, FR‑PO420, FR‑PO421,
FR‑PO422, FR‑PO424, FR‑PO428, FR‑PO434,
FR‑PO948, FR‑PO1065, SA‑PO038, SA‑PO389,
SA‑PO878, SA‑PO964, SA‑PO1129, PUB641,
PUB642
phosphate uptake.......................TH‑PO051, TH‑PO548,
FR‑OR071, FR‑OR073, FR‑PO405, FR‑PO409,
FR‑PO412, FR‑PO416, FR‑PO427, FR‑PO436,
FR‑PO438, FR‑PO1010, FR‑PO1022, SA‑PO763,
SA‑PO776, PUB205, PUB680, PUB715
platelets................. TH‑PO650, TH‑PO1148, FR‑PO685,
SA‑PO031, SA‑PO036, SA‑PO051, PUB414,
PUB574

podocyte................ TH‑OR026, TH‑OR071, TH‑OR076,
TH‑OR111, TH‑OR113, TH‑PO019, TH‑PO135,
TH‑PO152, TH‑PO166, TH‑PO217, TH‑PO218,
TH‑PO219, TH‑PO220, TH‑PO221, TH‑PO223,
TH‑PO224, TH‑PO226, TH‑PO227, TH‑PO231,
TH‑PO233, TH‑PO234, TH‑PO235, TH‑PO236,
TH‑PO238, TH‑PO239, TH‑PO246, TH‑PO247,
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TH‑PO254, TH‑PO261, TH‑PO262, TH‑PO273,
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TH‑PO423, TH‑PO424, TH‑PO425, TH‑PO427,
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FR‑OR053, FR‑OR085, FR‑OR115, FR‑PO002,
FR‑PO034, FR‑PO041, FR‑PO055, FR‑PO140,
FR‑PO141, FR‑PO143, FR‑PO144, FR‑PO145,
FR‑PO146, FR‑PO149, FR‑PO151, FR‑PO152,
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FR‑PO191, FR‑PO192, FR‑PO193, FR‑PO212,
FR‑PO290, FR‑PO296, FR‑PO303, FR‑PO316,
FR‑PO464, FR‑PO466, FR‑PO467, FR‑PO468,
FR‑PO469, FR‑PO470, FR‑PO471, FR‑PO475,
FR‑PO479, FR‑PO480, FR‑PO482, FR‑PO483,
FR‑PO485, FR‑PO487, FR‑PO488, FR‑PO491,
FR‑PO492, FR‑PO494, FR‑PO497, FR‑PO500,
FR‑PO501, FR‑PO504, FR‑PO505, FR‑PO506,
FR‑PO507, FR‑PO508, FR‑PO562, FR‑PO563,
FR‑PO607, FR‑PO645, FR‑PO665, FR‑PO918,
SA‑OR091, SA‑OR092, SA‑OR093, SA‑OR094,
SA‑OR095, SA‑OR097, SA‑OR098, SA‑OR066,
SA‑OR070, SA‑PO182, SA‑PO183, SA‑PO190,
SA‑PO258, SA‑PO273, SA‑PO296, SA‑PO311,
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PUB106, PUB107, PUB108, PUB338
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TH‑PO555, FR‑OR066, FR‑PO206, FR‑PO359,
FR‑PO509, FR‑PO511, FR‑PO512, FR‑PO517,
FR‑PO519, FR‑PO521, FR‑PO523, FR‑PO524,
FR‑PO526, FR‑PO531, FR‑PO532, FR‑PO534,
FR‑PO535, FR‑PO537, FR‑PO539, FR‑PO543,
FR‑PO553, FR‑PO557, FR‑PO1070, SA‑OR073,
SA‑OR075, SA‑OR076, SA‑OR078, SA‑PO582,
SA‑PO586, SA‑PO587, SA‑PO588, SA‑PO589,
SA‑PO591, SA‑PO597, SA‑PO600, SA‑PO603,
SA‑PO604, SA‑PO609, SA‑PO610, SA‑PO613,
SA‑PO615, SA‑PO617, SA‑PO623, SA‑PO957,
PUB248, PUB250, PUB251, PUB252, PUB254,
PUB258, PUB514
polymorphisms.......TH‑PO620, FR‑OR086, FR‑OR089,
FR‑PO287, FR‑PO586, FR‑PO609, FR‑PO651,
FR‑PO759, SA‑PO555, SA‑PO556, PUB055
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TH‑PO396, TH‑PO475, TH‑PO476, FR‑PO215,
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FR‑OR114
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TH‑OR098, TH‑PO352, TH‑PO551, TH‑PO699,
TH‑PO726, TH‑PO742, TH‑PO858, TH‑PO859,
TH‑PO872, TH‑PO877, TH‑PO878, TH‑PO881,
TH‑PO885, FR‑OR003, FR‑OR029, FR‑OR087,
FR‑PO233, FR‑PO429, FR‑PO665, FR‑PO674,
FR‑PO687, FR‑PO694, FR‑PO696, FR‑PO716,
FR‑PO724, FR‑PO731, FR‑PO736, FR‑PO739,
FR‑PO745, FR‑PO763, FR‑PO764, FR‑PO798,
FR‑PO802, SA‑PO185, SA‑PO451, SA‑PO508,
SA‑PO528, SA‑PO593, SA‑PO724, SA‑PO761,
SA‑PO778, SA‑PO782, SA‑PO866, SA‑PO883,
SA‑PO925, SA‑PO933, PUB135, PUB150,
PUB162, PUB167, PUB179, PUB181, PUB204,
PUB209, PUB210, PUB336, PUB675
progression of renal failure......TH‑OR028, TH‑OR104,
TH‑PO797, TH‑PO875, TH‑PO886, FR‑OR007,
FR‑OR075, FR‑PO009, FR‑PO038, FR‑PO626,
FR‑PO675, FR‑PO793, SA‑PO092, SA‑PO495,
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PUB223, PUB228, PUB488
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TH‑PO020, TH‑PO021, TH‑PO028, TH‑PO029,
TH‑PO032, TH‑PO166, TH‑PO221, TH‑PO223,
TH‑PO240, TH‑PO242, TH‑PO250, TH‑PO263,
TH‑PO275, TH‑PO281, TH‑PO291, TH‑PO304,
TH‑PO357, TH‑PO420, TH‑PO441, TH‑PO449,
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FR‑OR117, FR‑OR130, FR‑PO010, FR‑PO017,
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FR‑PO141, FR‑PO142, FR‑PO158, FR‑PO175,
FR‑PO183, FR‑PO192, FR‑PO331, FR‑PO440,
FR‑PO466, FR‑PO471, FR‑PO479, FR‑PO499,
FR‑PO504, FR‑PO604, FR‑PO618, FR‑PO623,
FR‑PO625, FR‑PO650, FR‑PO676, FR‑PO711,
FR‑PO728, FR‑PO757, FR‑PO830, FR‑PO1085,
SA‑OR058, SA‑OR081, SA‑PO190, SA‑PO237,
SA‑PO255, SA‑PO256, SA‑PO258, SA‑PO319,
SA‑PO388, SA‑PO430, SA‑PO530, SA‑PO565,
SA‑PO566, SA‑PO643, SA‑PO651, SA‑PO654,
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PUB577, PUB604, PUB661, PUB722, PUB727,
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proximal tubule.........................TH‑OR021, TH‑OR023,
TH‑OR079, TH‑OR114, TH‑OR128, TH‑PO110,
TH‑PO128, TH‑PO263, TH‑PO264, TH‑PO431,
TH‑PO573, FR‑OR052, FR‑PO052, FR‑PO086,
FR‑PO096, FR‑PO169, FR‑PO199, FR‑PO210,
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SA‑PO094, SA‑PO095, SA‑PO108, SA‑PO147,
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SA‑PO311, SA‑PO328, SA‑PO420, SA‑PO467,
SA‑PO491, SA‑PO651, SA‑PO668, SA‑PO669,
PUB026, PUB095, PUB110, PUB265, PUB420,
PUB680
pulse wave velocity.....................TH‑PO313, TH‑PO318,
TH‑PO913, TH‑PO1153, FR‑PO905, SA‑PO1132,
PUB303
pyelonephritis.........TH‑PO155, TH‑PO582, TH‑PO585,
TH‑PO587, TH‑PO810, FR‑PO064, FR‑PO389,
SA‑PO011, SA‑PO288, PUB572
quality of life......... TH‑OR049, TH‑OR050, TH‑OR106,
TH‑PO935, TH‑PO936, TH‑PO965, TH‑PO967,
TH‑PO1018, TH‑PO1032, TH‑PO1033,
TH‑PO1034, TH‑PO1038, TH‑PO1043,
TH‑PO1048, TH‑PO1103, TH‑PO1104,
TH‑PO1107, TH‑PO1108, TH‑PO1109,
TH‑PO1111, TH‑PO1113, TH‑PO1114, TH‑PO1115,
TH‑PO1136, TH‑PO1138, FR‑OR027, FR‑PO791,
FR‑PO823, FR‑PO966, FR‑PO1038, FR‑PO1048,
FR‑PO1049, SA‑PO364, SA‑PO379, SA‑PO382,
SA‑PO383, SA‑PO623, SA‑PO916, SA‑PO917,
SA‑PO934, SA‑PO937, SA‑PO943, SA‑PO944,
SA‑PO945, SA‑PO946, SA‑PO947, SA‑PO948,
SA‑PO949, SA‑PO951, SA‑PO952, SA‑PO954,
SA‑PO955, SA‑PO1055, SA‑PO1103, SA‑PO1114,
SA‑PO1127, SA‑PO1138, SA‑PO1147, PUB119,
PUB120, PUB121, PUB175, PUB208, PUB315,
PUB329, PUB579, PUB597, PUB629, PUB686,
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RAGE (receptor for AGEs)......................... TH‑PO1092
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TH‑OR044, TH‑OR096, TH‑PO756, TH‑PO758,
TH‑PO884, TH‑PO903, TH‑PO909, TH‑PO911,
TH‑PO914, TH‑PO994, FR‑OR083, FR‑PO815,
FR‑PO858, FR‑PO865, FR‑PO866, FR‑PO943,
SA‑OR002, SA‑PO1054, SA‑PO1114, PUB158


HI-OR01
Liraglutide and Renal Outcomes in Type 2 Diabetes: Results of the LEADER Trial

1Wessex Kidney Centre; 2London School of Hygiene & Tropical Medicine; 3Univ College London.

Background: Ischaemia reperfusion (IR) injury at transplantation contributes to damage that limits allograft longevity. The REPAIR study demonstrated a trend towards improved iohexol GFR (adjusted relative increase 3.08ml/min/1.73m²; p=0.13), and a significant improvement in eGFR (4.98ml/min/1.73m²; p=0.011) at 1 year in patients undergoing early RIPC prior to LD kidney transplantation. We analysed eGFR data up to 5 years.

Methods: 406 adult live donor/recipient pairs were randomised by factorial design to: sham RIPC/early RIPC (immediately pre-surgery)/late RIPC (24 hours pre-surgery)/dual RIPC (early+late RIPC). The primary outcome was iohexol GFR at 12 months. eGFR (CKD-EPI) up to 60 months was an important secondary outcome.

Results: eGFR data demonstrated a sustained benefit of early RIPC - adjusted mean differences between control & early RIPC groups were 3.94 (p=0.052), 5.16 (p=0.015), 5.55 (p=0.039) & 5.05 (p=0.104) ml/min/1.73m² at 2.3, 4 & 5 years (100% completed 3 years, 4 & 5 year follow up ongoing).

Conclusions: In conclusion, liraglutide in addition to standard of care therapy reduced the progression of diabetic nephropathy.

Funding: Pharmaceutical Company Support - Novo Nordisk

HI-OR02
Remote Ischaemic Preconditioning (RIPC) Leads to Sustained Improvement in Allograft Function Following Live Donor (LD) Kidney Transplantation: 5 Year Follow Up in the REnal Protection Against Ischaemia Reperfusion in Transplantation (REPAIR) Study

Kristin Søndergaard, Neil Poulter, Mark Daniels, Michael Nauck, Kristin Brown Frandsen, Gilbert Daniels, Peter Kristensen, Michael Nauck, Steve Nissen, Stuart Marson, Nicholas Pocock, Steve Nauck, Mette Steinberg, Mette Stockner, Bernhard Zinnman, Florian Baeres, Richard Bergenstal, Steve Marso, John Buse.

Nephrology, Friedrich Alexander Univ Erlangen, Erlangen, Germany.

Background: The effects of liraglutide, a long-acting glucagon-like peptide-1 (GLP-1) analog, on renal outcomes in type 2 diabetes are unknown. We conducted a randomized, double-blind, placebo-controlled trial comparing liraglutide vs placebo, both on a background of standard of care, in participants with type 2 diabetes and high cardiovascular risk.

Methods: The Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial was initiated in 2010 and completed in 2015. Renal events were key secondary outcomes. The primary renal outcome was a composite of persistent macroalbuminuria, persistent doubling of serum creatinine, end stage renal disease (ESRD), or death due to renal disease. Risk of renal outcomes was determined using intention-to-treat in time-to-event analyses; competing risk of death was taken into account. Change of eGFR and loss of eGFR by >30% was also analyzed.

Results: 9340 patients were randomized and median follow-up was 3.84 years. The primary renal outcome occurred in fewer participants treated with liraglutide (268 of 4668) than with placebo (337 of 4672; HR 0.787 [0.670,0.924]; p=0.003). The difference was primarily driven by new onset of persistent macroalbuminuria, occurring in fewer participants treated with liraglutide (161 of 4668) than with placebo (215 of 4672; HR 0.74 [0.61,0.91]; p=0.004). Doubling of serum creatinine and ESRD tended to be less frequent with liraglutide: eGFR decreased significantly less and albuminuria increased less with liraglutide than placebo. The difference in change of eGFR was driven exclusively by the subgroup with eGFR <60 ml/min at baseline (N=2458). The change in difference of albuminuria was independent of baseline of eGFR or albuminuria.

Conclusions: In conclusion, liraglutide in addition to standard of care therapy reduced lower graft loss & mortality was noted in all preconditioned groups.

Funding: Government Support - Non-U.S.
HI-OR05
AURA-LV: Successful Treatment of Active Lupus Nephritis with Voclosporin William Franklin Pendergraft,1 James A. Tumlin,2 Bradford H. Rovin,3 Mary Anne Dooley,1 David R. W. Jayne,4 David Wofsy,5 Frederic A. Houssiau,5 David Isenberg,6 Tak-nao Chan,7 Neil Solomon,8 Robert B. Huizinga,9 UNC; 10Penn Med; 11NYU Langone Health, New York, NY; 12Nephrology, Univ of WA, Seattle, WA; 13Retrophin, Inc., Cambridge, MA; 14Nephrology, Veterans Affairs Affairs Medical Center, West Haven, CT; 15Dept of Medicine, Perelman School of Medicine at the Univ of Pennsylvania, Philadelphia, PA; 16Dept of Medicine, Univ of Western Ontario, Ontario, Canada; 17Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: In lupus nephritis (LN), complete (CR) or partial remission (PR) is associated with improved renal survival. Voclosporin (VCS) is a novel CNIs with improved safety and predictable PK/PD profile.

Methods: The trial primary objective was CR defined as a urine protein/creatinine ratio (UPCR) of <0.5 mg/mg using an eGFR of 60 mL/min without a decrease of ≥20%. Entry criteria: renal biopsy within 6 months (Class III-V LN, ISN/RPS); UPCR>1.5 (III-IV) or 2.0 mg/mg (V);serologic evidence of active LN; and eGFR >45ml/min. Low (23.7 mg BID) or high dose VCS (39.5 mg BID) was administered with MMF and steroids.

Results: 265 patients were enrolled. Baseline UPCR (mg/mg) was 4.4 (placebo). 5.2 (low dose VCS) and 4.5 (high dose VCS). 24 week CR. 19.3% (placebo), 32.6% (low dose) and 27.3% (high dose) (OR: 2.03, p=0.045 low dose vs. placebo). The results were confirmed by 24 hour urine collections (p=0.047). Both the low and high dose VCS were statistically superior to placebo in PR and time to CR and PR. In the VCS groups, eGFR fell by a median of 8-9 ml/min by week 4 and then stabilized. Mean blood pressure between groups was similar. Over 90% of subjects experienced at least one adverse event with the most common being infections and GI events. More patients experienced serious adverse events in both voclosporin groups (25.8% low; 25.0% high, 15.8% placebo) with the nature of SAEs consistent with those observed in patients with highly active LN. There were 13 deaths (1 placebo, 10 low, 2 high) with 11/13 in Asia. Causes were multi-factorial including sepsis and other lupus-related complications. None were considered related to VCS by investigators.

Conclusions: The AURA study is the first global study to demonstrate the positive effects of VCS in the treatment of active LN. Adverse events were higher in the treated patient group, consistent with increased immunosuppression. There was a higher mortality rate in the low-dose group with heterogeneous causation. These favorable data will help plan subsequent studies of voclosporin in LN.

Funding: Pharmaceutical Company Support - Aurinia Pharmaceuticals Inc

HI-OR06
Efficacy and Safety of Sparsentan, a Dual Angiotensin II (Ang II) and Endothelin (ET) Type A Receptor Antagonist, in Patients with Focal Segmental Glomerulosclerosis (FSGS): A Phase 2 Trial (DUET) Howard Trachtman,1,2 Peter J. Nelson,1 Radko Komers.4 1Pediatric Nephrology, NYU School of Medicine, New York, NY; 2NYU Langone Medical Center, New York, NY; 3Nephrology, Univ of WA, Seattle, WA; 4Retrophin, Inc., Cambridge, MA.

Background: This phase 2, double-blind (DB), controlled trial (NCT01613118) evaluated the efficacy and safety of sparsentan (SPAR) as a treatment for primary FSGS.

Methods: After a 2-week ACEI/ARB washout, 109 patients, aged 8-71 yrs, with biopsy-proven FSGS were randomized to receive SPAR 200, 400, or 800mg/day, or the active control ARB irbesartan (IRB, 300mg/day) for 8 weeks. The primary endpoint was the change in urine protein-to-creatinine ratio (UPCR) from baseline. The proportion of patients with a decrease of ≥20% in UPCR was compared between groups (placebo vs those treated with IRB (45% vs 19%, P=0.006). A significant reduction in UPCR was also observed in pooled 400-800mg groups (47% vs 19%, P=0.01). The proportion of patients who achieved UPCR <3g/g with ≥40% reduction was 28% across all SPAR groups and 9% in IRB (P<0.05). Complete remission (UPCR <3g/g) occurred in 4 SPAR- and 0 IRB-treated patients. In the DB period, the most common treatment emergent adverse event (AE) was hypotension; 2 SPAR patients had serious AEs (anemia, unrelated hospitalization), which did not result in discontinuation of treatment; and 3 patients discontinued due to AEs (AKI and modest LFT elevation in SPAR; hypoa(iiubuminemia in IRB). All patients who completed the DB period were offered to continue on open-label SPAR treatment.

Conclusions: In summary, in patients with FSGS, dual Ang II and ET blockade with SPAR achieved significantly greater antiproteinuric effect compared with blockade of Ang II alone with IRB. In accord with prior studies in essential hypertension, SPAR appears to be safe and well tolerated in patients with FSGS.

Funding: Pharmaceutical Company Support - Retrophin, Inc.

FR-PO1121
Development and Validation of a Model to Improve Targeting of Electronic Alerts for Hospitalized Patients with Acute Kidney Injury Francis Perry Wilson,1,2 Aditya Biswas,3 Chirag R. Parikh,1,2 Harold I. Feldman,3 Amit X. Garg,4 Paul M. Palevsky,5 Stephen R. Latham.3 1Program of Applied Translational Research, Yale Univ, New Haven, CT; 2Clinical Epidemiology Research Center, Veterans Affairs Affairs Medical Center, West Haven, CT; 3Dept of Medicine, Perelman School of Medicine at the Univ of Pennsylvania, Philadelphia, PA; 4Dept of Medicine, Univ of Western Ontario, Ontario, Canada; 5Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: The proliferation of alerts in the hospital can lead to alert fatigue. Uplift modeling may allow for personalized targeting of alerts to reduce provider burden and increase effectiveness.

Methods: Using data from our prior randomized trial of electronic alerts for acute kidney injury (AKI), we trained a neural-network-based uplift model on the first 4/5ths of study participants. We then tested the model in the last 1/5 of study participants to identify a subgroup of individuals who would particularly benefit from alerts, manifested by a reduction in the risk of progression of AKI at 7 days.

Results: A total of 19.7% of patients had progression of AKI in the training set and 17.8% in the test set (p=0.35). Alerting showed no significant benefit on AKI progression in either the training or test set (p=0.12, p=0.60, respectively). The uplift-model identified 213 individuals in the test set predicted to benefit from alerts, and 265 predicted not to benefit. Among those expected to benefit, alerting significantly reduced progression of AKI (OR 0.48, 0.24-0.93, p=0.03). There was no significant alert effect in those not expected to benefit (p=0.19).

Funding: NIDDK Support

FR-PO1122

Background: Curcumin is a popular herbal supplement from the spice turmeric. It has anti-oxidant, anti-inflammatory and anti-apoptotic properties, and reduces ischemic reperfusion and nephrotoxic injury in animals. We tested whether oral curcumin reduces markers of injury and clinical acute kidney injury (AKI) in patients undergoing elective abdominal aortic aneurysm repair.

Methods: We randomized 606 patients at 10 centres to take oral curcumin or matching placebo for 4 days (2000 mg on 8 occasions) at the time of elective open or endovascular abdominal aortic aneurysm repair. The primary outcomes were 4 makers of injury after the repair. Secondary outcomes included clinical AKI, a composite of adjudicated clinical events, hospital length of stay and safety outcomes (diabetes, anemia). The methods and analyses were pre-specified (ClinicalTrials.gov NCT01225994).

Results: Oral curcumin was well tolerated with >90% scheduled pills taken. Curcumin (n=304) versus placebo (n=302) had no significant effect on any injury marker, nor any other outcome. Results were consistent in additional analyses.

Key: FR - Friday; OR - Oral; PO - Poster
Underline represents presenting author.
**FR-PO1123**

**Randomized Controlled Trial for Renal Denervation in Resistant Hypertensive Patients (SYMPATHY): Relevance of Medication Adherence**

Rosa de Jager,1 Michiel Bots,2 Peter J. Blankesteijn.1 Nephrology and Hypertension, UMC Utrecht, Utrecht, Netherlands; 2Julius Center, UMC Utrecht, Utrecht, Netherlands.

**Background:** Randomized controlled trials of catheter-based renal denervation (RDN) as therapy for resistant hypertension produced conflicting results. Medication adherence may be important in (partially) explaining that.

**Methods:** SYMPATHY is a prospective open label multicenter trial in Dutch patients with resistant hypertension (NCT01850901). Primary outcome was change in daytime systolic ambulatory blood pressure (ABPM) at 6 months. Patients were randomly assigned to RDN or not on top of usual care. Secondary outcome included medication adherence, which was qualitatively assessed by liquid chromatography/tandem mass spectrometry with spectra library search, using blood samples collected on the day of blood pressure (BP) measurements. Patients and physicians were unaware of adherence assessment.

**Conclusion:** SYMPATHY was approved by the Ethics Committee.

**Results:** SYMPATHY enrolled 139 patients (95 RDN; 44 control) from May 2013 to January 2016. Mean differences between control and RDN in changes in daytime systolic ABPM after 6 months was 2.0 mmHg (95% CI -6.1 to 10.2), in 24h systolic ABPM 1.0 mmHg (-1.7 to 1.9) and in office systolic BP -8.2 mmHg (-17.1 to 0.7). In four out of five patients fewer medications were detected than were prescribed. Baseline mean number of prescribed types of BP lowering drugs was 3.8±1.5 and was detected of 1.7±1.4. The better the adherence, the lower daytime systolic ABPM. A significant increase in number of detected drugs at 6 months (increase of 0.6 pills, (0.1 to 1.0), p=0.03) was found in the control, but not in the RDN group (0.5 pills (0.2 to 0.8)).

**Conclusions:** This is the second largest trial in the field of RDN and the first that objectively assessed medication use in both the intervention and the control arm. RDN as therapy for resistant hypertension was not superior to usual care. Medication adherence is poor, when patients were unaware of monitoring. Hypertension which seems "resistant" to treatment (partially) explained by poor medication adherence. Changes over time in adherence differ between RDN and control group. This complicates the interpretation of the results on BP.

**Funding:** Pharmaceutical Company Support - Medtronic, Government Support - Non-U.S.

**FR-PO1125**

**Renal and Vascular Effects of Uric Acid Lowering in Patients with Uncomplicated Type 1 Diabetes Mellitus**

Yuliya Lytvyn,1 Ronnie Lok-Hang Har,1 Amy Locke,1 Vesta S. Lai,1 Derek S. Fong,3 Andrew Advani,2 Bruce A. Perkins,2 David Cherney.1 Medicine/Nephrology, Univ of Toronto/Univ Health Network, Toronto, ON, Canada; 2Medicine/Endocrinology, Univ of Toronto/St. Michael’s Hospital, Toronto, ON, Canada; 3Medicine/Endocrinology, Univ of Toronto/Mount Sinai Hospital, Toronto, ON, Canada.

**Background:** Even within the normal range, higher plasma uric acid (PUA) levels are associated with lower GFR and higher blood pressure (BP) in young adults with type 1 diabetes (T1D). Our aim was to determine the impact of PUA lowering on renal and vascular function in patients with uncomplicated T1D.

**Methods:** T1D patients (n=49) were studied under eu- and hyperglycemic conditions at baseline and after treatment with the xanthine oxidase inhibitor febuxostat (FBX), for 8 weeks. Healthy controls (HC) were studied under euglycemic conditions (n=24). PUA, GFR (inulin), effective renal plasma flow (ERPF, paraaminohippurate), BP and hemodynamic responses to an infusion of angiotensin II (to assess the intrarenal RAAS) were measured pre- and post-FBX. Arterial stiffness, flow mediated and nitroglycerin mediated dilatation (FMD and GMD respectively) were measured pre- and post-FBX. Gomez’s equations were used to estimate afferent (R_a) and efferent (R_e) arteriolar resistances and glomerular hydrostatic pressure (P glomeruli).

**Results:** FBX decreased PUA in HC (303±71µmol/L to 131±55µmol/L, p<0.0001) and T1D (2406±224µmol/L to 124±53µmol/L, p=0.0001). FBX had a modest systolic BP lowering effect in T1D patients (112±1mmHg to 109±9mmHg, p=0.049), but not in HC, which was not accompanied by changes in arterial stiffness, FMD or GMD in either cohort. FBX enhanced the filtration fraction response to hyperglycemia in T1D patients, through larger increases in R_e and P glomeruli, but without impacting the RAAS.

**Conclusions:** PUA lowers systolic BP and may modulate the renal R_e responses to hyperglycemia. Ongoing longitudinal outcome trials will determine whether BP and renal hemodynamic effects of PUA lowering modify renal or cardiovascular outcomes in patients with T1D.

**Funding:** Government Support - Non-U.S.
FR-PO1126

Anti-Inflammatory Effects of Topiroxostat in Hyperuricemic Patients with Diabetic Nephropathy: A Multicenter, Open-Label, Randomized Trial

Toshihiro Mizukoshi,1 Sawako Kato,1 Masahiko Ando,1 Hiroshi Sobajima,1 Norimi Ohashi,2 Tomohiko Naruse,1 Hideaki Shimizu,2 Yosuke Sakai,2 Takanobu Nagata,1 Shioichi Maruyama.1 1Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan; 2Center for Advanced Medicine and Clinical Research, Nagoya Univ Hospital, Nagoya, Japan; 1ETUE Study Research Group, Japan.

Background: Proteinuria is an established risk factor for diabetic nephropathy. Recent studies indicate that some xanthine oxidase inhibitors (XOIs) have a renoprotective effect.

Methods: The ETUE study (Effect of Topiroxostat, a selective XO, on Urinary albumin in hyperuricemic patients with Diabetic nephropathy) was a 24-week, multicenter, open-label, randomized (1:1) trial of 80 patients. Hyperuricemic patients with diabetic nephropathy (estimated glomerular filtration rate [eGFR] > 20 mL/min/1.73 m2) and overt proteinuria (0.3 g to creatinine ratio (UPCR) > 3.5 g/g Cr) were assigned to either high dose (160 mg daily) or low dose (40 mg daily) topiroxostat. The primary endpoint was the change in albuminuria measured by urinary albumin-to-creatinine ratio (UACR) after 24 weeks relative to the baseline value.

Results: Baseline characteristics were similar between the groups. In the high dose group after 24 weeks of treatment the UACR significantly decreased by -12.2 mg/gCr (95% CI: 5.1 to -19.3, P = 0.003), while in the low dose group the decrease in UACR was not significant (-20.1 mg/gCr [95% CI: 16.5 to -41.7, P = 0.066]). In the linear mixed model including baseline albuminuria, eGFR, age, and sex as covariates, the decreases in UACR in patients treated with topiroxostat were still significant from baseline to 12 weeks by 22.7 ± 8.3 mg/gCr (P = 0.0075) in the high dose group and to 24 weeks by 203.9 ± 77.1 mg/gCr (P = 0.001) in the low dose group. There was no significant difference between the groups. Topiroxostat had mild and significant lowering effects on eGFR and systolic and diastolic blood pressure, and it steadily reduced serum uric acid levels. The adverse event profile during this study was not different between the groups.

Conclusions: Topiroxostat 160 mg daily reduced albuminuria in patients with diabetic nephropathy. Trial registration: UMIN 000015403.

Funding: Pharmaceutical Company Support - Sanwa Kagaku Kenkyusho Co., Ltd.

FR-PO1127

Abstract Withdrawn

FR-PO1128

Effects of Blisibimod, a Selective Inhibitor of B-Cell Activating Factor, in Patients with IgA Nephropathy

Jonathan Barratt,1 Colin Hislop,2 Jim Pennington,1 Monica Gangal,2 Renee Martin,3 Adrian Liew.1

1Infection, Immunology & Inflammation, Univ of Leicester, Leicester, United Kingdom; 2Pennington, Liew, 1St Georges Univ of London; 3Guy’s Hospital.

Background: IgA nephropathy (IgAN) is the commonest glomerulonephritis in the world. The elevated serum B-cell activating factor (BAFF) correlates with IgAN histological severity. We report interim results of a Phase 2, randomized, double-blind, placebo-controlled trial evaluating the effects of blisibimod, a BAFF inhibitor, in patients with IgAN (BRIGHT-SC Study, NCT02062684).

Methods: Subjects with biopsy-proven IgAN, urine protein:creatinine ratio (UPCR) 1-6 g/g, eGFR > 30mL/min/1.73m2 on renin-angiotensin blockade were randomized to subcutaneous blisibimod (100mg 3x/week for 8 weeks, then 200mg weekly) or placebo.57 subjects met the entry criteria, 47 of whom had been followed for at least 6 months at the time of analysis.

Results: B-cell subsets and immunoglobulin levels decreased significantly in the blisibimod group, demonstrating pharmacological inhibition of BAFF. Proteinuria reduction was seen in the blisibimod group, while a steady increase was seen with placebo, this effect persisted to week 96 (% change from baseline -8.7% vs+59.4%, P=0.017). Separation of analysis.

Conclusions: Blisibimod was well-tolerated with no safety concerns reported by the safety monitoring board.

Funding: Private Foundation Support

FR-PO1130

Abstract Withdrawn

FR-PO1131

Efficacy of LDL Apheresis in the Treatment of Drug-Resistant Nephrotic Syndrome

Naoki Takamatsu, Yufu Gochio, Takuto Maeda, Hideki Takizawa.

Nephrology, Teine Keijinkai Hospital, Sapporo, Japan.

Background: LDL apheresis (LDL-A) is an extracorporeal measure to correct dyslipidemia (DL). In Japan, LDL-A is approved as a treatment of secondary DL associated with refractory nephrotic syndrome (NS) due to focal segmental glomerulosclerosis (FSGS). In addition to correction of DL, LDL-A is thought to enhance responses of immunosuppressants leading to rapid resolution of NS. A frequently encountered dilemma is the management of clinically evident FSGS despite an otherwise established biopsy-proven diagnosis. We investigated the effect of LDL-A on biopsy-proven FSGS (pFSGS) and clinically-diagnosed FSGS (cFSGS).

Methods: 10 cases of LDL-A performed for the first time against drug-resistant NS of FSGS origin (pFSGS=3, cFSGS=7) between 4/2008-8/2016 were enrolled. Clinical parameters before and after LDL-A was compared between pFSGS and cFSGS, and between complete remission (CR) and incomplete remission (IR) groups. In addition, efficacy of LDL-A and length of hospital stay was evaluated among 3 of the relapsed cases thereafter, with complete remission (CR) and incomplete remission (IR) groups.

Results: All patients received concomitant treatment of immunosuppressants (prednisolone=10, cyclosporine=4), and all achieved remission from NS with LDL-A (Up

Table 1: The outcome variables at 52 weeks

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Placebo</th>
<th>Vitamin D</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass (g)</td>
<td>96±25</td>
<td>100±39</td>
<td>0.28</td>
</tr>
<tr>
<td>LV stroke volume (ml)</td>
<td>149±36</td>
<td>154±36</td>
<td>0.67</td>
</tr>
<tr>
<td>LV end systolic volume (ml)</td>
<td>108±36</td>
<td>118±34</td>
<td>0.25</td>
</tr>
<tr>
<td>LV stroke volume (ml)</td>
<td>97±24</td>
<td>98±33</td>
<td>0.74</td>
</tr>
<tr>
<td>RV end systolic volume (ml)</td>
<td>161±24</td>
<td>162±39</td>
<td>0.92</td>
</tr>
<tr>
<td>RV end diastolic volume (ml)</td>
<td>60±20</td>
<td>64±15</td>
<td>0.69</td>
</tr>
<tr>
<td>RV ejection fraction (%)</td>
<td>59±4</td>
<td>59±8</td>
<td>0.97</td>
</tr>
<tr>
<td>RA area (cm²)</td>
<td>204±5</td>
<td>204±5</td>
<td>0.68</td>
</tr>
<tr>
<td>LA area (cm²)</td>
<td>213±7</td>
<td>22±3</td>
<td>0.63</td>
</tr>
<tr>
<td>LV e/a ratio</td>
<td>1.02±22</td>
<td>0.96±27</td>
<td>0.41</td>
</tr>
<tr>
<td>LV septal wall</td>
<td>6.8±09</td>
<td>7.1±89</td>
<td>0.93</td>
</tr>
<tr>
<td>LV / septal wall</td>
<td>10.8±3</td>
<td>9.3±3</td>
<td>0.92</td>
</tr>
<tr>
<td>LV systolic pressure (mmHg)</td>
<td>22.5±8</td>
<td>22.4±5</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Legend: LV=left ventricle, RV=right ventricle, LVET=left axis, RVET=right axis, E/e’=e’ ratios at septum and lateral wall, pulmonary artery systolic pressure between the vitamin D and placebo groups [see table 1].

Conclusions: Cholesterol lowering through 52 weeks increased vitamin D levels but did not have an impact on cardiaic function in stable, non-diabetic, CKD patients with low vitamin D.

Funding: Private Foundation Support

Key: FR - Friday; OR - Oral; PO - Poster
Underline represents presenting author.

4B
Predicting Adverse Events with Non-Invasive Monitoring

Mark S. Segal,1 Robert W. Nappo,2 Matthew J. Banet,2 Susan M. Pede,2 1Nephrology, Univ of Florida, Gainesville, FL; 2Operations, UHHealth Dialysis, Gainesville, FL; 3ToSense.

Background: To investigate if adverse events can be identified prior to occurrence through non-invasive monitoring. Additional objectives were estimating true ‘dry weight’ and evaluation of waveforms to identify hypokalemia.

Methods: Prior to start of a dialysis session, research personnel applied ToSense’s CoVo™ Monitoring System (the ‘Sensor’) (1 figure) which made frequent measurements of stroke volume, cardiac output, thoracic fluid index, heart rate, respiration rate, and ECG waveforms and wirelessly communicated the data to a cloud based storage system to patients. Additional data captured and analyzed included patients’ weight before and after each dialysis session, blood pressure, fluid removed, adverse events during the dialysis session, and lab values.

Results: 28 males and 22 females participated in the study. 48 adverse events from 22 patients were captured including two patients with hypokalemia. Preliminary results indicate that: i) stroke volume decrease systematically during dialysis and precedes adverse events by 10 – 60 minutes; ii) changes in heart rate and heart rate variability precede adverse events by 10 – 60 minutes; iii) changes in blood pressure can be measured without a cuff semi-continuously. One patient experienced a 12.5-kilogram weight loss over 8 dialysis sessions. Thoracic fluid measurements indicated a plateau at a dry weight. Waveform data from the hypokalemia patients is still being analyzed.

Conclusions: This study demonstrates that the Sensor’s non-invasive measurements of stroke volume and fluid index may be able to predict adverse events during dialysis. Additionally, the ability to cufflessly measure blood pressure will provide earlier notification of hypotensive events during dialysis. In addition, repeated non-invasive measurements of thoracic impedance may provide insight into true dry weight for dialysis patients.

Funding: Pharmaceutical Company Support - ToSense, Inc.
FR-PO1137

Blood Pressure in Dialysis (BID) Trial Philip Zager,1,4,5 D. Miskulin,2,4,5 Jennifer J. Gassman,3,5 1UMN; 2Tufts; 4Cleveland Clinic; 5DCI; 6On Behalf of the BID Study Group.

Background: The KDQOI systolic blood pressure (SBP) guidelines for hemodialysis (HD) are based on expert opinion. Trial data are needed to determine if the benefits of intensive control of SBP in high-risk patients shown in SPRINT extend to HD patients. The BID Pilot assessed feasibility and safety of conducting a full-scale trial of intensive vs. standard control of SBP.

Methods: We randomized 126 patients to a predialysis SBP of 110-140 (n=62) or 155-165 (n=64) mm Hg for 1 year. We estimated mean SBP in each arm from a linear mixed model. We assessed the relationship of SBP to interdialytic weight gain (IDWG). We compared adverse events across arms. Change in left ventricular mass (LVM) was assessed by MRI.

Results: In days 91 to 365 the mean separation in SBP between arms was 12.9 mm Hg. The number of antihypertensive medications at baseline (2.9 vs. 2.4), 6 (3.3 vs. 2.4) and 12 (3.4 vs. 2.5) months was higher in the intensive vs. standard arm. We used Cox models (referred: standard arm) to assess time to first death (HR 4.29), all cause (HR 1.36) and cardiovascular (HR 2.72) hospitalizations (HI), all NS. There were 4 deaths in the intensive (not protocol related) and 1 in the standard arm (possibly protocol related). The numbers of HI and vascular access thromboses (VA) were higher in the intensive (12, 10) vs. standard arm (4, 7), both P=0.05. However, the number of patients with H and T was similar in the intensive (H 29, T 27) and standard arms (H 25, T 27) (NS). Intradialytic hypotension was more frequent in the intensive vs. standard arm. Overall there were no statistically significant relationships between IDWG and SBP. The median change in LVM was similar in the intensive (-0.8 g) vs. standard arm (1.5 g) (NS).

Conclusions: It is feasible to conduct a full-scale trial to determine if intensive control of SBP may improve clinical outcomes. However, the possible safety signal merits inclusion of a vanguard phase.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc. (DCI)

FR-PO1138

Blood Volume Monitoring Guided Ultrafiltration Biofeedback on Reduction of Intradialytic Hypotensive Episodes in Hemodialysis: Results of a Randomized Crossover Trial Kelvin C.W. Leung, Pietro Ravani, Robert R. Quinn, Jennifer M. MacRae. Medicine, Univ of Calgary, Calgary, AB, Canada.

Background: Intradialytic hypotension (IDH) is associated with significant patient morbidity. One type of biofeedback technology proposed for the prevention of IDH in hemodialysis (HD) is blood volume monitoring (BVM) guided ultrafiltration (UF) biofeedback which automatically adjusts the fluid removal rate based on blood volume parameters. The effect of BVM biofeedback on the reduction of IDH was tested in a randomized trial.

Methods: We performed a 22-week, single blind, randomized crossover trial in maintenance HD patients who had >30% of HD sessions in the preceding 8-weeks complicated by symptomatic IDH in 5 centres in Calgary, Alberta, Canada. Participants underwent a four-week run-in phase for dialysis prescription and dry weight optimization and those meeting inclusion criteria were randomized to best clinical practice HD (control) or best clinical practice plus BVM-guided UF biofeedback (intervention) for 8-weeks. This was followed by a two-week washout phase prior to crossing over for a second 8-week study phase. The primary outcome was the rate of symptomatic IDH. An intent-to-treat analysis was performed.

Results: Thirty-five participants entered the study, 32 met inclusion criteria for randomization and 26 completed the study. The rate of symptomatic IDH during the biofeedback intervention was 0.097/hr (95% confidence interval [CI] [0.055-0.139]/hr) and 0.0741/hr (95% CI 0.0498-0.0984/hr) during the control dialysis (P=0.05). There was no difference in the rate and proportion of sessions effected by asymptomatic IDH or symptoms alone between the two interventions. Results remained consistent when adjusted for randomization order and study week. There was no difference in intradialytic weight gain, proportion of patients achieving target weight, brain natriuretic peptide, cardiac troponin, body water content, ultrafiltration rate, and patient recovery time between the two interventions.

Conclusions: The use of BVM-guided UF biofeedback in IDH prone patients did not reduce the rate of symptomatic IDH events.

FR-PO1139

Study of the Effect of Dilution Mode on On-Line HDF on the Intra-dialytic Hemodynamic Stability: EDOIDEA Study Ikuto Masakan,1 Hideki Kawanishi,2 1Nephrology, Yabuki Hospital, Yamagata, Japan; 2Nephrology, Tsuchiya General Hospital, Hiroshima, Japan.

Background: On-Line hemodiafiltration (OL-HDF) is a rapidly developing dialysis modality, however, even in the latest systematic review the advantages of OL-HDF has been still controversial. OL-HDF is generally performed in post-dilution (Pre-HDF) in Europe and other many countries but pre-dilution (Post-HDF) has been the major in Japan. A Randomized control trial evaluating clinical advantages of pre-dilution OL-HDF has been thirsted for to clarify which dialysis modality is more effective to solve several issues in chronic dialysis patients. EDOIDEA study was designed and has been performed by Japanese Society for Hemodialysis (JSHDF) to answer the question.

Methods: EDOIDEA study is a randomized parallel crossover style for evaluating the influence of dialution method on intra-dialytic hemodynamic stability. The patients with informed consent were randomly divided into the next 2 groups, Group A and Group B. The patients were treated in the conventional therapy, Pre-HDF, Post-HDF, Pre-HDF in Group A and in the conventional therapy, Post-HDF, Pre-HDF, Post-HDF in Group B. The primary outcomes were about intra-dialytic hemodynamic stability and secondary outcomes were changes in blood chemistry, dialysis efficacy, albumin loss during dialysis session and patients’ subjective symptoms.

Results: Finally 99 patients were divided into 48 patients in Group A and 51 patients in Group B. The average substitution volumes were 54.3 L/session in Pre-HDF and 14.4 L/session in Post-HDF. There were no differences in blood pressure and intra-dialytic hypotension between pre-dilution and post-dilution. Kt/V area was greater in post-dilation than pre-dilution. The removal rate of beta2 microglobulin was not different between 2 Groups but albumin loss was greater in Post-HDF than Pre-HDF. There were no significant differences in the patients’ subjective symptoms.

Conclusions: There were no definitive differences on the hemodynamically stability between Pre-HDF and Post-HDF. The risks of albumin loss during dialysis session and hypoalbuminemia were greater in Post-HDF than Pre-HDF.

FR-PO1140

Elevated Tissue Na+ Deposition in Hemodialysis Patients with Insulin Dependent Diabetes Mellitus Detected by 23Na-Magnetic Resonance Imaging Anke Dahlmann,1 Christoph Kopp,1 Peter Linz,2 Matthias Hammorn,2 Daniela Ameslinger,1 Kai-Uwe Eckardt,1 Friedrich C. Luft,3 Jens Titze,4 Nephrology and Hypertension, Univ Hospital Erlangen-Nürnberg, Erlangen, Germany; 4Radiology, Univ Hospital Erlangen-Nürnberg, Erlangen, Germany; 3Max-Delbrück Center for Molecular Medicine and Charité Medical Faculty, Berlin, Germany; 5Clinical Pharmacology, Vanderbilt Univ, Nashville.

Background: Long-term elevated blood sugar, as observed in patients with insulin dependent diabetes mellitus (IDDM), results in matrix-compositional changes of skin and muscle tissue. We used 23Na-magnetic resonance imaging (23Na-MRI) to quantify tissue Na+ storage in skin and muscle of hemodialysis (HD) patients with or without concomitant IDDM. We hypothesized that tissue Na+ might accumulate to a higher extent in IDDM patients.

Methods: We determined tissue Na+ content by 23Na-MRI measurements pre- and post HD treatment in 13 HD+IDDM patients and in 46 age-matched control HD patients. Simultaneously, tissue water content was detected by H-MRI and blood samples were taken to determine HbA1c values.

Results: 23Na-MRI demonstrated increased Na+ content in muscle and skin tissue of HD+IDDM patients compared to control HD patients. Simultaneously measured tissue water content was detected by H-MRI was not significantly different. Ratio of tissue Na+ to water signal suggested edema-free Na+ storage. Muscle Na+ levels correlated with patients’ HbA1c values. Na+ and water mobilization during HD treatment lowered muscle Na+ and water content to a greater degree in HD+IDDM patients than in control HD patients.

Conclusions: 23Na-MRI detected increased Na+ in muscle and skin tissue of HD+IDDM patients compared to control HD patients. Muscle Na+ values were directly correlated with HbA1c levels. Our findings provide first evidence that impaired serum glucose metabolism is associated with disturbances in tissue Na+ and water content in the subpopulation of HD patients co-diagnosed with IDDM.

Funding: Private Foundation Support

Key: FR - Friday; OR - Oral; PO - Poster
Underline represents presenting author.
FR-PO1141

Intermittent HEMOdialysis Anticoagulation with TINzaparin versus Unfractionated Heparin (HEMA-TIN): A Multicentre Randomized Control Trial

Christine M. Ribic,1 Azim S. Gangji,1 Louise M. Moist,1 Michael Walsh,1 Deborah J. Cook,1 Mark A. Crowther,1 1Medicine, McMaster Univ, Hamilton, ON, Canada; 2Medicine, London Health Sciences Centre, London, ON, Canada.

Background: The predominant renal elimination of low molecular weight heparins (LMWHs) has raised safety concerns regarding their use as extracorporeal anticoagulants on hemodialysis (HD) due to potential bioaccumulation. Tinzaparin may be less dependent on renal clearance compared to other LMWHs. The safety and efficacy of tinzaparin for HD anticoagulation is unknown.

Methods: We conducted a double-dummy design, crossover RCT to evaluate the safety and efficacy of tinzaparin versus unfractionated heparin (UFH) for anticoagulation in patients maintained on facility-based, thrice weekly HD (NCT01930396). Patients received either UFH and tinzaparin placebo or tinzaparin and UFH placebo for 3 months followed by crossover to the alternate regimen for 3 months. Patients, health care providers and outcome adjudicators were blinded to treatment allocation. Dose titration for clinically apparent clotting of the HD circuit/filter or patient bleeding was protocolized. Primary outcomes were patient and study reported major, clinically important non-major or minor bleeds. Secondary outcomes included: a) anti-Xa and PTI levels pre and post HD; b) dialysis efficacy (Kt/V) and c) sessional HD tubing/membrane clotting using a novel scale which was validated in 205 participating dialysis nurses.

Results: 189 patients from 4 centres were randomized of which 157 crossed over and 125 completed the trial with a total of 126±11, 100 HD sessions evaluated. 125 pre and 125 post HD anti-Xa values underwent preliminary review by the data safety monitoring board and did not raise concern for bioaccumulation. 26 dose titrations occurred in 18 patients with 13 dose increases (6 UFH; 7 Tinzaparin) for clotting and 13 dose decreases (6 UFH; 7 Tinzaparin) for bleeding events. 159 (88.5 %) patients remained on 2500 units of tinzaparin throughout the trial.

Conclusions: Tinzaparin requires minimal dose titration for bleeding or clotting events in patients requiring HD. Full data with respect to minor and major bleeding, clotting scores, dialysis efficacy and anti-Xa levels will be presented.

Funding: Pharmaceutical Company Support - Leo Pharma

FR-PO1142

Roxadustat for the Treatment of Chronic Kidney Disease-Associated Anemia in Japanese Patients Not on Dialysis

Tadao Akizawa,1 Manabu Iwasaki,2 Tetsuro Otsuka,1 Michael Reusch,4 Toshihiro Misumi,4 1Showa Univ School of Medicine, Tokyo, Japan; 2Seikei Univ, Tokyo, Japan; 3Astellas Pharma Inc., Tokyo, Japan; 4Astellas Pharma Europe B.V., Leiden, Netherlands.

Background: Anemia is a complication of CKD. The purpose of this study was to evaluate the efficacy and safety of ASP1517 (roxadustat) in Japanese non-dialysis anemic CKD patients.

Methods: During the 1st 6 weeks of this phase 2, double-blind, 24-week study (NCT01964196), anemic Japanese patients with CKD were randomized to oral placebo (PBO) or roxadustat (50, 70, or 100mg) 3x weekly (TIW). During weeks 6 to 24, dose was adjusted to maintain hemoglobin (Hb) at 10–12 g/dL; patients who met pre-defined criteria were re-randomized to roxadustat TIW or once weekly (QW). The primary end point was rate of rise in Hb (ΔHb, g/dL/week) during the 1st 6 weeks; response rate over the whole study and mean Hb and change in Hb from baseline (BL) at Weeks 18–24 were also evaluated. Safety was assessed by adverse events (AEs). Data are presented as mean (SD).

Results: 107 patients were randomized to PBO (n=27) or roxadustat 50mg (n=27), 70mg (n=26), or 100mg (n=27). Hb (g/dL) at BL was 9.34 (0.66) for PBO, and 9.39 (0.59), 9.39 (0.60), and 9.36 (0.50) for roxadustat 50mg, 70mg, and 100mg, respectively. The primary end point, ΔHb (g/dL/week), was −0.052 (0.142) for PBO and +0.200 (0.160), +0.453 (0.256), and +0.570 (0.240) for roxadustat; differences from PBO for all roxadustat doses were statistically significant (P<.0001) by the closed testing procedure. Response rate was 14.8% for PBO and 93.8% for pooled roxadustat (n=81). Mean Hb at Weeks 18–24 was 9.42 (0.84) for PBO and 10.48 (0.64), 10.72 (0.56), and 10.88 (0.66) for roxadustat; change from BL in Hb was +0.17 (0.61) for PBO and +1.10 (0.71), +1.33 (0.82), and +1.55 (0.88) for roxadustat. No major adverse cardiac events (ie, myocardial infarction, stroke, death) occurred in roxadustat-treated patients.

Conclusions: These data demonstrate a dose-dependent and significant correction of Hb with roxadustat vs PBO. Roxadustat was well tolerated, which is consistent with previous studies. These results support the phase 3 investigation of roxadustat for the treatment of CKD-associated anemia in patients not on dialysis.

Funding: Pharmaceutical Company Support - Astellas Pharma Inc

Key: FR - Friday; OR - Oral; PO - Poster
Underline represents presenting author.

7B